APTI women's forum

APTI Women's Forum Newsletter

Novel Excipients
Fuelling Pharma Innovation

a quarterly newsletter published by Association of Pharmaceutical Teachers of India

Apr - Jun 2021

Editor's Note

Prof. Vandana B. Patravale

Chief Editor, APTI Women's Forum Newsletter

Dear Readers,

I take immense pleasure in welcoming you all, on behalf of APTI Women's Forum, to this quarterly issue of our Newsletter. It has always been our aim to bring forth thematic issues which can serve as a great learning experience for all our readers ranging from students and teachers to industry professionals. Continuing with this trend, our theme for the present issue "*Novel Excipients: Fuelling Pharma Innovation*" has been selectively handpicked for you all. The global excipients market is soaring high at USD 7.9 billion in 2021 and is projected to rise with a CAGR of 5.8% reaching USD 10.6 billion by 2026. The quality and functionality of pharmaceutical excipients play a crucial role in determining the integrity of the product, making it an extremely important component of formulation development.

I am elated to present to you a wide set of articles in this thematic issue which will enlighten you about numerous novel excipients along with their applications and innovative manufacturing techniques. We have a comprehensive compilation of excipients including Affinisol™ HPMC described with a focus on HME technology, functionalized alginates from marine source, modified chitosan, different types of potential polysaccharides and sustainable nanocellulose. Authors have also touched upon the emerging multifunctional excipients like mesoporous silica, polysaccharide-based excipients for ocular delivery and TPGS for overcoming multi drug resistance in cancer. It is a known fact that development of novel substances cannot be deemed successful without compliance of regulatory guidelines. We, hence, have an article talking about the various regulatory requirements and the strategic approaches that can be undertaken in order to conduct research to develop novel excipients.

Excipients do not impart any medicinal properties to the formulation; however, they have harder roles to play ranging from enabling pharmacological targeting to protecting the API and enhancing the ease of manufacturing process. This, in turn, drives the need for detailed research and effective development of multifunctional excipients for delivery of drugs as well as cosmetics. This area of research brings forth a lucrative growth opportunity for all of us to widen our scope of vision and venture into the world of excipients.

I and the entire editorial board want to express our heartfelt gratitude to all the contributing authors for sparing their valuable time and making this thematic issue impactful. I also thank the entire editorial team for their efforts in compiling this newsletter. I am hopeful that all my readers will gain knowledge and enjoy this newsletter to the same extent that we did while designing it!

Submit your thematic articles at: editor.aptiwomensforum@gmail.com

APTI Women's Forum
Editorial Board

Prof. Vandana B. Patravale
Professor of Pharmaceutics
Institute of Chemical Technology, Mumbai
(editor.aptiwomensforum@gmail.com)

Prof. Suneela Dhaneshwar
Director,
Amity Institute of Pharmacy & Deputy Dean of Research
Amity University, Lucknow Campus

Prof. Shubhini Saraf
Professor and Head (Department of Pharmaceutical Sciences)
Dean, School of Biomedical and Pharmaceutical Sciences
Babasaheb Bhimrao Ambedkar University, Lucknow

Dr. Purnima Ashok
Principal,
Acharya & BM Reddy College of Pharmacy,
Bengaluru

Prof. Kanchan Kohli
School of Pharmaceutical Education & Research (SPER)
Jamia Hamdard, New Delhi

Dr. Clara Fernandes
Associate Professor,
Bombay College of Pharmacy- Autonomous
(Affiliated to University of Mumbai)

Novel Polysaccharides: Fuelling Pharma Innovation

Nilima Thombre* & Sanjay Kshirsagar

MET's Institute of Pharmacy, Bhujbal Knowledge City, Nashik, Maharashtra

nilimat_iop@bkc.met.edu

Abstract

The development of any pharmaceutical dosage form includes a drug moiety and excipients where excipients have significant valuation with improved physicochemical characteristics of dosage forms. Polysaccharides are best natural excipients with wide applications in pharmaceuticals, cosmeceuticals, medical devices, as supplements in nutraceuticals and food industry from last few decades. Natural polysaccharides are biomacromolecules which have been explored for chemical, physical, and enzymatic modifications to develop unique characteristics with new applications. Alterations in structure due to modification of natural polysaccharides changes structure–activity relationships and aids in the development of improved functional polysaccharides with innovative bioactivities.

Nature has gifted extensive variety of natural materials to India that can help to advance and maintain health of all living beings directly or indirectly. From the last decade, important developments in various dosage forms of existing or recent active pharmaceutical ingredient (API) involved the use of natural products, synthetic as well as modified excipients for numerous purposes. Traditionally, excipients are used in drug formulations as inert vehicles to give necessary weight, consistency and volume for the correct administration of API, however in current pharmaceutical dosage forms, excipients play multifunctional roles such as providing modified drug release, better bioavailability of API along with stability, better acceptance by patient and assurance of ease of manufacture (1). Currently availability of huge number of natural plant-derived pharmaceutical excipients with various molecular weights and physicochemical properties motivates researchers to investigate new applications of these natural polysaccharides in drug delivery systems (2).

Natural, synthetic, and semisynthetic polymers have been investigated in various pharmaceutical dosage forms such as film coating agents, matrix controlled systems, nanoparticles, microspheres, buccal films, viscous liquid dosage forms like ophthalmic solutions, suspensions, and implants where their applicability and efficiency have been confirmed. These have been also applied as viscosity modifiers/ enhancers, stabilisers, disintegrants, solubilisers, emulgent, gelling agents, suspending agents, bioadhesives, and binders in various dosage forms. Natural, synthetic and semi-synthetic polysaccharides as drug-release-retardants have been utilised in sustained drug delivery systems to improve therapeutic efficacy of drugs as well as targeted drug delivery systems to target locations in the gastrointestinal tract. Synthetic polysaccharides have been used to obtain desired drug release profiles in combinations which make the process complicated and enhance the cost of formulation (3).

Currently, synthetic additives have been effectively replaced by numerous naturally derived polysaccharides like spaghula husk, guar gum, pectin, galactomannans from Mimosa scabrella, Gleditsiatria canthos Linn, Sesbania gum, tamarind seed gum, Hibiscus esculenta mucilage, gum dammar, gum copal, konjac, agar, chitosan etc. in sustained-release formulations, modified drug delivery systems and controlled release formulations. Seed polysaccharides in food industry have been applied for processing of food and improvement of mouthfeel and texture of food products. Seed polysaccharides are mainly of three types: nonstarch polysaccharides as reserved food material like locust bean, Caesalpinia pulcherrima, guar etc.; mucilaginous material in seed like yellow mustard seed, flaxseed, psyllium seed etc.; and cotyledons and endosperms cell wall materials like soybean seeds and tamarind. All polysaccharides vary in chemical compositions, structural properties, functional and physical characteristics as per plant sources, growing environments, and method of production. Non-starch seed polysaccharides are used as dietary fibre which is important in reduction in calorie intake, control of insulin and blood glucose levels, and reducing the risks of heart diseases and colon cancer (4).

Polysaccharides, also recognized as Cinderella of biopolymers, contain wide variation in functions. They can be energy storage materials like starch and glycogen in plant seed polysaccharides like locust bean gum, guar gum, panwar gum, and tara gum. They also contribute to the mechanical strength and structural integrity of tissues by hydration of cross-linked three dimensional network (pectins in land plants while carrageenans, agar, and alginate in marine species). Polysaccharides such as chitin and cellulose, xylans and mannans produce stiff, hard structures or strong fibres by compact packing of the chains. Polysaccharides also have protective roles, for instance, the antigenic and immunogenic exocellular microbial polysaccharides which are highly specific for particular organisms or the exudate gums from plants, which heal the injured area of the plant and prevent against bacterial infections (3).

Galactomannans (GMs) are polysaccharides containing (1→4)-β-D-mannopyranosyl residues with (1→6) linked α-D-galactopyranosyl residues. GMs (also known as "Pharaoh's Polysaccharides") are non-ionic, water miscible hydrocolloids with high molar mass and form stable highly viscous aqueous solutions. They are widely used for diverse applications such as thickeners, stabilisers in different industries; development of edible coatings or films in food products; gelling agents, emulgents and nutritional supplements. Their nontoxic nature allows applications in the biomedical, textile, cosmetics, food, and pharmaceutical industries. GMs form very thick solutions at comparatively low proportion which get affected by heat processing, ionic strength and pH. The viscosity of GMs solution (hence rheology) depends mainly on molar mass while the synergistic interactions are determined by the mannose/galactose ratio (M/G) and fine structure of a galactomannan chain. The functionality of GMs depends on M/G ratio of GMs and its distribution. GMs with a diverse M/G ratio have differences in thermal and mechanical characteristics and can be employed in film formulations used as edible packaging materials. Rheological behaviour of aqueous GMs solutions are valuable to study the polysaccharide structure and its potential functions

in the pharmaceutical field for controlled drug release formulations. M/G ratio of GM is inversely related to solubility whereas galactose side chains prevent mannan backbone from formation of hydrogen bonded aggregates. GMs solution generally exhibits a non-Newtonian behavior, whereas the shear rate is inversely related to viscosity. The substitution in galactomannans significantly influences their solution properties. GMs free from steric hindrance by galactose can form gels with certain metal salts. GMs are applied as absorbent in various industries as well as in paper industry because of its nature to develop hydrogen bond easily (5).

