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Editors

Dr. Manish Uniyal

Prof. S.C. Bhatt

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B. Sc. II YEAR

Elementary Solid State Physics

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Unit writing and Editing

Editing
Dr. T. C. Upadhyay, Professor
Department of Physics,
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Writing
Dr Madan Singh, Professor
Department of Physics and Electronics
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Dr. Mahipal Singh
Department Physics
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Dr. Girish Chandra
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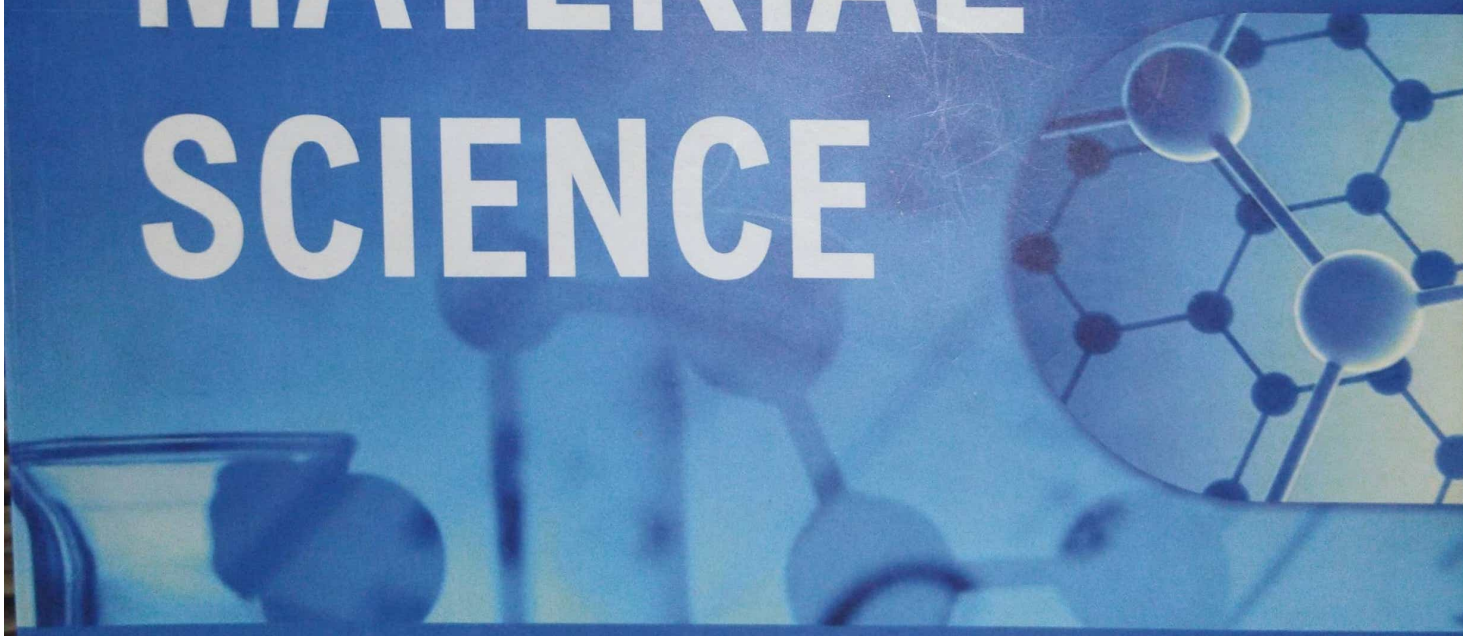

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Deptt. of Physics
HNBGU, Srinagar Garhwal

Shaurya Bhatt
Amity University
Noida (U.P.)

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Editorial

This book is a collection of research papers presented in the National Conference on recent Advances in Material Science (NCRAMS-13) which have been organized in the department of Physics, H.N.B. Garhwal University, Srinagar Garhwal from 26 to 27 october 2013. Dr. K.S. Bartwal was the key note speaker of the Conference. Dr.Bartwal is renown world famous Material Scientist in Raja Rammana Centre for Advance Technology (RRCAT), Indore. He delivered the talk on Advances in Materials Processing. Dr. L.P. Purohit from Gurukul Kangri University Haridwar, Dr. R.C. Ramola form SRT Tehri and number of eminient scientist, Faculties, Research Scholars from India participating the Conference and delivering the talks on Recent Advances in Material Science. This conference is organized by keeping in view to provide opportunities for interaction and discussion of the senior researchers working in the field of material Science and Recent Advances to the young faculties, Research Scholars of the University and the affiliating colleges. We are thankful to the Hon'ble Vice Chancellor Prof.S.K.Singh, Registrar Prof. P.S. Rana, Finance Officer Prof. J. S. Bisht, All Deans, Head Department of Physics Prof.R.P.Gairola and other University officers & officials for their kind Support and help. We are also thankful to the funding Agencies DAE-BRNS Mumbai, DST, UCOST, INSA and HNBGU for providing the financial assistance to organize the successful National Conference

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Temperature dependence of dielectric properties of H- phase $[Ta_2O_5]_{1-x} - [TiO_2]_x$, $(0.078 \leq x \leq 0.085)$

Aradhana Bhandari,[1] Alok S. Kandari,[1] and N. S. Panwar[1,*]

[1]University Science Instrumentation Centre, HNB Garhwal University, Srinagar (Garhwal) - 246174, India

Abstract

Observed temperature dependence of dielectric constant, loss tangent and dielectric conductivity of H- phase $[Ta_2O_5]_{1-x}$-$[TiO_2]_x$, $(0.078 \leq x \leq 0.085)$ pellets, prepared by solid state reaction method, has been presented. Dielectric constant was observed slowly increasing with temperature showing strong transition peaks at 495, 505, 510 and 520 °C for the compositions with x = 0.078, 0.080, 0.082 and 0.085, respectively. Dielectric loss and conductivity also show anomalous increase near the transition temperature, for all the prepared compositions. Near the transition temperature, anomalous dielectric behavior may be associated with the softening of the active phonon mode.

Keywords: Ceramics, Phase Transformation, Sintering

*Corresponding author, E-mail address: arru.srg@gmail.com

1. Introduction

To meet out the demand for miniaturized components with enhanced performance in microelectronics applications, tantalum pentoxide (Ta_2O_5) has been proposed as one of the promising alternatives [1-6] to the low dielectric constant silicon oxy-nitrides [7-10]. Dielectric constant of Ta_2O_5 can be enhanced further [11-15] by the addition of titanium dioxide (TiO_2). Both Ta- and Ti- oxide are compatible with the compounds as well as with the current fabrication procedures of microelectronics device fabrication. Dielectric permittivity of $[Ta_2O_5]_{1-x}$- $[TiO_2]_x$ ceramics was observed significantly dependent on fabrication process and composition (x value) [16] . Depending on the composition and process conditions, $[Ta_2O_5]_{1-x}$-$[TiO_2]_x$ ceramics may have mixture of low dielectric constant phase (L- phase) and higher dielectric constant phase (H- phase), in different proportions [16, 17] . The L- phase is orthorhombic [18-22], and the H- phase is monoclinic or triclinic [18-20, 23-30], at room temperature (RT). Appearance of H- phase (monoclinic or triclinic), and large and oriented grains may be associated with the enhanced dielectric permittivity, in TiO_2 added Ta_2O_5. Due to the structural distortion the increasing interactions of ions lead to the reinforcement of the internal electric field, and consequently to the enhanced dielectric constant. Composition dependence $(0.078 \leq x \leq 0.085)$ of dielectric constant, loss tangent and dielectric conductivity, at different frequencies has been reported in I. Dielectric constant was found increasing with x (≤ 0.080) having maximal value for x = 0.08; and for the compositions with $x > 0.08$ dielectric constant was observed decreasing with increasing x, in the measured composition range, for all the measured frequencies [16]. The loss tangent was observed increasing with x $(0.078 \leq x \leq 0.085)$, which may be associated with the oxygen- vacancies, other stoichiometric and impurity defects. Both phase and microstructure, and also density and homogeneity, significantly affect the dielectric properties of a ceramic. Being non-centrosymmetric at RT, H- phase $[Ta_2O_5]_{1-x}$-$[TiO_2]_x$ is a potential ferroelectric [21]. Dielectric properties of H- phase $[Ta_2O_5]_{1-x}$- $[TiO_2]_x$, were observed dominantly driven by composition rather than the frequency or temperature [16]. In continuation to I, the present paper reports the

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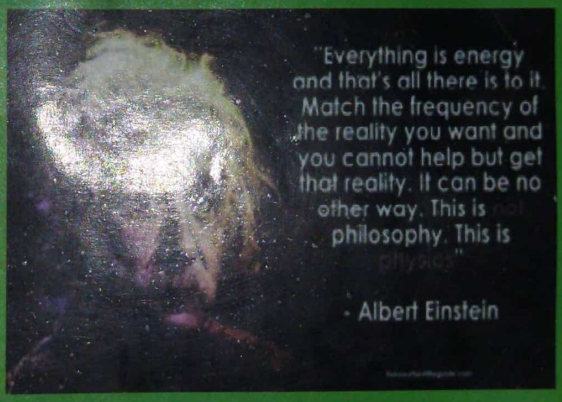

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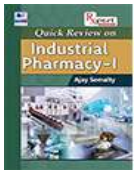

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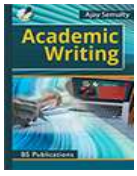

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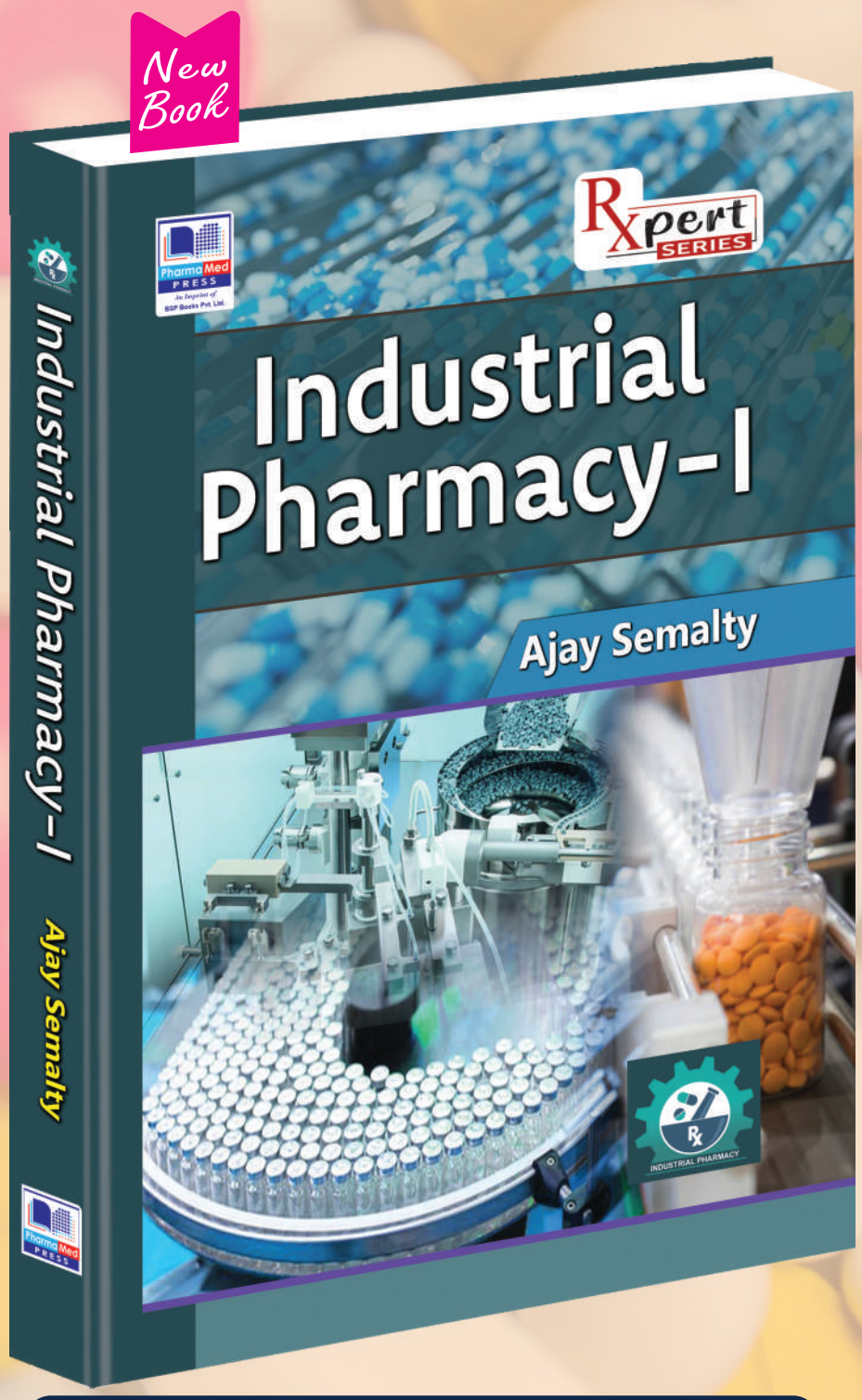

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Dr. Ajay Semalty, is Course Coordinator of India's most popular SWAYAM MOOC- "Academic Writing" & "Industirial Pharmacy - I"; and working as a faculty member in the Department of Pharmaceutical Sciences, H.N.B. Garhwal University (A Central University) Srinagar (Garhwal), Uttarakhand for the last 17.5 years with Academic, research, and industrial experience of more than 18 yrs. He is also University SWAYAM Coordinator and SPOC NPTEL Local chapter of Garhwal University. He is M. Pharm. (Pharmaceutics), MBA (Operations Management); Ph. D., PDF Meijo University, Nagoya Japan. He has been included in the World's top 2 % Scientist of Pharmacy and Pharmacology (by Stanford University research, 2020). He has completed 11 research projects funded by various agencies; He has published 80 papers, 6 books (including the best seller "Essentials of Pharmaceutical Technology" by Pharma Med Press), 2 patents (01 granted) and more than 150 conference papers. He is a highly cited researcher of the field (h index 26). He was awarded: Daiko Foundation Post-Doctoral Research Fellowship and invited by Meijo University, Nagoya, Japan; prestigious national Research Award by UGC, New Delhi, and Young Scientist Award of the year 2007 by Uttarakhand Council of Science & Technology (UCOST). He is expert reviewer of Iceland Research Foundation Iceland; Israel Science Foundation, Israel and Scientific Expert (REPRISE) for Ministry of Institution and University Research (MIUR), Italy, Elsevier Books; Member of The Asian Council of Science Editors, APTI and IPA; Editorial Board Member and Peer reviewer of various national and international reputed journals. He has supervised 28 M. Pharm research projects and supervising 02 Ph.D. candidates. He has delivered more than 200 invited lectures in various training programs in Faculty Development Centers (FDCs), Human Resource Development Centres (HRDCs) and other institutions. He has developed more than 100 hrs. of e-content for SWAYAM, SWAYAMPRABHA, and ARPIT courses. He has developed 20 online courses including two SWAYAM Massive Open Online Courses (MOOCs): "Academic Writing" (listed in top 30 world MOOCs and appreciated by Ministry of Education; ranked #1 in exam registration in 2019 and 2020) and "Industrial Pharmacy - I" (First and only Pharmacy MOOC in India) with more than 48000 learners from more than 95 countries.

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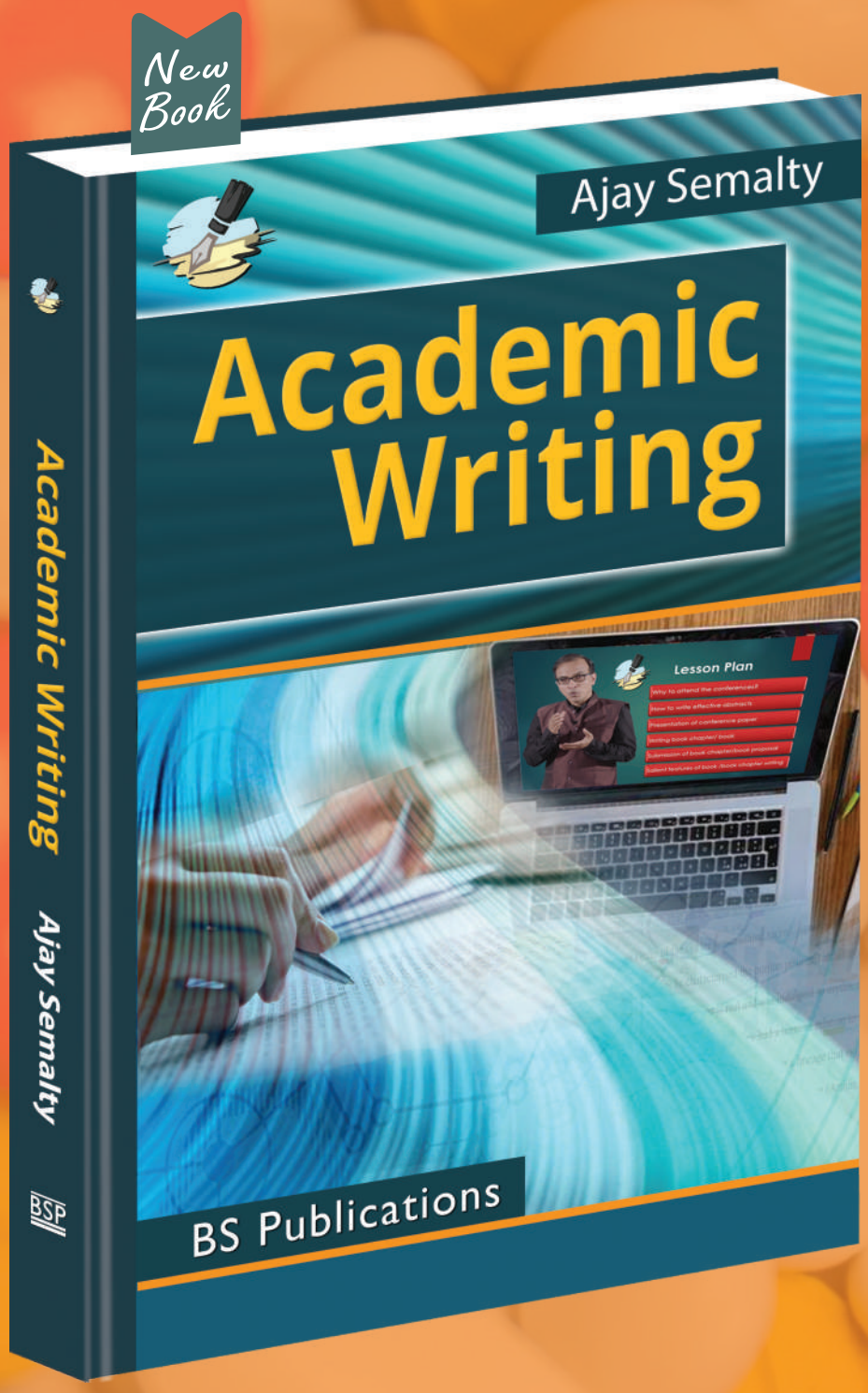

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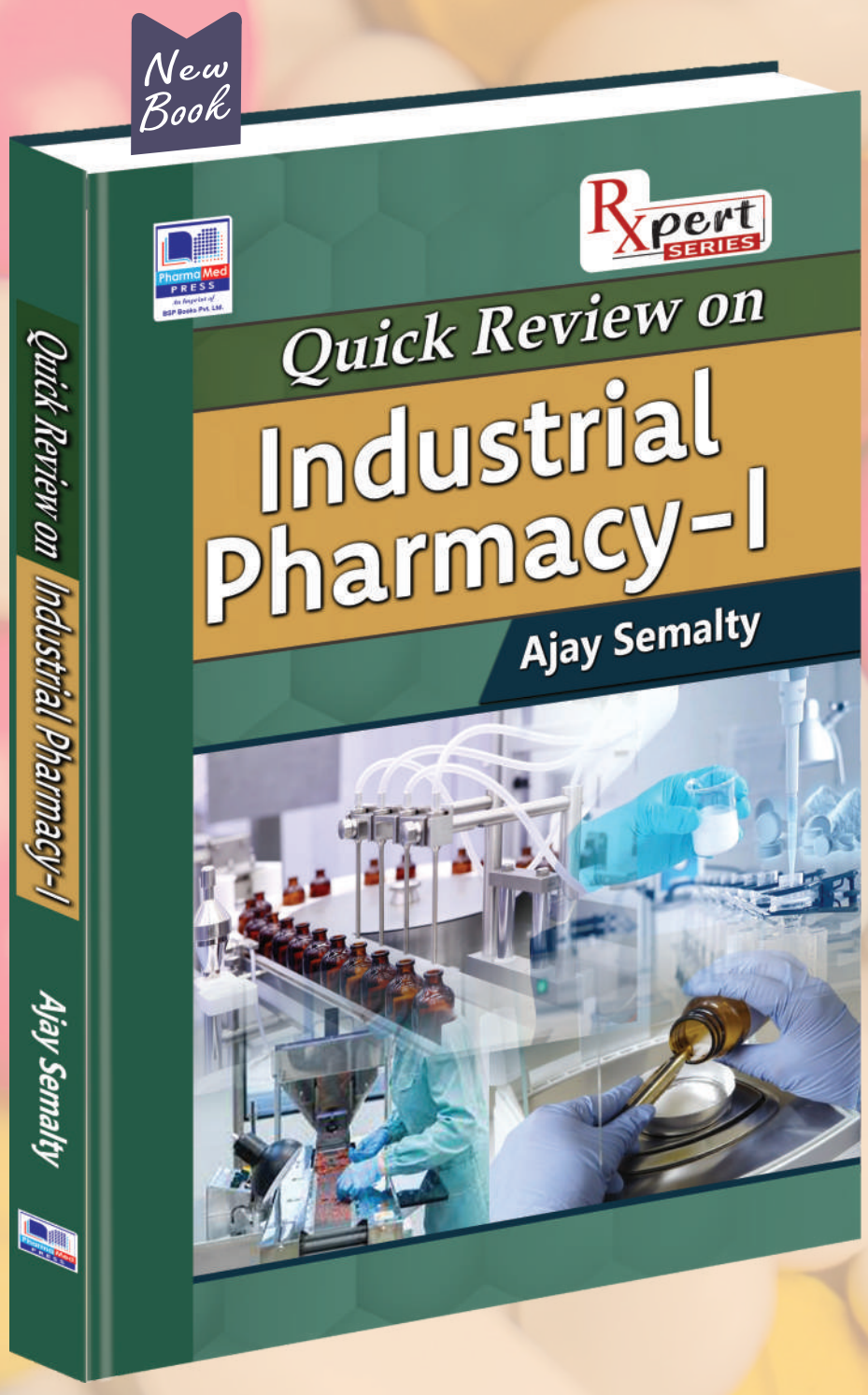

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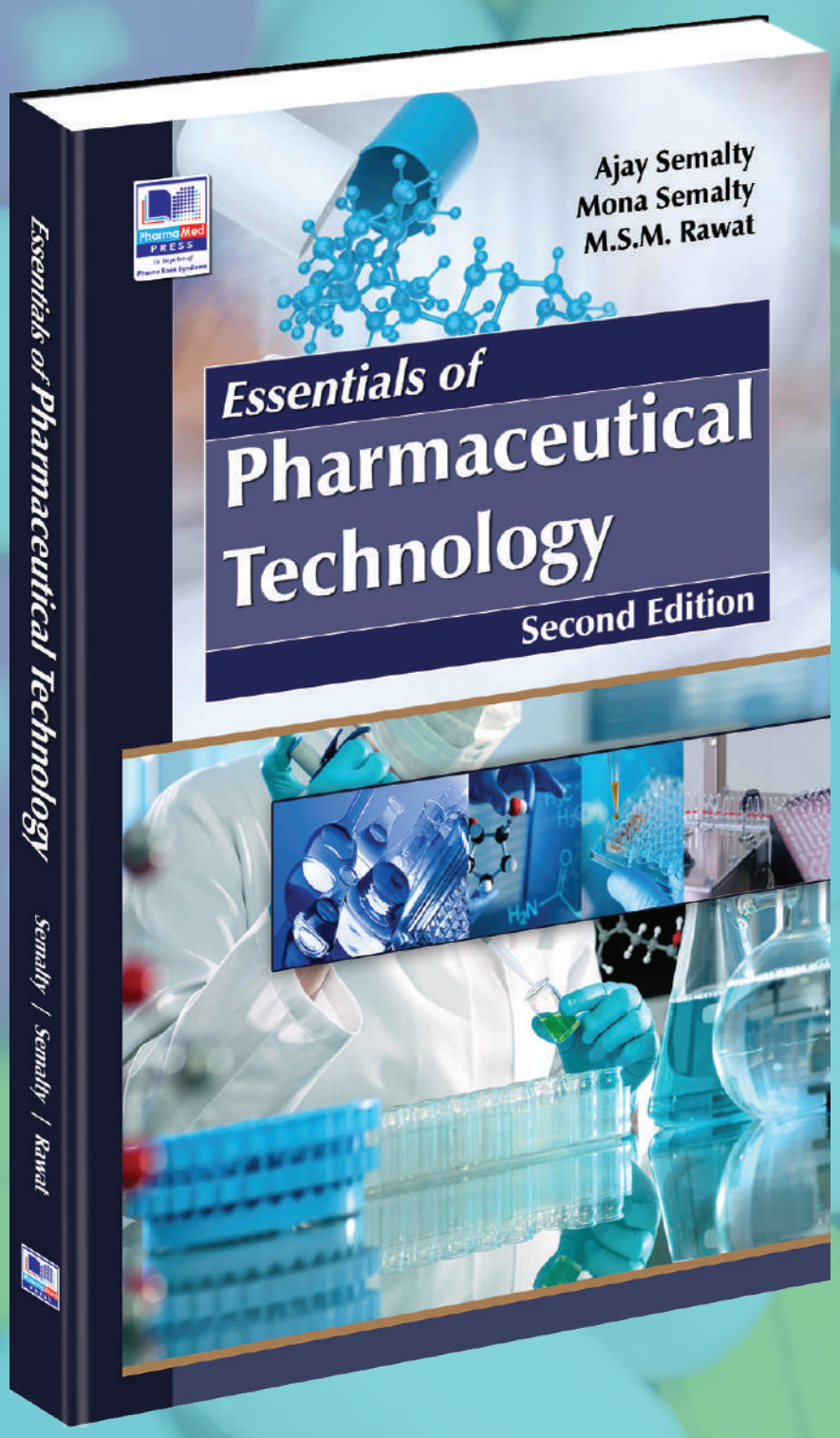
Dr. Ajay Semalty, is Course Coordinator of India's most popular SWAYAM MOOC- Academic Writing and working as a faculty member in the Department of Pharmaceutical Sciences, H.N.B. Garhwal University (A Central University) Srinagar (Garhwal), Uttarakhand for the last 17.5 years with Academic, research, and industrial experience of more than 18 yrs. He is also University SWAYAM Coordinator and SPOC NPTEL Local chapter of Garhwal University. He is M. Pharm. (Pharmaceutics), MBA (Operations Management); Ph. D., PDF Meijo University, Nagoya Japan. He has been included in the World's top 2 % Scientist of Pharmacy and Pharmacology (by Stanford University research, 2020). He has completed 11 research projects funded by various agencies; He has published 80 papers, 6 books (including the best seller "Essentials of Pharmaceutical Technology" by Pharma Med Press), 2 patents (01 granted) and more than 150 conference papers. He is a highly cited researcher of the field (h index 26). He was awarded: Daiko Foundation Post-Doctoral Research Fellowship and invited by Meijo University, Nagoya, Japan; prestigious national Research Award by UGC, New Delhi, and Young Scientist Award of the year 2007 by Uttarakhand Council of Science & Technology (UCOST). He is expert reviewer of Iceland Research Foundation Iceland; Israel Science Foundation, Israel and Scientific Expert (REPRISE) for Ministry of Institution and University Research (MIUR), Italy, Elsevier Books; Member of The Asian Council of Science Editors, APTI and IPA; Editorial Board Member and Peer reviewer of various national and international reputed journals. He has supervised 28 M. Pharm research projects and supervising 02 Ph.D. candidates. He has delivered more than 200 invited lectures in various training programs in Faculty Development Centers (FDCs), Human Resource Development Centres (HRDCs) and other institutions. He has developed more than 100 hrs. of e-content for SWAYAM, SWAYAMPRABHA, and ARPIT courses. He has developed 20 online courses including two SWAYAM Massive Open Online Courses (MOOCs): “Academic Writing” (listed in top 30 world MOOCs and appreciated by Ministry of Education; ranked #1 in exam registration in 2019 and 2020) and “Industrial Pharmacy - I” (First and only Pharmacy MOOC in India) with more than 48000 learners from more than 95 countries.



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Ajay Semalty, M Pharm, MBA, Ph D is presently working as Assistant Professor (Pharmaceutics), Department of Pharmaceutical Sciences, H.N.B. Garhwal (Central) University Srinagar (Garhwal), Uttarakhand for last 14 years.He has been awarded the prestigious "Research Award-2016" by UGC New Delhi and "Young Scientist Award-2007" by Uttarakhand Council of Science & Technology (UCOST), Govt. of Uttarakhand. He has been granted 8 research projects funded by DST, UGC, AICTE, DAE, BARC and Daiko foundation (Meijo University Nagoya Japan). He is one of the most widely cited researcher (h index 21) with 70 papers (36 International, 34 National) in various peer reviewed national and international journals of high impact. He has participated in various international & national conferences; presented his research work and published 64 (10 International, 54 National) Scientific Abstracts. He is peer reviewer for various pharmacy journals of Elsevier, Taylor & Francis, Informa, Springer and Bentham. He is member of editorial board of various national journals. He has also published a book entitled "Art of Writing and Publishing in Pharmaceutical Journals" (published by Pharma Book Syndicate, Hyderabad). He has 2 Indian patents (published) to his credit. He has been a visiting scientist for his post-doctoral research in Faculty of Pharmacy, Meijo University Nagoya, Japan in Year 2011-12.

Mona Semalty, M. Pharm., MBA, Ph D is presently working as Assistant Professor (Pharmaceutics), in Department of Pharmaceutical Sciences, H.N.B. Garhwal (Central) University Srinagar (Garhwal), Uttarakhand and has 14 years of academic and research experience. Her focus area of research is novel drug delivery by microparticulate systems and herbal drug delivery for diabetes and hair loss (alopecia). She has been granted 7 research projects by DST, UGC and AICTE and published 58 (29 International, 29 National) papers in various peer reviewed national and international journals of high impact (h index 21). She has participated in various conferences and published 61 (14 International, 47 National) Scientific Abstracts along with 2 Indian patents for effective herbal dosage forms for alopecia and obesity .She is peer reviewer for various pharmacy journals of Elsevier, Taylor & Francis, Informa, Springer and Bentham. She has also authored a book entitled "Art of Writing and Publishing in Pharmaceutical Journals" (published by Pharma Book Syndicate, Hyderabad). She is life member of IPA and APTI.

M.S.M. Rawat, Prof. (Retd.) and Former Vice Chancellor, HNB Garhwal (Central) University Srinagar Garhwal, Ph D (IIT Delhi) has a very rich teaching and research experience of more than 44 years. He is an eminent scientist and academician known for his outstanding research work on natural products, drug delivery and medicinal plants. He has guided 42 Ph D and 2 D. Sc. students. He has completed 11 research projects funded by various funding agencies (UGC, AICTE, DBT, UCOST etc.). He has more than 200 papers in various national and international journals of repute. He is editor and peer reviewer of various national and international journals of repute. He has also presented his research work and delivered invited lectures in various national and international conferences. He has published two books. He established Pharmacy Department in Garhwal University, Uttarakhand.

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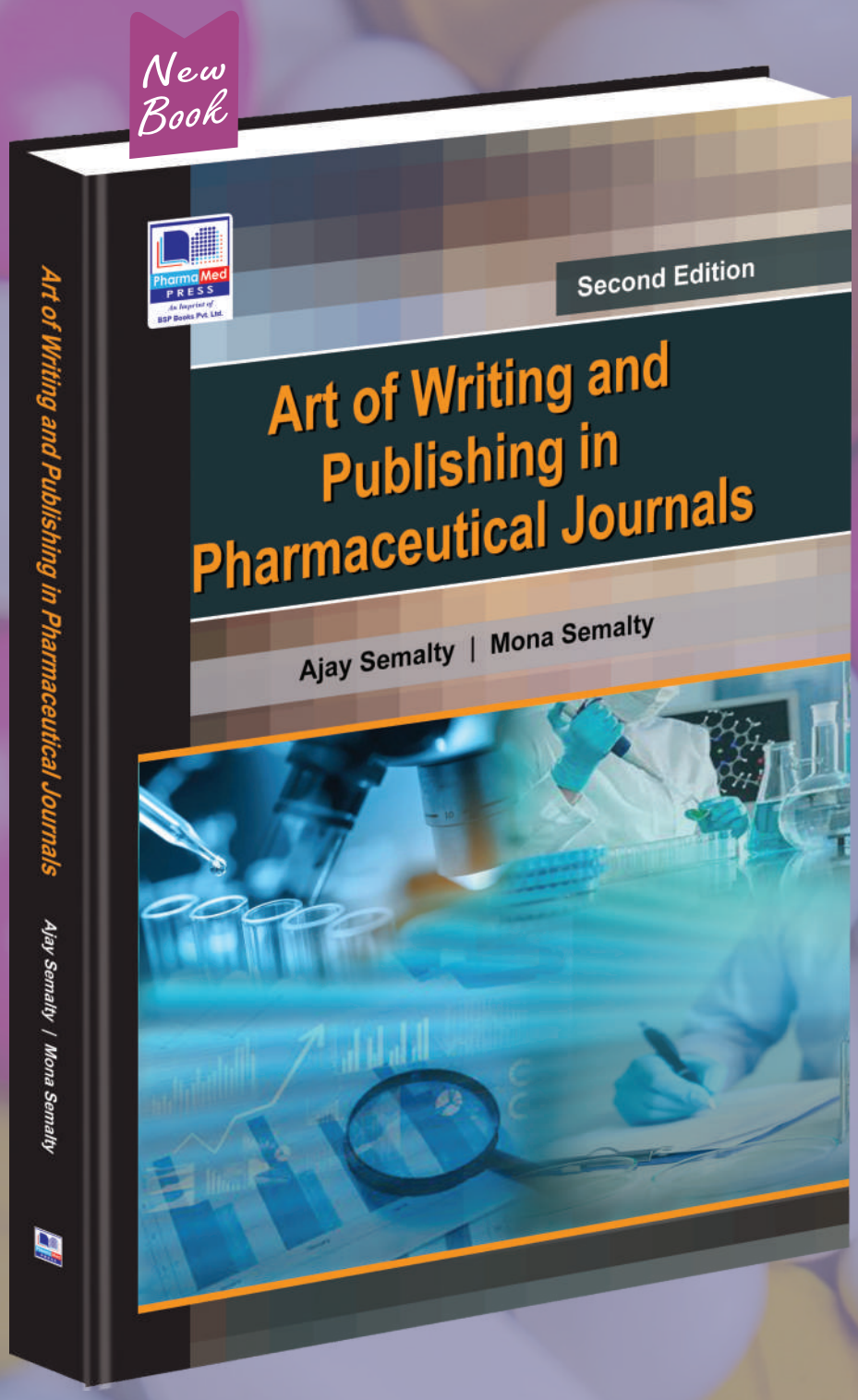

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Dr. Ajay Semalty, is the Course Coordinator of India's most popular SWAYAM MOOCs- Academic Writing and Industrial Pharmacy. He is working as a faculty member in the Department of Pharmaceutical Sciences, H.N.B. Garhwal University (A Central University) Srinagar (Garhwal), Uttarakhand for the last 18 years with Academic, research, and industrial experience of more than 19 yrs. He is also working as the University SWAYAM Coordinator and SPOC NPTEL Local chapter of Garhwal University. He is M. Pharm. (Pharmaceutics), MBA (Operations Management); Ph. D., PDF Meijo University, Japan; He has been included in the World's top 2 % Scientist of Pharmacy and Pharmacology (by Stanford University research, 2020& 2021). He has completed 11 research projects funded by various agencies; published 85 papers, 11 books, and 3 patents (02 granted). He is a highly cited researcher in the field (h index 26). He has been awarded Daiko Foundation Post-Doctoral Research Fellowship, Meijo University, Nagoya, Japan the prestigious national Research Award by UGC, New Delhi, and Young Scientist Award-2007 by Uttarakhand Council of Science & Technology (UCOST). He is an expert reviewer of Iceland Research Foundation Iceland; Israel Science Foundation, Israel and Scientific Expert (REPRISE) for Ministry of Institution and University Research (MIUR), Italy, Elsevier Books; Member of The Asian Council of Science Editors, APTI and IPA; Editorial Board Member and Peer reviewer of various national and international reputed journals; supervised 25 M. Pharm research projects and supervising 02 Ph.D. candidates. He has delivered more than 300 invited lectures and developed more than 100 hrs. of e-content for SWAYAM, SWAYAMPRABHA, and ARPIT courses.

Dr. Mona Semalty, Co-Course Coordinator of India's most popular SWAYAM MOOC- “Academic Writing” and “Industrial Pharmacy I”, is a graduate of Krupanidhi College of Pharmacy, Rajiv Gandhi University of Health and Sciences Bangalore (Karnataka), postgraduate (M. Pharm.-Pharmaceutics) from M.L.S. University Udaipur (Rajasthan) and doctorate from H.N.B. Garhwal (Central) University Srinagar Garhwal (Uttarakhand). She is also a postgraduate in Management- MBA with specialization in Operation Management from IGNOU, New Delhi. She is presently working as Assistant Professor (Pharmaceutics), in the Department of Pharmaceutical Sciences, H.N.B. Garhwal University Srinagar (Garhwal), Uttarakhand, India with more than 18 years of experience in teaching and research. Her focus area of research is novel drug delivery by microparticulate systems and herbal drug delivery for diabetes and hair loss (alopecia).