Thus, polysaccharides have garnered a lot of interest because of their interesting characteristics like low toxicity, biodegradability, biocompatibility, and relatively cost effective production from plentiful natural sources. However, there are certain problems associated with the use of polysaccharides. These include pH dependent solubility, hydration rate, thickening, possibility of microbial contamination, and drop in viscosity on storage. Structural modification of polysaccharides not only lessens these disadvantages but also facilitates their application for various drug delivery purposes. These modification can enhance their applicability as an excipient in pharmaceutical field (6). Polysaccharides exhibit various bioactivities like antioxidant, anti-tumor, anticoagulant, anti-virus, anti-radiation, anti-cancer and immunoregulatory activities and due to their potential nutritional and pharmaceutical benefits, they can be applied as healthy food supplement also. Although various natural and synthetic polymers are present, the application of natural excipients in pharmaceutical industry is much more preferred as it is economic, readily available, non-toxic, ability for chemical modifications, biodegradability and biocompatibility (7). Various polysaccharide modification methods are available such as methylation, carboxymethylation, phosphorylation, acetylation, sulfation, hydroxy-propylation, selenylation, and etherification etc. (8). Apart from these, molecular structure and various physicochemical characteristics of either natural or modified polysaccharides can be explored to widen their applicability as bioactive molecules in the pharmaceutical and food industries with desired functional features.

Conclusion

Applicability of natural, synthetic and semisynthetic polysaccharides are widely accepted in formulation development of pharmaceutical products, cosmetics, food products, nutraceuticals etc. as it is easy to access, economic, biocompatible, biodegradable, and free from toxicity. Natural and modified polysaccharides have been applied in the development of conventional dosage forms, modified release systems, novel drug delivery systems etc. Modified polysaccharides can be explored further for their applicability as excipients with innovative biological activities.

References

1. Avachat A, Dash R, Shrotriya S. Recent investigations of plant based natural gums, mucilages and resins in novel drug delivery systems. Indian Journal of Pharmaceutical Education and Research. 2011;45: 86-99
2. Prajapati V, Jani G, Moradiya N, Randeria N, Nagar B, Naikwadi N, Variya B. Review on Galactomannan: A versatile biodegradable seed polysaccharide. International Journal of Biological Macromolecules. 2013; 60: 83– 92.
3. Cerqueira M, Souza B, Simões J. Structural and thermal characterization of galactomannans from non-conventional sources. Carbohydrate Polymers. 2011; 83: 179–185.
4. Pollard M, Eder B, Fischer P, Windhab E. Characterization of galactomannans isolated from legume endosperms of Caesalpinioideae and Faboideae subfamilies by multidetection aqueous SEC. Carbohydrate Polymers. 2010;79: 70–84.
5. Morris E, Cutler A, Ross-Murphy S, Rees D. Concentration and shear rate dependence of viscosity in random coil polysaccharide solutions. Carbohydrate Polymers. 1981;1: 5–21.
6. Yong Xu, Yu-jiWu, Pei-long Sun, Fu-ming Zhang, Robert J. Linhardt, An-qiang Zhang. Chemically modified polysaccharides: Synthesis, characterization, structure activity relationships of action. International Journal of Biological Macromolecules.2019; 132: 970–977
7. Wang ZJ, Xie JH, Shen MY, Tang W, Wang H, Nie SP, Xie MY. Carboxymethylation of polysaccharide from Cyclocaryapaliurus and their characterization and antioxidant properties evaluation.Carbohydrate Polymers. 2016; 136: 988-994
8. Garner J and Park K. Chemically Modified Natural Polysaccharides to Form Gels. Springer International Publishing Switzerland 2015 K.G. Ramawat, J.-M.Me ´rillon (eds.), Polysaccharides.2015;1555-1582.

Contribute articles to APTI Women's Forum Newsletter

Dear Readers,

We would love to have your contribution to the thematic issues of this Newsletter.

The themes for the forthcoming issues :

Please contribute within **1st June, 2021**

1. July - Sep 2021 Issue

   New Education Policy 2020: Reforms, Opportunities and Challenges

2. Oct - Dec 2021 Issue

   Drug Repurposing: A Way Forward

Functionalized Alginates: Novel Excipients from Marine Source

Maushmi S. Kumar

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, V.L. Mehta Road, Vile Parle (west), Mumbai-400056

maushmiskumar@gmail.com

Introduction

Pharmaceutical excipients are miscellaneous group of materials, which are essential for the formulation development of drug products, facilitate an effective delivery of drug substances and can accommodate upto 80–90% of the drug product formulation (1). In the era of innovation and newness, the pharmaceutical industries await novel excipients approvals. According to the ICH Guideline M4Q definition, an excipient is considered novel if a new chemical entity or chemically modified or established excipient is being used in the drug product for the first time or via a new route of administration. A thorough physicochemical characterization, functionality and safety of the excipient is to be ensured (2). These strict requirements bring it very close to the strenuous and rigorous regulations process for the approvals in the development of Biosimilars. Soluplus®, Kollicoat®, Smartseal 30 D, Recombumin® are few novel excipients; even though albumin in Recombumin is a popular protein marker. A huge R&D investment with a high risk of failure and a long time span is one of the major drawbacks, which has limited manufacturers to invest in a novel excipient development. The International Pharmaceutical Excipients Council (IPEC) under ICH-Guidelines offers guidance on GMPs, stability studies, and certificates of analysis (3, 4). However, the absence of an independent approval process for excipients makes the whole process complex for both manufacturers and users of excipients, as the quality and safety is assessed in the context of a new drug application. Manufacturers prefer to maintain confidentiality with sensitive information for direct approval and want shorter launch period in order to compensate for the huge investment in the field (5). Currently, various polymers are being assessed as novel excipients in the formulation development of appropriate dosage forms. They are studied for their physicochemical properties for regulatory purposes and are finding applications as bioreagents, surface actives, and keratolytic agents.

Alginate - A Novel Excipient Marine Polymer

Ocean conserves a renewable source of bio compounds and have an everlasting positive impact on the development of drugs, drug delivery systems, and biomedical devices. Marine polysaccharides such as alginate, carrageenan, fucoidan, chitosan, and hyaluronan have been used since quite some time now as excipients in formulation development. They are extracted majorly from seaweeds and marine invertebrates, and have been largely studied for use in drug carrier device, particles, capsules and hydrogels. Among all the marine polysaccharides, alginates are most popular due their solubility at neutral and alkaline conditions, biocompatibility, low toxicity, high bioavailability and for the capability to be processed in the form of hydrogel matrices, beads and particles (6). One of the most common use of alginates is their use as an excipient in drug delivery as a stabilizing agent. Alginates have huge

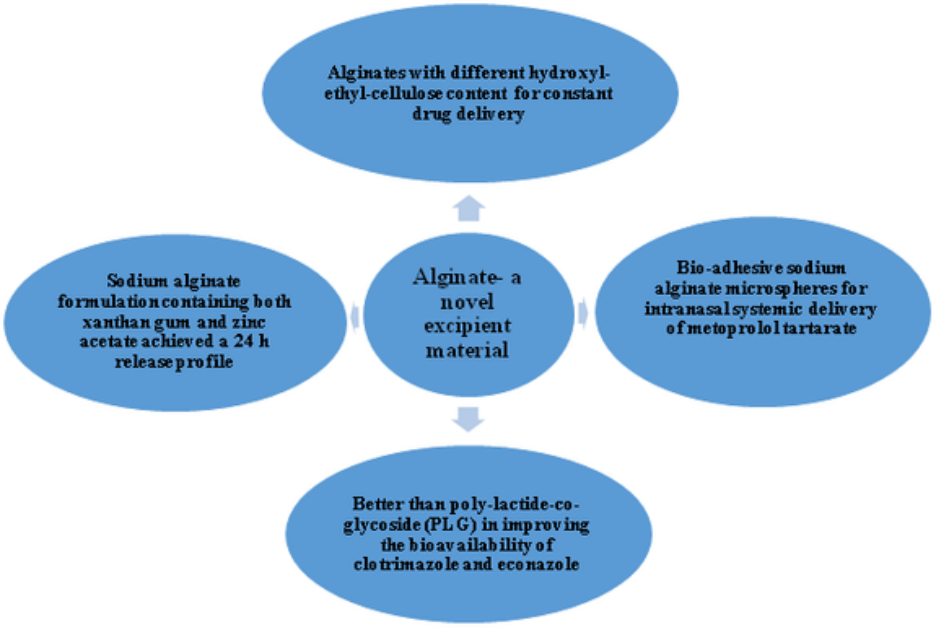


Figure 1. Few developments in alginate as a candidate of novel excipient (7-8)

potential to be identified as a novel excipient, where in few researchers have already reported its development. Chemically, the alginates are composed of linear units of monomers consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks. They are extracted from the brown Phaeophyceae group of seaweeds. Alginic acid is converted into sodium alginate, which is the most common water soluble form of alginic acid.

Alginates have excellent physicochemical and biological properties, due to which various grades of the polymer are substantially explored in various types of formulation as excipients. They are being successfully used not only in tablets, capsules and gels; but also in the synthesis of films, patches, beads, micro and nanoparticles. There are various tailor-made alginates being modified and used as improved excipient for better and smarter drug delivery systems for selected drug candidates (10). Another approach is developing alginates as an excipient which can help to adjust the drug release according to physiological changes especially to the pH changes or by magnet triggered delivery systems. Alginate oligosaccharides have been developed for improved antibacterial, antifungal therapy, probiotic and prebiotic activity, hypertension, immunomodulatory activity etc. Alginate has been tried for various routes of administration including oral, parenteral, pulmonary and transdermal and qualifies the criteria of a novel excipient (11).

Recently, methyl ester derivatives of alginic acid are evaluated for their use as potential multifunctional excipients for pharmaceutical direct compression. The results reported that the degree of methylation (DM) increased the physico-chemical and mechanical properties of the produced materials. With an increase in the DM, the produced tablets possessed increasedtensile strength with better compressibility. They also extended disintegration times of the tablet due to the hydrophobicity. The modified alginates were also tested for their binding properties to check its diverse function (12). In another work, alginate hexyl amide derivative was used in oral film's formulation. In another work, alginate hexyl amide derivative was used in oral film's formulation. The synthesized alginate derivative had good

mechanical and drug release profile which makes it an innovative film-forming material for buccal drug delivery application. It also complied with the Biopharmaceutics Classification System (BCS) class II drugs to increase solubility and improve bioavailability (13). A modified alginate copolymer, alginate nanoparticle and their cosmetic and medical application is patented in WO2018136012A1 (14). The modified copolymer comprised of an alginate backbone with a grafted moiety attached to one of the hydroxyl groups of the alginate backbone. The grafted moiety was made of a polymer and a stabilizing group. Another work by Cheaburu-Yilmaz et al. (2019) compared the interpolymeric complexes of alginate poly (N-isopropyl acryl amide (PNIPAAm) and related graft copolymers for their in vitro and in vivo release of theophylline, toxicity and biocompatibility (15). Goncalves et al. (2016) has already demonstrated that the alginate micro particles break under ultrasound waves vibration after 15 mins, giving promising application of alginate in acoustic environment (16). Alginic acid (AA) and microcrystalline cellulose (MCC101) was used to obtain a co-processed excipient. Optimized co-processed excipient yielded good tabletability, increased powder flowability, and faster disintegration time compared to the individual ingredients and to a commercial co-processed excipient named Prosolv® ODT (17). Various alginate graft copolymeric matrices and their effect on oral drug release pattern have been evaluated. Comparisons have been done for alginate graft copolymers against co-excipients in non-grafted formulations for drug release modulation. More extensive research is needed for commercialized application of these graft copolymers in oral drug delivery systems (18).

Conclusion

Novel excipients are being developed for new drug delivery systems and improving the overall quality of the drug product. Recently, modified or co-processed excipients have been introduced in the market. There are many important aspects of novel polymeric excipient such as performance, product safety, GMP, analytical methods, stability, cost, environmental issues, safety and reliability of manufacturer etc. Alginates can be engineered into various geometric shapes and as nanoparticles, micro spheres, and hydrogels. For drug delivery, they are used as drug carriers in modified, cross-linked and grafted forms. So far, alginates preparation has given positive results in controlled release of selected drugs. The development of a novel excipient is similar to a new drug development which is the real task. Manufacturers require an independent registration process for novel excipients from drug product registration. Such an approach can mitigate the introduction of more novel excipients in market.

References

1. Challenger CA. Novel Excipients Needed More Than Ever Before. Pharm. Tech [Internet]. 2021 Mar [cited 2021 Mar 9];45(3):24–29. Available from: https://www.pharmtech.com/view/novel-excipients-needed-more-than-ever-before
2. ICH M 4: ICH Harmonised Tripartite Guideline. 2002 Sept [cited 2021 March 9]; Available from: https://database.ich.org/sites/default/files/M4Q_R1_Guideline.pdf
3. ICH Q1A (R2), Stability testing of new drug substances and products. [cited 2021 Mar 11] Available from: http://www.ich.org.
4. The IPEC Excipient Stability Program Guide. 2010. [cited 2021 Mar 9] Available from: http://www. ipec-europe.org.
5. Guth F, Schiffter HA, Kolter K Novel excipients – from concept to launch. Chimica Oggi - Chem Today. 2013 Sept/Oct;31(5):78-81.
6. Ogaji IJ, Nep EI, Audu-Peter JD Advances in Natural Polymers as Pharmaceutical Excipients. Pharm Anal Acta. 2012;3(1):146.
7. Rajinikanth PS, Sankar C, Mishra B. Sodium alginate microspheres of metoprolol tartrate for intranasal systemic delivery: Development and evaluation. Drug Delv. 2013 10:21-28.
8. Fuchs-Koelwel B, Koelwel C, Gopferich A, Gabler B, Wiegrebe E, et al. Tolerance of a new calcium-alginate-insert for controlled medication therapy of the eye. Ophthalmologe. 2004;101:496-499.
9. Zeng WM. Oral controlled release formulation for highly water-soluble drugs: Drug--sodium alginate--xanthan gum-zinc acetate matrix. Drug Development and Industrial Pharmacy 2004;30:491–495.
10. Nayak AK, Ansari MT, Sami F, Kaur H, Singh B, Hasnain MS (2020) Alginates as drug delivery excipients. Academic Press, p. 19-39. ISBN 9780128176405.)
11. Hariyadi DM, Islam N. Current Status of Alginate in Drug Delivery. Advances in pharmacological and pharmaceutical sciences. 2020; Article ID 8886095,16 pages. Available from: https://doi.org/10.1155/2020/8886095
12. Sanchez-Ballester NM, Bataille B, Benabbas R, Alonso B, Soulairol I. Development of alginate esters as novel multifunctional excipients for direct compression. Carbohydrate Pol. 2020;240:116280.
13. Khames A. Hexyl alginate derivative, an amphiphilic innovative buccal film-forming material of promising mechanical and release characteristics for the improvement of repaglinide bioavailability. Drug Des Devel Ther. 2019;13:925-940
14. Kumar J. A modified alginate copolymer, alginate nanoparticle and applications thereof. 2018; WO2018136012A1.
15. Cheaburu-Yilmaz CN, Lupusoru CE, Vasile C. New Alginate/PNIPAAm Matrices for Drug Delivery. Polymers (Basel).2019;11(2):366.
16. Gonçalves VS, Gurikov P, Poejo J, Matias AA, Heinrich S, Duarte CM, Smirnova I. Alginate-based hybrid aerogel micro particles for mucosal drug delivery. Eur J Pharm Biopharm. 2016;107:160-70.
17. Benabbas R, Sanchez-Ballester NM, Bataille B, Sharkawi T, Soulairol I. Development and pharmaceutical performance of a novel co-processed excipient of alginic acid and microcrystalline cellulose. Powder Tech. 2021;378, Part A, 576-584.
18. Wong TW. Alginate graft copolymers and alginate–co-excipient physical mixture in oral drug delivery. 2011;63(12):1497-1512.

Modified Chitosan and their applications


Krishna Patel & Hetal Thakkar*

Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

hetal.thakkar-pharmacy@msubaroda.ac.in

Introduction

Chitin is amongst the most popular polysaccharides of natural origin. It is found in several organisms like cell wall of yeast and fungi, cuticles of several insects, and crustacean shells. Chitosan is also produced by some green microalgae. It is obtained by the process of deacetylation of chitin and is a copolymer of 2-amino-2-deoxy-β-d-gluco-pyranose(glucosamine) and 2-acetamide-2-deoxy-β-d-gluco-pyranose(N-acetyl-glucosamine). The molecular weight is in the range of 1 × 105 and 5 × 105 Da, with nitrogen content of 6.80% or above. Its solubility is affected by the molecular weight, extent of acetylation, as well as distribution of the acetyl and amino groups along the chain (1).

- Chitosan is poorly soluble in water, but it is soluble at low pH.
- Because of poor aqueous solubility, it has many limitations in terms of application in various areas.
- Derivatization of chitosan can be accomplished by performing some chemical reactions, such as substitution of some functional groups, which results in a superior chemical substitute compared to the unmodified chitosan.
- These modified chitosan derivatives having superior physicochemical and biological characteristics are more suitable for use as carriers in the various pharmaceutical formulations. (2)

Chemistry of chitosan

The presence of responsive amino (-NH2) and hydroxyl (-OH) groups facilitate the modification of chitosan. These modifications lead to improved biological and chemical characteristics as well as modified solubility as a function of the intended applications. There are many forms of modified chitosan such as quarternized chitosan, highly cationic, N-acyl derivatives, oxy chitosan, thiolated, cross-linked, sugar-modified, sulfated, chito-oligosaccharides, azidated, phosphorylated, EDTA-chitosan, thiourea derivatives, low molecular weight chitosan etc. (3)

Quaternized chitosan derivatives

Quaternization is a procedure to improve aqueous solubility of chitosan. Modifying the positive (NH3+) charge of chitosan leads to its improved solubility at a wider pH range. In an acidic environment, chitosan is positively charged, on the other hand, quaternized chitosan is permanently positively charged even at the basic pH. Quaternization of amino functional groups in chitosan can be accomplished by means of methyl iodide solubilized in N-methyl pyrrolidinone having basic pH.