She has to her credits 10 research projects, 3 patents (02 granted), 06 books and 40 book chapters,67 papers (31 International, 36 National) in various peer-reviewed national and international journals of high impact, h index is 25, 72 (14 International, 58 National)Scientific Abstracts. She is a peer reviewer for various pharmacy journals of Elsevier, Taylor & Francis, Informa, Springer and Bentham. She is an expert reviewer and Scientific Expert (REPRISE) for the Ministry of Institution and University Research (MIUR) Italy and DST-SERB India. She has developed more than 80 hrs. of e-content for SWAYAM, and SWAYAMPRABHA. She is a life member of IPA and APTI.

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Research and Advancements

Editors Vikas Kumar | Addepalli Veeranjaneyulu

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CONTENTS

CHAPTER 4

HERBAL MEDICINES IN NEUROPSYCHIATRIC ILLNESS: THE CASE OF L-STEPHOLIDINE

NITIN SATI[1], KEDAR S. PRABHAVALKR[2], SRIDHAR NATESAN[3], and LOKESH K BHATT[2*]

[1]Department of Pharmaceutical Sciences, Hemwati Nandan Bahuguna Garhwal University, Srinagar 246174, Garhwal, Uttarakhand, India

[2]Department of Pharmacology, Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle (West), Mumbai 400056, Maharashtra, India

[3]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, P.O. Box 53, De Crespigny Park, Camberwell SE5 8AF, London

[*]Corresponding author. E-mail: bhatt.lokesh@gmail.com

CONTENTS

ABSTRACT

Herbal researches have revealed panoply of promising compounds with neuroprotective activity and potential for treatment of psychopharmacological disorders. The numerous chemical structural templates of herbal products have led us to a plethora of synthetic chemical moieties that have been tested in biological models with some degree of success. In this chapter, we briefly explored the pivotal role played by herbal compounds in therapeutic modulation of neuropsychiatric illness and reviewed role of L-stepholidine in neuropsychiatry.

4.1 INTRODUCTION

Herbal compounds have played a pivotal role in our quest for understanding human biology. Their interaction with receptors, enzymes, and molecular targets has helped us understand basic physiology, neurotransmission, and consequences of therapeutic interventions in the case of neuropsychiatric illness. The numerous chemical structural templates of herbal products have led us to a plethora of synthetic chemical moieties that have been tested in biological models with some degree of success. In this chapter, we briefly explored the pivotal role played by herbal compounds in therapeutic modulation of neuropsychiatric illness and reviewed role of L-stepholidine in neuropsychiatry.

4.2 HERBS ACTING ON NERVOUS SYSTEM

Herbal researches have revealed panoply of promising compounds with neuroprotective activity and potential for treatment of psychopharmacological disorders. Some of herbs with neuroprotective and psychopharmacological disorders are mentioned below.

Ayurvedic Materia Medica mentions *Bacopa monniera* as a therapeutically useful herb for the treatment of cognitive impairment, suggesting its anti-Alzheimer's properties. The extract of *B. monniera* was evaluated for antioxidant activity by reduction of divalent metals, scavenging of reactive oxygen species, alterations of lipoxygenase activity and hydrogen peroxide-induced lipid peroxidation assays. The study revealed that the extract reduced divalent metals, dose-dependently scavenged reactive

oxygen species, decreased the formation of lipid peroxides, and inhibited lipoxygenase activity. The extract has also been reported to reduce beta-amyloid levels in the brain of an Alzheimer's disease doubly transgenic mouse model of rapid amyloid deposition. The results of the study also suggest possible mechanisms of action relevant to the treatment of Alzheimer's disease.[1]

Curcuma longa has been used as food additive and herbal medicine in Asia since antiquity. Curcumin, the active principle of *C. longa* has neuroprotective, anti-inflammatory, antioxidant, anti-protein-aggregate activities.[2]

Uncaria rhynchophylla (Miq.) Jack and *Gastrodia elata* BI. are traditional Chinese herbs that are usually used in combination to treat convulsive disorders, such as epilepsy, in China. Anti-convulsive effect of the mentioned herbs was evaluated using in vitro and in vivo studies. The study was carried out with either of the plants and the combination, separately. The results of the study indicated that *U. rhynchophylla* (Miq.) possesses anti-convulsive activity and its effect is synergized by *G. elata* BI. *U. rhynchophylla* has also been used to relieve various neurological symptoms. The methanolic extract of *U. rhynchophylla* also exhibited neuroprotective activity. Inhibition of β-amyloid protein generation, prevention of β-amyloid protein fibril formation or destabilization of β-amyloid protein may serve as attractive targets for treatment of Alzheimer's disease. The study revealed that *U. rhynchophylla* has remarkably inhibitory effects on the regulation of β-amyloid protein fibrils, and thus could have the potency to be a novel therapeutic agent to prevent and/or cure Alzheimer's disease.[3]

The genus *Stachys* (Lamiaceae) comprises of around 300 species that are mostly distributed in temperate and tropical regions of the world. *Stachys* species are used as herbal medicines and wild tea in many local regions of the world. Several studies have demonstrated anti-toxic, anti-proliferative, anti-microbial, anti-inflammatory, and antioxidant activities of *Stachys* species. *Stachys lavandulifolia* Vahl is used as sedative and anxiolytic in folk medicine in Iran.[4] The ethanolic extract exhibited neuroprotective effect and reduced permeability of blood brain barrier.[5] The neuroprotective effect of aqueous extract *S. lavundulifolia* was also reported.[6]

The compounds isolated from *Magnolia* spp. have exhibited neuroprotective effects. The phyto-constituent form *M. officinalis*

4-O-methylhonokiol possess the potential to be used in the treatment of Alzheimer's disease.[7] Similarly, phyto-constituents from other *Magnolia* spp. are also reported to possess neuroprotective effects. Lignans from *M. fargesii* have potential for use in the treatment of neuro-inflammatory diseases.[8] Neolignans from the fruits of *M. obovata* also exhibit neuroprotective effect.[9]

The extract of *Tripterygium wilfordii* Hook F, a Chinese herb, yielded a compound with neuroprotective activity and possible use in the treatment of Parkinson's disease.[10] The aqueous extract of Purslane herb also exerted neuroprotective effect.[11] The Chinese herb *Dihuang Yinzi* (*DY*) is well known to treat neurological diseases in traditional Chinese system of medicine. The extract of the herb were evaluated for neuroprotective and anti-dementia activity. The study revealed that the herb possesses neuroprotective and anti-dementia properties and may act by preventing the loss of neural cells and synapses in ischemic brain injury.[12]

Tianma is the rhizome of *G. elata* Blume, a traditional Chinese medicine used for the treatment of headache, convulsions, hypertension and neurodegenerative diseases. It exhibited neuroprotective and neurogenerative effect by inhibiting stress-related proteins and mobilizing neuroprotective genes.[13] It was hypothesized that Tianma promotes neuro-regenerative signaling cascades by controlling chaperone/proteosomal degradation pathways.[14] *G. elata* has been used traditionally for the treatment of epilepsy in Oriental countries and Asia. The ether fraction of methanolic extract was evaluated for its ability to protect neuronal damage. The study revealed that the extract possesses protective effect against neuronal damage. The ether fraction of methanol extract also possesses the ability to prevent neuronal damage against kainic acid-induced neuronal damage in mouse hippocampus.[15]

The plants of Huperziaceae have been used for medicinal purposes in China. Huperzine A, a novel alkaloid isolated from a Chinese herb exhibit neuroprotective effects and can improve learning and memory deficiency in animal models and AD patients.[16] Chinese herb Huanglian-Jiedu-Tang exhibited neuroprotective effect on chronic brain injury after focal cerebral ischemia in mice.[17] A prescription comprising *Panax ginseng*, *Acanthopanax senticosus*, *Angelica sinensis*, and *Scutellaria baicalensisis* is used in Traditional Korean Medicine for treatment of mental and physical weakness. The prescription was evaluated for neuroprotective effect in focal cerebral ischemia rat mode. The study revealed that the prescription

do exert neuroprotective effect by anti-inflammatory mechanism and may improve sensory-motor function by reducing damage.[18]

Acorus calamus is a traditionally used as neuroprotective and anti-convulsant. Effect of co-administration of methanolic extract of *A. calamus* and anti-epileptic drugs was studied. The study revealed that *A. calamus* exhibit synergistic anti-convulsant action.[19] *A. sinensis* and *Sophora flavescens* are herbs used in Chinese traditional medicine as neuroprotective. The essential oil isolated from these exhibited neuroprotective and antioxidant properties.[20] *Ixeris sonchifolia* Hance is an herb distributed in northeastern parts of China and has been used by natives to stimulate circulation. The extracts of the herb were evaluated for neuroprotective effects. The study revealed that the flavonoids in ethyl acetate extract contribute at least partly to the neuroprotective effect against ischemia-induced cellular injury and can be potentially developed for treatment of ischemia-reperfusion-induced diseases.[21]

The alkaloids isolated from *Erythrina mulungu* (Papilionaceae) exhibited anti-anxiety activity. The alkaloids erythravine and (+)-11alpha-hydroxy-erythravine were the phytochemicals responsible for the anxiolytic activity of the crude extract of *E. mulungu*.[22] Same alkaloids isolated from the extract of flowers of the *E. mulungu* also exhibited anxiolytic activity.[23] The hydroalcoholic extract of flowers of *E. mulungu* exhibited anti-convulsant and mild anxiolytic activity owing to the presence of alkaloid erythrosine. *Erythravine* (3, 10 mg/kg) and (+)-11alpha-hydroxy-erythravine (10 mg/kg) exhibited anxiolytic-like effect in animal models. Erythrosine (0.001–10 μg/mL) exhibited anti-convulsant and mild anxiolytic activities.[24]

Albizia julibrissin (Fabaceae) is used in traditional system of medicine for treatment of various ailments. The flowers of *A. julibrissin* are used as sedative in traditional Chinese medicine. Isolation of flavonoids with sedative property from the extract of the *A. julibrissin* flowers justified its use in traditional system of medicine.[25] *Sonchus oleraceus* L. has been used as a general tonic and as a pain reliever in Brazilian folk medicine. The hydroethanolic and dichloromethane extract of the aerial parts of *S. oleraceus* exhibited anxiolytic activity,[26] anti-nociceptive activity,[27] and anti-depressant[28] activity.

The aqueous extract of *Sphaeranthus senegalensis* Vaill. (Family: Compositae) was evaluated for sedative activity in behavioral animal models. The extract when subjected to preliminary phytochemical

investigation showed the presence of glycosides, saponins, and tannins. The extract (50 and 100 mg/kg p.o.) exhibited sedative action in the various animal models.[29] The aqueous extract of *Zizyphus spina-christi* Willd root bark was evaluated in various behavioral study models in mice for central nervous system (CNS) activity. The extract exhibited CNS depressant activity, with mode of action different from neuromuscular blockade. The study indicated that the aqueous extract of the plant might contain phyto-constituents with CNS depressant activity.[30]

The aqueous extract of *Diospyros mespiliformis* stem bark were screened in mice for CNS-related activities. The extract (100 and 200 mg/kg p.o.) exhibited sedative activity suggesting the presence of concerned phytochemicals in the aqueous extract.[31] The methanolic and aqueous extracts of *Wedelia calendulacea* stem were screened in rats and mice for neuropharmacological activity. The methanolic extract (20 and 50 mg/kg, i.p.) and aqueous extract (200 and 500 mg/kg, i.p.) exhibited sedative activity.[32]

Plants of genus *Utrica* are used in traditional system of medicine for treatment of various ailments. The hydroalcoholic extract of leaves and stems of *Urtica circularis* (Hicken) *Sorarú* (Urticaceae) were evaluated for neuropharmacological effects in animal models. The study revealed sedative activity of hydroalcoholic extract by facilitating GABAergic and cholinergic transmission.[33] Methanolic extract of *Newbouldia laevis* was evaluated for its effect on CNS in animal models. Spontaneous motor activity, exploratory behavior, apomorphine-induced climbing behavior in mice, and pentobarbital-induced hypnosis were the behavioral models used for assessing the CNS activity. The methanolic extract exhibited sedative property owing to possible presence of compounds with sedative action.[34]

Cecropia glazioui Sneth has been used in most Latin American countries as an anti-hypertensive, cardiotonic, and anti-asthmatic folk medicine. The aqueous extract of *C. glazioui* (0.25–1 g/kg p.o.) produced anxiolytic-like effect in mice.[35] The aqueous extract and its butanolic fraction of *C. glazioui* Sneth exhibited antidepressant-like effect, probably by blockade of monoamine uptake in CNS.[36] *Marsilea minuta* Linn. (Marsileaceae) has been referred in Indian traditional medicine system (Ayurveda) for the treatment of insomnia and other mental disorders.[37] The ethanolic extract (100, 200, and 400 mg/kg/day) exhibited antidepressant activity in animal model using rats, probably due to effect on serotonin density in rat prefrontal cortex.

4.2.1 HERBAL COMPOUNDS THAT HERALDED OUR UNDERSTANDING OF NEUROTRANSMISSION IN THE CNS

Our understanding of the monoaminergic system comprising mainly of histamine, dopaminergic, serotonergic, and adrenergic systems has been greatly enhanced with their interaction with natural products. Histamine was discovered as a contaminant of ergot generated by bacteria (not exactly one of herbal origin) by Sir Henry Dale in 1910.[38] We now understand it as a major excitatory neurotransmitter in the brain that keeps us awake and alert during the day. Depletion of monoamines by Reserpine, an indole alkaloid, discovered by analyzing extracts of *Rauwolfia serpentina* used in the Indian system of medicine (Ayurveda), led to the monoaminergic theory of depression as it induced a profound depressive state.[39] This spurred the discovery of anti-psychotics, antidepressants, and stimulants used to treat attention deficit disorders (ADD).

Muscarine, a natural product found in certain mushrooms (*Inocybe* and *Clitocybe* species, such as the deadly *Clitocybe dealbata*), led to our understanding of muscarinic receptors as it mimics the function of the natural neurotransmitter acetylcholine.[40] Nicotine, a potent agonist alkaloid found in some members of the nightshade family of plants (e.g., cultivated *Nicotiana tabacum*), widely smoked as a stimulant, led to our understanding of the nicotinic receptors.[41] The CNS depressant and painkiller morphine derived from opium poppy (*Papaver somniferum*) led to our appreciation of the opioid receptors.[42] Cannabinoids from the Cannabis plant used for recreational purposes for centuries led to the discovery of endocannabinoids.[43] Allosteric interactions with the GABA receptor of a number of substances (alcohol, flavonoids in St. John's Worth and Chamomile flowers) has led to the discovery of sedatives and muscle relaxants.[44]

There is no dearth of examples from the plant kingdom that can be highlighted against every neurotransmitter system that has been discovered. It is quite fascinating that plants expend so much energy in producing these complex compounds, albeit for their natural defense from being grazed by cattle or harvested by humans for food.

The chapter discusses the case of an herbal compound (L-stepholidine) extracted from the *Stephania* genus, a flowering plant in the family Menispermaceae, native to eastern and southern Asia and Australasia.[45] They are perennial vines and the name Stephania refers to the anthers being arranged in a crown-like manner from the Greek language. L-stepholidine interacts with the dopaminergic system and hence in the next section, the

role of dopamine and other neurotransmitters involved in neuropsychiatric illness has been described.

4.3 NEUROTRANSMITTERS IN NEUROPSYCHIATRIC ILLNESS

4.3.1 DOPAMINE

Dopamine makes over more than half of the CNS content of catecholamine, large amount are found in basal ganglia (especially the caudate nucleus), the nucleus accumbens, the olfactory tubercle, the central nucleus of amygdale, the median eminence, and restricted fields of frontal cortex.[46] Four dopamine pathways in the brain play a role in the pathophysiology of schizophrenia as well as the therapeutic and side effects of anti-psychotic agents.

- Nigrostriatal dopamine pathway—This pathway as part of the extrapyramidal nervous system controls the movements. This pathway degenerates in Parkinson's disease, and blockade of D2 receptors in this pathway causes the drug-induced movement disorders (DIMDs) and eventually tardive dyskinesia. Dopamine deficiency as well as receptor blockade in this pathway can also cause akathisia and dystonia.
- Mesolimbic dopamine pathway—Hyperactivity in the mesolimbic dopamine pathway is thought to cause psychosis and the positive symptoms of schizophrenia such as hallucinations and delusions. This pathway is also thought to be involved in emotion and sensations of pleasure. Blocking hyperactivity in this pathway reduces or eliminates positive symptoms.
- Mesocortical dopamine pathway—This pathway is thought to control cognitive function, and dopamine deficiency in this pathway is responsible for the negative and cognitive symptoms of schizophrenia. Dopamine receptor blockade in this pathway leads to worsening of negative and cognitive symptoms. So, the anti-psychotic drug has to decrease dopamine in the mesolimbic pathway to alleviate positive symptoms but increase it in the mesocortical pathway to treat negative and cognitive symptoms.
- Tuberoinfundibular dopamine pathway—Normal function of the tuberoinfundibular dopamine pathway is to inhibit prolactin

release. Blockade of dopamine receptors in this pathway leads to hyperprolactinemia.

4.3.2 SEROTONIN

Serotonin is a powerful modulator of emotional processes in the CNS. Dysfunction of serotonergic neurotransmission is implicated in the pathogenesis of neuropsychiatric disorders, including schizophrenia, depression, and anxiety. Serotonergic pathways are important as these modulate dopaminergic transmission and play a key role in control of mood, cognition, and motor behaviour.[46]

4.3.3 GLUTAMATE

Glutamate receptors are broadly classified into two subtypes: ionotropic glutamate receptors which are ligand-gated ion channels and metabotropic glutamate receptors (mGlu receptors) which are coupled via G proteins to second messenger systems. When activated, ionotropic glutamate receptors produce an influx of cations into the cell, directly depolarizing the postsynaptic neuron and thus transmitting excitatory inputs into the synapse. In contrast, mGlu receptors function to modulate glutamatergic transmission by presynaptic and postsynaptic mechanisms.[47] The mGlu receptors fall into three groups based on current pharmacology and the molecular properties of each receptor. Each mGlu receptor subtype is uniquely and differentially distributed in the CNS. Thus, the expression of mGlu receptors in different brain regions and selected synapses provides a mechanism for the CNS to modulate glutamatergic neuronal transmission within specific synapses.[48] The availability of novel drugs that modulate glutamate neurotransmission provides a new prospect for the treatment of schizophrenia. Impairment of glutamate functioning has been hypothesized in etiology of schizophrenia.[49]

4.3.4 GAMMA-AMINOBUTYRIC ACID (GABA)

An interaction between dopaminergic and GABAergic systems in schizophrenia is supported by the fact that GABA neurons in the middle layers

of pre-frontal cortex (PFC) receive direct synaptic input from DA terminals and exert inhibitory control over excitatory output of layer III pyramidal neurons, and undergo substantial developmental changes in late adolescence, the typical age of onset for schizophrenia. Evidence for reduced GABA uptake sites in the temporal lobe, increased $GABA_A$ receptor binding in superficial layers of cingulated cortex, and reduced gene expression or glutamic acid decarboxylase in the prefrontal cortex provides direct support for GABAergic involvement in this disorder.[50]

4.3.5 ADRENERGIC SYSTEM

Hyperactivity of noradrenergic system in psychotic patients has been reported. In human brain, all three adrenoceptor subtypes (α1A, α1B, and α1D) are present. A common feature of atypical anti-psychotics such as clozapine, sertindole, and olanzapine is nanomolar affinity for α1 adrenoceptor in addition to their affinities for dopamine D_2 and serotonin 5-HT_2 receptors. Hence, α1 adrenoceptor antagonists provide an area to explore for the treatment of schizophrenia.[51]

4.3.6 CHOLINERGIC SYSTEM

Cholinergic system has a primary role in hallucinations and delusional thinking. Alteration in cholinergic parameters may be primary component of the pathophysiology of schizophrenia or a down-stream effect from pathology in other neurotransmitter systems or structures. Dopaminergic system regulates the cortical cholinergic cell groups. The basal forebrain cholinergic complex, which projects throughout the cerebral cortex, is regulated by GABA-mediated output from nucleus accumbens. Output from nucleus accumbens is highly dependent upon its dopaminergic input. Abnormal dopaminergic tone in nucleus accumbens might alter the activity of cholinergic projections to the cortex thereby linking an alteration in cortical function to subcortical dopamine dysregulation.[52] It has been found that cholinergic blockade impairs cognitive function in normal human control subjects, including marked memory impairment and attention deficits. Learning and memory system traditionally associated with the hippocampus and hippocampal function is also found to be dependent upon cholinergic input. All these finding suggest that cholinergic

input to the hippocampal formation is the critical component of learning and memory and may be impaired in schizophrenia. Thus, the attention, learning, and memory deficits in schizophrenia might be attributed to abnormalities in a variety of cholinergic pathways.[53]

4.4 L-STEPHOLIDINE—A NATURALLY OCCURRING DOPAMINE D_1 RECEPTOR AGONIST AND D_2 RECEPTOR ANTAGONIST WITH NEUROPROTECTIVE PROPERTIES

The root extracts of the plants of the *Stephania* species is used in traditional Chinese medicine to treat pain and spasticity and is found in the Han Fan Ji (Fen Fang Ji) formulations(not be confused with Guang Fan Ji which contains the nephrotoxin aristolochic acid.[54] The root extracts contain tetrahydroprotoberberines of which L-stepholidine is a component of it.[55] In addition to the indications cited earlier, L-stepholidine has also been reported to decrease blood pressure without exerting any adverse effect on the heart, and also has been found to have sedative effects on the CNS.[56] Scientific investigations led to the pharmacological characterization of L-stepholidine which led to suggestion of its therapeutic use in neuropsychiatric illness.

It did come as a surprise that L-stepholidine has a unique receptor affinity profile that was not anticipated or seen in any other molecule. It had affinity to both the dopamine D2 receptor as well as the dopamine D1 receptor as a single molecular entity.[57] It acts as an antagonist at the dopamine D2 receptor while acting as a partial agonist at the dopamine D1 receptor. In addition to its effects on the dopaminergic system, it also has neuroprotective properties.[58] Given the context of its pharmacological profile, its ability to modulate the dopaminergic system is of importance in the context of neuropsychiatric illness.

4.5 PHARMACOLOGICAL USES OF L-STEPHOLIDINE

In Schizophrenia, the hypothesis that imbalanced dopaminergic signaling in the striatum and cortical regions leads to psychosis and negative symptoms present an ideal case where L-stepholidine could be an useful intervention.[59] The dopamine D2 receptor antagonism in the striatum would block excessive dopamine stimulation which is considered to be the main

cause for psychosis. In the cortical regions where dopamine D1 receptors predominate, D1 partial agonism would help overcome hypodopaminergia. Overcoming hypodopaminergia is hypothesized to play a key role in alleviating negative and cognitive symptoms. In preclinical models, this strategy has been evaluated and it needs clinical evaluation.[60–62]

L-stepholidine's ability to relieve motor deficits of Parkinson's disease-like symptoms when co-administered with Levodopa and its neuroprotective effects through an antioxidative mechanism that slows neurodegeneration in animal models provides clues as to its usefulness in treating Parkinson's disease.[63,64] It also has been documented that in animal experiments, SPD is well-absorbed in the digestive tract, can be widely distributed in body tissues, and can easily penetrate the blood–brain barrier.[65]

4.6 CONCLUSION

L-stepholidine presents a classical case where herbal drugs can provide useful therapeutic compounds and templates for further drug design. Currently, most anti-psychotics induce weight gain and cause metabolic disorders and it is hoped that this compound may turn out to be different.[66] In most instances, it may be not be economical to cultivate and harvest plants for herbal drugs and a synthetic route may be needed. In any case, a number of regulatory agencies now encourage herbal drugs for clinical trials or licensing and may not need stringent requirement as necessary for new chemical entities. Historical human use also infuses confidence while risk is assessed for human use. Efforts are currently underway to evaluate L-stepholidine in extensive clinical trials and hopefully it will prove to be therapeutically useful.

KEYWORDS

- **neuropsychiatry**
- ***Bacopa monniera***
- ***Uncaria rhynchophylla***
- **epilepsy**

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CHAPTER-13

PHARMACOGNOSY AND AYURVED

Vinod Nautiyal*
Assistant Professor
Gurukula Kangri
Vishwavidyala Haridwar

Ram Kumar Sahu
Assistant Professor
Dept. of Pharmaceutical Sciences,
Assam University (A Central University)
Silchar (Assam)

Somesh Thapliyal
Assistant Professor
Dept. of Pharmaceutical Sciences,
HNBG University (A Central University)
Shrinagar Garhwal

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Pharmacognosy

Whenever the word Pharmacognosy comes in mind, it gives a clue about pharmaceutical science and pharmacy. The word pharmacognosy was first coined by C.A Seydler a French chemist, in 1815, in his article *Analecta Pharmacognostica* the word pharmacognosy is derived from two wordsi. epharmac on and gnosis, meaning drug and study. It means in pharmacohnosy we study the drugs, particularly crude drugs obtained from plant, animal and mineral source.

Nowdayssomenovelsourceofdrugsisalsocoveredinpharmacognosysuchas marine source and tissue culture. Tissue culture is gaining popularity among pharma industry and research laboratory for the production of secondary metabolites of therapeutic value. Marine pharmacognosy also serve the source of numbers of potent secondary metabolites, such as Ara-C, Saxitoxin, ATX-II Terado toxin, Laminineetc are the novel pote compound obtained from various marine red green algae or animals.

Crude Drugs

These are the drugs of natural origin which are raw or unprocessed drugs. These are collected from its natural habitat and after cleaning and after natural dying or as fresh, are useddirectly. For example, Tulsi leaves are used as fresh with tea, milk, water for attaining lot of health benefits. Ginger, lemon, cinnamonetc can be used fresh and dried as well.

Organised vs Unorganised Drugs

The term itself indicates that these are the drugs which are obtained from organs of plant or animal (organised) and devoid of organs of the plant or animal. In other word organised drugs are the crudedrugs which have a fixed cellular structureeg. Cichona, Cinnamon, Ajuna are the crude drugs which are bark of the plants, having the fixed cellular structure. Unorganised drugs are not the part of the plants oranimal, the seare the secretion orgum sormucilageobtained after making incision or by microbial attack or by any other environmental adversity. Eg Opium, aloedried Vextract, gumacacia, as a foetida, benzoin, guggulet careun organised drugs. These drugs are also called as cellular and a cellular drugs, because of having a definite cellular structure or dividing of it.

History and Development of Pharmacognosy

Development of pharmacognosy goes back to 5000 years ago with Chinese herbal Pen-t-Sao containg 365 drugs each for a day, which was written by the emperor Shen Nung approximately 3000 years ago. Papyrus Ebers, containing seven hundred crude drugs and eight hundred formulae which describe their applications. It is a scroll sixty feet long with the width of one foot.

Ayurveda which is considered 'an ancient science of life' dates back to vedic period various well known texts in Ayurveda are Charaka and Sushurutasam hitas, apart from these. Dhanwntari is known as god of medicine.

In India 200-150 BC Charka described 50 groups of 10 drugs in each group according to some specific properties which he called Gunas. In near about same time period Shusruta also called the father of Surgery described seven hundred sixty herbs in seven distinct sects. Bheshajya Ratnawali (Ayurvedic Pharmacy) mention five basic dosage forms viz. Churna, Avaleha, Grita ,Bhasma, Sadhna Kalpa.

Hippocrates (460-360BC) also known as father of medicine, Aristotle (384-322 BC) Dioscorides (40-80 AD) Galen (131-200 AD) and many ancient practitioners of Arab made noteworthy contribution in the development of pharmacognosy. Paracelsus (1493-1541) a chemist developed the various therapeutic mineral salt remedies, was a mile stone in the advancement of pharmacognosy. Le'mery (1645-1715) first timed used alcohol for extraction of crude drugs. Willium Withering in 1785 based on his experimentations described the applications of Digitalis. Percolation process changed led fast advancement for extracting the constituents of the crude drugs. A benchmark was set by Derosne a German pharmacist in 1803, isolated the narcotine an alkaloid of opium. Morphine was isolated by Sertuerner in 1803 from Opium and its analgesic property was recognized.

In nineteenth century great advancement occurred in the field of pharmacognosy. Strychnine, emetine, brucine piperine, quinine, and colchicine were isolated in this century. Pelletier a French pharmacist isolated strychnine firstly from igatius beans and secondly from nux vomica seeds.

In 1852 Stass and Otto developed the method of isolation of Alkaloids. Posselt & Reimann (1828) Neumann (1860) Hardyand Gallow (1877) Geradand Hardy (1875) Nagai (1887) Kuerseten (1891) isolated nicotine, cocaine, pilocarpine ephedrine podophyllotoxin respectively.

In this century pharmacognosy was advanced with the isolation of digoxin, reserpine, the ophylline ergometrine and quinidine. The term material medica was in use during nineteenth century till the term Pharmacognosy was given by C.A Ceydler in 1815 in his work on sapsarila entitled “analectapharmacognostica” Swede Linnaeus (1707-1778) a great taxonomist gave binomial system of classification in which plants are classified in this system the generic name of the plant is composed of two parts i.e genus and species. This system of classification (binomial classification) is still in use today. In 1862-1863 Benthom and Hooker and other Taxonomist did advancement in plant taxonomy.

Invention of different magnification tools and techniques like clearing secti

-oning, mounting, staining and instruments viz. simple microscope, compound microscope and advanced electric microscope took pharmacognosy one step ahead. Observation of the crude drugs anatomy and histology gave more clear images of the crude drugs. Mendel's work on genetic and hybridization was milestone in the field of high yield giving verities development in cultivation, collection and commercialization of the medicinal plants. Food and crude drugs n 1865 Berg published the Anatomical Atlas of Crude Drugs. GGreenishand Collinin1904 published' anan atomical atlas of powdered vegetable drugs'

Voehl, Tschirch and other established a benchmark in detection of adulteration among by introducing the anatomical features of the powdered crude drugs. Pharmacognosy and pharmacognosist must enrich their knowledge through various plant and animal terminology and techniques viz. hybridization, breeding, genetics, plant pathology entomology etc.

Classification of Crude Drugs

Basis of classification of crude is considering certain characteristics, viz. morphology, chemistry, pharmacology or taxonomy or chemotaxonomy or alphabetically.

Alphabetical Classification

In this classificationcrude drugs are classified according to their Latin, English or any other vernacular name. eg Indian pharmacopoeia, British pharmacopeia, USP, NF, Epetc categorige the drug salphabetically. Acacia, benjoin, catechu, dill, ergot, fennel, ginger, henna, ipomea, jalap, kurchi bark, liquorice, and soon.

Morphological Classification

In this classification the crude drugs are categorized according to their morphological characters, means similar character shaving drugs are grouped in same category irrespective of their pharmacology orchemistry.

Bark

Cinnamon. Cinchona. Ashok, Arjun, Kurchi.

Root

Ashwagandha, Rauwolfia Liqorice.

Rhizome

Ginger, Turmeric, Fern.

Leaf

Digitalis, Senna, Cinnamon, Vasaka.

Flower

Pyrethrum, Rose, Jasmine.

Whole Fruit

Colocynth, Fennel.

Entire Drugs
Tulsi, Ephedra, Belladonna.
Dried Juices
Aloes, Red gum.
Dried Extracts
Agar, Curare, Catechu
This claasification is having its applicability for practical study and easy authentication of the drug.

Chemical Classification

In this classification crude drugs are classified according to chemical nature of their active principles. Phytoconstituents of the plants are responsible for the therapeutic effect, hencethis classification more practiced. Eg. all alkaloid containing drugs are categorised in a group.
Alkaloids
Belladona, Opium, Hyoscyamus, Datura.
Glycosides
Aloe, Cascara, Rhubarb.
Fats and Fixed oil
Wool fat, Castor oil, Olive oil, Almond oil.
Carbohydrates and Derived Products
Honey, Starch, pectin Agar, Isbagol.
Volatile oils
Eucalyptus, Lemon grass, Citronella, Turpentine.
Reins and Combinations
Asafoetida, Jalap, Colophony.
Vitamins & Hormones
Fish oil, Insulin, Yeast.

Therapeutic or Pharmacological Classification

In this classification crude drugs are classified according to pharmacological response shown by the chief active principles of the drugs on human body animals or on isolated muscles. The advantage of this categorisation that, all the similar therapeutic action having drugs are categorised in same group and disadvantage is that different morphological characters having drugs come together which some time may lead adulteration while studying or on storage.

Drugs Showing Response on Gastrointestinal Tract

Epecac-emetic
Asafoetida, Nutmeg, Fennel-Carminative
Isbagol, agar, aloe, castor oil- Laxative and purgative
Cinchona, Gentian-Bitters
Kurchi, Epecac- Antiamoebic

Drugs Showing Response on Respiratory System

Tea, coffee-BroncholdialatorsLiquorice,
Vasaka
Expectorant
Opium
Antitussive
Stramonium, Datura-Antispectorant

Drugs Acting on Cardiac System

Digitalis, squill-CardiotonicErgot, ephedra-vasoconstrictor Rauwolfia-antihypertensive.

Drugs Acting on Nervous System

CNS acting Drugs-Opium (Analgesic) tea & coffee (stimulant)
Hyoscyamus, belladonna opium (depressant) Cannabis resin & opium latex
(Hallucinogen)
Ans acting Drug-Ephedra (Adrenergic)
Pilocarpus(Cholinergic)
Belladona(Anti cholinergic)
Antispasmodic drugs- Datura& opium **(Smooth muscle relaxant)**
Curare **(Skeletal muscle relaxant)**
Vinca&Taxus**(Anticancer)**
Guggul& colchicum **(Used in rheumatics-antirheumatic)** Shatavar, Ginseng, Kutki, Tulsi**(Immunity Enhancer)** Coca **(Local anaesthetic)**
Olive oil, almond oil, arachis oil, wool fat, sesame oil **(Acting On Skin & Mucous Membrane)**

Biological (Taxonomical) Classification

This classification classify the drugs according to the phylogenic (natural relationship) similarities among plants and animals, in to kingdom, division, class, order, genus species and subspecies. For classification any accepted system of naming (eg.Binomial system) is applied.

Taxonomic Classification of Hyoscyamus, Datura and Belladona

Phylum
Spermatophyte
Division
Angiospermae Class Dicotylenous Subclass
Sympetalae Order
Tubiflorae
Family
Solanaceae

Genus

Atropa, Hyoscyamus, Datura

Species

Hyoscyamusniger, Daturastramonium, Atropa belladonna

Chemotaxonomical Classification

In this classification crude drugs are categorised in specific family according the distribution of a particular chemical compound. Eg distribution of tropane alkaloid in Hyoscyamus, belladonna, stramonium etc. this classification is very helpful regarding the investigation of biosynthetic pathways and secondary metabolite accumulation and their distribution in various families.

Ayurved and Ayurvedic System of Medicine

In India Ayurved is being practiced from vedic period, it is also believed, that before vedic period, there was an advanced civilization called Saraswati civilization, in existence on the banks of extincted river Saraswasti which was streaming in various parts of northwest India in between 12000 years BCE.

Ayurved is considered as ancient science of life, which is being practices from thousands of years with the principle to "maintain the health of a healthy person and to make an individual disease free if it is there" these is a verse in Sanskrit stating the above fact-

"स्वस्थस्यस्वास्थयरक्षणंव्याधितस्यब्याधिपररमोक्षः"

Ayurved is considered as sub ved of Atharvved, according to some scholar, it is the last part of Rigved, while other scholar also believe that Ayurved is the fifth ved. Ved were being practiced by ancient Aryans of India distributed to all over Indian subcontinent from Varma to Gulf of Persia. (Faraskikhadi) and from Himalay to deep ocean Java, Sumatra Thailand Indonesia etc.

Ayurved stand on three essential elements called tridosh viz. Vat, Pitt, Kaph, 9air, bile and phlegm respectively) when these doshas are inastateo fbalance the na person is considered healthy, when doshas are imbalanced then person be come unhealthy.

Concept of Panchmahabhoot, Tridosh, Panchsheeland Saptdhatu

In Ayurved it is believed that whole universe is made up of five basic elements viz. Jal agniprithvi, vaayu and aakash (Water, fire or energy, earth, air and space respectively) these five basic elements in combination form tridoshas called vat (space) pitt (energy and liquid) and kaph (liquid and solid) It is believed that the tridoshas are in harmony, but in every every out of three dosha, one prevail and dominates the rest of two dosha, the prakriti of that person is determined by according to the prevailing dosha in his body.

These tridosha exist in the humanbody in different forms and these forms are called as saptdhatuviz Ra (lymph) Rkta (blood) meda (adipose tissue) mansa (flesh) majja (nervine tissue) shukra 9reproductive tissues) asthi (bones) and mal (excretory material) when tridosh, and saptdhatu are in harmony to each other the person is considered as healthy and vice versa is considered as unhealthy or patholoci.

According to the Ayurvedic belief a herb is having five distict characteristic (properties 0 having the ability to treat a disease. These areras Gun, Veerya, Vipak, Prabhaav, and they may have further divisions. EgRas are of sixtpe like and hurkatuet candgun are10 like Guru, Sukshma, Lghu etc.

Ancient Ayurvedic Text and Practitioners

Charakawasan Ayurved a practitioner in the court of Kushana emperor Kanishka. He compiled the Ayurvedic treatise (Samhita) containg 50 different groups of 10 medicinal plants parts. According to Charaka these groups (gunas) fulfills the need of a practicisingphysician.

Sushruta was in the time period of Kushana empire and he compiled the Ayurvedic treatise (Samhita) known as Sushrut Samhita. this text describes 760 herbs in seven distinct sets on the basis of some of their common characters. Sushruta is believed the first surgeon of the India, who performed first plastic surgery.

Dhanwantri, Nagarjun, AtreyaPunarvasu, Jeevak, Charak, Sushrut, Vagbhattetc.are the most contributing Ayurvedic practioners. Famous ancient Ayurvedic texts are Charak Samhita, Sushrut Samhita, Agnivesh Samhita, Kashyap Samhita, Harita Samhita, Dravyagun Samhita. and different Nighantu etc.

Asav and AristhaLeha Pak or Avaleha Arka Bhasma Churna are five basic dosage forms of Ayurved.

Conclusion

Pharmacognosy serve the basis of all other streams of the therapeutics, hernatural medicines are most economic readily available, potent and with ought or less side effects. In context to the COVID-19 only Ayurvedic formulations became the hope of large population worldwide and a new hope for the further development of Pharmacognosy and Ayurved is in deep consideration.

Pharmacognosy is the modern scientific version of Ayurvedic system of medicine, and it is the need of time to do make Ayurved more scientifically validated and proven to spresad accept it in western world where modern medicinies are more popular. Overall pahramcognosy and Ayurved serve as a natural way tore main healthy wealthy and wise.

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CHAPTER-16

HEALTH AND SAFETY ISSUES

Vinod Nautiyal*
Assistant Professor,
Gurukula Kangri Vishwavidyalya
Haridwar

Somesh Thapliyal
Assistant Professor,
Dept. of Pharmaceutical Sciences,
HNBG University (A Central University)
Shrinagar Garhwal

Ram Kumar Sahu
Assistant Professor,
Dept. of Pharmaceutical Science,
Assam University (A Central University)
Silchar (Assam)

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Introduction

It can't be an overemphasis to specify that all the living organism on the earth are encompassed by microorganism. The few species of microorganism require the body of microorganisms for their survival. The microorganism might be pathogenic or non-pathogenic for the host cell. The pathogenic microorganism caused different types of diseases in immunocompromised or even in healthy ones. The human body as well as other living organism act as host for pathogenic microorganism such as bacteria, fungi and virus, and they cause different types of communicable and non-communicable diseases. The recent outbreak of Covid -19 which is a virus arising dreadful impacts on global health system & economy. The COVID-19 is communicable diseases, and its virus spread directly through respiratory droplet or saliva, and indirectly by contact with contaminated objects.

According to WHO the utmost common symptoms are fever, dry cough, tiredness, sore throat, diarrhoea, conjunctivitis, headache, loss of taste or smell, a rash on the skin, or discoloration of fingers or toes. The serious symptoms associated with COVID-19 are difficulty in breathing or shortness of breath, chest pain, loss of speech, or movement. Yet no specific drug or vaccination against the virus is accessible, so it will be good take preventive measures which boost our immunity in these times.

Ayurveda is considered as the science of life, it proliferates the nature gifts in preserving healthy and happy life. Ayurveda's broad information base on preventive consideration, gets from the ideas of "Dinacharya" - day by day systems and "Ritucharya" - occasional systems to keep up sound life. The Ayurveda are plant-based science and documented the immunity booster plant and their formulation. According to Ayurveda, our body can withstand infections only when all the seven layers of our body's tissues (Rasa, Mamsa, Rakta, Medha, Majja, Asthi and Shukra) are strong. When the seven layers are working together, our immunity will be boosted. Ayurveda documented that certain plants and plant products can empower our immunity.

The Different Measures can be used for the Prevention of COVID-19

I General Measures

1. Warm water should be drink throughout the day.

2. Steam inhalation with fresh Pudina (Mint) leaves or Ajwain (Caraway seeds) can be do twice in a day.

3. Do Yogasana, Pranayama and meditation for at least 30 minutes in early morning.

4. Add following spices like Haldi (Turmeric), Jeera (Cumin), Dhaniya (Coriander) and Lahsun (Garlic) in cooking.

5. Apply sesame oil/ coconut oil or Ghee in both the nostrils (Pratimash-Nasya) in morning and evening.

6. Take 1 table spoon sesame or coconut oil in mouth. Do not drink, Swish in the mouth for 2 to 3 minutes and spit it off followed by warm water rinse. This can be done once or twice a day.

II Ayurvedic Immunity Boosters

1. Take Chyavanprash 10gm (1tsf) in the morning, while Diabetics patient should take sugar free Chyavanprash.

2. Drink herbal tea / decoction (Kadha) made from Tulsi (Basil), Dalchini (Cinnamon), Kalimirch (Black pepper), Shunthi (Dry Ginger) and Munakka (Raisin) - once or twice a day. Add jaggery (natural sugar) and / or fresh lemon juice to your taste, if needed.

3. Drink golden milk once or twice a day. It contains half tea spoon Haldi (turmeric) powder in 150 ml hot milk.

III Dietary Therapy and Herbs Against COVID-19

There are different potential approaches for the application of dietary therapy and herbal medicine against COVID- 19:

- Using foods and herbs as diet or supplement to prevent infection and strengthen immunity.
- Coating the face masks with antiviral agent.
- Air-disinfectant (essential oil) can be applied in room to stop aerosol transmission.
- Use as a surface sanitizing agent to provide a disinfected environment.

III Concept of Health and Healthy Condition

Health as a word, reveals its auto healing power, because in abode of the nature we come across to the abiotic and biotic environmental factors. These environmental factors some time tends in such a way that it becomes life threatening to the biotic force on earth. Sometime the living world on earth get affected a lot from these environmental adversities, these environmental adversities may come in the form of different calamities viz. floods landslides cloud bursts draughts excessive cold and heat waves. When earth is affected by these natural calamities, it leads the initiation of some new epidemic and pandemic viz. COVID-19.

According to the Indian system of medicine, also called as ancient science of life that is Ayurved, a healthy person is that who's body is performing normally and he or she is not having any kind of health abnormalities in his/her body. Five basic elements viz earth water space air and fire, of a healthy body is in balance and they perform their functions normally. Balance in the three basic pillars i.e vat pitt and kaph is responsible for the health and healthy person while imbalance among these three pillars leads lot of health disorders. As a conclusion it is considered that healthy person is that who is disease, metabolic disorder of infection free and his/her body is not revealing any adverse symptoms and the person is working and performing normally at its daily routine life.

IV Factors Affecting Health

A. Biotic

Various biotic factors of the ecosystem when works in harmony to each other the ecosystem remains healthy and works normal, but when any of them is imbalanced aby any reasons the biotic world specially human is effected seriously, for example if the crops frown by farmers is destroyed by different type of animal pests, it may lead the serious life threatening for the survival of the humans, because without food no one can survive after certain time.

B. Pollution

It is the one of major issue remain from long back as a challenging factor for the humanity and other living world on earth. It has been observed that some time the pollution become graveyard of a big population at a particular time, such type of deaths of a large population is seen specially the industrial hazards for example the release of methyl isocyanate (MIC) gas from Union carbide factory at Bhopal India caused the deaths of thousands of innocent people. Some other industrial hazard has been reported from the various parts of the world. These type of hazard some may affect the health of people so deeply or it can be said that if adversely affect the health at genetic level and it leads the disorder from generation to generation.

C. Excessive Human Interventions

Man from ancient time is curious to explore the various parts of the nature for its own ease, comfort and some time for luxury, but mankind forgets that this exaggerated approach to explore the nature up to the level which become a threat to the nature hence for living world for example man is using air conditioning devices on almost every part of his living i.e. from home office vehicle etc. that the chloro- fluoro emission of this gas has become a serious threat to the ozone layer of earth and leading global warming. When ozone layer is depleted the harmful sunlight can cause serious health problems and initiation of new epidemic or pandemic. Global warming itself is so serious that it may prove a threat to the survival of the humanity and other living force on earth, and may get extinct like dinosaurs.

D. Climate Changes

In ancient time, climatic conditions were unlike today, nature itself was dominant, were acting as a controlling force. At present time human intervention is increasing day by day, hence introduction of new diseases leading to pandemic and epidemics, example is COVID- 19. Afforestation is a big cause for the climatic change, green plants acts as pollution absorbing medium, resulting in depletion of pollution from environment.

Second major reason for climate change is excretion of chlorofluoro carbon gases which causes global warming leading to new diseases and suitable conditions for the infective and communicable and transmittable diseases.

V Different Health Issues

Different Health Issues may be of following types

A. Metabolic Disorders

Various metabolic disorders in human body may occur due to some abnormal functioning of the body organ or system or they may be because of some autoimmune disorder. Sometime metabolic disorders may be because of some wrong life style or wrong food habbit.eg lipid metabolism disorder, glucose metabolism disorder Wasting syndrome, metabolic syndrome X.

B. Lifestyle Disorders

As the name itself is indicating the meaning of the disorder, means these are the disorders which occurs in the body due to the altered life style or in lay man language we can say that these type of disorders are due to the lazy lifestyle and over eating or wrong eating patterns. Some of the popular life style disorders are non-insulin dependent diabetes mellitus also called as type two diabetes. From recent study is clear that obese people having high risk of hyperglycaemia as compare to the non-obese person. Diabetes-particularly type-II is a metabolic disorder of glucose in which blood sugar level is elevate, which is responsible for a variety of other health issues like nephropathy cardiopathy and retinopathy. This disorder is primarily due to the stagnant or lazy or non-physically active life, at first which give rise to the fat and cholesterol gain and further its disorder. When we look world scenario of diabetes, India is the world diabetes capital. Lacs of people are dying every year from diabetes in India.

Another popular life style disorder is obese, which according to the world health organization (WHO) is a serious health disorder now. An obese people is at risk for communicable and non-communicable diseases. A fatty person is prone to hypertension, with associated health issues like high blood pressure, respiration problem, join pains arthritis and some other common health disorders etc.

Some other common life style disorders are-

- Hypertension
- Arthritis
- Heart diseases
- Metabolic syndrome
- Chronic kidney failure
- Asthma
- Atherosclerosis
- Depression
- Vascular dementia

Apart from above mentioned disorders there are lot of other life style disorder also which slowly make person compromised with immunity and prone to the various diseases, infection and at high risk of life threatening health issues and death also.

C. Food Habit Related Heath Disorders

There are many health disorders and issues which is directly associated to the food habit. Most popular health issues related to the uncontrolled food habits are as following-

- **Anorexia, Anorexia Nervosa**

Feeling of overweight, even they are not.

- **Bulimia Nervosa**

Eating unusual amount of food for a specific time period.

- **Binger Eating Disorder**
- This is similar to bulimia with shorter period of time.
- **Pica**

It's an overeating having of eating the thigs which are food in reality.

- **Rumination Disorder**

Regurgitating the food, swallowing and chewing it again.

- **Avoidant/ Restrictive food in take Disorder**

Above listed health disorder are not very common but often symptomatic in population.

Some common eating habit disorder are –

- **Obesity**
- **Type 2 sugar**
- **Hypercholesteraemia**
- **Hypertension**
- **Asthma**
- **Allergic Prophylactic Attack**
- **Various type of Skin Allergies**

D. India Approach of Heath and Treatment of Health Issues

As a health care system professional my exposure this system is as a registered pharmacist. I have studied both modern d traditional system of medicine thoroughly and I firmly feel that the approaches to be healthy and maintaining the health is the ancient Indian Ayurvedic and Yogic approaches. Which can be summarize in following points-

Sthool or Physical level

in which person have to live an active life he/she should adopt a healthy eating, sleeping and happy life living approach.

Skooshm or Microlevel

there are emphasis on the food and other material consumption, in such a way that the ingested food material should be easy to digest, healthy the body comprised with nutrients sufficient to meet out the requirement of the body. This approach also covers the exercises and different postures (Asanas).

Chetan or Consciousness level

this is the most important approach to be healthy wealthy and wise as per Indian mythology and ancient rich scientific scriptures. Today modern

science confirms that a healthy and happy person is healthier because his psychological attitude favours him to attain good immunity with healing power. If a person performs Yoga pranayama daily in his/her life definitely the person will be healthier. Stanford and NIMHAND the reputed institute of the world have scientifically validated the healing power of yog pranayama in different non-curable health issue with positive outcome.

Conclusion

Health is the most and primary object of humanity and all other living animals. A healthy person can live a happy and successful life he/she can change the or contribute for upliftment of the society by any means. So one should be focused for his/her health and healthy body coz it said in an Indian phrase that “healthy brain lives in healthy body' and we all know brain is master controlling power of the body. If body is ill or with some pathologic condition, person's both physical and mental approach will be affected largely.

Various natural and manmade factors affect our health; we the humans are the biggest enemy of our own by destroying the natures balance and leading to the irreparable damage to the mother earth. We are receiving the natures alarm time to time, even we are not taking these alarms seriously, example is CCOVID-19. So in final words I want to spread my call- please be natural, eat natural, live natural and your nature will be very natural with natural joy happiness with fabulous health withought any health issues.

Innovations in Plant Science for Better Health: *From Soil to Fork*

Herbs, Spices, and Medicinal Plants for Human Gastrointestinal Disorders

Health Benefits and Safety

Editors Megh R. Goyal | Preeti Birwal
Durgesh Nandini Chauhan

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CHAPTER 1

Ethnopharmacology and Therapeutic Potential of *Carica papaya*

GURPREET SINGH, POOJA CHAWLA, ABDUL FARUK, and VINEY CHAWLA

ABSTRACT

Papaya (*Carica papaya* Linn) has been widely used as traditional herbal remedy for the prevention and management of several conditions and diseases. During the past few decades, it has been used in the treatment of digestive problems, wounds, dengue, and jaundice, etc. Its major bioactive phytoconstituents are: papain, chymopapain, alkaloids, flavonoids, lycopene, carotenoids, anthraquinones glycoside, antioxidants, and vitamins. This chapter has highlighted various ethnopharmacological and traditional uses of different parts of *Carica papaya.*

1.1 INTRODUCTION

Carica papaya is a member of the family *Caricaceae* (a family of dicots plants with four genera).[56] *Papaya* is a delicious fruit in most tropical and semitropical countries and is cultivated mostly for its consumption as fresh fruit, and for use in drinks, jams, salads, and candies.[2] The papaya plant has been well-documented in the literature for a number of medicinal properties and has been used against diseases, such as gastroenteritis, urethritis, typhoid fever, wound infection, asthma, rheumatism, fever, diarrhea, boils, and hypertension, etc.[7,11,37,59,60,67,71] All parts of papaya (seeds, roots, rinds, and fruits) have beneficial therapeutic and protective properties (Fig. 1.1). Different parts of the papaya plant have been used in

the food (nutraceuticals), skincare products, leather, and pharmaceutical production.[41] Scientists have reported the activity of papaya for antifertility, anthelmintic, and anti-inflammatoryeffects.[50,53,55,58,97] The latex of unripe fruit is widely used in pharmaceutical and cosmetics products.[18,69,78]

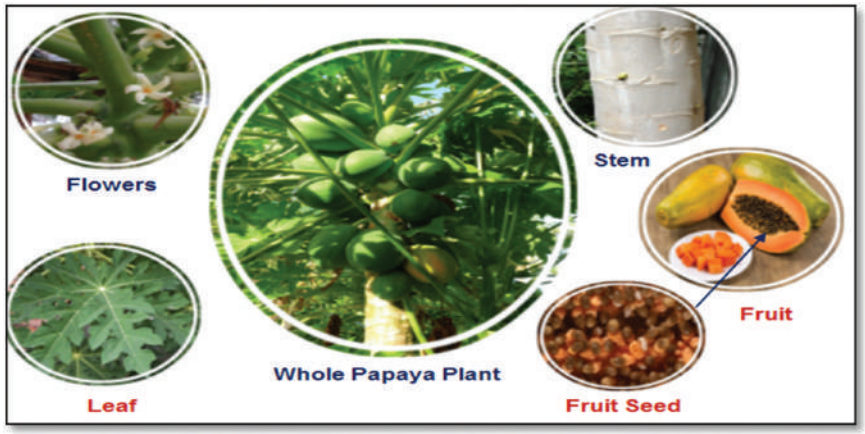

FIGURE 1.1 Major parts of *Carica papaya* plant.

The Spanish chronicler Oviedo indicated the papaya on Panamanian and Colombian coasts in 1526. Due to the high viability of papaya seeds, the fruit was rapidly produced in the tropics.[23] During this century, papaya has been cultivated in tropical regions with fertile soils and heavy rainfall. Then, papaya seeds were introduced to Southeast Asia and India by Spanish and Portuguese mariners. Later, papaya seeds reached Hawaii between 1800 and 1820.[77] In the 20th century, papaya seeds were taken to Barbados, Jamaica, Mexico, and Florida.

1.2 GEOGRAPHICAL DISTRIBUTION

It is local to the tropics of the Americas, however, now it is generally developed all through the world, and is accessible consistently.[3] It is cultivated in different parts of the world and the significant cultivators of papaya plants include India, tropical America, Europe, Australia, Hawaii, and South-East Asia.[30] Papaya is cultivated in all five continents due to its capability of growing in all soil types, but it requires good drainage.[1,73]

The major contribution of its total production[98] comes from Asia, Central America, and other countries as shown in Figure 1.2, and major cultivars of papaya plant are listed in Table 1.1. Different vernacular names of *C. papaya* and the taxonomic hierarchy of *C. papaya* have been illustrated by many investigators.[20,44,73]

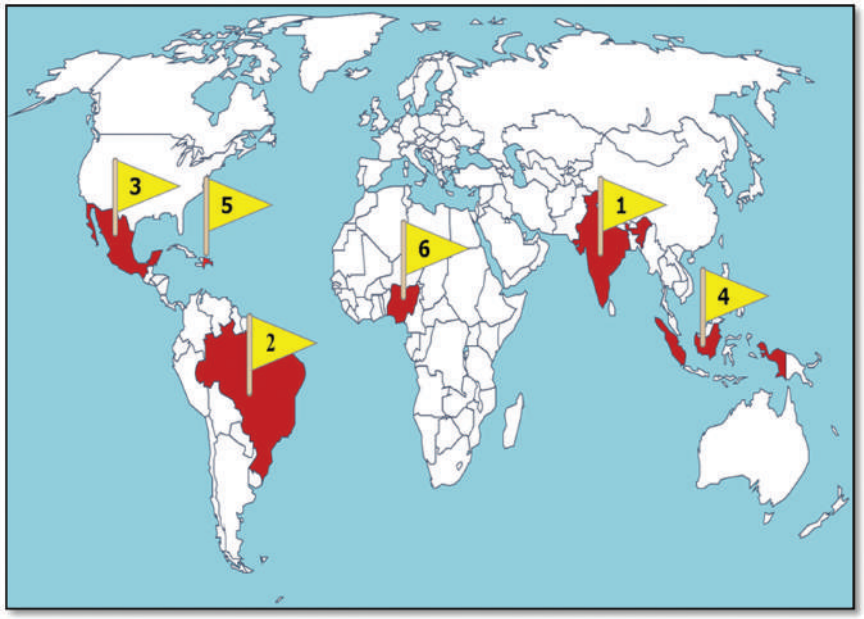

FIGURE 1.2 Major producers of papaya plant: (1) India, (2) Brazil, (3) Mexico, (4) Indonesia, (5) Dominican Republic, and (6) Nigeria.

1.3 MORPHOLOGY

Papaya is a small softwood and unbranched tropical fruit tree of 5–10 m in height with the spirally arranged leaves. The seven lobed leaves are large in diameter of about 50–70 cm, vary in sizes and shapes in different maturity stages. Fruits are commonly green while young and yellow-greenish or orange when ripe with the large ovoid smooth surface.[1,10] The fruit has a hollow berry, which contains small black seeds that constitute about 15% of the total weight and the seeds are lined in five rows to the interior wall

of the fruit. Papaya tree starts to bear fruit within 1–2 years.[72] It can be cultivated in either home gardens or outdoors.

TABLE 1.1 Major Cultivars of Papaya in the World.

Country	Variety
Australia	Improved Petersen, Guinea Gold
Barbados	Wakefield, Graeme
Cuba	Maradol
Dominican Republic	Cartagena
Florida	Cariflora, Betty, Homestead
Hawaii	Kapoho Solo,Waimanalo, Rainbow
India	Coorg Honey Dew, Coimbatore Varieties (CO1–CO8)
Indonesia	Semangka, Dampit
Malaysia	Eksotika, Sekaki
Mexico	Verde, Gialla, Cera, Chincona
Philippines	Cavite, Sinta
South Africa	Hortus Gold, Kaapmuiden
Taiwan	Tainung five
Thailand	Sai-nampueng, Khaek Dam
Trinidad	Santa Cruz Giant, Cedro
Venezuela	Paraguanera, Roja

On the basis of reported literature, papaya plant is categorized into three primary sexes (Fig. 1.3), such as male (staminate) (♂), hermaphrodite (bisexual) (⚥), and female (pistillate) (♀). A typical male and female plants bear individual unisexual flowers, while hermaphrodite plant bears a combination of male unisexual and hermaphroditic flowers.[33,54] The typical female flower is mostly large and conical in shape when it is mature with five petals spread from the base. The ovary is large in structure with a circular smooth surface, which produces spherical or ovoid-shaped flowers. Fruit progresses from globular to egg-shaped. In the case of hermaphrodite intermediate type, the flower is undefined and petals may be fused in their length or may be free from the base. Hermaphrodite elongated type of flower has fused petals from one-fourth to three-fourths of their total length with 10 anthers, out of which five are long and five are short. The long ovary contains five or more carpels and forms the fruit which is cylindrical to pear-shaped and is of great commercial value.

The typical male flower has a long and thin corolla. It contains anthers in two series of five; one series is longer than the other. The male flowers have nonfunctional rudimentary pistil.[33,61] Multiple species of papaya have been documented in the scientific literature, which belong to five genera, that is, *Jacaratia*, *Jarilla*, *Horovitzia*, *Carica*, and *Vasconcellea*.[24]

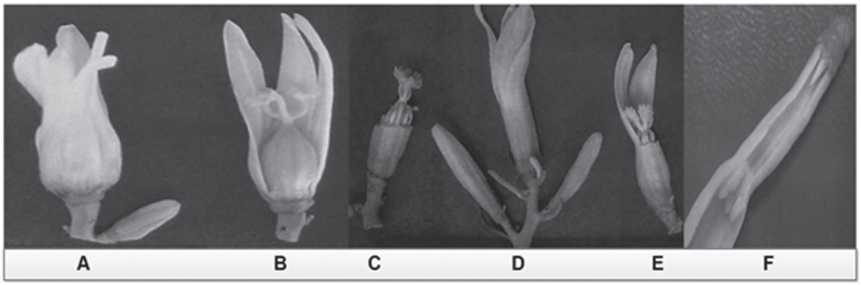

FIGURE 1.3 Six varieties of flowers of papaya plant: Typical female (A, B). Hermaphrodite intermediate (C). Hermaphrodite elongated (D). Hermaphrodite sterile (E). Typical male (F).

1.4 PHYTOCONSTITUENTS

Primary phytoconstituents reported from various parts of the *C. papaya* plant include papain (proteolytic enzyme), lycopene (tetraterpene), carotenoids, alkaloids, monoterpenoids, flavonoids, mineral (potassium, etc.), vitamins (A, C, and E; thiamine, niacin, and riboflavin), malic acid, and glycosides.[1,34,69,74,81,96] Fresh fruit juice contains flavonoids, tannins, and anthocyanins with antioxidant ability as free radical scavengers.[68] Young leaves of papaya include carpaine, pseudocarpaine, dehydrocarpaine, choline, carposide, and vitamins (C and E). Phytochemical analysis of the different parts of the plant revealed the presence of various bioactive phytochemicals, which have pharmacological importance (Fig. 1.4).

Papaya fruit exhibits wide range of medicinal properties (i.e., antimicrobial, antiviral, anti-inflammatory, healing of wound and dressing aid, anticancer, neurodegenerative, diuretic, abortifacient agent, and contraceptive).[43] It is highly well-known for its nutritional values and it aids in digestion. Extract of the whole fruit contains immunity boosters (i.e., vitamin C, ferulic, caffeic acid, and *p*-coumaric) that protect human cells against oxidative stresses.[13]

Unripe fruit of papaya contains proteolytic enzyme papain (cysteine protease), which acts like pepsin in gastric juice. The papain is more active

in green fruit and shows extensive proteolytic activity toward proteins. The extract from the seeds of papaya shows antioxidant and anticancer activities due to the presence of various phenolic compounds, vanillic acid, and vitamin C.[52,62,86]

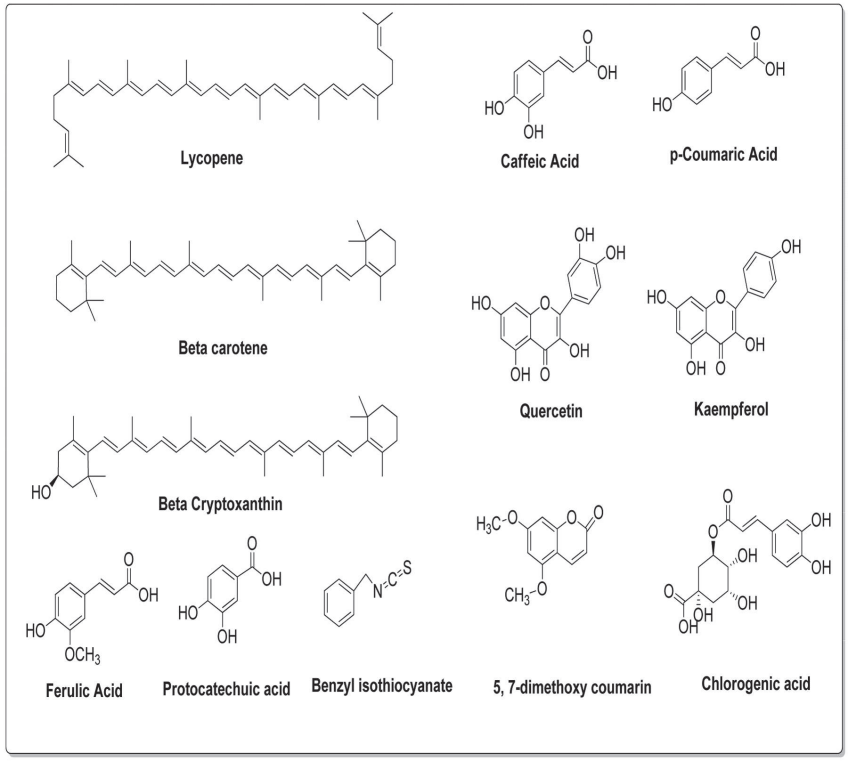

FIGURE 1.4 The structures of some phytoconstituents isolated from *C. papaya*.

Another source of papain is latex, which is harvested by incision on the surface of unripe fruit. After 4–5 days, latex is collected and further processed into dry powder for various uses in pharmaceutical and food industries.[51] The process of isolation of papain from unripe fruit latex is shown in Figure 1.5.

The papaya fruit is suitable for human consumption due to its nutritional and digestive value, with a low caloric content, which provides a favorable cost-benefit to human health.[69] Furthermore, scientific studies report the nutritional content of 100 g of ripe and unripe papaya fruits as summarized

in Table 1.2. Results revealed that unripe papaya has the highest concentrations of different vitamins and minerals as compared with ripe fruits.[22,79]

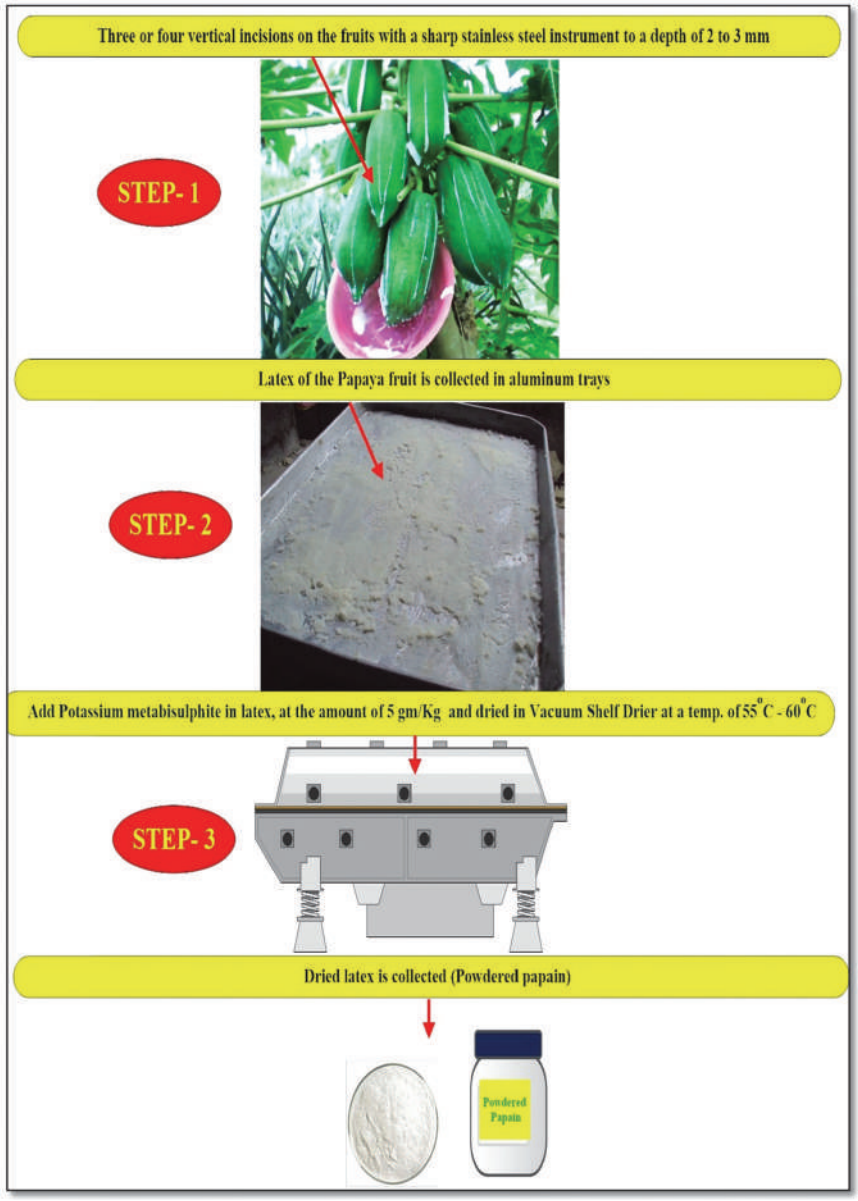

FIGURE 1.5 Isolation of papain powder from the latex from the papaya fruit.

TABLE 1.2 Nutritional Value of a Papaya Fruit.

Constituent	Ripe fruit (g)	Unripe fruit (g)
Water	89.1	92.6
Proteins	8.26	10.8
Total lipid	0.93	1.35
Ash	0.00459	6.76
Carbohydrates	86.2	81.1
Mineral Macronutrients:		
Sodium	0.1284	0.2838
Potassium	1.238	2.743
Magnesium	0.2294	0.6351
Calcium	0.1468	0.4324
Micronutrients:		
Iron	0.01284	0.00811
Copper	0.00018	0.00014
Zinc	0.00092	0
Vitamins:		
Vitamin C	0.5688	0.0003919
Thiamine	0.00028	0.00054
Riboflavin	0.00028	0.026
Niacin	0.0028	0.00405
Carotene	7.807(µg)	0

1.5 PHARMACOLOGICAL ACTIVITIES AND THERAPEUTIC USAGES OF *CARICA PAPAYA*

Every part of papaya plant holds the therapeutic value from leaves to roots.[56,69] The fruits, latex, and juice of papaya plant are the main source of many vitamins, which aid in dyspepsia, intestinal irritation, and habitual constipation.

The main constituent papain plays a vital role to improve the immune system.[9] In traditional veterinary medicine, papaya seeds are used as de-wormers and is also used in tropical folk medicine. The fresh latex is used as a vermifuge.[6] Papain is a proteolytic digestive enzyme that is used in several herbal formulations. Fresh juice of papaya prepared from peeled or unpeeled fruit is also sold as immunity booster drink because of its low cost, easy availability throughout the year and high nutritive value. In certain countries, the latex of the plant is used for tumors of uterus,

psoriasis, and ringworm. The root infusion is used against syphilis.[82] Through several scientific studies, the traditional, pharmacological, and biological effects of *C. papaya* have been validated.[10,44,74,78]

1.5.1 Anthelmintic Activity

A wide collection of papaya and their extracts have been used traditionally for the management of helminths (parasites). Papaya contains many biologically active compounds with varying properties in fruit, latex, leaves, and roots that aid in digestion. It has also been employed for treating intestinal worms.[6,16] Papain, which is present in the latex of unripe green fruits of papaya, has been commercialized in various forms. Dried seeds of papaya have shown significant activity in the management of human intestinal parasites, which have increased the stool clearance rate of parasites without any side effects. It is represented as a novel class of antihelminthic due to the efficacy of papaya latex and cysteine proteinases against *Heligmosomoid espolygyrus* (nematode).[89] Shaziya et al. reported the antihelminthic action of papaya leaves on *A. Caninum* nematode infecting mice.[87]

Papain is a protein enzyme with cysteine protease, chymopapain, and lysozyme, which can accelerate the reaction within body cells. During the digestion process, pancreas commonly produces enzymes in the human body, these enzymes break down the foods into micronutrients, which can be used by the body for energy and other functions.[12] Two main proteolytic enzymes (papain and chymopapain) in the latex of the papaya simply break down the proteins into amino acids through cleavage of the peptide bond. These proteins contained peptide bonds and can be easily broken down by enzymatic action into easily digestible micronutrients. It also helps to promote the digestion of wheat protein.[40]

1.5.2 Antioxidant Activity

Antioxidant properties of aqueous extract of papaya leaves were evaluated in alcohol-induced acute gastric damage. The outcomes revealed that gastric ulcer index was significantly better in rats pretreated with the extract of papaya leaf as compared with the alcohol-treated rats. Further, leaf extract also offered reduced blood oxidative stress level in rats via the reduction

of lipid peroxide levels in plasma and amplified red blood cell glutathione peroxidase activity.[39]

Another study showed strong in vivo antioxidant actions of ethyl acetate fraction of unripe pulp of papaya on antioxidant enzymes (i.e., glutathione peroxidase (GPX), glutathione S-transferase (GST), glutathione reductase (GR), catalase, and glucose-6-phosphate dehydrogenase (G6PD)) in albino mouse. It has been suggested that it can be used for protection against gastric ulcer and oxidative stress.[64] Natural source of antioxidants may responsible for total antioxidant effect due to the presence of carotenoid, polyphenols, vitamin C, and vitamin E.[57] Several studies showed that the antioxidant property is related to the diminished DNA damage and decreased lipid peroxidation, which maintained the immune function.[46,48]

1.5.3 Antiviral Activity

The published studies on dengue specified that the juice of papaya leaves could help to increase the platelets and white blood cells count in these patients.[15,80] A study in 2012 has reported about in vitro studies of papaya leaf extracts on persons infected with dengue. Papaya leaf extract inhibited the heat- and hypotonicity-induced hemolysis of red blood cells and has membrane-stabilizing properties.[76] In a randomized controlled trial in dengue patients, there was an increment in platelets-related genes like arachidonate 12-lipoxygenase and platelet-activating factor receptor gene and that contributed to the prevention of platelet lysis. In folk medicine, papaya leaves have been used for the management of dengue fever with hemorrhagic symptoms.[91]

1.5.4 Antimicrobial Activity

Osato et al.[65] and Calzada et al.[17] reported the ability of papaya seeds as antimicrobial agent against several Gram-positive and Gram-negative bacteria like *Trichomonas vaginalis* trophozoites, *Bacillus subtilis, Escherichia coli* and *Salmonella typhi*.[17,65] The aqueous extract of papaya leaves and roots at different concentrations showed antimicrobial effects against pathogenic bacteria.[8] The pulp and fruits of papaya also showed remarkable antibacterial effect against *B. subtilis, K. pneumonia, P. vulgaris, E. coli, P. aeruginosa, S. typhi, E. cloacae*, *and S. aureus*.[11]

1.5.5 Antifungal Activity

The papaya leaves and seeds of ripe and unripe fruits were evaluated against phytopathogenic fungi (i.e., *R. stolonifer*, Fusarium spp. and *C. gloeosporioides*), which exhibited good antifungal activity. The antifungal activity was observed to increase in a concentration-dependent manner.[19] The latex of papaya also inhibits the growth of *Candida albicans*. The latex shows antifungal activity due to partial degradation of the outermost layers of fungal cell wall, which lacks polysaccharides.[26] The synergistic effect of latex of papaya with fluconazole in *C. albicans* was also reported.[25]

1.5.6 Anti-Inflammatory Activity

It has been well documented in the literature that the dried papaya leaves are used for the management of inflammation, arthritis, rheumatism, and as wound dressing material. The ethanolic extract of the leaves was examined in rats using a paw edema model with indomethacin-treated control group. The results showed that the extracts significantly reduced edema and amount of granuloma. Similar results were confirmed with other models, that is, cotton pellet granuloma model and formaldehyde-induced arthritis model.[67,92,93]

Papaya leaves are a rich source of carpaine, nicotinic acid, which may be accountable for the anti-inflammatory effect. Ahmed et al.[4] assessed the inflammation at acute, subchronic, and chronic phase using the cotton pellet granuloma model, formaldehyde-induced arthritis and carrageenan-induced paw edema models. They suggested that the anti-inflammatory activity of the ethyl alcohol extract of papaya was due to the inhibition of *prostaglandin*- mediated inflammation.[4] Papaya leaf extract also exhibited anti-arthritic activity by the modulation of inflammatory mediators, such as, cytokines or chemokines, prostaglandins or leukotrienes.[67]

1.5.7 Antifertility Effects

The antifertility activity of papaya fruit was evaluated in adult rat and pregnant rat model. The results revealed that the unripe fruit disturbed the estrous cycle and encouraged the abortion.[27] Seed extract showed antifertility activity due to gradual degeneration of Sertoli and Leydig cells,

which induced long-term azoospermia.[95] A recent report revealed that seeds possess reversible male contraceptive potential by directly rendered the spermatozoa process.[90] It is further reported that root extract exerts morphological changes in the endometrium of rat uterus[83] and the aqueous extract of seeds has shown miscarriage in female *Sprague Dawley* rats.