N,N,N-trimethyl chitosan chloride is a popular quaternized chitosan, which is synthesized by reacting CH3I with chitosan in the environment with higher pH and using N-methyl-2-pyrrolidinone as a solvent, followed by using ion exchange resin to substitute iodides with chloride. A variety of quaternized chitosan can be obtained by changing the number of carbon in alkyl chain of alkyl halides. Enhancing the number of carbons in alkylated chitosan leads to enhancement in transfection efficiency up to 8 carbons (3).

Highly cationic chitosan derivatives

The cationic chitosan derivatives are synthesized by reacting chitosan with dialkylaminoalkyl chloride in basic medium. The cationic character plays an important role in applications such as enhanced mucoadhesiveness, improved transfection efficiency and absorption. Moreover, it elicits some biological activities such as anticancer, hypocholesterolemic, and anti-inflammatory action. In addition to this, it is used in skin care as well as hair care products (4).

N-acyl chitosan derivative

Chitosan can be made hydrophobic by amidation amongst the carboxyl groups of fatty acids and amino groups of chitosan. Acyl halide or acid anhydride are used as reactors (3). The addition of hydrophobic moiety usually leads to formation of an improved carrier with new physicochemical properties. Earlier hydrophobic molecules were synthesized by acylation, followed by complexation with DNA. This complex showed improved transfection efficiency because of cell membrane destabilization or rise in interaction between carrier and cell membrane (4).

Oxy-chitosan derivatives

This derivatization leads to production of water soluble moiety of chitosan. Production of carboxylated chitin/chitosan or soluble chitouronic acid sodium is possible with the help of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as a catalyst to oxidize hydroxyl groups to aldehyde in presence of NaOCl and NaBr. This moiety has higher biocompatibility which widen the extent of the applications in various areas. New bioactive C6 oxy-chitosan derivative showed good activity against Leishmania. An environment friendly process has recently been developed for the C6 oxidation of chitosan with the help of TEMPO/laccase redox resulting in a water-soluble chitosan derivative (3).

Thiolated chitosan

Production of thiolated chitosan includes substitution of the primary amino group of chitosan with the thiol group of the coupling agent. This polymer exhibits some great properties such as mucoadhesiveness, biodegradability, cohesiveness, enhanced permeation etc. (4) Formation of the disulfide bond with mucus glycoprotein which is having cysteine leads to higher mucoadhesiveness as these bonds are relatively stronger than the non-covalent bonds (5).

Cross-linked chitosan derivatives

Cross-linking process produces three dimensional network of the polymer, considered as a hydrogel (1). To do so, one needs cross-linking agents, such as glyoxal, formalin, or glutaraldehyde. Glutaraldehyde is the most popular cross-linking agent. However, it is toxic and natural alternatives such as citric acid, inorganic phosphate, and genipin are preferred (3). Hydrogels of chitosan tend to control the release of a drug from carrier. It is also used for the

production of the biodegradable sutures, hemodialyzing membranes, healing agents for skin burn and to immobilize enzymes and cells (1).

Sugar-modified chitosan

Sugar incorporated chitosan is synthesized by reductive N-alkylation. Sugar has an ability to recognize specific cells, viruses and bacteria and so sugar modified chitosan derivatives are used to incorporate cell-specific sugar moiety into chitosan.

Sulfated chitosan

Sulfated chitosan derivatives are synthesized by sulfation reaction. This reaction involves interaction between sulfating agents and reaction media. Various reagents which are used as sulfating agents are concentrated sulfuric acid, chlorosulfonic acid–sulfuric acid, oleum, sulfur dioxide, sulfur trioxide etc., but the most commonly used reagent is chlorosulfonic acid. Chitosan-sulfates possess structural similarity with heparin, due to which they have shown inhibitory effect to heamagglutination. Other than that, they have shown enzyme inhibitory, antisclerotic, antioxidant, and antibiotic activities (4).

Chito-oligosaccharide and low molecular weight chitosan

Due to greater viscosity of high molecular weight chitosan, it has less commercial use. By cutting off the molecular weight of chitosan, one can eliminate issues regarding viscosity and can improve biological characteristics. This can be done via production of chito-oligosaccharides and low molecular weight chitosan. The production of chito-oligosaccharide and low molecular weight chitosan include depolymerization process, which is mainly achieved by physical cleavage, chemical cleavage, and enzymatic cleavage of unmodified molecule (table 1). These processes also improve the solubilization of chitosan in water or acetic acid solutions. Mostly, cleavage of chitosan is performed by acid chitosanolysis (physical, chemical and enzymatic lysis). However, the main issue of enzymatic process is high cost and issue with chemical process is the use of non-green chemicals and their removal. To overcome this, there are recent superior methods such as high pressure homogenization and electrochemical processes to produce chito-oligosaccharide and low molecular weight chitosan (3).

Table 1: Depolymerization methods of chitosan (3)

Category	Depolymerization Method
Physical	High pressure homogenization
	Sonication
	Gamma radiation
	Autoclave
Chemical	Acid hydrolysis
	Free radical methods
Enzymatic	Specific enzymes such as chitinase, chitosanase
	Non-specific enzymes such as pepsin, protease, cellulase

Miscellaneous derivatives

In addition to the above discussed derivatives, other studied derivatives include azidated chitosan, phosphorylated chitosan, EDTA-chitosan, thiourea derivatives etc. All the reported derivatives and their applications have been summarized in table 2.

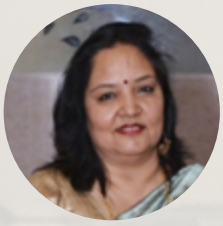
Table 2: Applications of modified chitosans

Derivative	Uses	References
Quaternized chitosan	Targeted peptide drug delivery, DNA delivery, microcarrier for drug.	(4)
Highly cationic chitosan derivatives	Improved mucoadhesion, higher absorption efficiency, enhanced transfection efficiency and some biological activities such as anticancer, anti-inflammatory, hypocholesteromic effect, and antimicrobial activity.	(4)
N-acyl chitosan	Textiles, membranes, and medical aids	(4)
Oxy-chitosan	Anti-parasitic activity	(4)
Thiolated chitosan	For the administration of hydrophilic molecules without any invasive technique, carrier for vaginal, ocular, buccal delivery, oral delivery of protein and peptides.	(4, 5)
Cross-linked chitosan	Epidermal and intracorporeal implants, biodegradable sutures, hemodialysis membranes, artificial substituents for skin burns, wound dressings, and for enzymes and cells immobilization.	(1, 4)
Sugar-modified chitosan	Liver specific drug delivery	(4, 6)
Sulfated chitosan	Anticoagulant, enzyme inhibition, inhibitory heamagglutination effect, antisclerotic, antimicrobial, antioxidant, and tear substitute.	(4, 7)
Chito-oligosaccharide and Low molecular weight chitosan	Plant defense elicitors, growth stimulators, food additives, antimicrobial agent, hypocholesteromic,blood pressure normalizers, anti-infective, anti-arthritis, improved calcium uptake and antineoplastic properties.	(8)
Azidated chitosan	Biological adhesive in surgical applications	(4)
Phosphorylated chitosan	Controlled drug delivery, additives in calcium phosphate cement.	(9)
EDTA-chitosan	Drug carrier to prevent enzymatic drug degradation, controlled drug delivery.	(4)
Thiourea derivatives	Antimicrobial agent.	(10)

References

1. Ruiz GAM, Corrales HFZ. Chitosan, chitosan derivatives and their biomedical applications. Biological activities and application of marine polysaccharides. 2017;87.
2. Zhao D, Yu S, Sun B, Gao S, Guo S, Zhao K. Biomedical applications of chitosan and its derivative nanoparticles. Polymers. 2018;10(4):462.
3. Brasselet C, Pierre G, Dubessay P, Dols-Lafargue M, Coulon J, Maupeu J, et al. Modification of chitosan for the generation of functional derivatives. Applied Sciences. 2019;9(7):1321.
4. Mourya V, Inamdar NN. Chitosan-modifications and applications: opportunities galore. Reactive and Functional polymers. 2008;68(6):1013-51.
5. Esquivel R, Juárez J, Almada M, Ibarra J, Valdez MA. Synthesis and characterization of new thiolated chitosan nanoparticles obtained by ionic gelation method. International Journal of Polymer Science. 2015;2015.
6. Park JH, Cho YW, Chung H, Kwon IC, Jeong SY. Synthesis and characterization of sugar-bearing chitosan derivatives: aqueous solubility and biodegradability. Biomacromolecules. 2003;4(4):1087-91.
7. Pires NR, Cunha PL, Maciel JS, Angelim AL, Melo VM, de Paula RC, et al. Sulfated chitosan as tear substitute with no antimicrobial activity. Carbohydrate polymers. 2013;91(1):92-9.
8. Lodhi G, Kim Y-S, Hwang J-W, Kim S-K, Jeon Y-J, Je J-Y, et al. Chitooligosaccharide and its derivatives: preparation and biological applications. BioMed research international. 2014;2014.
9. Wang X, Ma J, Wang Y, He B. Structural characterization of phosphorylated chitosan and their applications as effective additives of calcium phosphate cements. Biomaterials. 2001;22(16):2247-55.
10. Zhong Z, Xing R, Liu S, Wang L, Cai S, Li P. Synthesis of acyl thiourea derivatives of chitosan and their antimicrobial activities in vitro. Carbohydrate Research. 2008;343(3):566-70.