The crude extract of papaya bark showed antifertility activity in rats due to its effect on sperm motility; and while the aqueous/petroleum ether/alcoholic extracts in rabbits inhibited ovulation cycle. Therefore, it can be utilized as an effective contraceptive in animals.[47] It was further reported that the unripe or half-ripe fruits contain a high concentration of the latex, which increased the uterine contraction. Normal consumption of ripe papaya is safe in pregnancy, but unripe papaya is unsafe.[2]

1.5.8 Anticancer Activity

Many studies scientifically validated the anticancer effects of papaya leaves. The aqueous extract of papaya leaves exhibits a dose-dependent significant activity against the cells of breast and lung adenocarcinoma, cervical, hepatocellular and pancreatic epithelial carcinoma, and mesothelioma. These results indicate that extracts may inhibit the growth of different types of cancer cell lines. However, the precise cellular mechanism of action remains unclear.[29,66] Several studies have claimed that mechanisms in the inhibition of proliferation by papain include the production of cytokines by human peripheral blood mononuclear cells, interfering in cancer cell wall and cleavages of proteins into amino acid form.[21]

Leaves of *C. papaya* (which contain a high concentration of tocopherol, lycopene, flavonoid, and benzyl isothiocyanate) potentially contribute to anti-tumor activity.[79] Similarly, fermented product of papaya (FPP®) claimed the immunity booster and antioxidant activity. The role of free radicals in propagating cancer is fully documented. Thus, by acting as an antioxidant, it helps to control cancerous growth.[49]

1.5.9 Antihypertensive Activity

Methanolic extract of papaya elicited the antihypertensive effects due to in vivo inhibition of angiotensin-converting enzyme and it improved the effect on the baroreflex. It was reported that angiotensin-converting

enzyme inhibitory activity was similar to those of enalapril and reduced the cardiac hypertrophy.[14]

1.5.10 Antimalarial Activity

Daily consumption of papaya leaves is a common practice in tropical communities for preventing malaria caused by *Plasmodium* genus. In vitro antiplasmodial effect of the leaf extracts was reported to be due to carpaine, which is an alkaloid.[42,94] Petroleum ether extract of the rind of papaya fruit also exhibits antimalarial activity.[99]

1.5.11 Hematological Activity

The study revealed that phytochemicals in seed, leaf, and pulp produced significant effects on certain blood parameters in treated rats. A dose-dependent effect was observed, which could be attributed to the existence of folic acid, vitamin B_{12}, alkaloids, and glycosides. It can be used for the treatment of sickle-cell anemia.[36,38]

1.5.12 Wound Healing Activity

Papaya latex contains papain, which can break down the necrotic tissue contributing to wound healing process. The study showed that the latex of *C. papaya* decreases the oxidative tissue damage thus ensuring the clot formation process during healing and the increase in di-hydroxyproline content.[28] It is also known to be effective in diabetic wound healing by preventing infection due to its antimicrobial activity.[5]

1.5.13 Hepatoprotective Activity

Ethanol and aqueous extracts of papaya fruit hold the hepatoprotective effect against carbon tetrachloride (CCl_4)-induced hepatotoxicity in rats. Results revealed significant hepatoprotection by reduction in biochemical parameters, such as, SGPT (serum glutamic pyruvic transaminase), SGOT (serum glutamic-oxaloacetic transaminase), ALP (alkaline phosphatase), and serum bilirubin, which are indicators of liver damage.[75]

1.5.14 Topical Use

Various topical applications of papaya fruits have been used in developing countries, such as topical ulcer dressings and burn dressing. It is a cost-effective remedy for desloughing necrotic tissue and preventing burn wound infection.[31] It also provides a granulating tissue, which is suitable for the application of skin graft. Now-a-days, papaya is commonly used in children's burns dressing. Papaya fruit is crushed and is daily applied on the infected burns as a layer.[88]

1.6 SUMMARY

Scientists around the globe have focused on papaya plant for its high medicinal value with simple availability in nature. *C. papaya* has the potential of capturing the global market of herbal formulations for therapeutic potential in digestive disorders. However, this needs a clinical validation. The presence of secondary metabolites has been identified, which may help in the planning of such clinical studies, which are needed to understand and explore the exact pharmacological and molecular mechanisms action of *C. papaya* activity. It will also help to establish its toxicity profile along with drug interactions.

KEYWORDS

- **abortifacient**
- **anthelmintic activity**
- **antifertility**
- ***Carica papaya***
- **caricaceae**
- **chymopapain**
- **dengue**
- **digestion enhancer**
- **nutraceutical**
- **papain powder**

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The Impact of Aerosol in Weather Variation, Environment and Human Fitness

Peeush Singhal*[1], Ritu Vishnoi Singhal[2], Prince Prashant sharma[1], Vijay Jyoti Kumar[3]

Abstract

Aerosol is a vital part of the atmosphere, and its supply, composition, distribution, and effects are extremely difficult. Governments and scientists have given abundant attention to aerosol issues and it's become a hot topic because of the necessary role it plays in global climate change and also the Earth's setting. Through this paper, a) The importance of aerosol in Weather Variation, the the atmospheric environment, and human Fitness is summarized; b) The recent serious issues of aerosol pollution and also the shortage of current aerosol analysis in Asian country are pointed out and c) The need to reinforce aerosol research in India is emphasized.

Keywords: *Aerosol, Weather Variation, Environment, Human Fitness.*

*[1]Department of Pharmaceutical Sciences, Gurukul Kangri University, Haridwar-249404 (India)

[4]Department of Botany, Chinmaya Degree College, Sector 6 BHEL complex, Opp Shivalik Nagar, Ranipur, Hardwar, Uttarakhand.

[4]Department of Pharmaceutical Sciences, H.N.B. Garhwal Central University, Srinagar, Uttarakhand 246001 (India)

Introduction

The effect of Aerosol on the atmosphere is broadly recognized as one of the foremost critical and questionable angles of climate alter projections[1]. The watched worldwide warming slant is impressively less than anticipated from the increment in nursery gasses, and much of the distinction can be clarified by aerosol impacts[2, 3]. Mist concentrates affect climate through coordinate diffusing and assimilation of approaching sun powered radiation and catching of active long-wave radiation as well as through modification of cloud optical properties and the arrangement of clouds and precipitation[4, 5, 6]. There is developing concern for the effect of aerosols on human wellbeing and intrigued by numerous divisions such as climate forecast, the green vitality industry (with respect to their impact on sun powered vitality coming to the ground) [7, 8] and the commercial flying machine industry (with respect to the effect of volcanic cinder and dust storms on operations and aircraft) [9, 10]. Territorial issues incorporate potential impacts on human wellbeing and mortality and natural effect such as visibility impairment[11]. Major sources of aerosols incorporate urban/industrial emanations, smoke from biomass burning, and auxiliary arrangement from vaporous vaporized antecedents, ocean salt and dust[12, 13, 14]. Exceptional issues incorporate deciding the common sources of aerosols products and the organic fraction[15]. It is known that there are thousands of possibly hurtful living beings that can seriously hurt human wellbeing in inhalable atmospheric aerosols[16, 17]. Prove moreover appears that mist concentrates affect climate, in spite of the fact that this affect is to a great extent questionable[18]. Numerous papers related to aerosols have been as of late distributed in universally famous journals such as Nature and Science, demonstrating that the subject of climatic airborne has become one of the foremost vital inquires about directions[19]. In this studies, the significance of investigating aerosol will be talked about, and both the seriousness of aerosol contamination and the deficiency of relative ponders will be pointed out[20, 21, 22].

Aerosols

Aerosols are collections of tiny particles of solid and/or liquid suspended in a gas. The size of particles in an aerosol ranges from about 0.001 to about 100 microns[24]. (A micron is one-millionth of a meter.) The most familiar form of an aerosol is the pressurized spray can, which can dispense anything from hair spray to enamel paint to whipping cream. Aerosols are produced by a number of natural processes and are now manufactured in large quantities for a variety of commercial uses. They are also at the root of a number of environmental problems, including air pollution and destruction of ozone, a natural component of Earth's atmosphere[26, 27].

Classification

Aerosols are commonly classified into various subgroups based on the nature and size of the particles of which they are composed and, to some extent, the manner in which the aerosol is formed. Although relatively strict scientific definitions are available for each subgroup, these distinctions may become blurred in actual practical applications. The most important of these subgroups are fumes, dusts, mists, and sprays[28, 29, 30].

Fumes

Fumes consist of solid particles—ranging in size from 0.001 to 1 micron—suspended in a gas. Probably the most familiar form of a fume is smoke. Smoke is formed from the incomplete combustion of fuels such as coal, oil, or natural gas. The particles that make up smoke are smaller than 10 microns in size[29, 31].

Dusts

Dusts also contain solid particles suspended in a gas, usually air, but the particles are larger in size than those in a fume. They range from about 1 to about 100 microns in size, although they may be even larger. Dust is formed by the

release of materials such as soil and sand, fertilizers, coal dust, cement dust, pollen, and fly ash into the atmosphere. Because of their larger particle size, dusts tend to be more unstable and settle out more rapidly than do fumes, which do not settle out at all [30, 31].

Mists

Mists are liquid particles—less than about 10 microns in size—dispersed in a gas. The most common type of mist is that formed by tiny water droplets suspended in the air, as on a cool summer morning. If the concentration of liquid particles becomes high enough to affect visibility, it is then called a fog. A particular form of fog that has become significant in the last half century is smog. Smog forms when natural moisture in the air interacts with human-produced components, such as smoke and other combustion products, to form chemically active materials[32, 33, 34].

Sprays

Sprays form when relatively large (10+ microns) droplets of a liquid are suspended in a gas. Sprays can be formed naturally, as along an ocean beach, but are also produced as the result of some human inventions such as aerosol can dispensers of paints, deodorants, and other household products[35, 36].

Sources

About three-quarters of all aerosols found in Earth's atmosphere come from natural sources. The most important of these natural components are sea salt, soil and rock debris, products of volcanic emissions, smoke from forest fires, and solid and liquid particles formed by chemical reactions in the atmosphere[37, 38, 39, 40].

Volcanic eruptions are major, if highly irregular, sources of atmospheric aerosols. The eruptions of Mount Hudson in Chile in August 1991 and Mount Pinatubo in the Philippines in June 1991 produced huge volumes of aerosols that had measurable

effects on Earth's atmosphere.

Words to Know

- **Acid rain:** A form of precipitation that is significantly more acidic than neutral water, often produced as the result of industrial processes[41, 42].
- **Chlorofluorocarbons (CFCs):** A group of organic compounds once used widely as propellants in commercial sprays but regulated in the United States since 1987 because of their harmful environmental effects [43, 44].
- **Dust:** An aerosol consisting of solid particles in the range of 1 to 100 microns suspended in a gas[45].
- **Electrostatic precipitator:** A device for removing pollutants from a smokestack[46].
- **Fume:** A type of aerosol consisting of solid particles in the range 0.001 to 1 micron suspended in a gas[47, 48].
- **Micron:** One-millionth of a meter[48].
- **Mist:** A type of aerosol consisting of droplets of liquid less than 10 microns in size suspended in a gas[49, 50].
- **Ozone layer:** A region of the upper atmosphere in which the concentration of ozone is significantly higher than in other parts of the atmosphere[51].
- **Smog:** An aerosol form of air pollution produced when moisture in the air combines and reacts with the products of fossil fuel combustion[52].
- **Smoke:** A fume formed by the incomplete combustion of fossil fuels such as coal, oil, and natural gas[53].
- **Spray:** A type of aerosol consisting of droplets of liquid greater than 10 microns in size suspended in a gas[54].
- **Stack gases:** Gases released through a smokestack as the result of some power-generating or manufacturing process[55].

The remaining atmospheric aerosols result from human actions. Some, such as the aerosols released from spray-can products, go directly to form aerosols in the atmosphere. Others

undergo chemical changes; for example, oxides of nitrogen and sulfur are produced during the combustion of fossil fuels such as coal and oil. These oxides may be converted to liquid or solid nitrates and sulfates, which are then incorporated into atmospheric aerosols[56].

Aerosols Effect on Environment

Aerosols impact climate in two essential ways: by changing the sum of heat that gets in or out of the atmosphere, or by influencing the way clouds form Some aerosols, like numerous sorts of dust from ground-up rocks, are light-colored and indeed a small bit reflective[57,58]. When the sun's beams pillar down on them, they bounce the beams back out of the climate, anticipating that warm from ever coming to Earth's surface. The impact can be dramatic[50, 60]: The Mt. Pinatubo volcanic emission in 1991, within the Philippines, retched the proportionate of 1.2 square miles of little, reflective rock particles into the high stratosphere—cooling the planet for two full a long time a short time later. The 1815 Tambora emission, so also, produced an epic, globe-spanning "Year without a Summer" so cold and disheartening it motivated Mary Shelley's dark horror novel, *Frankenstein*[61, 62].

But other aerosols, like small bits of dark carbon from burned coal or wood, do the inverse, retaining warm from the sun because it beats down. That closes up warming the climate, in spite of the fact that it cools the surface of the Earth by anticipating the heat from getting away. Generally, that impact is likely littler than the cooling most aerosols induce—but it's distant from nonexistent, and the more carbon-based material that collects within the atmosphere, the more warming the environment experiences[63, 64].

Aerosols moreover impact how clouds frame and develop. Water droplets coalesce promptly around particles, so a particle-rich air advances cloud arrangement. White clouds reflect approaching sun, anticipating it from getting to the surface and warming land or water—but they too assimilate the heat that the planet is always emanating back outward,

catching it within the lower atmosphere. Depending on the cloud sort and area, they can either warm their environment or cool them[65, 66].

Ozone depletion: An especially genuine natural impact of aerosol technology has been harm to Earth's ozone layer. This harms shows up to be caused by a gather of compounds known as chlorofluorocarbons (CFCs) which, for more than a half century, were by far the most popular of all propellants used in aerosol cans. Scientists initially felt small concern around the utilize of CFCs in aerosol products since they are profoundly steady compounds at conditions experienced on Earth's surface. They have since learned, in any case, that CFCs carry on exceptionally in an unexpected way when they diffuse into the upper environment and are uncovered to the strongly sun based radiation display there. Under those circumstances, CFCs break down and discharge chlorine molecules that, in turn, react with ozone within the stratosphere (the climatic locale around 7 to 31 miles over Earth's surface). As a result, the concentration of ozone in portions of the environment has been relentlessly diminishing. This alter might demonstrate to be exceptionally perilous, since Earth's ozone layer retains bright radiation from the Sun and secures living things on our planet from the destructive impacts of that radiation[67,68,69,70].

Aerosols have a complicated suite of distinctive impacts on the planet, but people have straightforwardly affected their nearness, plenitude, and dissemination. And whereas the climate impacts are complex, the wellbeing impacts are clear: More fine fabric within the atmosphere harms human health[71,72].

Health Effects of Aerosols

Effects of airborne particles[73,74,75]

- Health effects (epidemiology as the main trigger);
- Effects on atmospheric properties;
- Visibility reduction;
- Fog formation and precipitation;
- Solar radiation reduction;

- Temperature and wind distribution alteration (e.g. climate change);
- Effects on materials;
- Effects on vegetation.

1. Health effects of particles – seldom with direct proofs about the mechanism. In general, inhalation of airborne particles contributes to excess mortality and morbidity (not all adverse effects result in death). Specific health "end points" include[77]:

- Declines in lung function;
- Increased respiratory symptoms such as cough, shortness of breath, wheezing and asthma attacks;
- Chronic obstructive pulmonary disease;
- Cardiovascular diseases (diffusion across the epithelium of alveoli, changes coagulation of blood);
- Lung cancer.

a) Syndromes, illnesses and sensitivities exhibited or acquired as a result of indoor environment exposures - The indoor exposures causing these responses are believed to be a function of the synergistic effects of two or more pollutants (or even among particles)[78,79,80]:

- Sick Building Syndrome (goes away once building is avoided).
- Building Related Illness (acquisition due to exposure to that building).
- Multiple Chemical Sensitivity (synergistic effects to a number of chemicals).

b) Factors influencing particle deposition in the respiratory tract

- The physiochemistry of aerosol (particle size/size distribution; density; shape; hygroscopic/hydrophobic character; chemical reactions).
- The anatomy of the respiratory tract (diameter; length; breathing angles of airway segments).
- The physiology of the respiratory tract (airflow pattern; breathing pattern).

c) Particle deposition in respiratory tract; can be either total or fractional deposition (extra thoracic in nose or mouth; bronchial; bronchiolar; or alveolar).

d) Determination of particle deposition in respiratory tract can only be determined via experimental studies involving human or animal experiments; lung cast experiments in post mortem. Alternatively, computational modeling: NB: Experimental studies show significantly higher deposition rates than predicted by modeling[82, 83, 84].

Conclusion

Because of the significance and indecision of the results of aerosols on weather change, research on aerosol became a hot topic, drawing consideration from researchers, the public, and governments worldwide. Aerosol pollution in Asian country is serious; examine aerosols, therefore, is urgent. Because of its low vegetation coverage, massive population, and absence of water resources, the final living surroundings in Asian country is fragile. Over the past few times, high frequency dust storm events coming back from the northeast of Asian country have drawn the consideration of scientists globally. Additionally, human activities (e.g., urbanization and modernizations in vehicles, industry, and agriculture) have introduced serious air pollution to Asian country, and therefore the high concentrations of particle pollutants and their wide coverage space create matters tough to manage. Currently, atmospheric aerosol concentrations of black carbon and sulphate are extraordinarily high in Asian country. It's anticipated that this poor environmental state of affairs in Asian country can last for an extended time, for that Asian country can endure high pressure from alternative governments to cut back aerosol emissions. Besides affecting human health, aerosols will make dangerous variations to the regional atmosphere and climate. Recently, aerosol-related researches in Asian country have enhanced significantly, and these studies have obtained sensible results. However, these studies still exhibit shortcomings concerning qualities like depth of investigation, creativity,

information sharing, interdisciplinary, and synthesis of results. To confirm the property development of the social economy and to reinforce people's commonplace of living, the Indian government and scientists should pay a lot of consideration to the aerosol downside and must place more effort into learning the impacts of aerosol on climate change, the surroundings, and human health.

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11

Microfluidics and its Role in Monitoring Environmental Health

Prince Prashant Sharma[1], Vijay Jyoti Kumar[2], Peeush Singhal[1], Ashwani Kumar[1]

Abstract

Today, investigators of various fields are working in microfluidics to extend its application in the fields like Environmental Science, Atmosphere Science, biological Science, Analytical Sciences and Biomedical Sciences.

Keywords: *Microfluidics, Lab-on-a-chip, Environment, Contamination, Health Care*

Introduction

A lab-on-a-chip (LOC) is a device that incorporates one or several laboratory functions on a millimeters sized "chip" (single integrated circuit) to achieve computerization and HTS (high- throughput screening). These devices can handle

[1]Department of Pharmaceutical Sciences (FMSH), Gurukul Kangri Vishwavidyalaya, Haridwar, India
[2]Department of Pharmaceutical Sciences, H.N.B. Garhwal Central University, Srinagar, Uttarakhand, India

pico-liters fluid volumes which are are a division of micro-electro-mechanical systems (MEMS) devices also known as microTAS (total analysis systems). LOCs may be used to study the behaviour, precise control and manipulation of minute amounts of fluids (**micro-fluidics**). However, through scale lengths a smaller than a millimetre to achieve automation and high-throughput screening. Rigorously lab-on-a-chip indicates the use of single or many lab procedures positioned onto chip-format, while "microTAS" is committed to the incorporation of the total sequential lab methods to execute a chemical investigation. microTAS technologies were found to be relevant for many investigations so a new term "lab-on-a-chip" was announced. One of the important current issue is the improved monitoring and detection system for environmental changes and its effect on microorganisms, since classical detection approaches are expensive and tedious often requires 48–72 hrs. Alternatively, MEMS (microfluidic-chip-based) technologies provide eventually quick, less tedious, easy job. Most of the public health problems are due to presence of bacterial, viral, and parasitic pathogens and their toxins and other environmental contaminants. So, their detection in environmental samples is the initial step in identify and check the presence of these organisms and protecting human and animal health and safety from the infection caused by them. This chapter reports the prevailing and state-of-the-art technologies for the recognition of environmental contaminants present in the samples.

Microfluidic Application Fields (MAF)

Acoustic droplet ejection (ADE)	DNA chips (microarrays)
Astrobiology	Droplet-based microfluidics
Cell behaviour	Evolutionary biology
Cellular biophysics	Fuel cells
Continuous-flow microfluidics	Molecular biology
Digital microfluidics	Open microfluidics
	Paper-based microfluidics

Table 1: Microfluidics in time-line

Period	New techniques	Old methods
50s	invention and development of the first transistors	substituted the lamps formerly used in the production of electronic devices like radios, and computers
60s	first integrated circuits and then the first microprocessors were developed using photolithography	reduction and incorporation of thousands of transistors
80s	developed first device containing mechanical micro-elements integrated on a silicon wafer known as MEMS (Micro Electro Mechanical Systems)	Replaces pressure sensors and printer heads.
90's,	MEMS introduced in biology, chemistry and biomedical fields and developed as Laboratories on a Chip (LoC) Development of microfluidics Microfluidic devices	Reduction in use of laboratory work and in-vivo methods
2000s	Microfluidic-chip made of PDMS	—
Today	Today, investigators of various fields are working in microfluidics to extend its application in the fields like Environmental Science, Atmosphere Science, biological Science, Analytical Sciences and Biomedical Sciences.	

Microfluidic-Chip (MFC) Materials

1. Materials for microfluidic-chip (MFC) fabrication: inorganic materials
   a. Silicon microfluidic-chip (MFC)
   b. Glass microfluidic-chip (MFC)
   c. Ceramic microfluidic-chip (MFC)
2. Materials for microfluidic-chip (MFC) s fabrication: polymers
   a. Elastomers
      i. PDMS microfluidic-chip (MFC)

   ii. Thermoset polyester (TPE) microfluidic-chip (MFC)
b. Thermoplastic polymers
   i. Polystyrene (PS) microfluidic-chip (MFC)
   ii. Polycarbonate (pc) microfluidic-chip (MFC)
   iii. Poly-methyl methacrylate (PMMA) microfluidic-chip (MFC)
   iv. Poly-ethylene glycol diacrylate (PEGDA) microfluidic-chip (MFC)
   v. Microfluidic-chip (MFC) made of teflons: perfluorinated compounds (pfa/ pfep/ pfpe)
   vi. Polyurethane (PU) microfluidic-chip (MFC)
c. Paper microfluidic-chip (MFC)
d. Hydrogels

3. Materials for microfluidic-chips (MFC) fabrication: composite materials
   a. Cyclic-olefin copolymer (COC) microfluidic-chip (MFC)
   b. Paper/polymer hybrid microfluidic-chip (MFC)

Microfluidic-chip (MFC) Construction Technologies

The origin for most lab-on-a-chip construction processes is the standard method of printed circuit board (PCB) and microprocessor construction (Photolithography). Initially silicon was used for utmost processes, as these tools were developed directly derivatized from semi-conductor assemblies. But due to lesser production costs and quick prototype demands for bio-chemical compatibility and specific optical characteristics, innovative routes have been industrialized such as

1. Technique for print making on metals and glass
2. Off-stoichiometry thiolene (OSTEmer) polymers processing
3. Deposition and bonding
4. Soft lithography using elastomeric materials processing most notably PDMS (polydimethylsiloxane)
5. Thick-film and stereolithography

6. Fast replication methods
7. Electroplating
8. Injection moulding
9. Embossing

The demand for cheap and easy lab-on-a-chip prototyping resulted in development of simple methodology for the construction of PDMS microfluidic devices: **E-SCAR-GOT** (**E**mbedded **SCA**ffold **R**emovin**G** **O**pen **T**echnology). This procedure creates microfluidic networks by using a solitary PDMS block like 3D printing.

Microfluidics (Micro-Chip) Technologies Employed for Monitoring Environmental Health

Soft Lithographic Microfluidics

Soft lithographic microfluidics is a low cost and easy moulding microfluidic fabrication technique with high optical transparency that makes multilayer stacking through which large microfluidic networks can be prepared on industrial scale. It is the best method for quantitative measurements of automated cell culture systems and single cell resolutions. However, this technique requires some additional equipment such as valves and pressure sources for device operations. Another drawback is that it needs additional detection elements are required and also each layer is required to precisely aligned for nonstop fluid flow inside a micro-channel.

Droplet Microfluidics

Droplet microfluidics technology is new and highly fascinating platform in microfluidic fabrication. Droplets can precisely screen and govern entire microfluidic fabrications and this technique is more efficient as compared to the conventional bulk techniques. This technique can precisely measure femto- and pico- liter volume. It is relatively fast and simple technique to study mixed, transported, spited, recombined, and

analysed samples. However, there are less chance of interaction between surface leading and non-fouling and the possibility of cross contamination is also very less. This technique is very useful for analyses done using high- throughput technique. But this technique offers some restriction during detection of analytes in small droplet quantities that requires the use of highly sensitive analytical instrumentations. Integration with other techniques is difficult and not suitable.

Electro-Wetting-On-Dielectric Driven Droplet (EWODDD) Microfluidic Systems

Droplet manipulation does not require large external appliances such as pumps. Microfluidic procedures including mingling, merging, sorting and separation can be achieved on the same set of electrodes in moderately simple way by appropriate programming of the actual signal. It is relatively modest platforms for executing complex bio-analytical procedures and useful for the purpose of diagnostics. But large range of microelectrodes are separately for high-throughput screening. Also, it has son drawbacks like cross contamination and sample loss due to non- précised adsorption of sample and reagents on microelectrode surfaces. Storage conditions are also need to be considered for reagents and analytes for the reason that there is a direct contact between droplets and hydrophobic surface.

Centrifugal microfluidics or Lab-on-a-Disc (LoD)

Centrifugal microfluidics technique also provides a good platform for pumping, mixing, and routing using a modest motor. This method can be employed for multiplexed analyses. Reactions can be achieved in profitable manner due to high level integration with raw materials. Sample composition is not a problem during a reaction. Some disadvantages of this techniques are Sample loss during processing, valving and precise manipulation of the rotational speed are needed to be done for the smooth working. Network design is complicated.

Paper-based Microfluidics

Paper-based microfluidic technology provides an economical portable background to on-site investigative applications with a special advantage the sample can also be elated through a semi- automatic function i.e. capillary force. With help of this technique colorimetric assays can also be performed. Some limitations are that its operational cost is very high because of antibodies are required which are expensive, reagent coated paper's shelf-life also quantification analyses are tough to perform.

Conclusion

The Microfluidic-chip technology, however has previously demonstrated its mark as important tool for R&D, it is silently viewed in its preliminary phases and more improvement in this technology still need to endures in many fields to encounter the upcoming needs for miniaturization, not only the overheads but also to grow it as a green instrumentation tool to diminish the impact of research on the surrounding environment. The developing and under developed areas still do not benefit from this technology. It can be projected that in the coming years, bio-medical sciences, chemical sciences and biotechnological sciences will move from macro-laboratories to micro-laboratories.

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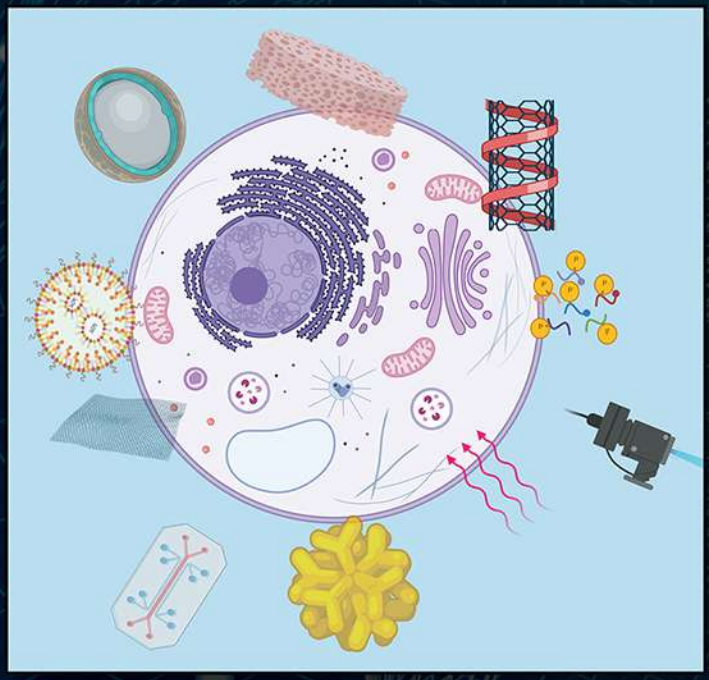
NANOPHARMACEUTICALS IN REGENERATIVE MEDICINE



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HARISHKUMAR MADHYASTHA
DURGESH NANDINI CHAUHAN

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9

Extracellular Matrix: The State of the Art in Regenerative Medicine

Gurpreet Singh
Guru Nanak Dev University, Amritsar, Punjab, India

Pooja A Chawla
ISF College of Pharmacy, Moga, Punjab, India

Abdul Faruk
HNB Garhwal University (A Central University) Srinagar-Garhwal, Uttrakhand, India

Viney Chawla
Baba Farid University of Health Sciences, Faridkot, Punjab, India

Anmoldeep Kaur
Guru Nanak Dev University, Amritsar, Punjab, India

CONTENTS

Introduction

Regenerative medicine gained significant interest in the treatment of life-threatening diseases and disorders, especially in cardiovascular and neurodegenerative diseases (Mao and Mooney 2015). It is a multidisciplinary approach, which restores the normal physiological functions of the human body by replacement or repair of tissues and organs (Christ et al. 2013). Regenerative medicines are innovative therapies that involve various strategies of tissue engineering, stem cell biology, gene, and cellular therapeutics (Lorden et al. 2015). All regenerative medicine approaches depend upon cellular level events and their constituents, which are involved in various developmental or repair processes of human tissues, i.e. replacing damaged cells in the brain and pancreas (Mao and Mooney 2015). These transplanted cells perform all normal functions and functionally participate in the all tissue events (Chen and Liu 2016). Presently, regenerative medicine-based treatment is very expensive and not affordable by all (Mahalatchimy 2016).

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Regenerative medicine is defined as a cellular therapeutic approach which "substitutes or repair human cells, various tissues or organ systems, to restore normal physiological function of human body" (Han et al. 2020; Sampogna et al. 2015).

There are a number of regulatory issues that influence the development of regenerative medicine and thus, in this scenario, need additional focus on legislation for regenerative medicine (Kleiderman et al. 2018). Recent research reports suggested that stem cell-based therapy has a promising role in the treatment of deadly human diseases, i.e. leukaemia, breast cancer, and others (Aly 2020). The ultimate objective of regenerative medicine is the isolation of specialised cell constituents and implanted into a patient where it replaces or repairs damage part of tissue or cells through self-repair remodelling (Mao and Mooney 2015). Therefore, it regulates the functioning of native tissues or cells. It offers transformative and effective outcomes for targeting life-threatening acute and chronic conditions and also an alternative for degenerative and genetic disorders (Mahla 2016).

According to the status of the Global Regenerative Medicine Market forecast, the international market of regenerative medicine is continuously growing and expected to reach USD 17.9 billion by 2025 (marketsandmarkets 2020). Food and Drug Administration (FDA, United States) implemented the 21st Century Cures Act in 2016 for the regulation of regenerative medicine therapies under a special section 3033, which describes the term and conditions for designation of drug under Regenerative Medicine Advanced Therapy (RMAT) (Barlas 2018). The Cures Act improves the ability of scientific, technical, and professional experts regarding clinical trial designs for regenerative medicine. It will accelerate the production of regenerative medicine products with safety of patients (FDA 2020).

The Cures Act defines the regenerative medicine as:

> cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products intended to treat, modify, reverse, or cure a serious or life threatening disease.
>
> (FDA 2021b)

There are currently four main categories of stem cells that have the clone ability and differentiate into particular types of cells.

i. **Embryonic stem cells:** Derived from the initial developmental phase of few days old embryos at the blastocyst stage. It has the potential to differentiate into various cells with a distinct biological response. Such cells are known as pluripotent (Romito and Cobellis 2016).
ii. **Foetal stem cells:** Isolated from aborted human foetuses, especially foetal blood, foetal tissues, and also bone marrow. They have the ability to differentiate but not all cells. They are known as multipotent and have been utilised in the regeneration and repair of damaged tissues/organs (Biehl and Russell 2009).
iii. **Cord blood and placental stem cells:** Obtained from umbilical cord blood and placentas. They possess the therapeutic potential and used in bone-marrow replacement therapies. They are not able to differentiate into all types of cells (Weiss and Troyer 2006).
iv. **Adult stem cells:** They are the most abundant cells, which are used for various therapies/conditions. They are isolated from almost all human tissue and organs. They are known as "somatic stem cells" (Liras 2010).

There is no doubt that regenerative medicine products provide a better treatment option than conventional drugs. But still, there are certain limitations and challenges for researchers and pharmaceutical companies that need to be addressed for the improvement of these specialised products (Dodson and Levine 2015). The following are the few noticeable points that should be considered during the design and production of regenerative medicine (Herberts et al. 2011):

i. **Safety:** The derived product should be safe and effective without any tumour formation or production of unwanted cell types.

ii. **Regulatory aspects and standardisation:** Must meet regulatory requirements which ensure product quality, safety, and efficacy as mention by standards (Rosemann et al. 2019).
iii. **Imaging and Monitoring:** Need sophisticated techniques with the features of observing all the changes and variation during cell behaviour (Leahy et al. 2016) and also, monitoring the migration of cells after administration (Naumova et al. 2014).
iv. **Manufacturing:** Manufacturing of viable (living) cells for regenerative medicine must follow through optimised process protocol to avoid cell variability (Martin et al. 2014).
v. Multidisciplinary research involves in regenerative medicine requiring effective communication within all research communities for better outcomes (Shineha et al. 2017).
vi. **Animal Models:** Appropriate animal models are needed for the comparison of animal embryos/human genetic or cellular material information (Ribitsch et al. 2020).
vii. **Scale up/Technology Transfer**: Large-scale production reduces the overall cost of the product. The scalable production processes provide safe and effective products (Pigeau et al. 2018).
viii. **Immunogenicity:** In regenerative therapies, a major issue is the rejection of transplanted cell by the patient. This could be overcome by exploring the research for new generation of immunosuppressant drugs (Charron 2013).
ix. **Cell Viability:** Cell viability and storage conditions (Yu et al. 2018).

A number of regenerative medicine which have already received FDA approval (FDA 2021a) and are commercially available are listed in Figure 9.1. This chapter explores the role of extracellular matrix (ECM) in regenerative medicine.

The Extracellular Matrix

Regenerative strategies mainly focus on stem cell-based or tissue engineering applications for remodelling and regeneration of defective cells, tissues, and organs. Stem cell differentiation is modulated by signals from the extracellular microenvironment including the extracellular matrix (ECM) (Chen and Liu 2016). Cellular migration and differentiation events are the main key factors that are considered for the design of regenerative medicine (Mata et al. 2017). The ECM is composed of several types of collagens, proteoglycans, glycoproteins, and glycosaminoglycans, which are assembled into a complex structure (Yue 2014). The composition of ECM varies from tissue to tissue and organ to organ (Kular et al. 2014). The distinctive functions of the ECM include cell adhesion, the physical barrier for different tissues. It also impacts many cellular functions, including mechanical stimulation from substrates, activation of intracellular signalling by cell adhesion molecules, and availability and action of soluble factor (Muncie and Weaver 2018).

The extracellular matrixes (ECM) define the tissue architecture and biochemical and biophysical features. The main organisational unit of the ECM called core matrisome, which includes different kinds of collagen (divided into several families), glycoproteins, and proteoglycans (Hynes and Naba 2012). Other than ECM, there are numerous non-ECM varying factors, which also participate in different cellular events, i.e. remodelling and cell behaviour. They mainly include proteases, growth factors, cytokines, and cross-linking enzymes (Vaday and Lider 2000). Collagen is the most abundant protein of mammalian ECM and accountable for the structural and functional integrity of the tissue (Frantz et al. 2010). Other structural molecules of ECM belong to the glycosaminoglycans class which includes hyaluronic acid (HA, non-sulphated glycosaminoglycan), chondroitin sulphate (CS, sulphated glycosaminoglycan), and heparin (natural glycosaminoglycan) Figure 9.2 (Pomin and Mulloy 2018). They play a vital role in elasticity, water retention, and resistance to compressive forces, while adhesion proteins play a significant role as molecular glue for a structural network of ECM complex. Examples of adhesion molecules are laminin, fibronectin, and tenascin-C (Walker et al. 2018).

Early in the 20th century, cell biologists worked in a two-dimensional (2D) framework, which includes separating and culturing cells from living tissue for replacing damaged or diseased tissue (O'Brien and Duffy 2015). With the advancement in the field of bioengineering and regenerative medicine, it is

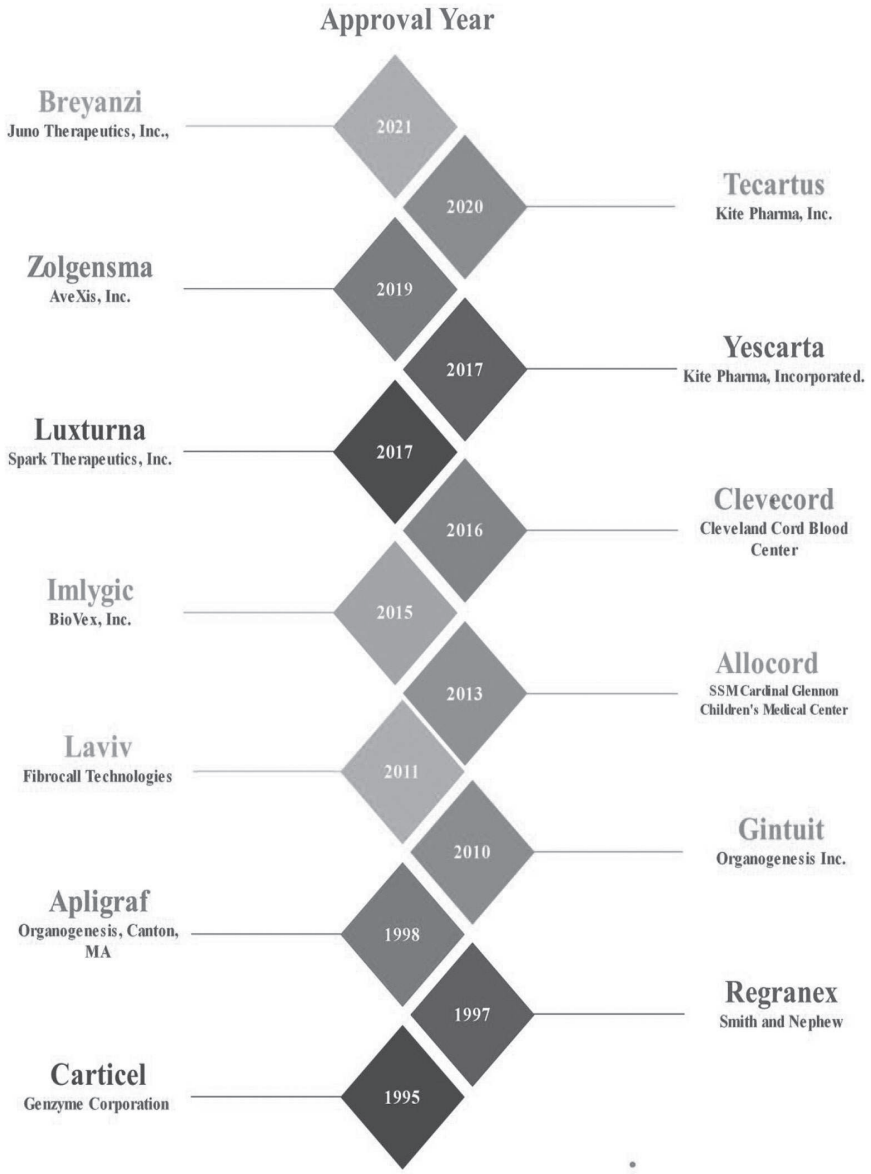

FIGURE 9.1 List of FDA Approved Products.

observed that multicellular organisms require a three-dimensional (3D) framework for structural integrity with specific microenvironments (Chen and Liu 2016). It is required to incorporate the knowledge of cell biology and cell transplantation with the discipline of material science for providing a 3D environment for growing cells and tissues. The evolution in the medical field has opened a new horizon for use of ECM in regenerative medicine. Various ECM analogues have been developed from synthetic scaffolds (Nikolova and Chavali 2019), hydrogels, and ceramic-based scaffolds (Hussey et al. 2018). These scaffolds are commonly made-up of synthetic and biodegradable polymers (Chaudhari et al. 2016). Commonly used polymers include polycaprolactone, polyethylene glycol, polyacrylic acid, hydroxyapatite or tricalcium phosphate, alginate, chitosan, and cellulose derived from plants (Hussey et al. 2018). Biomaterials used in regenerative medicine are broadly classified into two groups, i.e. naturally obtained and synthetic

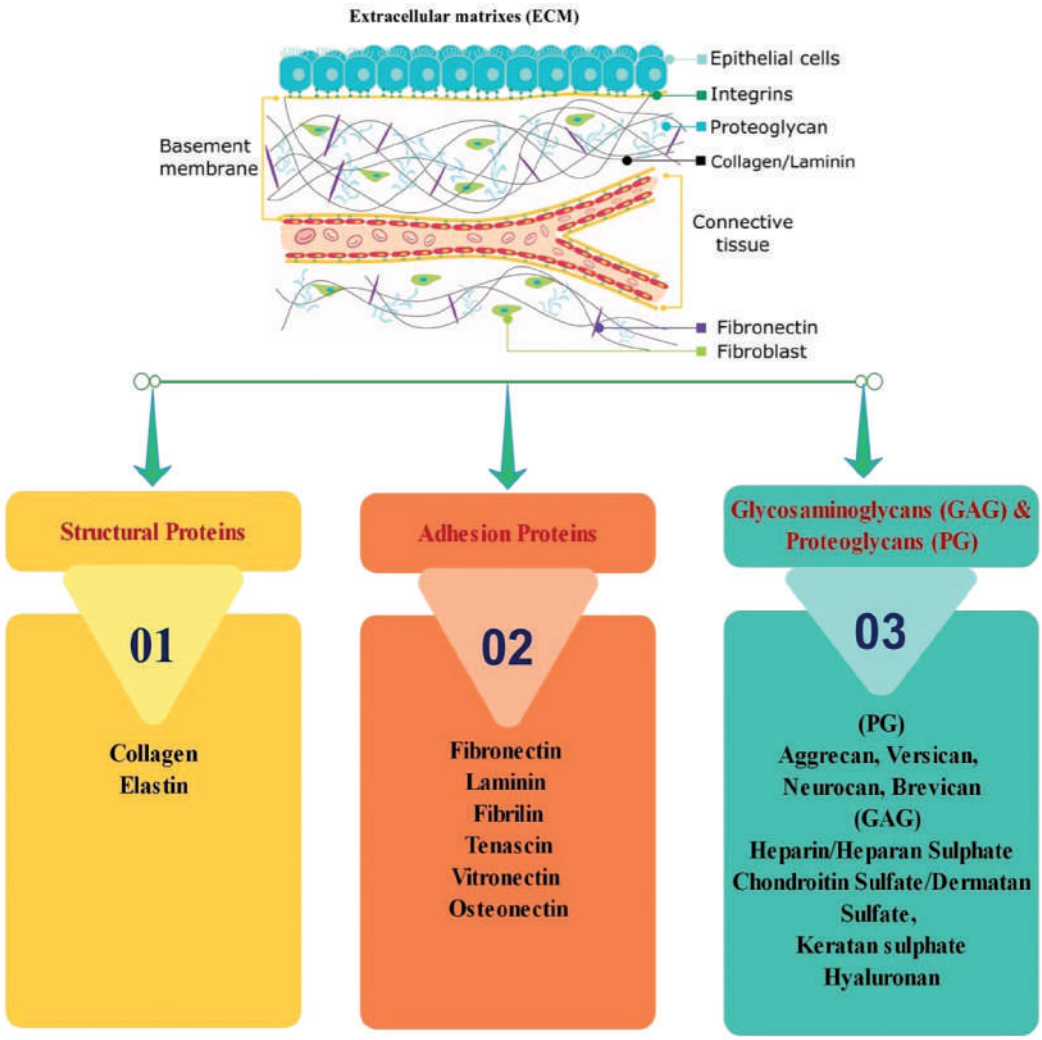

FIGURE 9.2 Composition of ECM (Kular et al. 2014).

materials (Fernandes et al. 2009). Natural materials are generally extracted or purified from ECM or its components such as collagen, laminin, and fibronectin (Frantz et al. 2010). Synthetic materials include polymers, metals or derived substrates. Both synthetic and natural materials have distinct pros and cons in regenerative medicine. Ideally, they are selected on the basis of condition and requirement of treatment. Biomaterials isolated from ECM show more unpredictability than synthetic polymers. In the case of synthetic polymers, immune response and their antigenicity is the major issue (Chen and Liu 2016). New trends and technologies in the bioengineering field reveal the functions of the ECM in regenerative medicine. This enriched the knowledge of ECM signalling in the functions of stem cells. These outcomes revealed the use of synthetic ECM scaffolds, which promote the endogenous stem cell repair and healing of damaged cells/tissues and mimic the native microenvironment (Chan and Leong 2008). A list of potential components of the extracellular matrix which are utilised in regenerative medicine (Traphagen and Yelick 2009) are summarised in Figures 9.3 and 9.4.

ECM-based biomaterials promote tissue remodelling in a precise and controllable manner. The decellularised ECM (DECM), which is water-insoluble matrix obtained after removal of cellular constituents

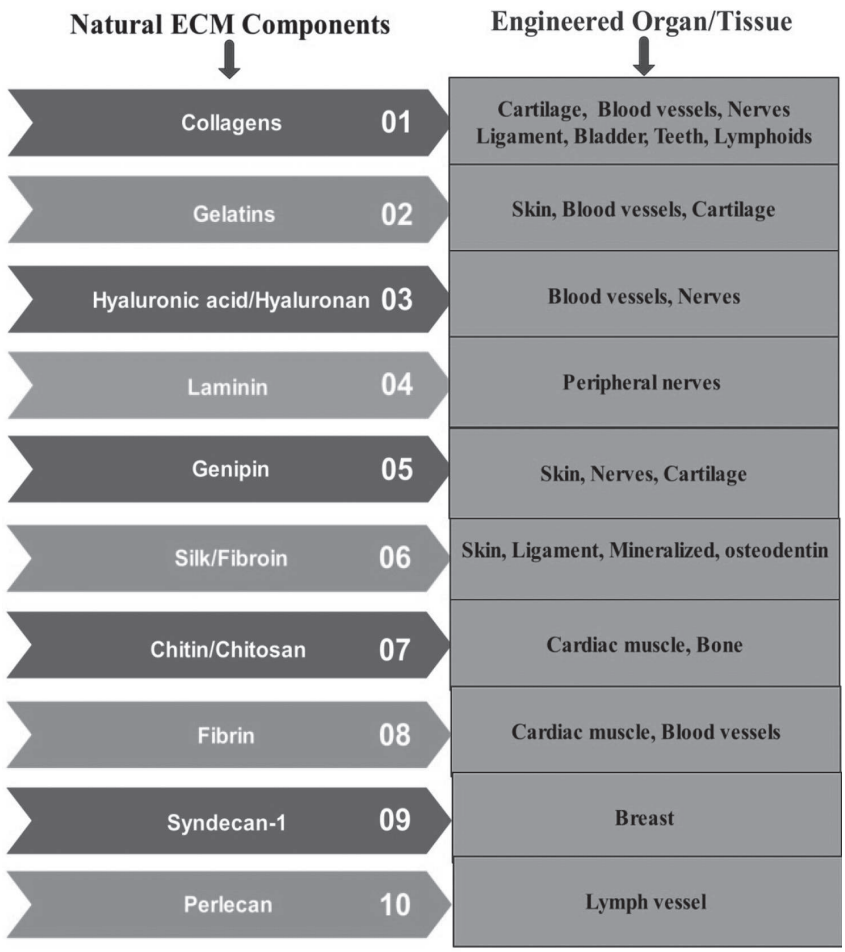

FIGURE 9.3 List of Engineered Organs and Tissues Based on ECM.

from ECM, also plays a significant role in the remodelling and repair process (Chakraborty et al. 2020). Due to biocompatibility and biodegradability, the DECM offers better results than other commonly used biomaterials (Liao et al. 2020). DECM-based tissue/organ, hydrogel, and microparticles have high demand in regenerative medicine (Parmaksiz et al. 2016).

Biomimetic materials can be fabricated using different techniques, i.e. soft lithography (Whitesides et al. 2001) (micro-contact printing), electrospinning (Braghirolli et al. 2014), and 3D printing (Atala and Forgacs 2019). Cellular constituents present within all tissues are required for tissue morphogenesis, differentiation, and the homeostasis process. Fundamentally, ECM can resolve various syndromes, physiological conditions, and defects in the body (Theocharis et al. 2019). In recent years, many studies indicate the role of native ECMs/DECM in regenerative medicine (Ramos and Moroni 2020). The main applications of ECMs include 3D tissue culturing (Edmondson et al. 2014), stimulate the wound healing process (Agren and Werthen 2007), activate stem cell differentiation (Gattazzo et al. 2014), and drug screening assays (Langhans 2018). It's also applied in cell repair pathways and functional recovery of kidney (Bulow and Boor 2019), adrenal glands (Ruiz-Babot et al. 2015), and reproductive organs (Yalcinkaya et al. 2014). ECMs have many applications due to their biocompatibility and *in vivo* replicate ability (Aamodt and Grainger 2016). This chapter summarises some research investigations based on EMCs in regenerative medicine.

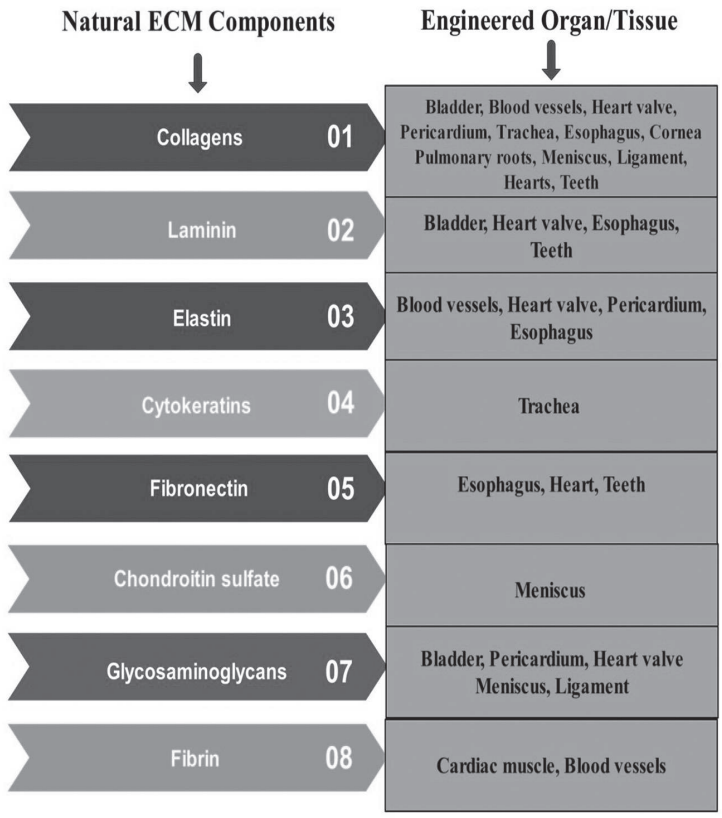

FIGURE 9.4 ECM Identified in Decellularised Organ and Tissue Studies.

Application of Extracellular Matrix

The chief proteins of the ECM are collagens and elastin. They are considered for biomedical applications because of their tensile strength and viscoelasticity to tissues. Other proteins include fibronectin, laminin, and nidogen, which act as connectors or linking proteins in the matrix network. Glycosaminoglycans (GAGs), proteoglycans, and growth factors are also promoting the *in vivo* construction of functional tissue (Mouw et al. 2014). Overall it is a challenging task due to limited knowledge and tissue to tissue variability. Ultimate goals of regenerative medicine can be achieved only if biomaterials maintain desired morphology, differentiation, proliferation, and metabolism of the cell.

Extracellular Matrix in Cardiac

The heart is a vital and delicate organ of our body that requires sophisticated tissue architecture for normal functioning. It acts as a circulatory motor for our body that supplies the blood and fulfils the variable demands during the rest and exercise phase (Lee and Walsh 2016). This excitation-contraction, the cycle of the heart, developed a physical force at the cellular level of the myocardial structure. Overall, this process is regulated by the delicate organisation of the cardiac extracellular matrix. In each excitation and contraction cycle, a number of mechanical events are involved in myocardial elements (Stoppel et al. 2016).

Recent investigations suggest that ECM is found in all the segments of the heart. However, it is particularly present in mesenchyme structures and plays a role in valvuloseptal morphogenesis (Lockhart et al. 2011). Any impairment in the composition of ECM in mesenchyme structures often leads to congenital

heart disease. Several reported animal studies describe the involvement of ECM in congenital heart diseases (Hacker 2018). Studies indicate the involvement of aggrecan, hyaluronan, versican, collagen type I-V, fibulin1, and fibronectin (Wight 2018). The common complications are vascular defects, blood vessel rupture, and cardiomyopathy. ECM involves in the regulation of cell differentiation and proliferation, which serve the cell survival (Ponticos and Smith 2014).

Extracellular Matrix in Brain

A major part of the brain is occupied by ECM, which contains collagens, fibronectin, vitronectin, laminin, and perlecan especially in amyloid deposits of the brain (Bonneh-Barkay and Wiley 2009). These ECM components play the main role in the development of nervous tissue and also regulate cell adhesion (Barros et al. 2011). Matrix proteins are almost absent in the adult brain (Ruoslahti 1996). Any change that occurs in the composition of ECM after neural injury may result in drastic consequences. Brain injury may induce changes in chondroitin sulphate proteoglycans, which influence myelin repair (Rhodes and Fawcett 2004). During the early stage of neural growth, the ECM provides structural support and stimulates signalling pathways of proliferation, especially by proteoglycans, laminins, and integrins. Proteoglycans provide structural support while laminins and integrins enhance neural progenitor proliferation (Bonnans et al. 2014). They also modify the shape of neural progenitors and neurons. In addition to this, ECM components affect the migration of newborn neurons during cortical growth. The role of the ECM in the brain is highly complicated (Lu et al. 2011). The same ECM component performs multiple roles during neural development and also influences the functioning of neighbouring cells (Rozario and DeSimone 2010). Recently reported evidence indicates the involvement of the ECM in several disease conditions, such as traumatic brain injury (George and Geller 2018), Alzheimer's disease (Lepelletier et al. 2017), age-associated cognitive deficits (Richard and Lu 2019), and schizophrenia (Lubbers et al. 2014). ECM-based regenerative approaches are widely used in the repair of peripheral soft tissue but not in the case of the brain due to the invasive route of administration. It requires a very specific narrow needle-guided administration approach for specific targeting. Current research efforts in regenerative medicine suggest that ECM-based biomaterials could serve as regenerative therapies in the brain (Hwang et al. 2020). A variety of underlying factors and mechanisms are still under observation and site-specific administration of ECM-based biomaterials is another issue in development of regenerative medicine (Chen and Liu 2016).

Pulmonary Extracellular Matrix

Pulmonary ECM is a structural complex system of protein molecules, which participate in various biochemical processes (Burgstaller et al. 2017). The remodelling mechanism is important for tissue homeostasis and any change in it may result in conditions like chronic obstructive pulmonary disease (COPD). Impaired expression of ECM proteins seen in COPD leads to the degradation and disruption of alveolar walls and stiffening of minor airways, which result in obstruction of airways (Ito et al. 2019). Alterations in ECM composition also influence the immune cell movement and their maintenance in the lung (Bonnans et al. 2014). Any abnormal functioning of ECM and response of inflammatory cell surface receptors may modify the collagen microstructure of the lung (Hussell et al. 2018). It is observed that there is a change in collagen organisation in COPD lung as compared to normal lung. The imbalance of enzymes like lysyloxidase and transglutaminase2 may involve structural changes of ECM during COPD (Burgess et al. 2016). ECM regulates normal interstitial fluid dynamics and strength and elasticity, tissue repair, and remodelling in the lungs. Versican and perlecan participate in the balancing of tissue fluid homeostasis (Pelosi et al. 2007). In the area of regenerative medicine, several studies reported lung scaffolds from small and large animals as an alternative to lung transplantation (Ohata and Ott 2020). These lung scaffolds were decellularised and reseed with lung perfusion culture in bioreactors. The resulting bioartificial lungs are probable to solve the problem of donor organ shortage and also reduced the immunogenicity (Panoskaltsis-Mortari 2015).

Extracellular Matrix in Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a global health issue and the specific aetiology of IBD is unknown. Ulcerative colitis and Crohn's disease are the two mainforms of IBD and they are characterised by an unusual immune response linked with defects functioning in the intestinal epithelial cell barrier (Zhang and Li 2014). Macroscopic tissue injury and clinical features of IBD are developed by changes in the ECM. Any change in ECM constituents may result in intestinal inflammation and progression of IBD (Petrey and de la Motte 2017). The conventional treatments merely target treatment of inflammation not repair/recovery of damaged tissue. Recently published work reports the use of hematopoietic or mesenchymal stem cells (HSCs or MSCs) for the management of IBD (Martinez-Montiel Mdel et al. 2014). It may help to establish an effective regenerative medicine for IBD patients. The development of decellularisation techniques in biomedical engineering greatly assisted the site-specific applications of ECM bio-scaffolds in the gastrointestinal tract (Almeida-Porada et al. 2013).

Conclusion

In conclusion, it is clear that the manipulation of ECM may serve as natural mimicking scaffolds in the arena of regenerative medicine. Regenerative medicine will change the traditional methods of management of various life-threatening diseases and conditions. Moreover, there is no doubt that all classes of stem cells (embryonic, adult, and induced pluripotent stem cells) have the potential to control the variety of diseases. ECM and ECM-like materials are biocompatible and having integration with the physiological microenvironment and mimic the ECM structure of the target tissues. ECM supports various biological functions and preserves the structures of entire organs. Ideally, they are preferred over synthetic polymers for biomedical engineering because of their immune tolerance. ECM regulation can play a significant role in several body conditions such as COPD, spinal cord injury, and neurodegenerative disorder. Furthermore, innovative interdisciplinary approaches and advancements in methodologies may lead to the improvement and discovery of new treatments for human disease.

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Chapter

Preparation and *in vitro* Characterisation of Solid Dispersion Floating Tablet by Effervescent Control Release Technique with Improved Floating Capabilities

Peeush Singhal, Rajneesh Dutt Kaushik and Vijay Jyoti Kumar

Abstract

In this research, an effort has been done for the development of effervescent controlled release floating tablet (ECRFT) from solid dispersions (SDs) of diclofenac sodium (DS) for upsurge the solubility and dissolution rate. ECRFT of DS was prepared by using SDs of DS and its SDs prepared with PEG as carrier using thermal method (simple fusion). SDs of DS was formulated in many ratios (1:1, 1:2, 1:3 and 1:4). Prepared SDs were optimised for its solubility, % drug content and % dissolution studies. Tablets were formulated by using optimised SDs products and all formulation was evaluated for various parameters. A clear rise in dissolution rate was detected with entirely SD, amid that the optimised SD (SD4) was considered for ECRFT. Among all the tablet formulations, its F3 formulation was better in all the terms of pre-compression and post-compression parameters. It had all the qualities of a good ECRFT, based on this F3 formulation was selected as the best formulation. Data of *in vitro* release were fitted in several kinetics models to explain release mechanism. The F3 formulation shows zero order release. From this study, we can conclude that ECRFT containing SDs of DS can be successfully used for achieving better therapeutic objective.

Keywords: solid dispersion, diclofenac sodium, polyethylene glycol, dissolution enhancement, floating tablets

1. Introduction

Diclofenac sodium (DS) is an effective NSAID with high affinity for both COX-1 and COX-2 receptors and it is one and only maximum frequently recommended drugs in India for the cure of pain, inflammation and joint stiffness caused by arthritis. According to BCS classification system DS belonging from class II means to say having poor solubility and poor dissolution rate [1] hence the focus of this study was on converting BCS class from II to I by increasing its solubility and

dissolution rate of DS Which was taken as model drug [2]. The release rate can be improved by increasing surface area of existing drug by using several techniques but among these methods solid dispersion technique is one of the best techniques for increasing the surface area [3]. Hence, an effort was made to increase the dissolution characteristics using the solid dispersion technique [3, 4]. It has absorption site in upper part of gastro intestinal tract. Gastric retention of DS was very short that is why the bioavailability of drug is 54% which is very low because near about 50% portion of orally given drug misses the absorption window. The pharmacokinetic profile of DS showed that the half-life is about ~1.2–2 h and hence there is a requirement of frequent dosing (3–4 tablets daily) [5] but this requirement of frequent dose is very dangerous for patients because due to this frequent dosing fluctuation in plasma drug level in body and need constant monitoring of patient for adjustment of dose regimen. That is why this reason may consequently support faster absorption of drug in stomach with higher concentrations for bioavailability improvement. Therefore in order to improve drug dissolution and reduced dosing frequency, it was attempted to formulate solid dispersion of DS [6, 7] and then develop effervescent controlled release floating tablet [8]. The emphasis of the current research was to increase the release rate and bioavailability of DS through preparing ECRFT (effervescent control release floating tablets) with dual approach [9] using solid dispersion product of DS in order to regulate the drug release and make available security from first pass metabolism.

2. Methodologies

2.1 Preformulation studies

Prior to the development of dosage forms, it is essential that certain fundamental, physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined and should be considered in the formulation in relation to the proposed dosage form and route of administration.

These studies should focus on those physiochemical properties of the drug that could affect drug performance and development of an efficacious dosage form.

A typical preformulation program should begin with the description of the organoleptic qualities of the drug substance. The colour, odour and taste are of immense value in developing an aesthetically acceptable formulation.

2.1.1 Identification and characterisation of diclofenac sodium

2.1.1.1 Physical appearance

Drug sample has been noted for its organoleptic properties. The drug is white to slightly yellowish crystalline powder, odour: slight and characteristic [1]. Drug was received as gift sample (15 g) from Kwality Pharmaceuticals Ltd., Amritsar.

2.1.1.2 Melting point determination

The melting point of compound is the temperature at which it changes from a solid to liquid [10]. This is a physical property often used to identify compounds.

2.1.1.2.1 Procedure

a. A capillary melting tube was taken.

b. A small amount of compound was placed on a clean surface. The compound was put in to open end of capillary tube.

c. The capillary melting point tube was placed in melting point apparatus (Macro scientific works).The sample was observed continuously, so that the melting point of the sample was not missed. Slow heating was done for most accurate results. The melting range was recorded which beings when the sample first starts to melt and ends when the sample completely melted.

2.1.1.3 Solubility studies

Solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous dispersion [11]. The solubility of diclofenac sodium was studied in various aqueous and non-aqueous solvents. About 10 mg of drug was taken in 10 ml of each solvent at room temperature in screw-capped test tubes and shaken for 30 min in a sonicator. The solubility was checked by U-V spectroscopy in all cases and reported in **Table 1**.

2.1.1.4 U.V. spectrophotometer

The organic molecule in solution when exposed to light in the ultra-violet region of the spectrum, absorbed light of particular wavelength depending on the type of electronic transition associated with absorption [12].

2.1.1.4.1 Diclofenac sodium

The solution (10 μg) of diclofenac sodium was prepared in simulated gastric fluid pH 1.2 and scanned spectrophotometrically (Systronics, Double beam UV-VIS Spectrophotometer: 2201). The scanning range was in between 200 nm to 400 nm. Standard solution of diclofenac sodium was then scanned and graph plotted. The

Parameter	**Evaluation**
API	DICLOFENAC SODIUM
Description	Crystalline
Colour	White
Odour	Odourless
Bulk Density	0.56 gm/ml
True Density	0.64 gm/ml
Carr's Index	14.28%
Hausner's Ratio	1.14
Melting Point	STD: 280°C OBS: 282–283°C
Solubility	Sparingly soluble: Water Freely soluble: methanol Soluble: 0.1 N HCl Insoluble: ether, chloroform and toluene
Partition coefficient	1.25

Table 1.
Preformulation characters of diclofenac sodium.

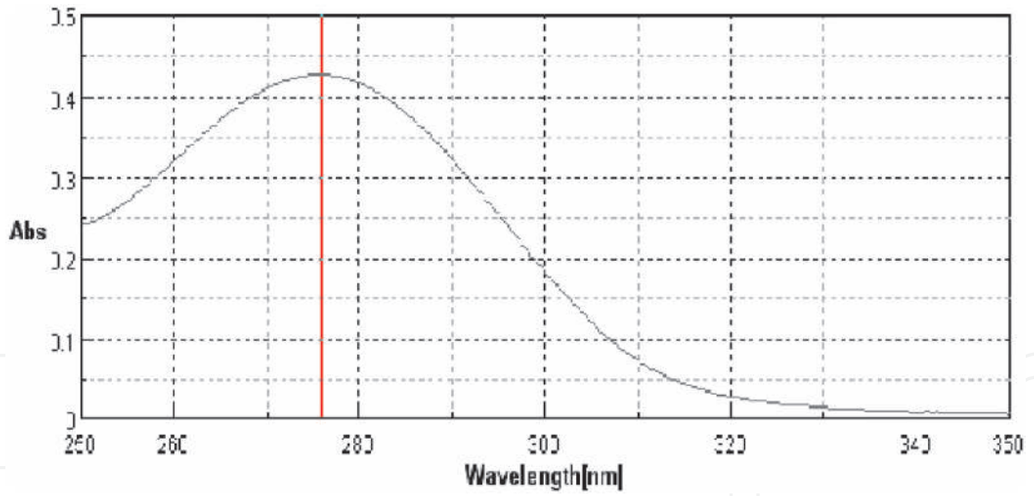

Figure 1.
U.V. scan of diclofenac sodium in simulated gastric fluid (PH 1.2).

determined λmax, 276 nm (**Figure 1**) was similar as reported in the literature (276 nm).

2.1.1.5 I.R. spectrophotometry

About 1 mg of the sample and 100 mg of the potassium bromide (KBr) was taken in a mortar and triturated [13]. A small amount of triturated sample was taken into a pellet maker and compressed at 10 kg/cm^2. The pellet was kept onto the sample holder and scanned from 4000 to 400 cm^{-1}.The I-R spectrum of drug sample was obtained using FTIR-8400 s, shimadzu. Important peaks are reported in **Table 2** and graphically represented in **Figures 2**, **3**. This I-R spectrum was found concordant with the IR of diclofenac sodium reported in the official monograph.

2.1.1.6 Quantitative estimation of drug

For the present study the spectrophotometric method given in the official books was selected for its sensitivity, specificity, simplicity, reproducibility, rapidity and accuracy [14].

2.1.1.7 Preparation of calibration curve of diclofenc sodium in simulated gastric fluid (pH 1.2)

Accurately weighed 50 mg of drug (diclofenac sodium) was dissolved in 100 ml of simulated gastric fluid pH 1.2 to give a solution of 500 μg/ml concentration and

IR spectrum	Standard peaks value	Observed peaks value cm^{-1}	Groups	Stretching/ deformation
DICLOFENC SODIUM	1600–1475	1556.61, 1498.74	C═C(aromatic)	Stretching
	1320–1210	1305.85	C—O stretching	Stretching
	1556	1556.61	Dichlorophenyl ring	Stretching
	1300–1000	1284.63	C—CO—C stretching	Stretching

Table 2.
Characteristic peaks of diclofenac sodium.

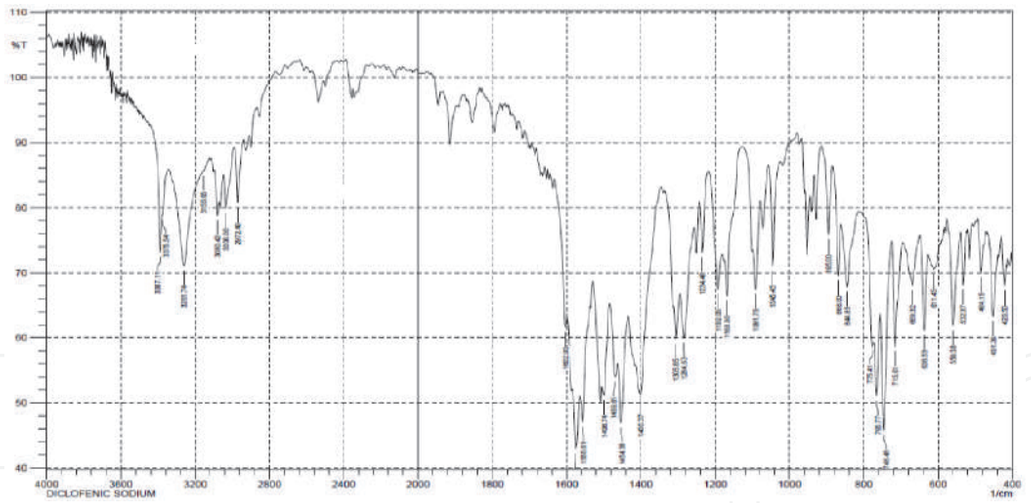

Figure 2.
FTIR spectroscopy of pure diclofenac sodium.

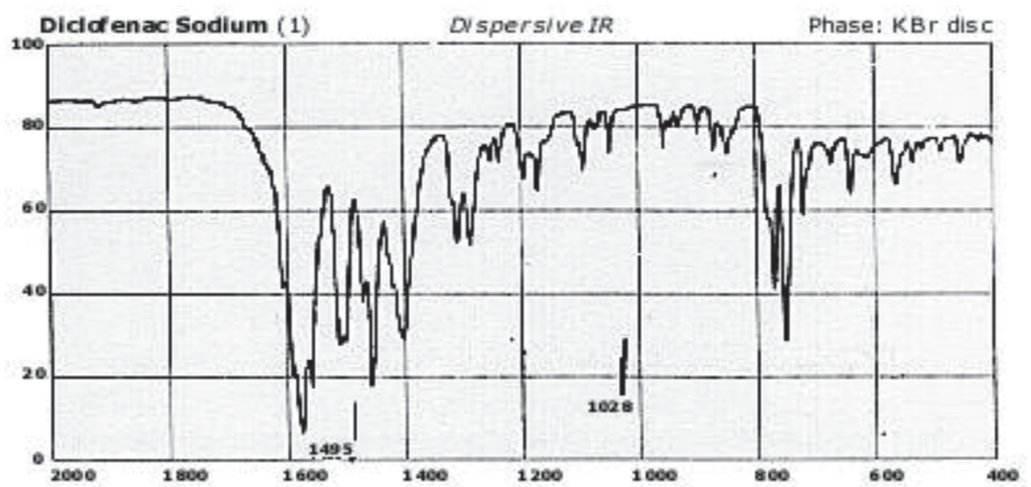

Figure 3.
I-R spectra of pure diclofenac sodium from I.P. 1996.

this was served as a standard solution [15, 16]. From this solution 10 ml was taken and diluted to 100 ml using simulated gastric fluid pH 1.2 to get a solution of 50 μg/ml concentration and this solution was served as the standard solution. In to a series of 10 ml volumetric flasks, aliquots of standard solution (i.e. 0.4, 0.8, 1.2, 1.6, 2.0, 3.0, 4.0, 5.0, 6.0 ml) were added and made up the volume up to 10 ml using simulated gastric fluid pH 1.2. The absorbance of these solutions was measured against reagent blank at 276 nm (**Table 3**). A standard curve between concentration and absorbance was plotted (**Figure 4**). A straight line passing through origin is obtained.

2.1.1.8 Partition coefficient

The partition coefficient directly influences the permeability of drug through various membranes [17–19]. The study has been designed to determine partition coefficient of drug in 1-octanol and pH 1.2 solutions. The partition coefficient between 1-octanol and Simulated gastric fluid (pH 1.2) was determined by shake flask method. About 10 mg of drug was dissolved in one of the phases, and is shaken with the other partitioning solvent for 30 min, allowed to stand for 5 min and then majority of the lower aqueous phase was run off. The drug concentration in both the

S. No	Concentration (μg/ml)	Abs(λmax-276 nm) (mean ± SD)
1	0	0.000 ± 0.00
2	2	0.068 ± 0.002
3	4	0.128 ± 0.005
4	6	0.190 ± 0.0015
5	8	0.246 ± 0.0021
6	10	0.315 ± 0.0022
7	12	0.329 ± 0.004
8	14	0.401 ± 0.001
9	16	0.445 ± 0.0032
10	18	0.522 ± 0.0051
11	20	0.589 ± 0.0059

Table 3.
Data for calibration curve of diclofenc sodium in simulated gastric fluid pH 1.2 at 276 nm (n = 3).

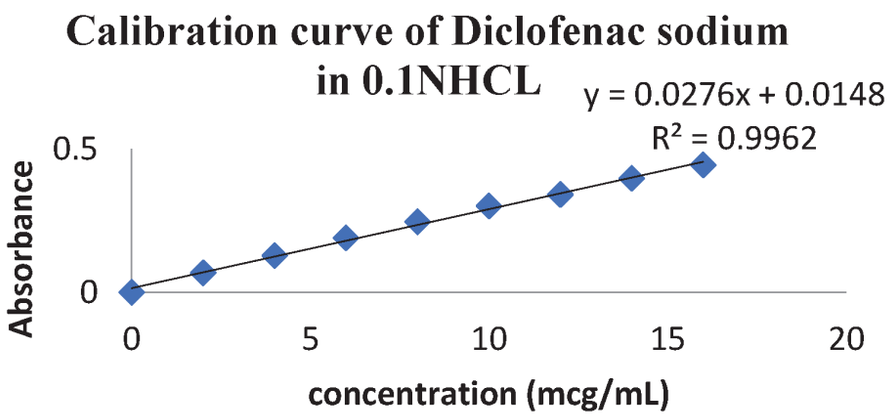

Figure 4.
Calibration curve of diclofenac sodium in pH 1.2 at 276 nm.

aqueous and 1-octanol phases was determined spectrophotometrically at 276 nm and calculated the partition coefficient. The partition coefficient was found to be 1.25.

Partition Coefficient = Conc.of drug in oil phase/Conc.of drug in aqueous phase (1)

2.1.2 Result and discussion

Samples of diclofenac sodium obtained as a gift sample from kwality pharmaceuticals pvt. Ltd., Amritsar was identified and characterised as per the identification test given in official monograph. Physical appearance and melting point of the drug sample under investigation was found to be same as that of the official reports. The results are given in **Table 4**. The solubility of diclofenac sodium was determined in aqueous and non-aqueous solvents. Diclofenac sodium was found to be soluble in 0.1NHCl and ethanol; sparingly soluble in water, practically insoluble in ether, chloroform and toluene. Partition coefficient of the drug was found to be 1.25.The results are given in **Table 1**.

S. No	Melting ranges	Melting point (mean ± SD)
1	288–290°C	289.12 ± 0.21

Table 4.
Melting point result of diclofenac sodium.

The drug was identified by IR spectroscopy and the characteristic peaks obtained (**Figure 2**) compared with standard spectra (**Figure 3**) of pure drug reported in official monograph (IP1996). The IR spectra of drug sample are in agreement with the standard IR spectra of pure diclofenac sodium given in official monograph [1]. Important peaks are reported in **Table 2**.

In the present study, a reported U-V spectrophometric method was used for the estimation of diclofenac sodium. The calibration curve of diclofenac sodium was prepared in simulated gastric fluid pH 1.2. The data was regressed to obtain straight line. The correlation coefficient was found to be 0.996 in simulated gastric fluid pH 1.2 indicating good linearity. The calibration curve was found to obey Beer-Lamberts Law in the concentration range studied (0–20 μg/ml).

3. Materials

Diclofenac Sodium (Batch no. A5/206), hydroxyl propyl methyl cellulose (HPMC) K100M (Batch no. HP121406 MC) and crosspovidone (Batch no. YPVPP09319040) were obtained from kwality pharmaceutical pvt ltd Amritsar, as gift samples. Sodium bicarbonate (NaHCO3), citric acid, polyvinyl pyrrolidone (PVP K-30), magnesium stearate, lactose and Isopropyl alcohol were purchased from local suppliers. Marketed product, "Voveran SR100 or Voveran 50", (Manufactured by Ranbaxy, India; Batch no.131003 AU or 320,028), used for comparative studies, was purchased from the local retail pharmacy.

4. Methods

4.1 Preparation of physical mixtures (PM)

Physical mixtures were prepared by mixing the appropriate amounts of the drug and carrier (PEG 6000) in the different weight ratios of 1:1, 1:2, 1:3 and 1:4 in mortar [3, 4, 6, 7]. The resulting mixtures were sieved through sieve no. 80, collected and stored in closed container away from light and humidity until use.