Affinisol™ HPMC HME: Solubilizing the insoluble

Reshu Virmani[1] &
Kamla Pathak*[2]

1School of Pharmaceutical Sciences, MVN University, Palwal, Haryana, India
2 Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, 206130, Uttar Pradesh, India

kamlapathak5@gmail.com

Introduction

High throughput data screening in the innovation and development of new molecules is gaining momentum due to poor solubility of drug substances (1). Increase in aqueous solubility of poor soluble drug is the major challenge in designing of new dosage form. Scientists are putting in tremendous efforts on advancing the drug delivery systems wherein the excipients play a significant role.

This write up emphasizes on providing key information about the newly developed polymer Affinisol. AFFINISOL™, hydroxypropyl methylcellulose (HPMC) is a hydrophilic polymer that enhances the solubility of poorly soluble drugs by prolonging the stability of solid dispersions and prevention of crystallization of active pharmaceutical ingredient. About 90% of the drugs in drug discovery pipeline have poor solubility which leads to low bioavailability. There are various approaches by which we can improve the solubility of drugs such as surfactant, co-solvent, pH modification, salt formation, hydrotrophy, and solid dispersion (2). Among various techniques for solubility enhancement, solid dispersion is the key technique to increase the bioavailability of drugs. Various approaches for the preparation of solid dispersion are spray drying, hot spin mixing, supercritical fluid processing, co evaporation, hot spin mixing, and roll mixing (3-7).

AFFINISOL™ HPMC has found applications in pharmaceutical industries for the preparation of solid dispersions using spray drying and hot melt extrusion (HME). HME is an advanced solubility enhancement technique bearing advantages of solvent free and continuous processing. It is more suitable to prepare amorphous solid dispersions resulting solubility enhancement followed by enhancement in bioavailability of drugs. HME was first used for pharmaceutical formulations in 1971 by El Egakey. The technique is more reliable in improving solubility of poorly soluble drugs (8-11). Various solid dosage forms mainly granules, tablets, pellets, implants, suppositories, and stents (9-12) can be manufactured using this technique.

In this method, melted polymeric components with active substances and other additives or plasticisers are forced through an orifice or die under controlled operational conditions (temperature, pressure, feeding rate, and screw speed) (13-15). This technique involves the compaction and conversion of a powder or a granular mix blend into a uniformly shaped product. The crucial parameters for HME are extrudate, solubility of drug, stability of excipient and properties of excipient like glass transition temperature.

Hypermellose is an extensively used pharmaceutical excipient which is amorphous in nature and has broad glass transition temperature of 160°C to 210°C while comparatively low degradation temperature of 200°C to 250°C (16-18). The broad glass transition temperature and low degradation temperature makes it very difficult to process hypermellose by HME technique. Recent studies reported that processing of hypermellose by HME can be improved using the high concentration of plasticizer and other additives. Hypermellose improves the bioavailability of poorly soluble drugs (19) by acting as an effective recrystallization inhibitor. Hence, it is very advantageous to include hypermellose in HME formulation without addition of plasticizers. Although some recent studies have reported that existing grades of hypermellose can be processed by HME at very high temperatures, these high temperatures cause thermal degradation of most of the drugs (20-21).

The Dow Chemical Company has recently introduced AFFINISOL™ HPMC HME, modified hypermellose. It was manufactured using conventional manufacturing methods for HPMC having comparatively lower transition temperature of 117°C–128°C making it more prone to HME. AFFINISOL™ HPMC HME is white to off-white crystalline hydrophilic amorphous polymer available in three grades: HPMC HME 15 LV, HPMC HME 100 LV, and HPMC HME 4M. The grades are different on possession of molecular weight. The selection of the grade to be used depends on required degree in enhancement of solubility and required drug release profile. AFFINISOL™ HPMC HME provides flexibility for selection of grade of polymer in HME process leading to optimization of drug release characteristics. It enables thermal processing during HME technique leading to preparation of stable solid dispersions of poorly soluble drugs.

Thermal properties

Affinisol (HPMC HME) has a glass transition temperature of 115°C (22). Lower transition temperature is useful for the processing of polymer. Thermal degradation temperature of Affinisol is approximately 250°C. This polymer does not change color at higher temperature. Color resistant property of the polymer makes it different from other grades of HPMC. This unique feature of thermal stability of Affinisol with low melt viscosity is helpful to process the HME without use of plasticizers. This property of the polymer minimizes toxicity problems, decreases formulation requirements, and helps in improving the physical stability of the preparation. This property is applicable for all three grades of Affinisol which helps in adjustment of dissolution of the drugs by selecting the optimum viscosity grades. Formulated systems of Affinisol can be extruded at a temperature of 200°C. Above and below these temperatures, minor modification in the process may be done to get the accuracy in the results.

Moisture sorption

Moisture is considered as one of the major causes of degradation of drug substances. Uptake of moisture may disturb the physical stability of formulation. Therefore, in pharmaceutical industry care must be taken to ensure the appropriate storage conditions. Affinisol HPMC HME has the capability to reduce the uptake of moisture compared to other grades of HPMC as well as other non-cellulosic material commonly used in HME. The presence of moisture may plasticize the formulation which results in reduction in glass transition temperature and raises physical instability risk of product. But as compared to other various HME polymers, Affinisol shows mild change in estimated glass transition temperature with increase in moisture content (23).

Solubility

Affinisol is a magical polymer, soluble in many organic solvents and mixtures of solvents which is beneficial for formulation in aqueous free systems for preformulation studies. Solubility of Affinisol depends on various grades of polymers and types of solvents used for the preparation.

Down Stream Processing

Milling is a widely applied process among various downstream processing techniques for AFFINISOL™ HPMC HME. On the basis of formulation, the conditions for milling will alter, for example, Fitz mill or Alpine impact mill is used to obtain fine powder from extrudate of AFFINISOL™ HPMC HME. Mill with smaller diameter screen 0.5-1 mm is used because mill having larger diameter screen causes obstacle in production of fibrous product.

Khatri P et al. evaluated applications of Affinisol® HPMC polymer for direct compression process and found that these polymers have better compressibility at lower compression pressure and can be easily processed using the HME technique. They studied different physical properties of Affinisol® HPMC like bulk density, tapped density, angle of repose, friability, loss on drying, influence of compression force etc. and found that Affinisol® HPMC has low friability as compared to HPMC 15. The polymer also has good flow properties and low moisture content. It was concluded that Affinisol® HPMC is a good binder and a controlled release matrix polymer required for direct compression (24).

Thermal and viscoelastic properties of Affinisol™ HPMC HME polymers were studied by Gupta et al. They found that cellulosic polymers have high melt viscosity and thermal degradation behavior, and thus are not suitable for preparation of solid dispersion of drugs by HME. Various characterization tests were performed such as X-ray diffraction, modulated differential scanning calorimetry, moisture sorption, rheology, and torque to check the nature of amorphous nature of Affinisol. According to thermogravimetric analysis, the degradation temperature for all polymers was more than 220 0C. The Affinisol™ polymers showed less hygroscopicity (moisture absorbing capacity) than Methocel™ K100LV and Kollidon® VA 64. At different temperatures, the viscosity of different grades of Affinisol™ was reported similar but it is highly sensitive to the applied shear rate. With increased angular frequency, the viscosity decreased significantly (unlike Kollidon® VA 64). Affinisol™ polymers showed great capability of being extruded at processing temperatures as compared to that of Kollidon® VA 64 as very high shear rate is required during melt extrusion procedure (25).

Conclusion

This article focused on providing the updated information about the Affinisol, its thermal properties, moisture sorption, solubility, and related research work. Improvement in the aqueous solubility of drug is a major challenge for the pharmaceutical industry. Literature supports the use of Affinisol for the improvement of aqueous solubility of BCS class II drugs, which makes it an excellent polymer candidate for further research in different research and formulation areas.