4.2 Preparation of solid dispersion

Melt method was used to prepare solid dispersions of diclofenac sodium with PEG 6000 containing different weight ratio (1:1, 1:2, 1:3, 1:4, and 1:5) (**Table 5**). Diclofenac sodium and PEG 6000 were weighed according to their weighed ratios. PEG 6000 was melted at 60°C. In this melted PEG 6000, diclofenac sodium was added. It was mixed well and flashed cooled on an ice bath and then stored overnight in desiccators. The prepared solid dispersion was then grounded by using a mortar and pestle, sieved through a mesh no. 40 and stored over a fused calcium chloride in a desiccators' for further use.

S. no.	Ratio (diclofenac sodium:PEG6000)	Batch code
1	1:1	SD1
2	1:2	SD2
3	1:3	SD3
4	1:4	SD4
5	1:5	SD5

Table 5.
Composition of solid dispersion and there assign batch code.

4.3 Characterisation of solid dispersion/ physical mixtures of diclofenac sodium with PEG-6000SDs

4.3.1 FTIR spectroscopy

FTIR spectra of drug, PEG 6000 and solid dispersion of DS were obtained. About 1 mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 min. The resultant disc was mounted in a suitable holder in perkin elmer USA spectrum 65 IR spectrophotometer and the IR spectrum was recorded from 4000 to 400 cm^{-1} in a scan time of 12 min [20]. The resultant spectra were compared for any spectral changes. **Figure 5** shows the FTIR spectra of the (i) drug, (ii) carrier and (iii) Surface solid dispersion. There was no significant change in the spectrum of solid dispersions, as incorporation of diclofenac into the carrier (PEG6000) did not modify the position of its functional groups.

4.3.2 Determination of saturation solubility

Saturation solubility was determined by using shake flask method [20]. Excess quantities of pure DS, prepared SDs and PMs were added in 25 ml distilled water in

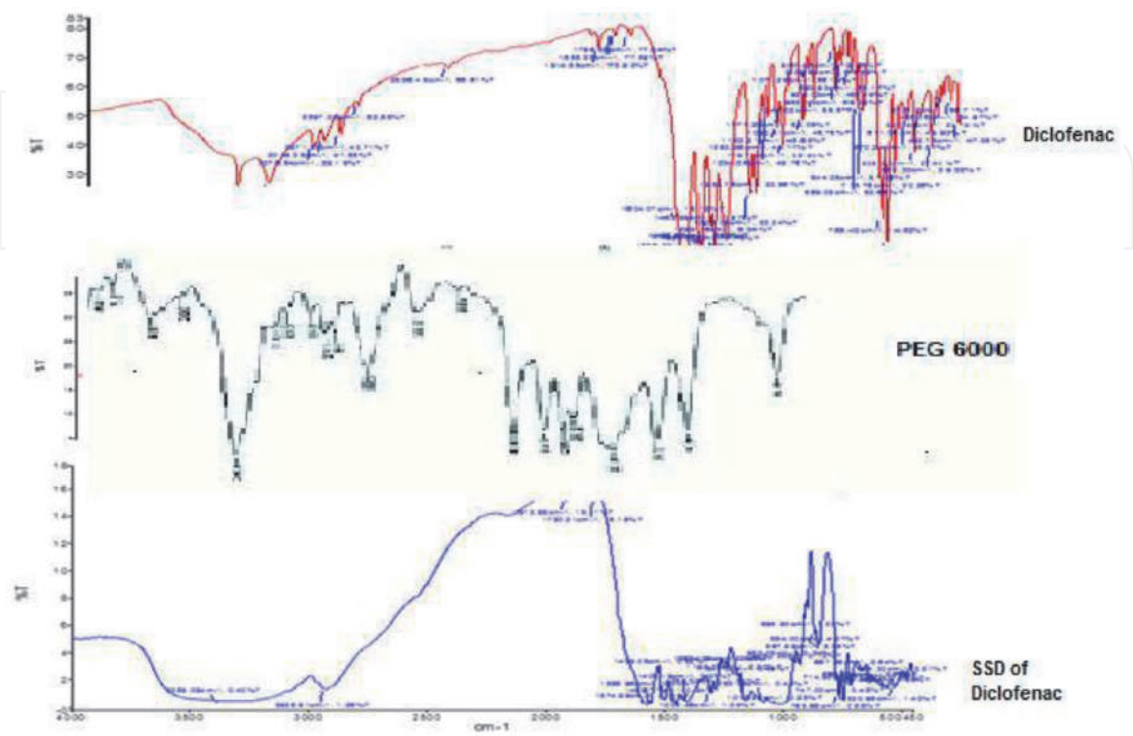

Figure 5.
Comparative FTIR spectra of diclofenac, PEG6000, & solid dispersion of diclofenac with PEG6000.

conical flasks which were then put in orbital shaker at 37°C and at 100 rpm for 72 h. Absorbance of resulting solution was measured on UV/Visible spectrophotometer (UV-1800 Shimadzu, Japan) at 276 nm.

4.3.3 Determination of pH dependent solubility

Shake flask method same as that for saturation solubility [20] was used with 0.1 N HCl.

4.3.4 Percent drug content

SDs equivalent to 50 mg of diclofenac sodium were weighed accurately and dissolved in 50 ml of ethanol by using mechanical shaker for 30 min. The solutions were filtered using whatman filter paper and drug content was determined by measuring absorbance at 276 nm by UV/visible spectrophotometer [6, 20]. From above evaluation tests, optimised formulation was confirmed (SD4 in **Table 6**) which was then subjected to *in vitro* dissolution studies.

4.3.5 In vitro *dissolution studies*

In vitro dissolution studies of prepared SDs were carried out in 900 ml of 0.1 N HCl as a medium using USP type 2 test apparatus with three replicates. The paddle rotation speed was 75 rpm and a temperature of 37°C ± 0.5 was maintained. In all experiments, 5 ml of dissolution sample was withdrawn at 5 min interval, filtered using a 0.45-mm Whatman filter, and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples were analysed on UV/Visible spectrophotometer at 276 nm**.**

4.4 Results and discussions

IR study was carried out to check the compatibility between the selected Polymers, with the drug. When the spectra were compared it was found that there was no shifting of functional peaks and no overlapping of characteristic peaks and also there was no appearance of new peaks. **Figure 5** shows the IR spectra of various samples. No significant change in the IR spectra of diclofenac sodium complexes was obtained, except for the broadening of the peaks. The broadening of peaks may be probably due to the restriction of bending and stretching vibrations of the

Formulation code	Saturation solubility in 0.1 N HCl (mg/ml)	pH dependent solubility in 0.1 N HCl (mg/ml)	Percent drug content (in 50 mg)
Pure DS	0.3886 ± 0.0044	6.020 ± 0.038	—
PM1 (1:1)	0.4481 ± 0.0045	8.328 ± 0.069	82.75 ± 1.54
PM2 (1:2)	0.4603 ± 0.0073	9.765 ± 0.0073	86.68 ± 1.27
PM3 (1:3)	0.5168 ± 0.0034	10.278 ± 0.086	88.01 ± 0.94
PM4 (1:4)	**0.5947 ± 0.0046**	**11.265 ± 0.101**	**90.92 ± 1.44**
SD1 (1:1)	1.1802 ± 0.0136	11.984 ± 0.064	93.87 ± 1.89
SD2 (1:2)	1.2612 ± 0.0097	12.735 ± 0.028	94.50 ± 2.11
SD3 (1:3)	1.4894 ± 0.0036	13.324 ± 0.071	95.16 ± 1.34
SD4 (1:4)	**1.9261 ± 0.0154**	**14.291 ± 0.144**	**96.72 ± 1.53**

Table 6.
Saturation solubility, pH dependent solubility and percent drug content studies of pure DS, SDs and PMs.

molecule. Various SDs of DS were prepared using PEG-6000, as carriers by thermal method (Simple fusion) technique to increase the solubility as well as dissolution of poorly aqueous soluble drug DS. The prepared SDs and PMs of DS were evaluated for saturation solubility, pH dependent solubility; percent drug content and *in vitro* dissolution studies. The saturation solubility and pH dependent solubility of pure DS, various prepared SDs and PMs of DS in 0.1 N HCl were measured and the results are given in **Table 6**. All PMs showed higher saturation solubility as compared with pure DS. Again, SDs of DS showed higher saturation solubility than their respective PMs of DS and carrier. This might be attributable to an improvement of wetting of drug particles and localised solubilisation by the hydrophilic polymeric carriers.

Based on the saturation solubility, pH dependent solubility in 0.1 N HCl and drug content among the 8 formulations, PM4 and SD4 were selected to carry out *in vitro* dissolution study and were compared with that of pure DS. The *in vitro* dissolution study of the pure DS, SD4 and PM4 using PEG-6000 as carrier was carried out in 0.1 N HCl at 37°C ± 1°C for 60 min and it was examined by plotting % drug dissolved against a function of time (**Figure 6**). SD4 and PM4 showed improved dissolution of DS over that of pure DS. Pure DS alone yields the slowest dissolution with only 35.65% drug and the dissolution of PM4 (70.76%) was found to be significantly faster when compared with pure DS. SD4 showed the fastest dissolution (92.99%) than PM4 and pure DS. This observation (**Table 7**) indicated that the increased dissolution of DS from SD4 due to presence of drug in amorphous state as compared PM4 and pure DS. As the proportion of PEG-6000 increased, dissolution rates have also been increased. The improvement of dissolution may be due to its hydrophilic nature of the carrier. Thus it can be concluded that the solubility of the poorly soluble drug, DS can be improved markedly by using solid dispersion technique and the carrier, PEG-6000 has increased the dissolution of the drug.

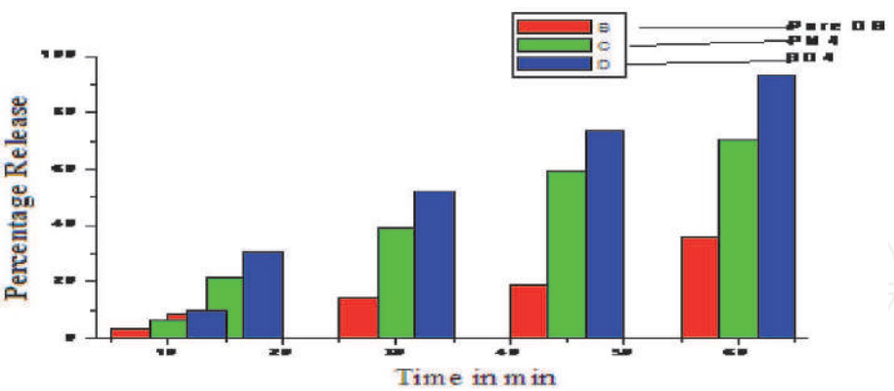

Figure 6.
Dissolution of the pure DS, SD4 and PM4.

	Percentage of diclofenac sodium dissolved from				
***Time in min*/formulation code**	**10**	**15**	**30**	**45**	**60**
Pure DS	3.37	8.50	14.35	18.85	35.65
PM4	6.67	21.23	39.44	59.41	70.76
SD4	**9.73**	**30.51**	**52.25**	**74.00**	**92.99**

Table 7.
Dissolution of the pure DS, SD4 and PM4.

4.5 Preparation of floating gastro retentive tablets

Various ratios of solid dispersions of diclofenac sodium with PEG-6000 were evaluated for percent drug content and out of them the best ratio was selected for preparation of floating tablet of diclofenac sodium. Tablets were prepared by conventional wet granulation method using HPMC K4M, HPMC K15M as a release retardant, carbopol as a swelling agents and $NaHCO_3$ as gas generating agent. Citric acid was also incorporated in the formulation to provide sufficiently acidic medium for $NaHCO_3$ to react and maintain buoyancy. The composition of various formulations is given in **Table 8**. All ingredients (except gas generating agents and magnesium stearate) were passed through sieve no. 60 and mixed in a polybag for 10 min and granulated using PVP K30 (in isopropyl alcohol). The wet mass was passed through sieve number 14 and dried in hot air oven at 50°C for 1.5 h. Dried granules were mixed with magnesium stearate as lubricant, talc as glidant and compressed using 16-station rotary tablet press (Rimek Minipress-I, India) using 13 mm flat punch in order to obtain controlled release floating gastro retentive tablets containing 50 mg of diclofenac sodium. Prior to compression, granules were evaluated for their flow and compressibility characteristic**.**

4.6 Characterisation of granules

4.6.1 Drug-polymer interaction studies

To study the interaction between drug and polymer, interaction study were performed, drug polymer study were carried out according to the following procedure. Drug and polymer were mixed in 1:1 ratio and put into the glass vials. The glass vials were sealed and placed in the stability chamber at 40°C and 75% RH for 21 days. The sample was analysed for colour change, liquification and bad odours after 7, 15 and 21 days. The IR spectra were taken after 21 days and analysed for any shift in major peaks. No shift was observed in the IR spectrum and no additional peak observed indicating no interaction between drug and polymer.

Ingredient (mg)	**Formulation code**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
SD4 (solid dispersion of diclofenac sodium)	250	250	250	250	250	250
HPMC K4	70	—	93	—	105	—
HPMC K15M	—	70	—	93	—	105
Carbopol 934P	70	70	47	47	105	105
Sodium bicarbonate	45	45	45	45	65	65
Citric acid	30	30	30	30	40	40
Avicel PH 102	50	50	50	50	50	50
Magnesium stearate	5	5	5	5	5	5
PVP K-30 5% PVP IN IPA						
Total weight	520	520	520	520	620	620

Table 8.
Composition of different formulations of diclofenac sodium floating tablets.

4.6.2 I-R spectrum of pure drug

About 1 mg of the sample and 100 mg of the potassium bromide (KBr) was taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet maker and compressed at 10 kg/cm$^{2.}$ The pellet was kept onto the sample holder and scanned from 4000 to 400 cm^{-1}.The I-R spectrum of drug sample was obtained using FTIR-8400 s, Shimadzu (**Figure 2**).

4.6.3 I-R spectra for diclofenac sodium with HPMC K4M + HPMC K15M and carbopol 934P

Sample mixture of diclofenac sodium with HPMC K4M + HPMC K15M and carbopol 934P were prepared in KBr discs (1 mg sample in 100 mg KBr). A small amount of triturated sample was taken into a pellet maker and was compressed at 10 kg/cm^2. The scanning range was 4000–400 cm^{-1}, and the resolution was 4 cm^{-1} (**Figures 7** and **8**).

4.7 Evaluation of granules properties

4.7.1 Angle of repose

The angle of repose of was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface [9, 21]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}(h/r) \tag{2}$$

where, h and r are the height and radius of the powder pile, respectively.

4.7.2 Bulk density

Both bulk density (BD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any

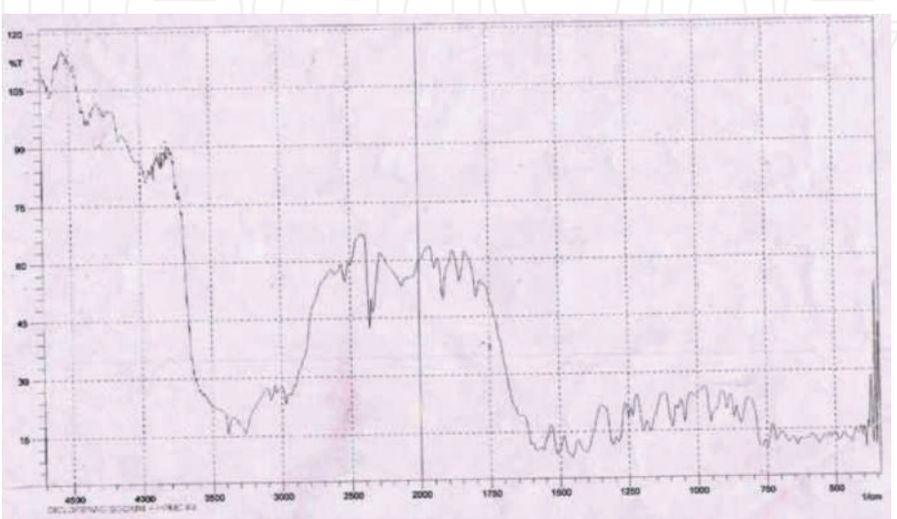

Figure 7.
FTIR of diclofenac sodium + HPMC K4M + HPMC K15M.

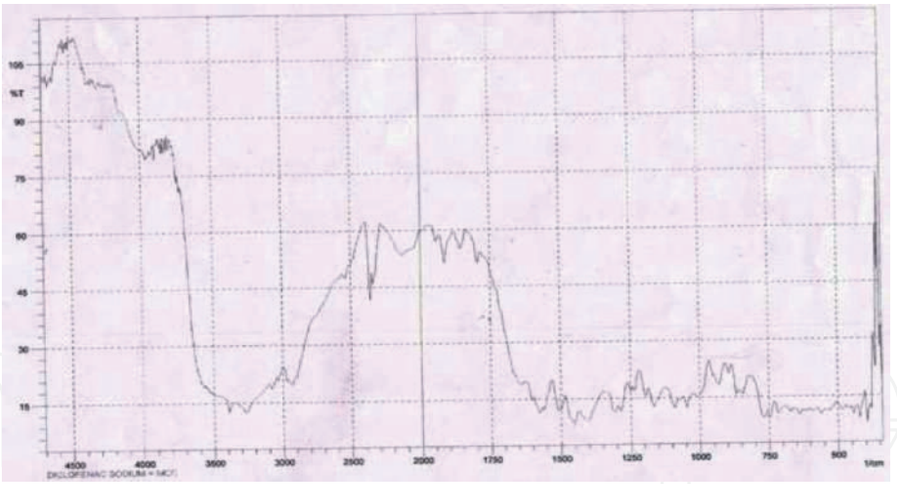

Figure 8.
FTIR of diclofenac sodium + carbopol 934P.

agglomerates formed, was introduced into a 10 ml measuring cylinder [9]. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was noted.

BD and TBD were calculated using the following formulas**.**

$$\text{BD} = \text{Weight of the Powder/Volume of the packing.} \quad (3)$$

$$\text{TBD} = \text{Weight of the powder/Tapped volume of the packing.} \quad (4)$$

4.7.3 Compressibility index/carr's index

The flow property was also determined by measuring the compressibility index. It is an important measure that can be obtained from the BD and TBD. According to the theory, the less compressible materials are more flowable. A material having values of less than 20–30% is defined as the free flowing material [9, 21]. Based on the BD and TBD, the percentage compressibility of the bulk drug was determined by using the following formula.

$$\text{Compressibility Index} = \frac{\text{Tap density–Bulk density}}{\text{Tap density}} \times 100 \quad (5)$$

4.8 Evaluation of floating tablets

4.8.1 In vitro *buoyancy determination studies*

In vitro buoyancy studies were performed for all the formulations as per the method described by Rosa *et al* [22]. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT) [9, 23–25].

4.8.2 General characteristic

The formulated tablets were assessed for its general appearance.

4.8.2.1 Thickness and diameter

Thickness and diameter of tablets was determined using vernier calliper. Three tablets from each batch were used, and average values were calculated.

4.8.2.2 Weight variation

Formulated floating tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limits or not.

4.8.2.3 Friability test

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre-weighed tablets were placed in the apparatus, which was given 100 revolutions, after which the tablets were reweighed. The percentage friability was calculated.

$$\%F = \{1 - (\text{loss in weight}/\text{initial weight})\} \times 100 \quad (6)$$

4.8.2.4 Hardness test

Hardness of the tablet was determined using the monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

4.8.2.5 Percent drug content

Ten tablets were weighed and powdered. An amount of the powder equivalent to 50 mg of diclofenac sodium was dissolved in 100 ml of 0.1 N HCl, filtered, diluted suitably and analysed for drug content at 276 nm using UV/Visible spectrophotometer.

4.8.2.6 Determination of percent swelling index (percentage water uptake)

The swelling properties of floating tablet containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37°C ± 0.5°C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain. Swelling characteristics were expressed in terms of percentage water uptake (%WU) according to the equation shows relationship between swelling index and time.

$$WU\% = \frac{\text{Weight of swollen tablet–Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100 \quad (7)$$

4.8.2.7 Dissolution studies using USP type II apparatus with wire sinker

Dissolution test was carried out using USP type II apparatus with wire sinker. The drug release study was carried out for 12 hr. in 900 ml of 0.1 N HCl dissolution

media, maintained at 37°C ± 0.5°C and agitated at 50 rpm. Periodically 5 ml samples were withdrawn and filtered through whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The absorbance of DS was measured UV/Visible spectrophotometrically at 276 nm. The percentage cumulative drug release was calculated and amount of CP released from tablets was determined. The floating tablet is wound with the helical wire sinker.

4.8.2.8 Kinetic of drug release

The result of *in vitro* dissolution studies of tablet were fitted with various kinetics models, like zero order (% cumulative drug release vs. time), first order (log % drug remaining vs. time), Higuchi's model (% cumulative drug release vs. square root of time) but these models failed to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer and Peppas semi-empirical model to ascertain the mechanism of drug release.

$$\mathbf{log}\ (Mt/M\infty) = \log k + n \log t \tag{8}$$

Where, M∞ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the tablets; and n is the diffusional exponent; indicative of the mechanism of drug release. **Table 9** shows an analysis of diffusional release mechanism obtained by various value of n. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

4.8.2.9 Biodegradability studies of floating tablet

The biodegradability studies were carried out using USP rotating basket apparatus. A tablet (50 mg) were introduced into the baskets which were rotated at 50 rpm in 900 ml of different pH buffer solution (5.0, 6.8, 8.0) maintained at 37°C ± 0.5°C.

4.8.2.10 Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The promising formulation F4 was tested for accelerated testing for a period of 2 months at 40°C ± 2°C/ 75% RH ±5% for their drug content and other parameters.

S. No	n value	Mechanism
1	$n \leq 0.5$	Quasi-fickian diffusion
2	0.5	Fickian diffusion
3	$0.5 \geq n \leq 1.0$	Anomalous (non-fickian) diffusion
4	$n \geq 1.0$	Non-fickian super case 11
5	1	Non-fickian case 11

Table 9.
Release mechanism with variation of n values.

5. Result and discussion

The effervescent floating tablets of SDs of DS were formulated in 6 different batches F1 to F6 by using hydrophilic polymers HPMC K4M, HPMC K15M and hydrophobic polymer carbopol 934P along with effervescing agents, sodium bicarbonate and citric acid (**Table 8**). All the formulations were prepared by wet granulation method. In order to get the longer duration of floating time the high viscosity polymer selected, HPMC K4M was chosen and it was found that, increased viscosity of a polymer prolongs the drug delivery from the dosage form. IR study was carried out to check the compatibility between the selected polymers with the diclofenac sodium drug. This study was performed to assure that there is complete physical entrapment of the drug into the polymer matrix without any mutual interaction. IR spectra were taken for samples like pure drug, and drug-polymer physical mixture at a wavelength of between 4000 and 400 cm^{-1}. All the spectra were compared for shifting of major functional peaks and also for the loss of functional peaks for identification of incompatibility, if any. When the spectra were compared it was found that there was no shifting of functional peaks and no overlapping of characteristic peaks and also there was no appearance of new peaks. **Figures 2**, 7 and **8** shows the IR spectra of various samples. No significant change in the IR spectra of diclofenac sodium complexes was obtained, except for the broadening of the peaks. The broadening of peaks may be probably due to the restriction of bending and stretching vibrations of the molecule [6]. The preformulation studies such as angle of repose, bulk density, tapped density, and carr's index evaluated were found to be within prescribed limits and indicated good free flowing property (**Table 10**).

In vitro Buoyancy of all the prepared tablets formulations were determined using 100 ml beaker containing 0.1NHCl medium shown in (**Table 11**) and the results can be concluded that the batch F3 containing HPMCK4M and carbopol 934P in higher concentration showed good buoyancy lag time is 4.3 min and total floating time is 15 hrs. TFT depends upon the amount of HPMC as the polymer content increased the floating time was increased due to the formation of thick gel which entrapped the gas formed due to $NaHCO_3$ firmly. Among these formulations, the *in vitro* buoyancy was increased in the following order: F3 > F1 > F4 > F2 > F5 > F6. The **Table 9** revealed that FLT minimum for F3 formulation, while its TFT was maximum i.e. 24 h; hence, F3 was selected for further evaluations and *in vitro* drug dissolution studies.

Formulation F3 was evaluated for physical characters like tablet thickness, diameter, hardness, friability, weight variation, percent swelling index, *in vitro* drug release studies. The thickness, diameter and hardness of the formulations satisfied the acceptance criteria. The friability and weight variation was found to be within the limits specified in pharmacopoeia. The drug content was found

Parameter	F1	F2	F3	F4	F5	F6
Angle of repose	22.53°	22.17°	23.42°	21.57°	22.87°	23.34°
Bulk density	0.953 ± 0.026	0.948 ± 0.031	0.975 ± 0.0.098	0.881 ± 0.102	0.836 ± 0.057	0.899 ± 0.083
Tapped density	1.05 ± 0.011	1.041 ± 0.019	1.031 ± 0.026	0.978 ± 0.020	0.981 ± 0.017	0.969 ± 0.038
Carr's index	7.64 ± 0.94	6.66 ± 0.71	5.69 ± 0.56	8.99 ± 0.62	8.68 ± 0.83	7.97 ± 0.49

Table 10.
Pre-compression parameters of granules.

Parameter	F1	F2	F3	F4	F5	F6
Floating lag time (FLT) (s)	160	182	158	163	221	223
Total Floating time (TFT) (h)	22	21	24	20	24	21

Table 11.
In vitro *buoyancy determination.*

spectrophotometrically indicating good content uniformity in the prepared formulation results were shown in **Table 12**.

The swelling index was calculated with respect to time. As time increase, the swelling index was increased because weight gain by tablet was increased proportionally with rate of hydration. The direct relationship was observed in **Table 13**.

The floating formulation F3 was subjected for the dissolution studies using USP type II apparatus with wire sinker in 900 ml of 0.1 N HCl medium. The results are given in **Table 14**. The formulation showed a constant rate of release in a sustained manner similar to zero order kinetics with good buoyancy property. Diclofenac sodium effervescent floating controlled release tablet formulation using solid dispersion (F3) showed far better release than marketed products.

5.1 Effect of sodium bicarbonate concentration on lag time of tablets

The concentration of sodium bicarbonate was found to be critical factor that influenced buoyancy of tablets (**Table 15**). Sodium bicarbonate released CO_2 gas that was trapped into the polymeric matrix of HPMC that made the tablets float. Various concentrations of sodium bicarbonate ranging from 5–12% of tablet weight were used. From the results, it was concluded that with the increasing

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	4.3 ± 0.016	4.8 ± 0.4	0.24 ± 0.08	542.4 ± 1.9	99.86 ± 0.15
F2	4.4 ± 0.013	5.1 ± 0.3	0.51 ± 0.03	555.8 ± 1.5	99.45 ± 0.08
F3	**4.5 ± 0.015**	**5.4 ± 0.6**	0.17 ± **0.04**	**554.3 ± 1.1**	**100.01 ± 0.04**
F4	4.5 ± 0.013	4.9 ± 0.4	0.46 ± 0.03	545.1 ± 1.8	99.96 ± 0.18
F5	5.5 ± 0.014	4.4 ± 0.1	0.35 ± 0.05	649.1 ± 1.7	98.90 ± 1.05
F6	5.7 ± 0.011	5.8 ± 0.3	0.41 ± 0.04	647.3 ± 0.4	99.02 ± 0.01

Table 12.
General characteristic of floating tablets.

% Swelling index (percentage water uptake)	
Time (h)	**Formulation F3**
1	24
2	37
3	48
4	63
5	71
6	88

Table 13.
% Swelling index (percentage water uptake) of floating tablets.

Time (mins)	Marketed tablet (Voveran-50) (% drug release)	Physical mixture	Diclofenac sodium-solid dispersion (% drug release)	Marketed tablet (Voveran-SR100) (%drug release)	Floating tablet of diclofenac sodium solid dispersion (3) (%drug release)
0	0	0.00	0.00	0.000	0.000
15	15.25 ± 0.64	21.23 ± 0.61	30.51 ± 0.54	12.706 ± 0.67	15.266 ± 0.41
30	37.37 ± 0.53	39.44 ± 0.64	52.25 ± 0.49	16.258 ± 1.27	18.365 ± 0.38
60	51.77 ± 0.86	70.76 ± 0.58	92.99 ± 0.78	19.353 ± 0.98	26.548 ± 0.51
90				24.930 ± 0.79	27.897 ± 0.50
120				27.966 ± 0.93	31.377 ± 0.43
150				32.220 ± 0.76	38.323 ± 0.45
180				38.922 ± 1.22	45.233 ± 0.29
210				45.875 ± 0.96	54.320 ± 0.27
240				51.519 ± 1.23	61.522 ± 0.30
270				60.865 ± 1.31	64.267 ± 0.31
300				64.037 ± .55	69.613 ± 0.35
330				68.561 ± 1.53	73.670 ± 0.51
360				73.686 ± 0.77	76.568 ± 0.42
390				77.371 ± 1.16	80.179 ± 0.44
420				82.957 ± 0.98	85.363 ± 0.47
450				86.414 ± 0.74	87.573 ± 0.58
480				89.213 ± 1.78	96.769 ± 1.19

Table 14.
Comparative in vitro *release study of marketed tablets, physical mixture, solid dispersion and floating tablets of diclofenac solid dispersion.*

S. No.	Concentration of sodium bicarbonate (%)	Floating lag time (s)
1	5	280
2	6	220
3	7	198
4	8	164
5	9	158
6	10	159
7	11	160
8	12	165

Table 15.
Comparison of floating lag time prepared from concentration of sodium bicarbonate.

concentration of sodium bicarbonate, the lag time decreased. A concentration of 8.5–9% w/w sodium bicarbonate was found to be optimal that resulted in tablets having lag time < 3 min and floating time of over 12 h. Similar conclusions were also drawn by other researchers working on floating delivery systems. In both the reported works, optimum concentration of sodium bicarbonate was found to be around 10% w/w of the tablet weight [26, 27] which is slightly higher than our optimal concentration.

5.2 Effect of HPMC grade on lag time of tablets

It was interesting to note that the grade and quantity of HPMC used in the formulations has impact on floating lag time of the tablet. With the increasing molecular weight/quantity of HPMC, the viscosities of the gel matrix around the tablet also increased which in turn in- creased the floating lag time. The lag time for HPMC K15M tablets was slightly higher compared to HPMC K4M tablet. This may be attributed to the increased density of tablet with increasing molecular weight of HPMC (**Table 16**).

5.3 Kinetic of drug release

The various release kinetic models (**Figures 9–12**) were applied to determine the mechanism of drug release from gastro retentive floating tablets and the data is tabulated in **Table 17**. The *in vitro* drug release of optimised formulation (F3) showed the highest regression coefficient values for zero order model, thus indicating absolute correlation between the two variables for the zero order model. Optimised formulations followed Zero order equation proving that the release is by diffusion mechanism. The values of release exponent (n) were calculated from korsmeyer and peppas equation and the 'n' value was determined to be 0.5665 indicating **Anomalous (non-fickian) diffusion.**

So it can be conclude that the optimised formulation follows the zero order plot to a major extend along with other plots to some extent.

S. No.	Quantity of HPMC (mg)	Floating lag time (s)
1	70 (HPMC K4M)	160
2	93 (HPMC K4M)	158
3	105 (HPMC K4M)	163
4	70 (HPMC K15M)	182
5	93 (HPMC K15M)	221
6	105 (HPMC K15M)	223

Table 16.
Comparison of floating lag time prepared from different grade or quantity of HPMC.

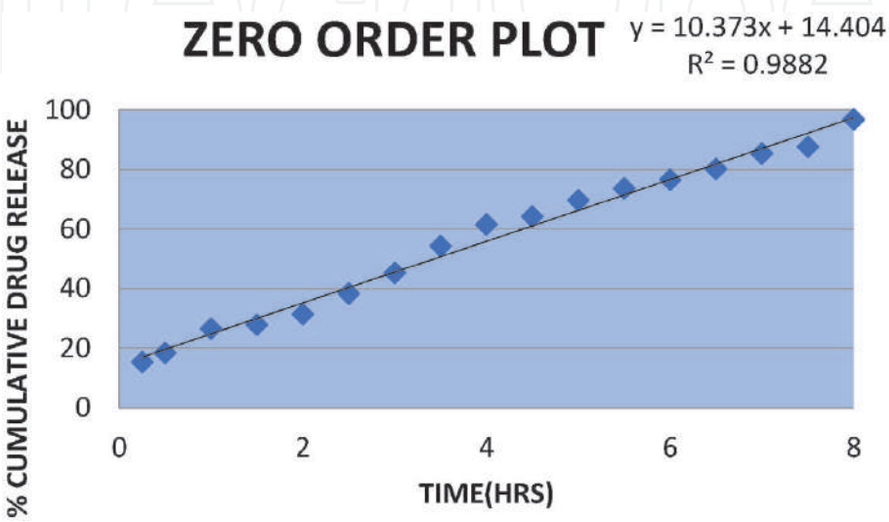

Figure 9.
Zero order release kinetics of optimised formulation.

Figure 10.
First order release kinetics of optimised formulation.

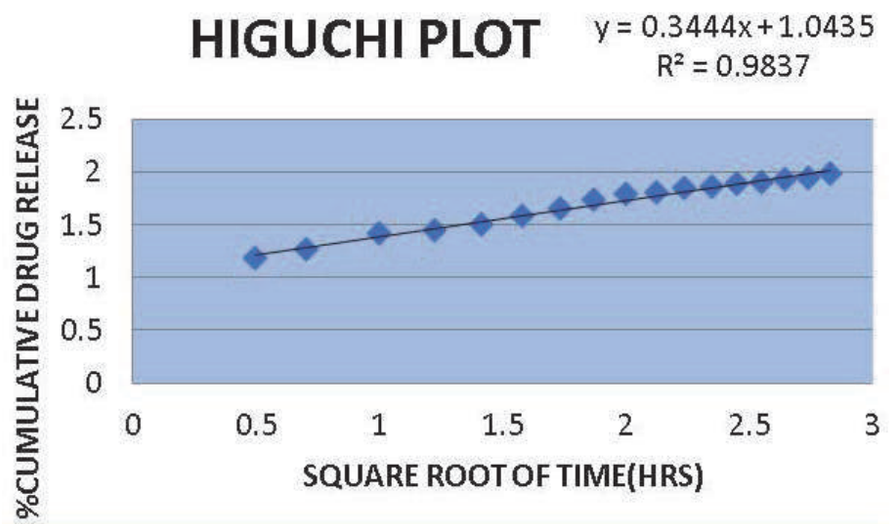

Figure 11.
Higuchi kinetics of optimised formulation.

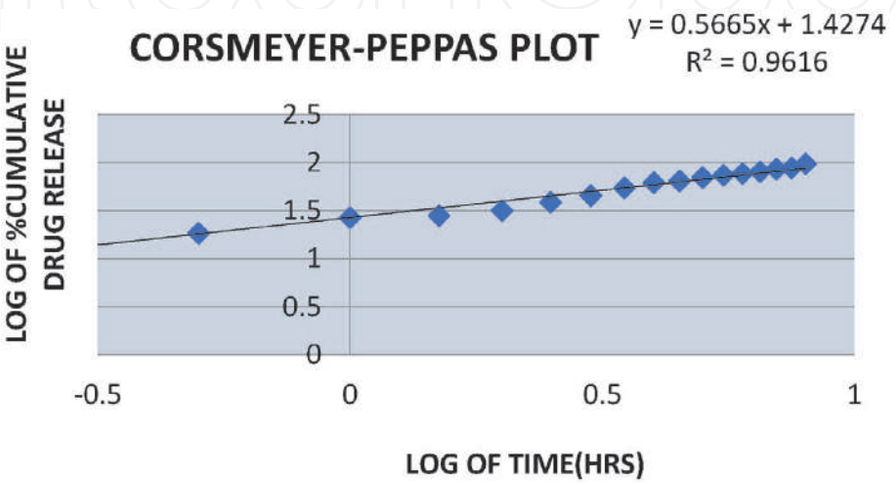

Figure 12.
Korsmeyer-Peppas kinetics of optimised formulation.

S.No	Formulation	Zero order		First order		Higuchi		Korsmeyer-peppas	
1	F3	K	R^2	K	R^2	K	R^2	N	R^2
		10.373	0.9882	−0.1373	0.8541	0.3444	0.9837	0.5665	0.9616

Table 17.
Release kinetic equation values of the optimised formulations.

5.4 Biodegradability studies of floating tablet

Biodegradability studies revealed that the gastro retentive floating tablet of diclofenac (F3) was found to disintegrate and dissolve in intestinal pH within 3 h (**Figure 13**).

Formulation F3 seemed to completely biodegrade in intestinal fluid, and it is the pH of media, which is responsible for slow dissolution of the tablet in intestinal fluid. This indicates that after gastric emptying the regular shaped tablet, gradually become rough with an irregular surface and thereafter was degraded. Thus the gastro retentive floating tablets of diclofenac proved to be suitable gastro retentive dosage form, as they have a rigid structure that resist biodegradation in gastric pH but exhibit complete biodegradation in phosphate buffer pH 8.0.

5.5 Stability studies

Pharmaceutical dosage forms are complex systems composed not only of drug substances but also of various excipients. These excipients, which are non-therapeutic, are intended to contribute desirable, practical properties to the dosage form. These dosage forms may undergo both chemical and physical degradation [28]. Thus, the success of the effective formulation can be evaluated only through the stability studies. This study pursues two particular aims:

- Determination of the optimum formulation and shelf life during developmental stages.

- Derivation of the stability of a product, which guarantees the safety and efficacy of the product up to end of the shelf life at a defined storage condition and pack profile.

So, stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container, to remain in its physical, chemical, microbiological, therapeutic and toxicological specifications. Ability of a

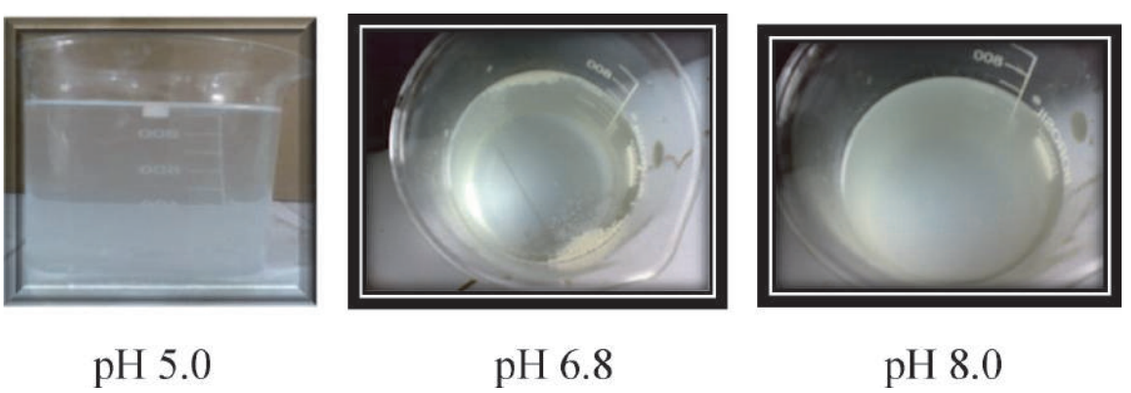

Figure 13.
Images of complete biodegradation of F3 floating tablet after 3 h.

formulation to retain properties in specified limits throughout its shelf-life is referred as stability [28].

The stability of finished pharmaceutical products depends on several factors. On the one hand, it depends on environmental factors such as ambient temperature, humidity and light. On the other hand, it depends on product related factors such as chemical and physical properties of active substance and pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of container closure system and properties of packaging materials.

A study of stability of a pharmaceutical product is essential for safety of the patients, legal requirements concerned with the identity, strength, purity and quality of the drug and to prevent the economic repercussions of marketing an unsuitable product [29, 30].

5.5.1 Experimental

Optimised formulations were stored in screw capped small glass bottles at room temperature and in stability chamber at 40 ± 1°C and 75% relative humidity. Samples were analysed for physical appearance, Hardness (kg/cm^2), Friability (%), Uniformity of weight (mg), Drug content (%), Thickness (mm), Buoyancy lag time (s), Floating time (h) and *in vitro* release after a period of 15, 30, 45, 60, 75, 90 days. Initial drug content was taken as 100% for each formulation. Observations are recorded in **Tables 18** and **19**.

5.5.1.1 Physical characteristics

Various physical parameters were evaluated such as appearance, Buoyancy lag time (s), floating time. Observations are recorded in **Table 18**.

S. No.	Physical parameters	0 days	15th days	30th days	60th days	90th days
1	Appearance	+	+	+	+	+
2	Floating time	+	+	+	+	+
3	Buoyancy lag time (s)	+	+	+	+	+

+, no change.

Table 18.
Effect of ageing on physical parameters.

Parameter	Optimised formulation (F3) (n = 3)			
	At 0 day	At 15 days	At 30 days	At 60 days
Hardness (kg/cm^2)	5.4 ± 0.08	5.4 ± 0.1	5.4 ± 0.09	5.2 ± 0.07
Friability (%)	0.17 ± 0.02	0.17 ± 0.01	0.19 ± 0.02	0.20 ± 0.01
Uniformity of weight (mg)	554.3 ± 1.1	554.3 ± 1.1	554.3 ± 1.1	554.3 ± 1.1
Drug content (%)	100.01 ± 0.04	100.01 ± 0.04	99.50 ± 0.58	98.89 ± 0.12
Thickness (mm)	4.55 ± 0.12	4.55 ± 0.09	4.55 ± 0.10	4.55 ± 0.11

Table 19.
Effect of ageing on physico-chemical parameters of optimised formulation.

5.5.1.2 Physcio-chemical parameters

Various parameters were evaluated such as Hardness (kg/cm^2), Friability (%), Uniformity of weight (mg), Drug content (%), Thickness (mm), and *in vitro* release after a period of 15, 30, 45, 60, 75, 90 days. Observations are recorded in **Table 19**.

5.5.1.3 Drug content was assayed by U.V. spectrophotometry

Gastro retentive floating tablet of diclofenac sodium (50 mg) was dissolved in 100 ml of 0.1 N HCl (pH 1.2) by stirring for 6 h using magnetic stirrer. The resulting solution was then filtered using 0.45 m millipore filter, 1 ml of this solution was taken and added to 100 ml of 0.1 N HCl (pH 1.2). It was then analysed spectrophotometrically at the predetermined λ max (276 nm) to determine concentration of the drug. The determinations were made in triplicate.

5.5.1.4 In vitro *dissolution studies*

In vitro dissolution studies were carried out using simulated gastric fluid (pH 1.2).

5.5.2 Result and discussion

5.5.2.1 Physical parameters of the optimised tablets formulation

The Physical parameters after 15th, 30th, 60th, 90th days are as mentioned in **Table 18**. All the Physical parameter are within the acceptable limits which indicated that gastro retentive floating tablet of diclofenac sodium showed no significant change in the physical appearance at room temperature and in stability chamber at 40°C ± 2°C and 75 ± 5% relative humidity indicating that the formulations were physically stable at these temperatures.

5.5.2.2 Physico-chemical parameters of the optimised formulation

Various parameters were evaluated such as Hardness (kg/cm^2), Friability (%), Uniformity of weight (mg), Drug content (%), Thickness (mm), and *in vitro* release

S. No.	Sampling interval (days)	% Residual drug content Mean ± S.D. (n = 3)	
		At room temp.	At 40 ± 2°C/75 ± 5% RH
1	0	100.01 ± 0.03	100.01 ± 0.03
2	15	99.82 ± 0.12	99.66 ± 0.09
3	30	99.56 ± 0.09	99.25 ± 0.18
4	45	98.75 ± 0.14	98.40 ± 0.15
5	60	98.56 ± 0.05	97.72 ± 0.9
6	75	98.07 ± 0.09	97.51 ± 0.10
7	90	97.69 ± 0.07	96.66 ± 0.06

Table 20.
Effect of ageing on residual drug content at room temperature &40 ± 2 °C/ 75 ± 5%RH.

after a period of 15, 30, 45, 60, 75, 90 days. Observations are recorded in **Table 6**. All the physico-chemical parameters are within the acceptable limits which indicated that formulation were stable over the period of 90 days.

5.5.2.3 Residual drug content of stability batch

Initial drug content of formulations was 100.01 ± 0.04.the drug contents at the end of 15th, 30th, 60th, 90th days were found to be as given in **Table 20**. The drug content was within the permissible limits. The percent residual drug content was determined and the log percent residual content was plotted against time t (**Figures 14–17**), which reflected almost linear relationship.

5.5.2.4 In vitro *dissolution studies*

The dissolution results obtained were as given in the **Table 21**.

The dissolution behaviour of samples withdrawn at different interval was similar and the difference in dissolution pattern of samples kept at two different conditions of storage was negligible.

The log % residual drug content vs. time graph was also plotted in order to evaluate shelf-life and half-life of formulations.

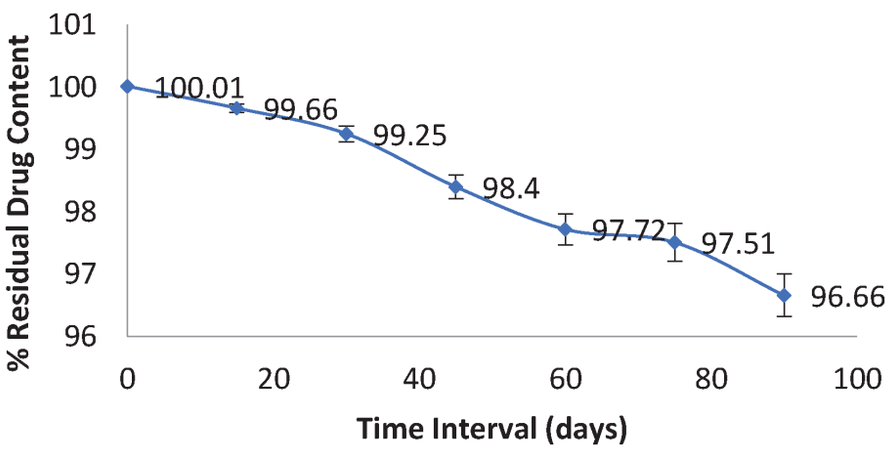

Figure 14.
Effect of ageing on residual drug content at 40 ± 2°C/75 ± 5%RH.

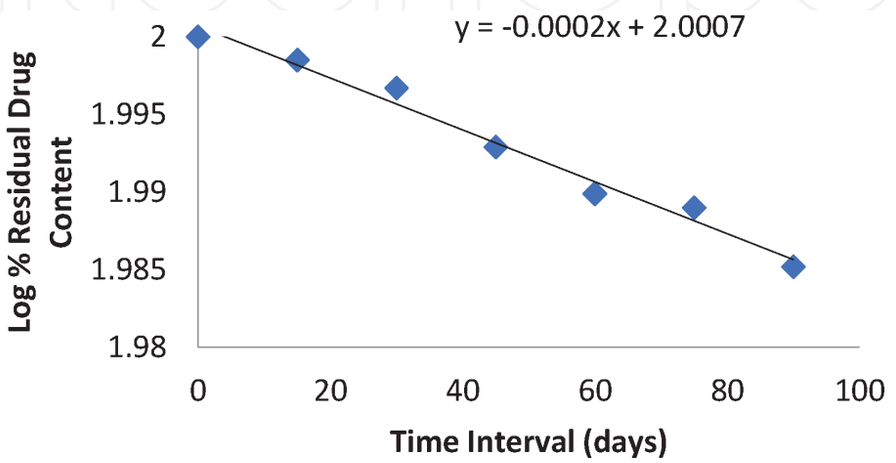

Figure 15.
Plot of log % residual drug content Vs time at 40 ± 2°C/75 ± 5%RH.

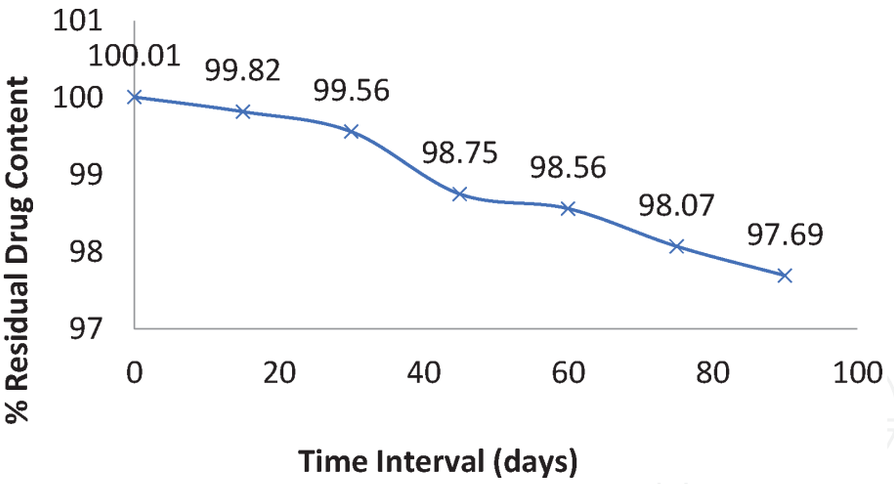

Figure 16.
Effect of ageing on residual drug content at room temperature.

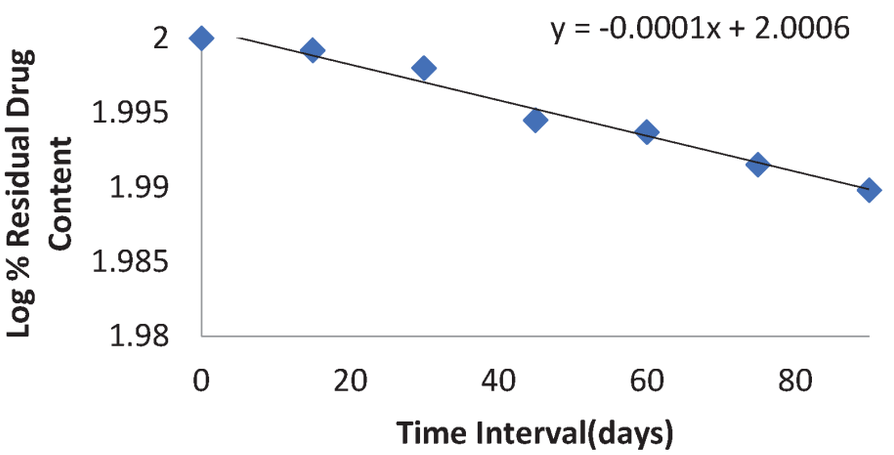

Figure 17.
Plot of log % residual drug content vs. time at room temp.

Time interval (days)	% Cumulative drug release in 8 h ± SD (n = 3)	
	Room temperature	40 ± 2°C/75 ± 5% RH
0	96.769 ± 1.19	96.769 ± 1.19
15	95.78 ± 0.84	94.34 ± 1.52
30	94.81 ± 1.64	93.05 ± 0.81
60	94.45 ± 0.56	92.89 ± 0.69
90	93.97 ± 0.93	92.45 ± 1.21

Table 21.
Effect of ageing on % cumulative drug release at room temperature & 40 ± 2°C/75 ± 5%RH.

Shelf-life was evaluated by the equation:

$$T_{10\%} = 0.104/K \quad (9)$$

Degradation rate constant K was calculated from the slope of straight line between log of % residual drug and time interval. The time required for degradation of 10% drug was calculated as $T_{10\%}$.

S. No.	Storage condition	K (day^{-1})	$T_{10\%}$ (days)	$t_{1/2}$ (days)
1	40 ± 2 °C/75 ± 5%RH	3.822×10^{-4}	272.039	1812.72
2	Room temperature	2.303×10^{-4}	451.58	3009.11

Table 22.
Shelf life of optimised formulation.

Half-life was evaluated by the equation:

$$T_{1/2} = 0.693/K \quad (10)$$

Gastro retentive floating tablet of diclofenac sodium stored at 40 ± 2°C/75 ± 5% RH showed K value as 3.822×10^{-4} and $t_{10\%}$ value as 272.039 days, while those stored at room temperature showed K value as 2.303×10^{-4} and $t_{10\%}$ value as 451.58 days (**Table 22**).

The $T_{10\%}$ obtained in case of formulation stored at 40°C ± 2°C/75 ± 5%RH was found to be lower in comparison with the formulation stored at room temperature which indicated that the formulations tend to degrade faster at higher temperatures and humidity.

The results of stability studies suggest that for adequate shelf life of optimised gastro retentive floating tablet of diclofenac sodium, it should be stored in cool and dry place.

6. Conclusions

In the above research work, ECRFT has been developed by using dual approach; one is solid dispersion (for solubility enhancement) and other is effervescent floating technique (for achieving extended retention in upper G.I.T.), which was prepared from previously optimised solid dispersion of diclofenac sodium. Formulated tablets showed outstanding physicochemical properties, biodegradation studies, stabilities studies, and prolong gastric retention with control release. When compared with marketed tablets of immediate release (Voveran-50) and control release (Voveran-100SR), the optimised formulation F3 was found to be favourable for improving bioavailability of drug, enhancing its therapeutics efficacy and improving patient compliance due to less frequent dosing requirement. Hence, it can be concluded that the prepared formulation can be used positively as a particular oral controlled release-floating tablet for once a day administration.

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Conflict of interest

There is no conflict of interest.

Acronyms and abbreviations

SEM	scanning electron microscopy
PM	physical mixtures
DT	disintegration time
ECRFT	effervescent controlled release floating tablet
SDs	solid dispersions
DS	diclofenac sodium
BD	bulk density
TBD	tapped bulk density
TFT	total floating time
%WU	percentage water uptake
FLT	floating lag time

Author details

Peeush Singhal[1]*, Rajneesh Dutt Kaushik[1] and Vijay Jyoti Kumar[2]

1 Department of Pharmaceutical Sciences (FMSH), Gurukul Kangri Vishwavidyalaya, Haridwar, India

2 Department of Pharmaceutical Sciences, H.N.B. Garhwal Central University, Srinagar, Uttarakhand, India

*Address all correspondence to: peeushpharma@gmail.com

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Dr. Somesh Thapliyal
M. Pharm., Ph.D.
Assistant Professor
Department of Pharmaceutical Sciences
Hemvati Nandan Bahuguna Garhwal University
(A Central University)
Srinagar Garhwal, Uttarakhand, INDIA

Vinod Nautiyal
M. Pharm.
Assistant Professor
Department of Pharmaceutical Sciences
Faculty of Medical Sciences and Health
Gurukul Kangri (Deemed to be) University
Haridwar, Uttarakhand, INDIA

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of the Pharmacy Council of India

Dr. Somesh Thapliyal
M. Pharm., Ph.D.
Assistant Professor
Department of Pharmaceutical Sciences
Hemvati Nandan Bahuguna Garhwal University
(A Central University)
Srinagar Garhwal, Uttarakhand, INDIA

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- Variation Concentration of Sulfur Dioxide and Correlation with Metrological Parameters over Alaknanda Valley, Garhwal Himalaya Uttarakhand
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- Characterization and Morphological Analysis of Airborne Pm10 and Pm2.5 in Srinagar Garhwal
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Editor

Dr. Alok Sagar Gautam is an Assistant Professor & Scientist at Hemvati Nandan Bahuguna Garhwal University (A Central University), Uttarakhand. Earlier, he worked in Instrumentation & Observational Techniques Division, Indian Institute of Tropical Meteorology, Pune. He is currently working on physical and chemical characteristics of aerosols/cloud dynamics to understand the extreme weather events i.e. cloud burst events in Himalayan region. He took part in South Pole Antarctica Expedition on a research project. He has published very good scientific papers in peer reviewed International/Nationals journals. He has also organized/participated in many scientific International/Nationals conferences, seminars, workshops. As a result of his very good research work, Dr. Gautam has been awarded Junior Associate at International Centre for Theoretical Physics (ICTP) Italy, Young Scientist Award by Uttarakhand State council for Science & Technology (UCOST), Young Scientist of the Year 2018 by International Academy of Science and Research (ISAR) Kolkata and "Promising Indian" by Promising Indian Society New Delhi.

Co-Editor

Dr. Tushar Kandari is working as an Assistant Professor in Govt. P.G. College, Sri Dev Suman University Campus, Gopeshwar, District Chamoli, Uttarakhand, India. He is specialized in Natural background environmental radioactivity and presently working in the same field. His research work purely emphasizes upon the level of natural radiation in the environment and its effect to the human being exposed. In his earlier work, he has developed a theoretical model which predicts the indoor radon concentration by using various parameters responsible for it and hence validated it to the measured indoor radon concentration. During his research study, he has published various papers in peer reviewed journals.

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ADVANCEMENT IN BASIC AND APPLIED SCIENCES

DR. ALOK SAGAR GAUTAM
DR. TUSHAR KANDARI

Advancement in BASIC AND APPLIED SCIENCES

Dr. Alok Sagar Gautam & Dr. Tushar Kandari

About the Book

Development of science and technology depends on the way of its application in the right direction. The present manuscript will surely attract the readers because of its interdisciplinary nature which covers atmospheric science, material science, computer science, remote sensing, environmental science, mathematical science, health and agricultural science. Some of the key findings of the book are study of various atmospheric factors i.e. climate change due to various pollutants and the aerosol content in the environment, the radioactivity level and the dose absorption level along with its correlation to the aerosols. The results discussed in the chapters were experimentally performed using the latest technology to get some impactful results. The chapters in the book shows a high impact over the society as it covers the hot and burning topic such as atmospheric and environmental science which deals with the factors responsible for the climate change and our environment. As we all know, learning is a never ending process to explore new horizons in science and technology, therefore this book somewhere reflects the above lines and is a small step towards advancement of science.

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4

A Review on Effects of Radon, Thoron and their Daughter Products on Human Beings in Uttarakhand Himalayan Region

Tushar Kandari, Preeti Pant, Poonam Semwal, Amar Deep, A.A. Bourai, R.C. Ramola

Introduction

Radon being a radioactive element present in the earth crust enters into the human environment through exhalation from top layer of the soil and this infiltration of gas becomes a major source for the environment. Radon and its isotopes get exchanged to the indoor air via. window and doors in the houses and through the building material used in the walls, floor, ceiling etc (Nazaroff and Nero, 1988). Sometimes, these gases and their decay products remain in the houses for a longer duration due to the poor ventilations conditions.

Inhalation of radon, thoron and their daughter products causes more than 50% of the ionizing radiation received by human population (UNSCEAR, 2000) and is studied in various countries (Jonsson, 1988; Letoureau et al., 1994; Kreinbrock et al., 2001; Kandari et al., 2016). Based on the epidemiological studies in European and American countries, World Health Organization (WHO, 2009) recommended to bring down the reference limit from 200 Bq/m^3 to 100 Bq/m^3 and also marked it as second leading cause to lung cancer next to smoking. In the past, thoron was neglected due to very short life span and was

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Thoron, Whether it Should be Neglected or Not: A Review

Tushar Kandari, Alok Sagar Gautam, A.A. Bourai, R.C. Ramola

Introduction

Radon and its progeny are present in the dwellings and houses according to the radium content present in the building materials and the soil beneath the houses. Radium being the daughter product of uranium which is a radioactive element, hence it is important to study its parent element. The presence of uranium, radium and thorium vary largely upon the geological variation in the soil beneath the houses, building material and various other factors. Indoor radon contributes maximum (52%) to the ionizing radiation dose received to human being (UNSCEAR, 2000). According to world health organization, the epidemiological study performed in various countries of the world says that the recommendation level for indoor radon reference level should bring down from 200 Bq/m^3 to 100 Bq/m^3 (WHO, 2009). Based on this epidemiological study in Europe and North America, WHO has declared that radon-222 has been regarded as the second leading cause of lung cancer after smoking. In addition to the earlier study, the conservative radon risk estimate was being revised on the basis of recent studies in Czech and France, and thereafter the dose conversion factor of radon progeny inhalation will increase by a factor of 2 (Tomasek, 2008a; Tomasek, 2008b).

ABOUT THE EDITORS

- **Dr. Alok Sagar Gautam** is an outstanding researcher, mentor and academician of National and International repute holds Post Graduate (M.Sc.), and Doctoral Degree (Ph.D) in the field of Atmospheric Physics and Space Science, associated as Assistant Professor of Department of Physics, Hemvati Nandan Bahuguna Garhwal University (A Central University), Uttarakhand. Earlier, he worked in Instrumentation & Observational Techniques Division, Indian Institute of Tropical Meteorology, Pune. He took part in South Pole Antarctica Expedition. He has published some very good scientific papers in peer reviewed International/Nationals journals. He has also organized/participated in many scientific International/Nationals conferences, seminars, workshops. As a result of his very good research work, Dr. Gautam has been awarded Junior Associate at International Centre for Theoretical Physics (ICTP) Italy, Young Scientist Award by Uttarakhand State council for Science & Technology (UCOST), Young Scientist of the Year 2018 by International Academy of Science and Research (ISAR) Kolkata and "Promising Indian" by Promising Indian Society New Delhi, Research Excellence Award for best research paper on "First report on Chemical Characteristics of atmospheric pollutants over Garhwal Region Uttarakhand "by Institute of Scholars Bengaluru, Young Scientist Award in Atmospheric and Space Science by Glocal Environment & Social Association (GESA) New Delhi.
- **Dr. Seema Dhawan** is a Professor at Department of Education, Birla Campus, HNB Garhwal Central University, Srinagar, Uttarakhand. She has completed his Master in Zoology, Doctorate in forestry and Education. Her research area of specialization is Education for sustainable development, Educational Technology and Research. She has 25 years of research and teaching experience at graduation and post graduation levels, Administrative practice of 6 years in Teacher's Training Institutions. She has supervised more than sixty five students for Dissertation and Ph. D. works, Published three books and 21 chapters in different books, Published 127 papers in National and International journals, Developed 13 psychological tools for research work and 7 Programmed Instructional Materials, Contributed expertise in training modules for Pupil teachers and teacher educators on Environmental Education developed by Center for Environmental Education and NCTE., Expert and Course writer for NIOS-CEE modules for Diploma Program in Elementary Education, Contributed as an expert for ARPIT courses and Swayamprabha 32 Channel. She has received Eight Awards in the Educational field viz. Prof. Satya Pal Ruhela Best Educational Sociologist Award, 2014; Women Educationist Award, 2014; Gyan Jyoti Award, 2017.
- **Dr. Tushar Kandari** is working as an Assistant Professor in Govt. P.G. College, Sri Dev Suman University Campus, Gopeshwar, District Chamoli, Uttarakhand, India. He is specialized in Natural background environmental radioactivity and presently working in the same field. His research work purely emphasizes upon the level of natural radiation in the environment and its effect to the human being exposed. In his earlier work, he has developed a theoretical model which predicts the indoor radon concentration by using various parameters responsible for it and hence validated it to the measured indoor radon concentration.
- **Dr. Poonam Semwal** has worked as a research fellow in the area of natural environmental radioactivity in Board of Research in Nuclear Sciences (BRNS) project. Her research work purely accentuates on the natural radiation along with numerical and theoretical modelling and its consequence on the exposed human being. In her earlier work, she has developed a numerical model which predicts the indoor radon, thoron and their progeny concentration by using various parameters and also validated the measured indoor radon, thoron and their concentration in tectonic regions. She has authored 20 research articles published in renowned International/National journals and conferences. She has organized two international conference and two webinars. She has been awarded as a Yong Scientist in the year 2016 and 2018.

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Air Quality, Climate Change and the Environmental Effects Referring to the Pandemic COVID-19 LOCKDOWN

Dr. Alok Sagar Gautam | Prof. Seema Dhawan
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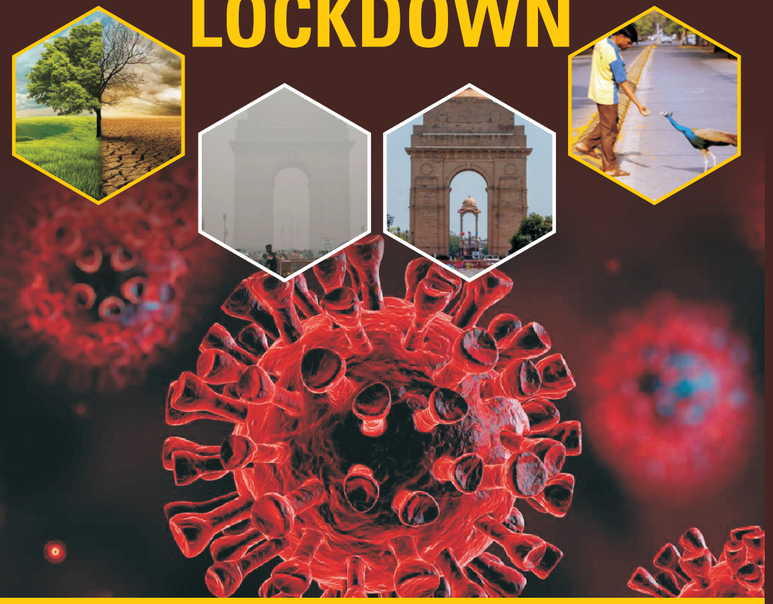

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4

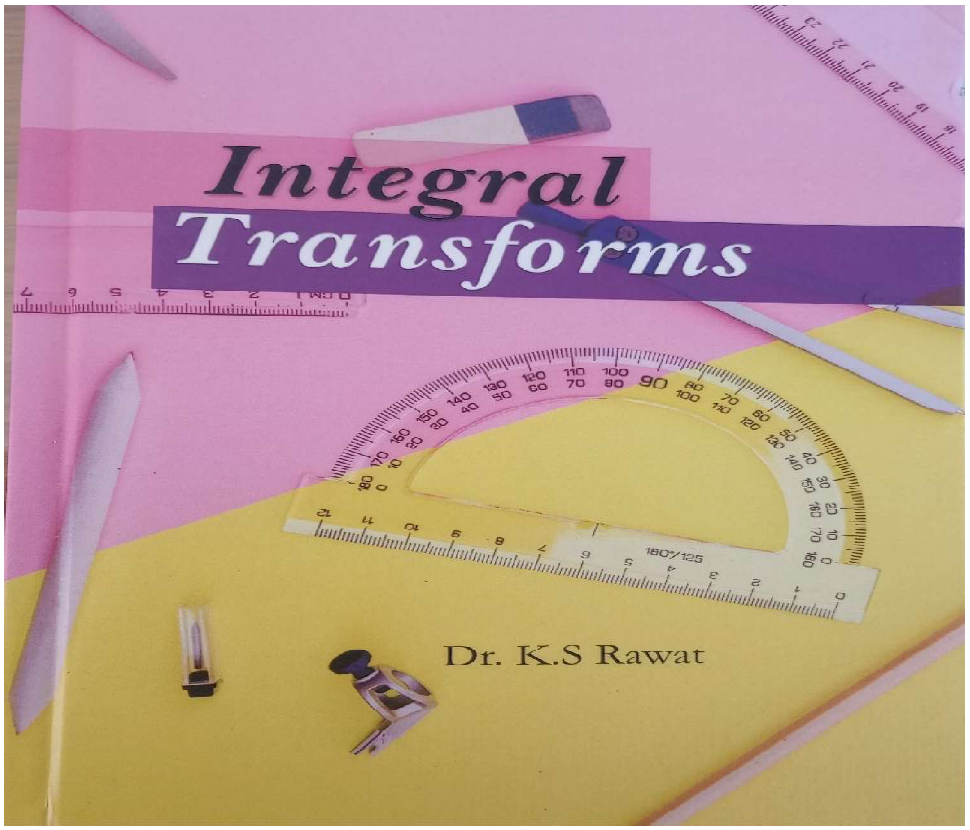
Exposure of Miners and Residential due to Radon and their Progeny, hence causing Health Effects

Tushar Kandari[1], Poonam Semwal[2], Alok Sagar Gautam[3], A.A. Bourai[4], R.C. Ramola[4]

Abstract

Radon is a naturally occurring radioactive gas that is produced from the process of radioactive decay of radium, thorium and uranium in soils and rocks. Exposure to radon accounts for more than 50% of the annual effective dose of natural radioactivity. Radon causes approximately 21,000 deaths annually from lung cancer, which makes it's the second leading cause of lung cancer after smoking. However, the extent of public knowledge about radon is unclear. Though many epidemiological studies regarding occupational exposure among miners and residential exposure among the general population, radon has

[1]Govt. P.G. College, Sridev Suman University Campus, Gopeshwar, Uttarakhand
[2]Govt. P.G. College, New Tehri, Uttarakhand
[3]B.C.C. Campus, H.N.B. Garhwal University, Srinagar Garhwal, Uttarakhand
[4]S.R.T. Campus, H.N.B. Garhwal University, Badshahi Thaul, Tehri, Uttarakhand



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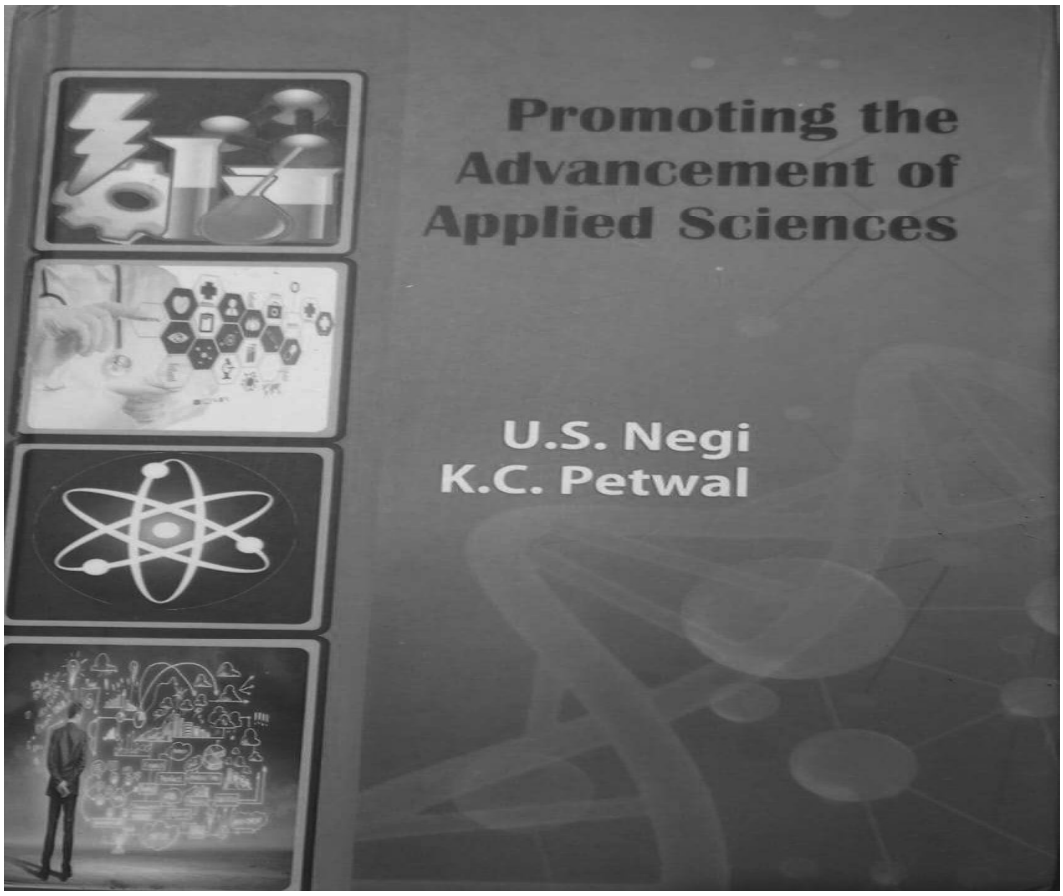

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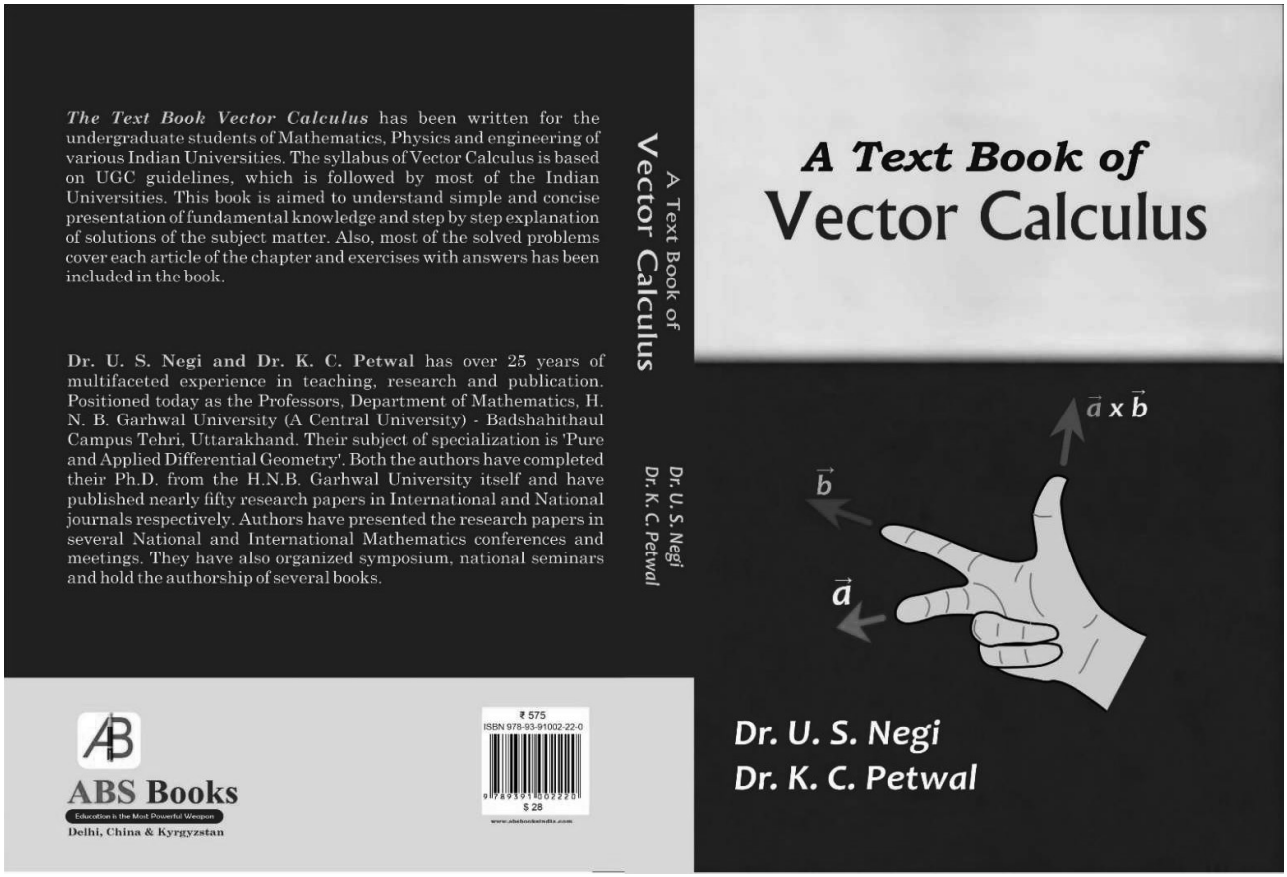

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Editors
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Department of Geography
Kumaun University
Nainital, Uttarakhand
India

Etienne Nel
Department of Geography
University of Otago
Dunedin, Otago
New Zealand

Stanko Pelc
Faculty of Education
University of Primorska
Koper-Capodistria
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Chapter 4
Socio-economic Wellbeing and Mental Health Profile of Rural Hill Women of Uttarakhand, India

Lata Pande, Jyoti Tiwari and Chhavi Arya

4.1 Introduction

Bounded in the north by Tibetan autonomous region of China and in the east bounded by Nepal, Uttarakhand is located at the northern margin of India. It is marginal not only in its physical setting but economically it is underdeveloped. It is characterized by small and fragmented land holdings. Fragile ecosystem, rain-fed agriculture poor productivity of the crop. Meager means of transport and communication, women-centered agriculture and economic migration of males in search of employment. The state also faces several challenges due to climate change and deforestation. As a result of which water and agricultural produce are adversely affected. The impact of development is witnessed at a very slow pace in the hilly regions of the state. Majority of the rural people in Uttarakhand belong low economic status and marginalized families.

The women belonging to this region bear the brunt of all these conditions and problems. Here the role of women is multi-dimensional and they shoulder the responsibility of agricultural and livestock production, making arrangements for water and fuel and also managing the chores of the entire household. Women in hilly region are the most disadvantaged people in terms of their health and nutritional status. They have less access to basic resources such as health care facilities,

L. Pande (✉) · C. Arya
Home Science Department, Kamoun University, DSB Campus, Nainital 263002, Uttarakhand, India
e-mail: latanutrition@yahoo.co.in

C. Arya
e-mail: chhavi_arya@hotmail.com

J. Tiwari
Home Science Department, HNB Garhwal University Srinagar Campus, Srinagar, Uttarakhand, India
e-mail: j.tiwari_7@yahoo.co.in

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Dr. Anamika Chauhan
Dr. Deepika Dhawan

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CAREER OPPORTUNITIES THROUGH HOME SCIENCE EDUCATIONAL TRAINING

Anjali Yadav[1] & Jyoti Tiwari[2]

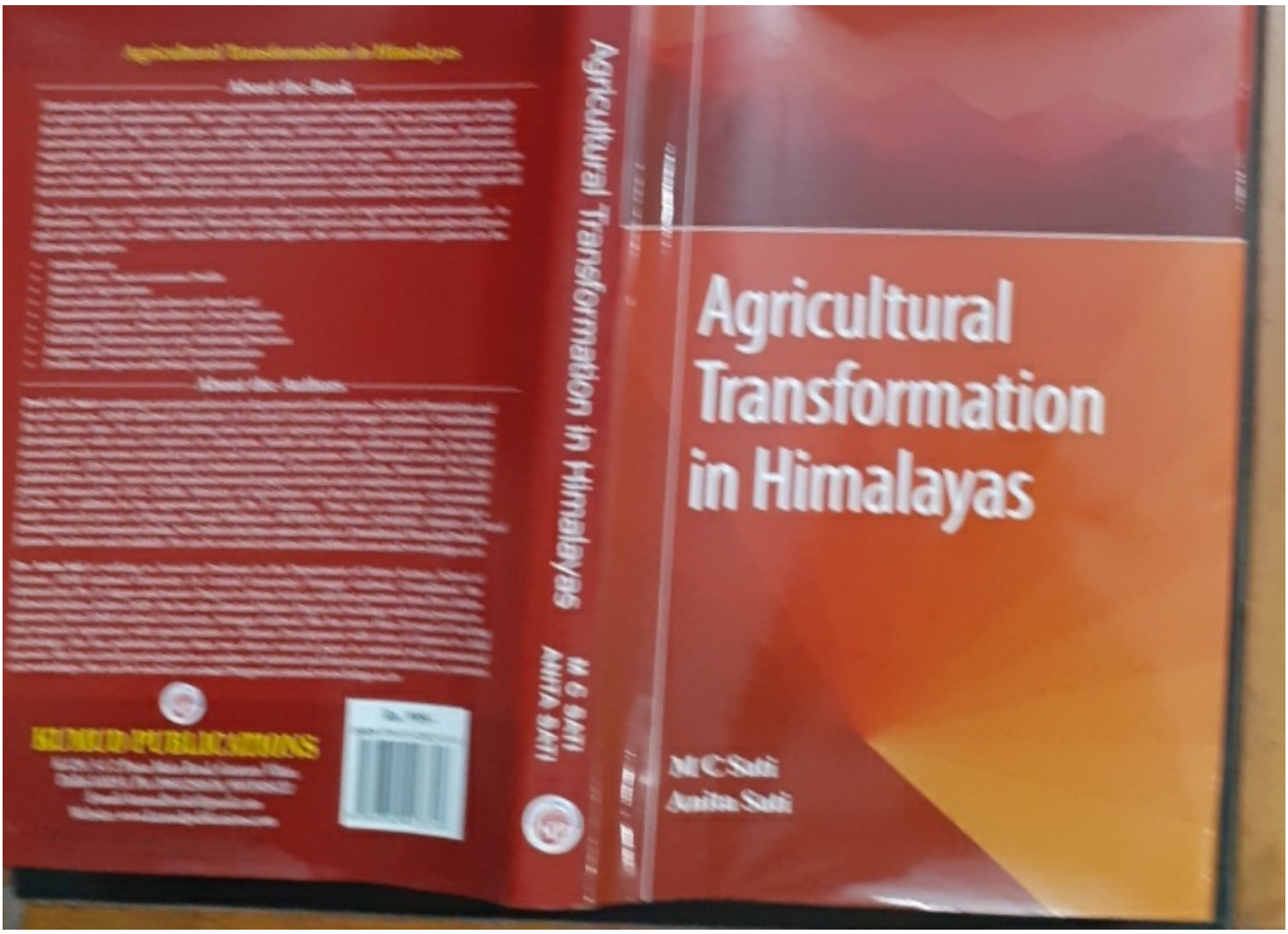
INTRODUCTION:

'Home Science is not only the science of family and society but also the science of employment'[3]

There is no other useful and multi-faceted subject like Home Science. Home Science teaches the person to improve the economic condition of himself and his family by giving employment, ways or methods of self-employment. It provides an opportune stage to move forward with the development of society with a wider range of thinking tools. Home Science consists of 2 words, that's 'Home' and 'Science'. The word *'Home'* is the place of residence wherever the family lives and the 2nd word *'Science'* refers to data-supported facts, principles & laws. With the combination of these 2 words, Home Science is derived as the Application of knowledge domain in an exceedingly systematic manner towards raising the standard

[1] Research Scholar, Department of Home Science, Birla Campus, H.N.B.G.U. (Central University) Srinagar, Uttarakhand. banjmau@gmail.com 7905425534

[2] Professor, Department of Home Science, Birla Campus, H.N.B.G.U. (Central University) Srinagar, Uttarakhand. j.tiwari_7@yahoo.com.in 7895706187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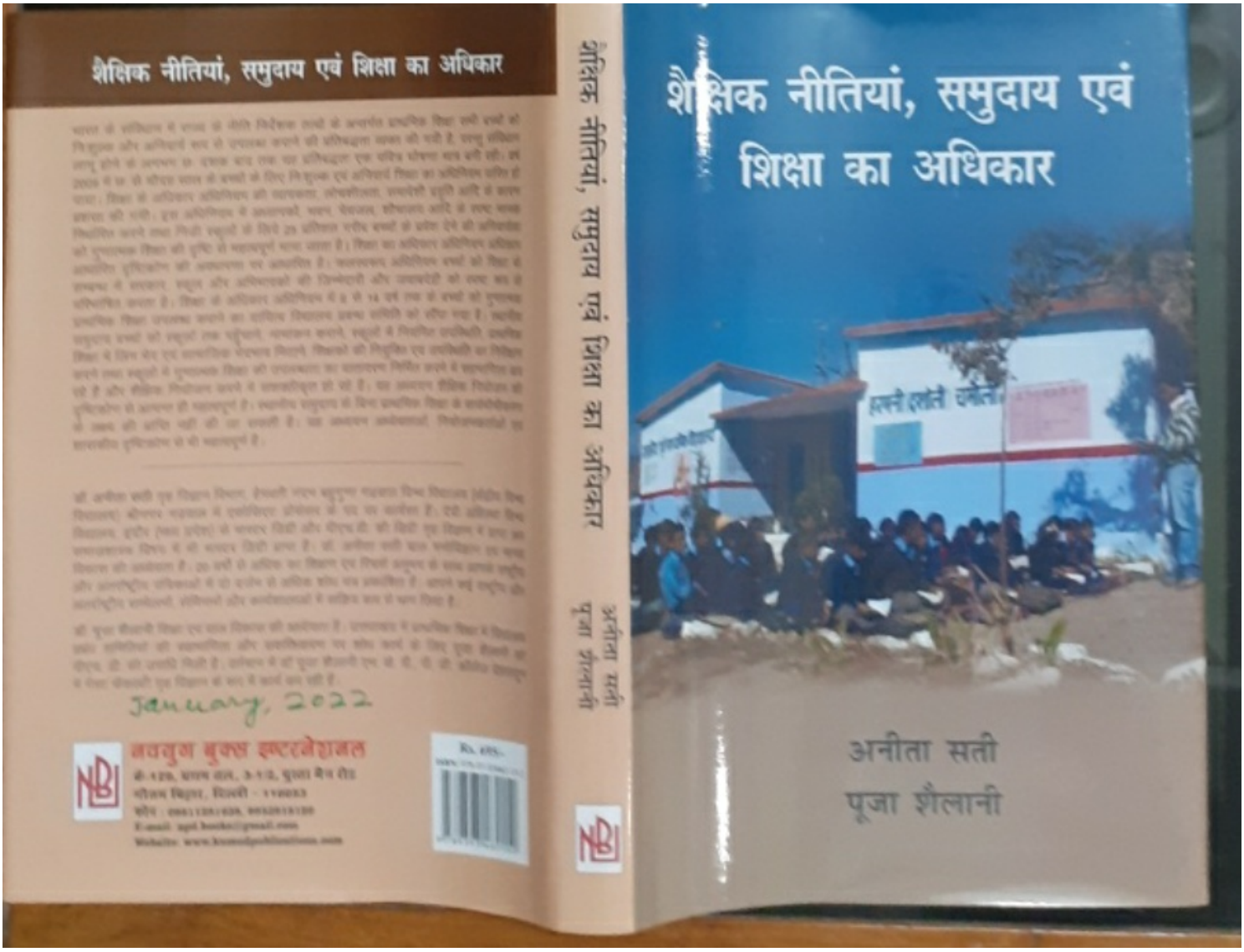
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अनीता सती
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COVID-19, HUMAN HEALTH AND NUTRITION

Anamika Chauhan
Dr. Deepika Saini

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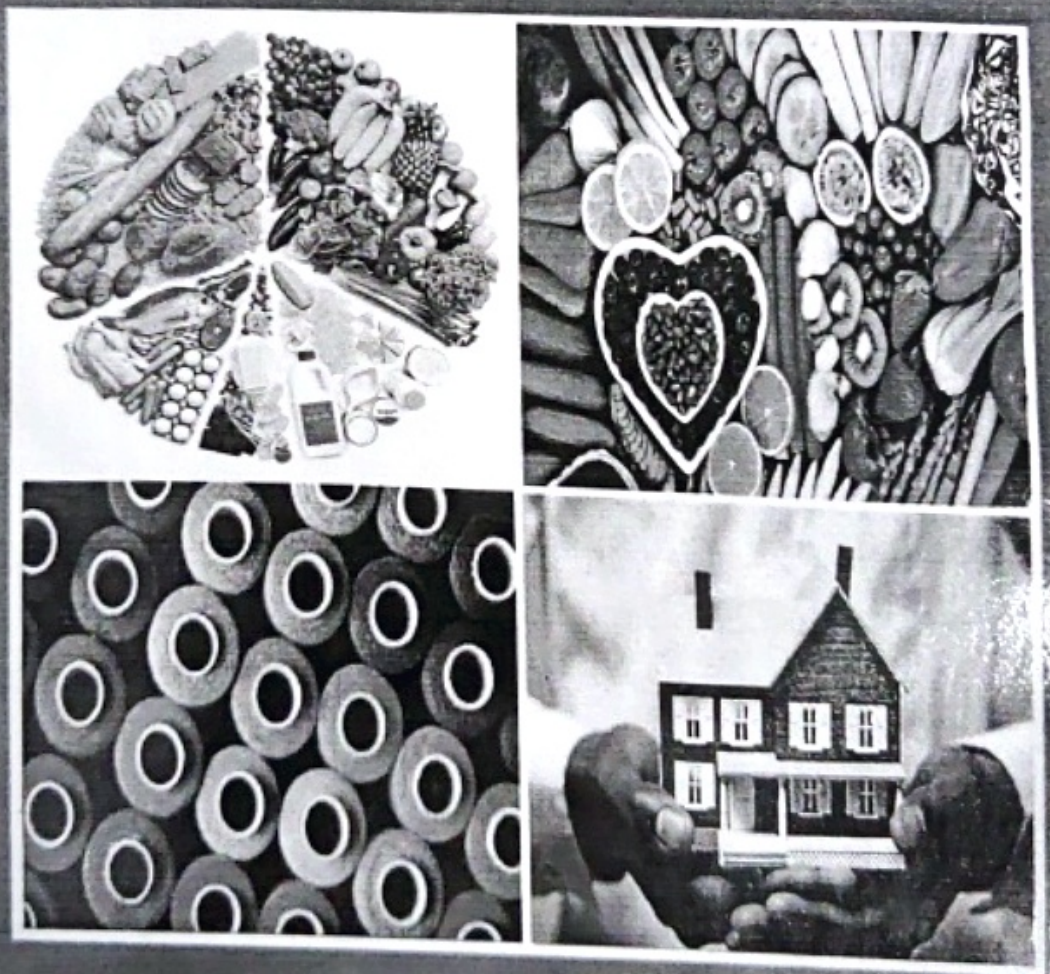
Home Science As a Vocational Subject : Challenges and Opportunities

Dr. Anamika Chauhan
Dr. Deepika Dhawan



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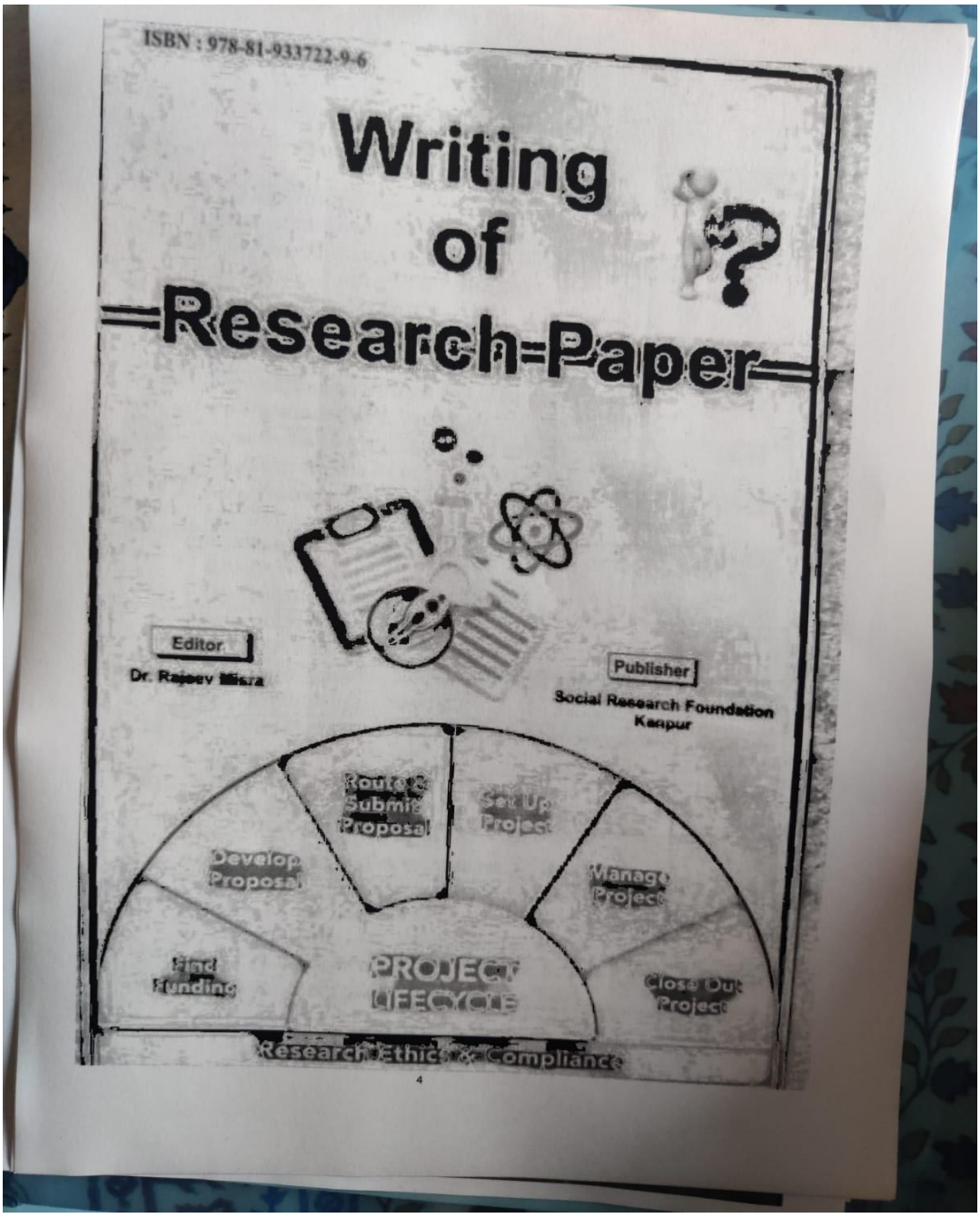

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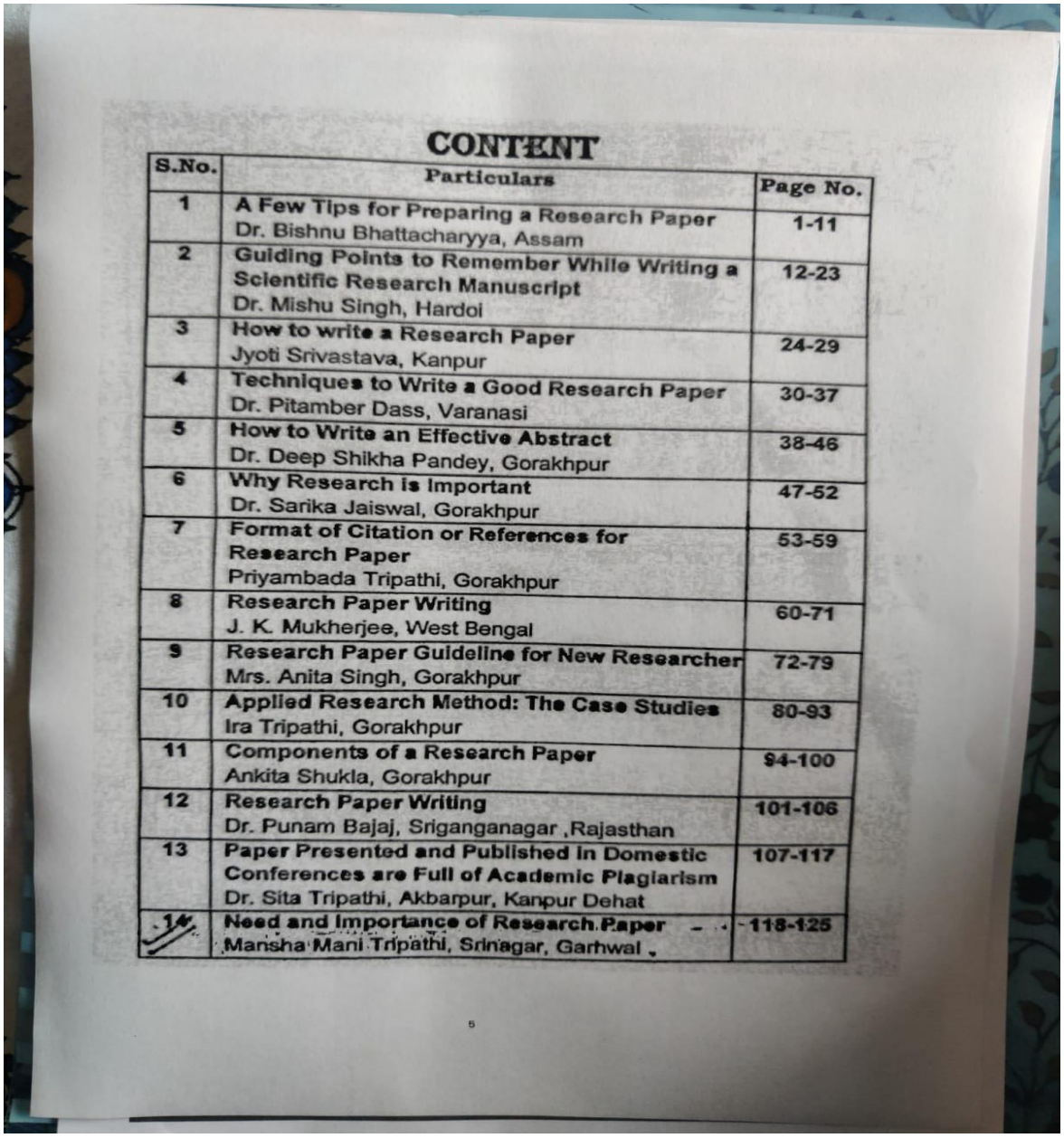

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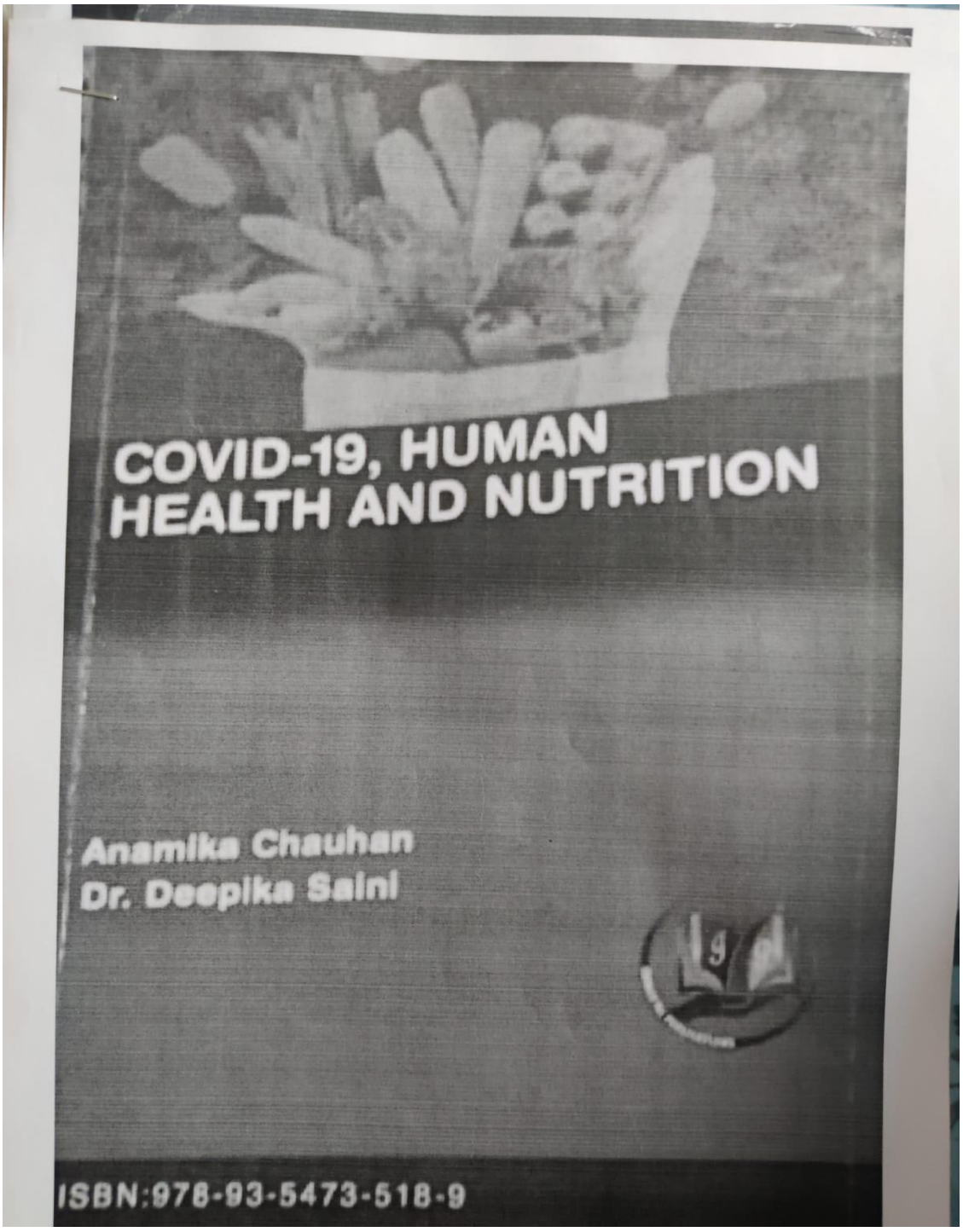

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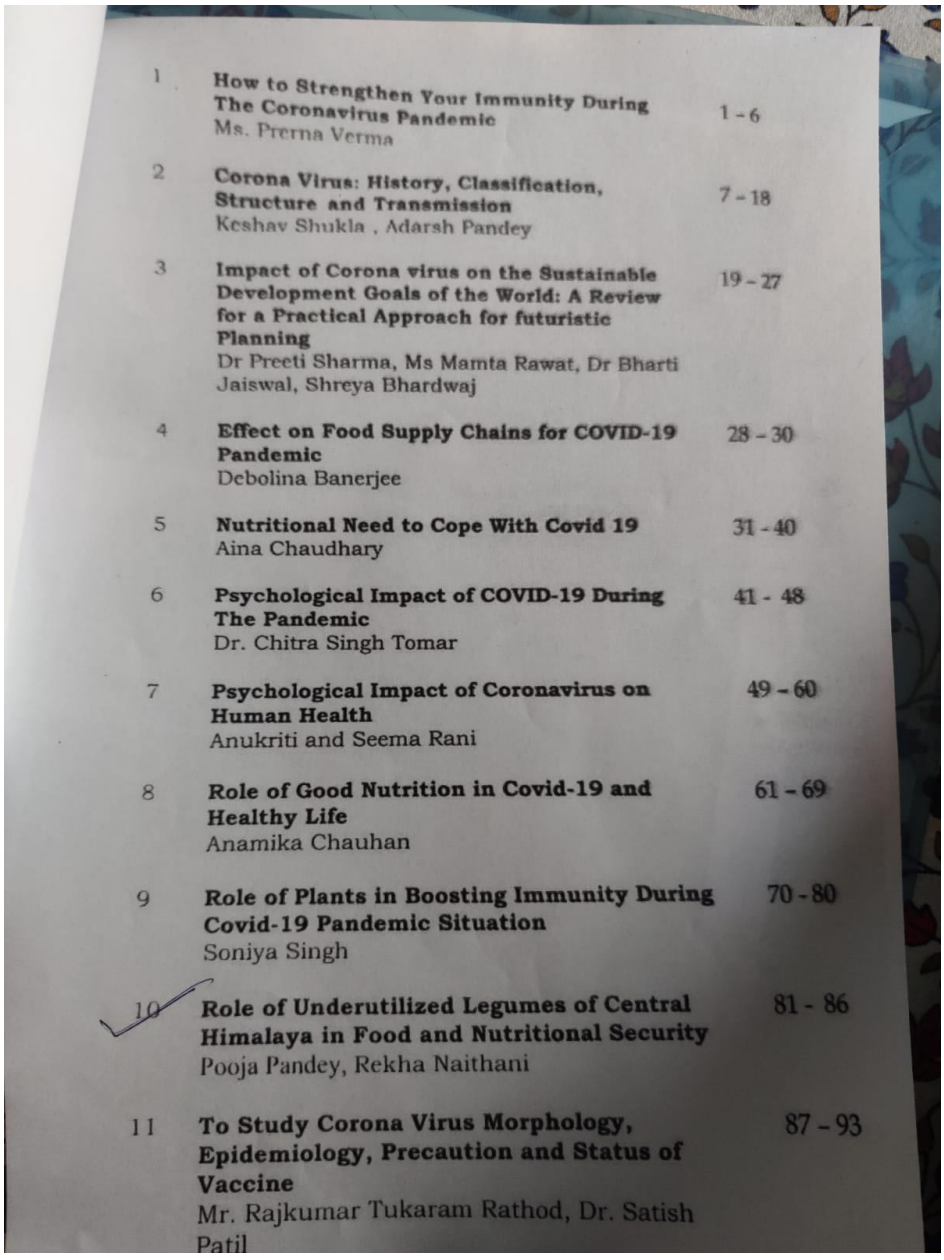

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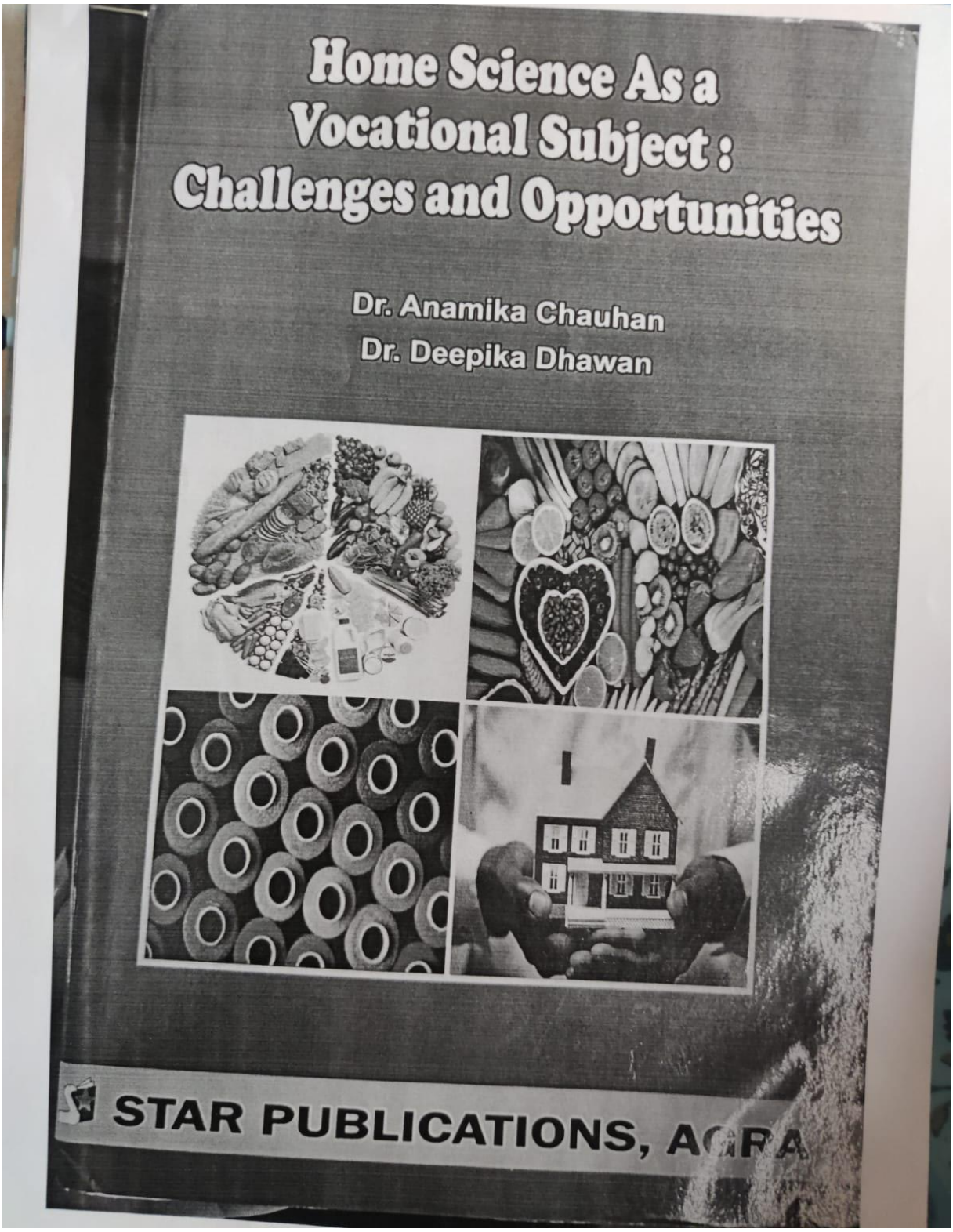

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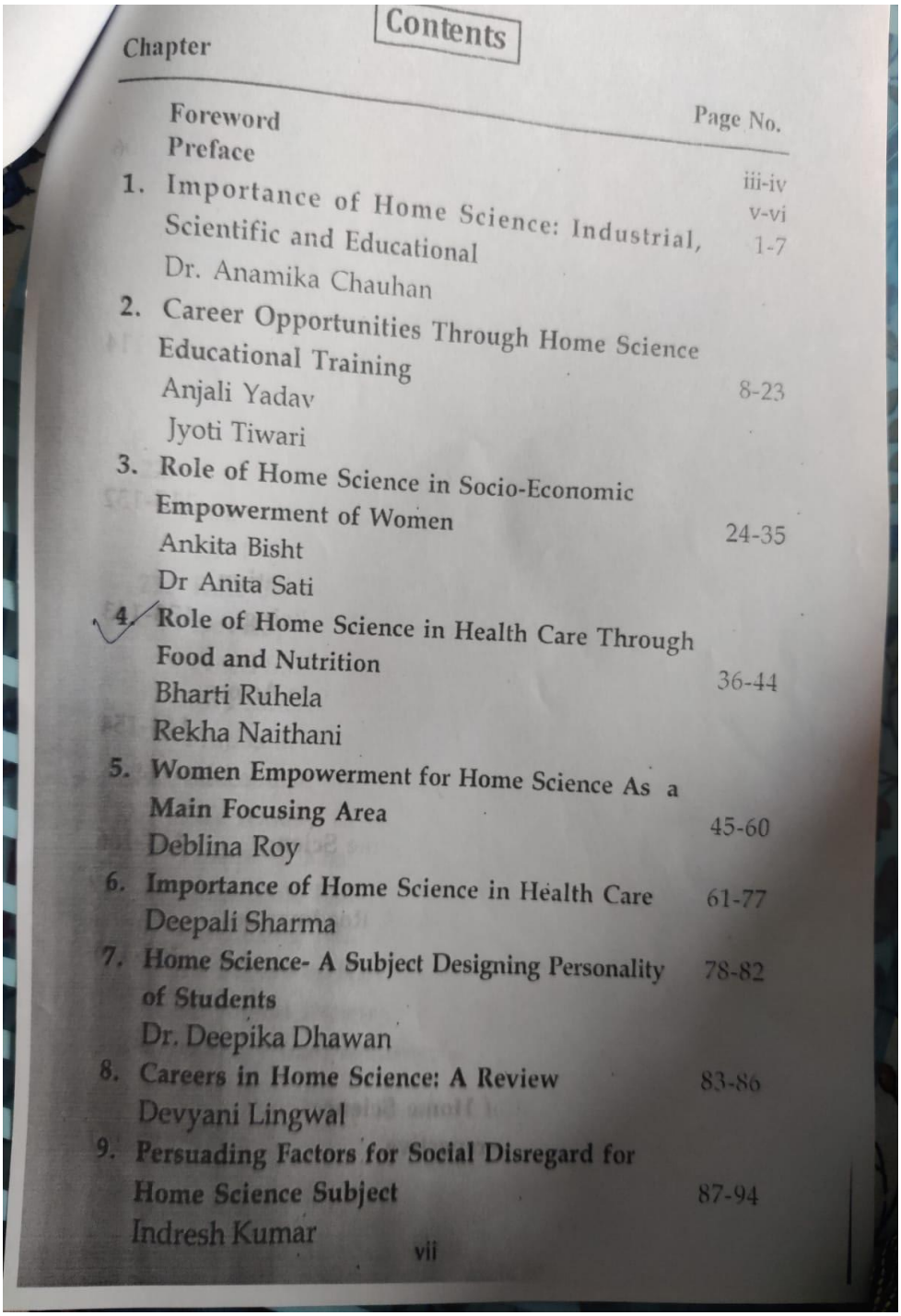

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Role of Applied Statistical Techniques in Interdisciplinary Research

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This book contains detailed studies on the consequences of out-migration and the further effects of migration on fertility. Pauri Garhwal (Uttarakhand, India) was selected as study area because it is currently facing negative population growth rate (-1.51%) as per the latest census of 2011. The Book has detailed study on migration and the declined fertility of the population of the area. The purpose of the study was to isolate the effects of migration on women by the demographic factors and to identify the patterns and levels of migration in the area. The results of the study indicated that the reasons behind the migration is due to lack of adequate employment opportunities, basic amenities and their desire for a better standard of living. Usually, the male members of the family migrate to towns to earn a decent living for their families that leads to the migration of whole family which induces others to follow the same. The study employs different regression models to estimate the impact of various factors of migration on declined fertility in the study area. The author of the book has extensively visited the district Pauri Garhwal and made personal interactions for the study.

Dr. Pankaj Bahuguna, obtained M.Sc. and Ph.D. in Statistics from H.N.B. Garhwal University (A Central University), Srinagar Garhwal Uttarakhand (India). He has worked extensively on demography of Pauri Garhwal district of Uttarakhand state. Presently, he is working as Assistant Professor (Statistics) at VCSG UUHF Bharsar.

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Demographic Study of Pauri Garhwal

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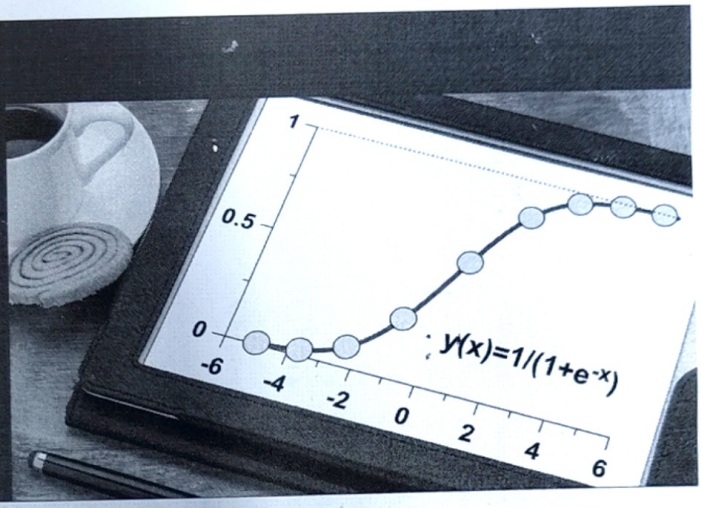

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