References

1. Keseru GM, Makara GM. The influence of lead discovery strategies on the properties of drug candidates. Nat Rev Drug Discov. 2009;8(3):203–12. doi:10.1038/nrd2796.
2. Alonzo D, Zhang GZ, Zhou D, Gao Y, Taylor L. Understanding the behavior of amorphous pharmaceutical systems during dissolution. Pharm Res. 2010; 27(4):608–18. doi:10.1007/s11095-009-0021-1.
3. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999; 88(10):1058–66. doi:10.1021/js980403l.
4. O'Donnell KP, Cai Z, Schmerler P, Williams 3rd RO. Atmospheric freeze drying for the reduction of powder electrostatics of amorphous, low density, high surface area pharmaceutical powders. Drug Dev Ind Pharm. 2012; 39(2):205–17. doi:10.3109/03639045.2012.669385.
5. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. AAPS PharmSciTech. 2005;6(3):E405–E9. doi:10.1208/pt060350.
6. Hughey J, Dinunzio J, Bennett R, Brough C, Miller D, Ma H, et al. Dissolution enhancement of a drug exhibiting thermal and acidic decomposition characteristics by fusion processing: a comparative study of hot melt extrusion and Kinetisol® dispersing. AAPS PharmSciTech. 2010; 11(2):760–74. doi:10.1208/s12249-010-9431-y.
7. Shah N, Sandhu H, Phuapradit W, Pinal R, Iyer R, Albano A, et al. Development of novel microprecipitated bulk powder (MBP) technology for manufacturing stable amorphous formulations of poorly soluble drugs. Int J Pharm. 2012; 438(1–2):53–60. doi:10.1016/j.ijpharm.2012.08.031.
8. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm. 2002; 54(2):107–17. doi:10.1016/S0939-6411(02)00061-9.
9. El-Egakey MA, Soliva M, Speiser P. Hot extruded dosage forms. I. Technology and dissolution kinetics of polymeric matrices. Pharm Acta Helv. 1971; 46(1):31–52.
10. Forster A, Hempenstall J, Rades T. Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. J Pharm Pharmacol. 2001; 53(3):303–15. doi:10.1211/0022357011775532.
11. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Kumar Battu S, et al. Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm. 2007;33(9):909–26. doi:10.1080/03639040701498759.
12. Prodduturi S, Urman K, Otaigbe J, Repka M. Stabilization of hot melt extrusion formulations containing solid solutions using polymer blends. AAPS PharmSciTech. 2007;8(2):E152–E61. doi:10.1208/pt0802050.
13. J B. Melt extrusion: From process to drug delivery technology. Eur J Pharm Biopharm. 2002 Sep 1;54(2):107–17.
14. Gryczke A. Melt extrusion with EUDRAGIT solubility enhancement modified release. Degussa. RÖHM GmbH & Co. KG, Darmstadt, Germany, 2006.
15. Chokshi R, Hossein Z. Hot-melt extrusion technique: A review. Int J Pharm Res. 2004: 3(1):3–16.
16. Bennett R, Keen J, Bi Y, Porter S, Dürig T, Mcginity J. Investigation of the interactions of enteric and hydrophilic polymers to enhance dissolution of griseofulvin following hot melt extrusion processing. J Pharm Pharm. 2015; 67(7):918–38. doi:10.1111/jphp.12388.
17. Swarbrick J, Boylan JC. Encyclopedia of Pharmaceutical Technology: 20 (3): CRC; 2000.
18. Jani R, Patel D. Hot melt extrusion: an industrially feasible approach for casting orodispersible film. Asian J Pharm Sci. 2015; 10(4):292–305. doi:10.1016/j.ajps.2015.03.002.
19. Konno H, Handa T, Alonzo D, Taylor L. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine. Eur J Pharm Biopharm. 2008;70(2):493–9. doi:10.1016/j.ejpb.2008.05.023.
20. Six K, Berghmans H, Leuner C, Dressman J, Van Werde K, Mullens J, et al. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion, part II. Pharm Res. 2003; 20(7):1047–54. doi: 0724- 8741/03/0700-1047/0.
21. Verreck G, Six K, Van den Mooter G, Baert L, Peeters J, Brewster ME. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion—part I. Int J Pharm. 2003; 251(1):165–74. doi: 0378-5173/02.
22. O'Donnell, K. P. and W. H. H. Woodward. Dielectric spectroscopy for the determination of the glass transition temperature of pharmaceutical solid dispersions. Drug Dev Ind Pharm. 2014: 1–10.
23. Lakshman, J.P., Cao, Y., Kowalski, J., Serajuddin, A.T.M., Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. Mol Pharm, 2008. 5(6): p. 994-1002
24. Khatri P, Katikaneni P, Desai D, Minko T. Evaluation of Affinisol® HPMC polymers for direct compression process applications. J Drug Deliv Sci Technol. 2018 Oct;47:461–7.
25. Gupta SS, Solanki N, Serajuddin ATM. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion, IV: AffinisolTM HPMC HME Polymers. AAPS PharmSciTech. 2016 Feb 1;17(1):148–57.

Mesoporous Silica: An Emerging Excipient for Drug Delivery Applications



Shrikant Dhage, Mansi Shah, & Vandana Patravale*

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, N. P. Marg, Matunga Mumbai 400019, India

vb.patravale@ictmumbai.edu.in

With the advancement in material science, significant progress has been made in exploring various materials at the nanoscale level for drug delivery and medical diagnostic applications. Among the varied inorganic materials explored, mesoporous silica nanoparticles (MSNs) have been widely used for developing various novel formulation strategies, thanks to their unique morphological, and structural features to act as carriers for drugs as well as imaging agents. MSNs with a pore size ranging from 2 nm to 50 nm and having an ordered arrangement in the pore structure, possess excellent properties such as high surface area with tunable pore geometry, functionalization potential for enhanced absorption and targeting, inert nature with good chemical/thermal stability, increased cellular permeability, biocompatibility & biodegradability etc., due to which they remain as one of the most sought after excipient for the formulation scientist (1). Recently, remarkable progress has been made to explore their potential in the stimuli-responsive targeted drug delivery systems, which have been widely reported (2). Besides, MSNs have been explored for various applications such as bioavailability enhancement, achieving modified drug release, increasing cellular permeability and endosomal escape, targeted drug delivery etc. In this article, we will have an overview of the latest advancements in MSNs based drug delivery systems.

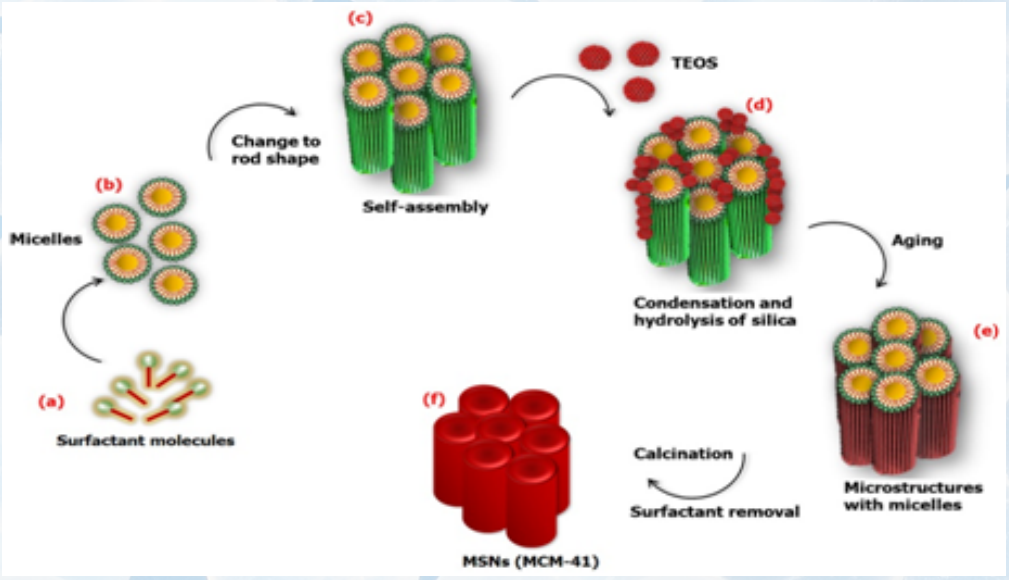


Figure 1: Schematic representation of the synthesis procedure for the formation of MCM-41 (Murugan et al., 2020).

Overview of types and critical properties of MSNs

Credit for the development of the first mesoporous solid goes to Mobil Research & Development, which synthesized mesoporous solids from aluminosilicate gels using a liquid-crystal template mechanism in the year 1992. This material designated as (Mobil Crystalline Materials or Mobil Composition of Matter) MCM-41, is hexagonal with a pore diameter of 2.5 to 6 nm and is widely used as a drug delivery carrier (Fig. 1)(3). Later, several modified versions such as MCM-48 (cubic arrangement), and MCM-50 (lamella-like arrangement) were developed. Further, Santa ionic triblock copolymers to achieve varying geometry such as cubic (SBA-11), 3-d hexagonal (SBA-12), hexagonal (SBA-15) and cubic cage-structured (SBA-16). Till now MSNs with varying geometry have been synthesized to achieve the desired physicochemical properties such as Technical Delft University (TUD-1), Hiroshima Mesoporous Material-33 (HMM-33) etc. (Fig. 2) (3).

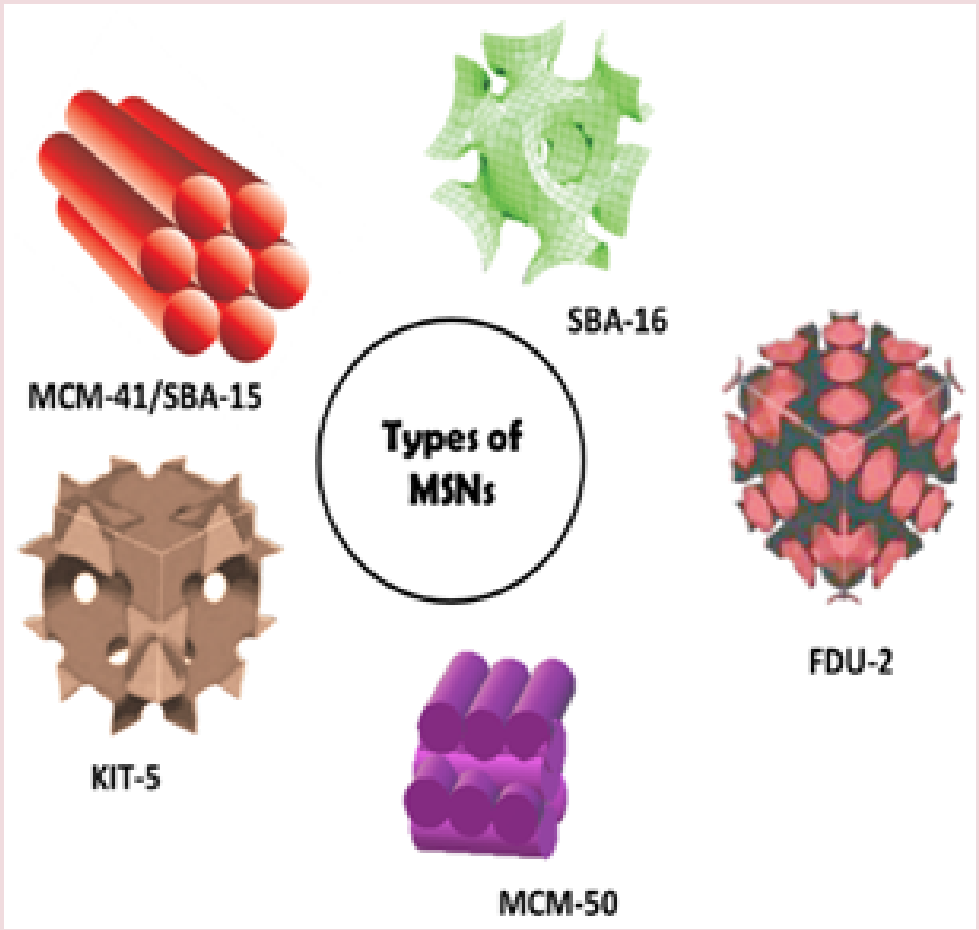


Figure 2: Representation of different types of MSNs

The physicochemical properties of MSNs hold the key to control their efficiency to carry the cargos for desired applications. Various properties such as particle size, shape, pore-volume, total surface area, surface charge, and hydrophilic-hydrophobic property govern their actual application in terms of drug loading, mucoadhesion and mucus penetration, cellular uptake and endosomal escape, targeted delivery etc. Therefore, it is of utmost importance to adjust these properties precisely while synthesizing MSNs to exploit them for clinical applications (1).

MSNs particle size plays important role in their permeation through biological barriers and affects overall behaviour in physiological condition. Various studies reported effects of MSNs particle size on cellular uptake by clathrin and caveolae-mediated endocytosis. Besides it is also shown to affect rapid clearance by mucus or the mononuclear phagocytic system. Numerous studies reported surface charge modified MSNs to achieve greater mucus layer penetration and cellular internalization. Recently, 'charge-reversal MSNs' have been proposed with a unique feature comprising negatively charged surface under normal physiological conditions to facilitate mucosal penetration and increase circulation time but upon exposure to an acidic environment, it gradually becomes positively charged, which helps in increasing the cellular uptake via. electrostatic interaction (4). Similarly, the shape of MSNs also has shown to possess a great influence on mediating biological effects. Huang and coworkers demonstrated that aspect ratios of MSN have a significant impact on cellular uptake as well as cell function in A375 cells (5). Recent reports suggest that there are relentless efforts to understand how physicochemical properties affect MSNs biological behaviour to harness its potential completely (1).

Recent advances in MSNs based drug delivery systems

For the past two decades, researchers are exploring MSNs in various therapeutic applications. Initially, MSNs were explored for solubility enhancement of BCS class II & IV drugs. MSNs due to their large surface area and high pore volume offer very high drug loading and are capable of keeping these drugs in the amorphous or non-crystalline state by confining within the pores, which facilitates drug dissolution. Also, it markedly improves the chemical stability of cargo and exerts protective effects (6,7).

Targeting strategies

To utilize efficient transport potential and site-specificity of MSNs, they have been functionalized with different moieties for redox-responsive, pH-responsive, light-responsive, temperature-responsive, magnet-responsive, enzyme-responsive, glucose-responsive, DNA-based, and multiple-responsive controlled delivery (8). MSNs have been widely explored for stimuli-responsive targeted drug delivery especially for cancer using passive as well as active targeting strategies for enhancing retention and selective uptake by tumour cells. Due to their tunable geometry, MSNs have been modified w.r.t. particle size (50-300 nm), particle shape (different aspect ratios) and surface characteristics (stealth effect with PEGylation) etc. to achieve passive targeting. For achieving active targeting, various targeting ligands have been conjugated with MSNs to enhance specific recognition and uptake by cancer cells such as antibodies, peptides, aptamers, saccharides, small molecules etc. Various receptors or molecules overexpressed in the diseased organ, cell or organelles are considered to select specific ligand. Among the different conjugation strategies, carbodiimide-mediated COOH/NH2 coupling, maleimide/SH coupling have been widely reported (2).

Stimuli-Responsive drug delivery strategies

MSNs based systems are widely explored to achieve spatial &/or temporal release of cargo in response to internal as well as external stimuli. Stimuli-responsive behaviour is imparted by grafting the MSN's external surface with moieties responsive to pH, enzyme, redox species etc. Chen et al. developed multifunctional pH-sensitive MSNs grafted with a mixture of PEG and poly(2-(pentamethyleneimino)ethyl methacrylate) (PPEMA), which acts as an ultra pH-sensitive gatekeeper (9). Murugan et al. prepared a redox stimuli responsive MCM-41 based system by thiol functionalization with organosilane group 3-mercapto propyltrimethoxysilane (SH group). Upon oxidation, these thiol groups spontaneously oxidized to form the disulphide cross-links, which on exposure to thiol reducing agents get lysed resulting in drug release (10). Liu et al. developed MSNs based matrix metalloproteinases (MMPs) responsive drug delivery system intending to achieve tumour targeted delivery of doxorubicin with minimal side effects. In this study, amino-functionalized MSNs grafted with MMPs substrate peptide containing PLGLAR via an amidation reaction. Bovine serum albumin was covalently coupled to the linker as end-cap for sealing the mesopores of MSNs. Further, this was conjugated with lactobionic acid as a targeting moiety (11).

Further, various external stimuli such as light, temperature, magnetic field, ultrasound etc. have been explored to get a site-specific release of payload. Peralta et al. developed thermoresponsive polymer grafted magnetic MSNs to achieve temperature-controlled release of the drug from mesopores. In this system, iron oxide coated MSNs shell was grafted with poly(N-isopropylacrylamide-co-3-(methacryloxypropyl) trimethoxysilane), a thermoresponsive copolymer that acted as a gatekeeper to release the drug below 25 °C and above 40 °C at lower critical solution temperature (LCST) (12). Picchetti et al. developed novel provitamin D3 loaded light-breakable organobridged MSNs coated with the bis-alkoxysilane linker. This system triggered the release of the provitamin D3 upon UV-light exposure (13). Researchers have also attempted various strategies with MSNs employing more than one stimuli-responsive strategies for targeted and/or controlled delivery of loaded drugs.

Biosafety assessment

Although structural modifications of MSNs such as particle size, shape, pore structure, surface chemistry etc. yield great benefits, it has also been observed that it affects their biodistribution and toxicity. Traditionally MSNs have been proved to be degradable, however, their biodegradability is correlated with organosilanes in the silica structure, residual structuring agents, and composition of the dissolution medium (14). Also, the safety and toxicity of MSNs greatly depend on the exposure route as well as the dose administered. Majorly, biosafety concern with MSNs arises from the interaction of their silanol groups with the membrane components which may lead to cell lysis as well as cellular components leaking (15). Capping of silanol with various agents such as poly (ethylene glycol), serum albumin etc. tends to decrease the toxicity of MSNs. Wang et al. had summarized various toxicity issues with MSNs ranging from inflammation, severe renal lesion, including haemorrhage and renal tubular necrosis, haematological toxicity to the different degree of cytotoxicity etc. (1).

Clinical translation, challenges and future outlook

Despite the great progress in MSNs synthesis and structural modifications, the biological effects of these inorganic materials are yet to be understood completely, as these are greatly influenced by many factors such as size, shape, surface properties, ligand chemistry and interactions with biological components etc. For novel MSNs based drug delivery systems improving the penetration capability within targeted tissues, achieving the colloidal stability in complex biological fluids and ensuring that their stimuli-responsive performance is preserved in complex biological media are paramount. Also, large scale manufacturing of nanomaterials based systems always remain a subject of concern. Reports have implied that to harness the large scale manufacturing of MSNs major limitations to tackle include cost-effective calcination of organic templates and poor resistance of these materials to hydrothermal environments (16). In the coming years, it is expected that these systems will meet the standards of clinical evaluation proving to be effective therapeutic carriers for future drug delivery strategies

References

1. Wang Y, Gou K, Guo X, Ke J, Li S, Li H. Advances in regulating physicochemical properties of mesoporous silica nanocarriers to overcome biological barriers. Acta Biomater. 2021 Mar;123:72–92.
2. Baeza A, Colilla M, Vallet-Regí M. Advances in mesoporous silica nanoparticles for targeted stimuli-responsive drug delivery. Expert Opin Drug Deliv. 2015 Feb;12(2):319–37.
3. Narayan R, Nayak UY, Raichur AM, Garg S. Mesoporous Silica Nanoparticles: A Comprehensive Review on Synthesis and Recent Advances. Pharmaceutics [Internet]. 2018 Sep [cited 2021 Mar 17];10(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6160987/
4. Zhou M, Xing Y, Li W, Li X, Zhang X, Du X. Thioether-bridged mesoporous organosilica nanocapsules with weak acid-triggered charge reversal for drug delivery. Microporous Mesoporous Mater. 2020 Aug 1;302:110242.
5. Huang X, Teng X, Chen D, Tang F, He J. The effect of the shape of mesoporous silica nanoparticles on cellular uptake and cell function. Biomaterials. 2010 Jan 1;31(3):438–48.
6. Stephen S, Gorain B, Choudhury H, Chatterjee B. Exploring the role of mesoporous silica nanoparticle in the development of novel drug delivery systems. Drug Deliv Transl Res [Internet]. 2021 Feb 18 [cited 2021 Mar 15]; Available from: http://link.springer.com/10.1007/s13346-021-00935-4
7. Veloso DFMC, Knopp MM, Löbmann K. Chapter 8 - Amorphous drug stabilization using mesoporous materials. In: Shegokar R, editor. Drug Delivery Trends [Internet]. Elsevier; 2020 [cited 2021 Mar 16]. p. 151–66. Available from: https://www.sciencedirect.com/science/article/pii/B9780128178706000080
8. Li Z, Zhang Y, Feng N. Mesoporous silica nanoparticles: synthesis, classification, drug loading, pharmacokinetics, biocompatibility, and application in drug delivery. Expert Opin Drug Deliv. 2019 Mar 4;16(3):219–37.
9. Chen T, Wu W, Xiao H, Chen Y, Chen M, Li J. Intelligent Drug Delivery System Based on Mesoporous Silica Nanoparticles Coated with an Ultra-pH-Sensitive Gatekeeper and Poly(ethylene glycol) [Internet]. American Chemical Society; 2015 [cited 2021 Mar 19]. Available from: https://pubs.acs.org/doi/abs/10.1021/acsmacrolett.5b00765
10. Murugan B, Ramana LN, Gandhi S, Sethuraman S, Krishnan UM. Engineered chemoswitchable mesoporous silica for tumor-specific cytotoxicity. J Mater Chem B. 2013 Jun 26;1(28):3494–505.
11. Liu Y, Ding X, Li J, Luo Z, Hu Y, Liu J, et al. Enzyme responsive drug delivery system based on mesoporous silica nanoparticles for tumor therapy in vivo. Nanotechnology. 2015 Apr 10;26(14):145102.
12. Peralta M, Jadhav S, Magnacca G, Scalarone D, Mártire D, Parolo M, et al. Synthesis and in vitro testing of thermoresponsive polymer-grafted core-shell magnetic mesoporous silica nanoparticles for efficient controlled and targeted drug delivery. J Colloid Interface Sci. 2019 Feb 1;544.
13. Picchetti P, DiMarco BN, Travaglini L, Zhang Y, Ortega-Liebana MC, De Cola L. Breaking with Light: Stimuli-Responsive Mesoporous Organosilica Particles. Chem Mater. 2020 Jan 14;32(1):392–9.
14. Bindini E, Chehadi Z, Faustini M, Albouy P-A, Grosso D, Cattoni A, et al. Following in Situ the Degradation of Mesoporous Silica in Biorelevant Conditions: At Last, a Good Comprehension of the Structure Influence. ACS Appl Mater Interfaces. 2020 Mar 25;12(12):13598–612.
15. Carvalho GC. Highlights in Mesoporous Silica Nanoparticles as a Multifunctional Controlled Drug Delivery Nanoplatform for Infectious Diseases Treatment. Pharm Res. 2020;30.
16. Prouzet E, Kacheff A, Aubert G, Bentaleb A, Backov R, Aymonier C. Toward a sustainable preparation of tunable mesoporous silica. J Supercrit Fluids. 2019 Jan 1;143:139–45.

TPGS: Multifunctional Excipient to Overcome Multi Drug Resistance in Cancer





Nandini Nimbalkar, Poorva Ambre, Swarnadeep Banerjee, Ashroba Shinde & Clara Fernandes*

Department of Pharmaceutics, Bombay College of Pharmacy Autonomous, Kalina, Santacruz, Mumbai 400098, India

clara.fernandes@bcp.edu.in

Introduction

Multidrug resistance (MDR) is reported to be a causative factor for nearly 90% of cancer-related mortality in patients undergoing treatment (1). Typically, MDR in any cancer population arises due to a variety of intrinsic and extrinsic factors which may include reduced cellular drug uptake, extensive drug outflow, enhanced drug digestion, induced DNA restore activation, inactive programmed cell death, and drug-target modulation, to name a few. Numerous mechanisms have been ascribed to MDR activity, prominent being inhibition of P-glycoprotein (P-gp) efflux transporter. ATP-binding cassette (ABC) transporter family includes P-gp which is responsible for the outflow of drugs from tumor cells leading to insufficient in-cell concentration and poor therapeutic efficiency. In contrast, inadequate cellular absorption, an acrid condition, and lysosomal enzymes can all reduce drug intracellular concentrations. As a consequence, an increase in chemotherapeutic agent intracellular concentrations is important (2). Various strategies have been designed to achieve MDR reversal which includes promoting enhanced solubilization of chemotherapeutics i.e., nanocarriers, improved cellular uptake of drug-using nanocarriers, combining drug delivery strategy with external aid i.e., photothermal therapy, stimuli/ smart drug delivery system, etc. (3). Literature also cites examples of various types of excipients i.e., lipids, surfactants, polymers, etc. capable of overcoming MDR. For example, surfactants like Pluronic, Cremophors, Tween, TPGS, etc., help in inhibiting P-gp pumps by decreasing the ATP (4). TPGS (D-α-tocopheryl polyethylene glycol succinate) is one of the safe components approved by the FDA and widely used as a novel multifunctional excipient in various administering medicine.

TPGS as an excipient

TPGS is an amphiphilic synthetic analog of the fat-soluble vitamin tocopherol, which occurs naturally. Tocophersolan or Tocofersolan are other names for it. It is an amphiphile obtained by esterification of tocopherol with polyethylene glycol with succinate diester linkage resulting in a lipophilic alkyl tail (tocopherol succinate moiety) and a hydrophilic polar head (polyethylene glycol chain) (5). It has a molecular weight of 1513 Da, a hydrophile-lipophile

balance value of 13.2, and a critical micelle concentration of 0.02% w/w (6). In drug delivery, it is widely exploited for its emulsifying, solubilizing, absorption-enhancing, and antioxidant properties in a formulation intended for intravitreal (7), ocular (8), dermal (9), intravenous (10), and nasal route of administration (11,12). According to the US FDA Inactive Ingredient Database, the approved dose of TPGS in oral administration is 45-300 mg (13). According to European Food Safety Authority (EFSA), TPGS is not found to be genotoxic. The safety profile of TPGS was evaluated by considering the no observed adverse effect level (NOAEL) which is equal to 1000 mg TPGS/kg body weight/day. The permit intake for infants and teenagers varies from 5 mg/kg body weight to 13 mg/kg body weight. For infants and young children, the margin of safety which is the ratio between NOAEL and the intake was found to be 80 to 200. However, TPGS is not recommended for children having serious kidney impairment (14).

The hydrophilic head group has been shown to majorly contribute to micellar property thereby enhancing solubility of a hydrophobic drug and P-gp inhibitory activity of TPGS-containing formulations. Besides this, it is known to modulate the wettability and induce partial polymorphic modifications of few compounds resulting in increased aqueous solubility (15). Also, the long-chain structure of TPGS enables the drug molecule to remain in the systemic circulation for longer, resulting in a prolonged systemic circulation time. Sheu MT et al. (2003) demonstrated the solubility enhancement of model drug estradiol by micellar solubilization using TPGS (16). The role of TPGS in increasing paclitaxel (PTX) solubility and intestinal permeability was investigated by Varma MV et al. (2005), TPGS concentrations above 0.1 mg/ml were found to linearly increase the aqueous solubility of drugs. The maximum PTX permeability was achieved with 0.1 mg/ml TPGS (17). In vivo, TPGS in presence of esterases undergoes enzymatic hydrolysis leading to the liberation of free alpha-tocopherol which prevents lipid peroxidation and protects the cellular damage by free radical mechanism (18). Using hydroxyethylcellulose (HEC) and TPGS, Singh H et al. (2017) formulated mucoadhesive sublingual films of Frovatriptan succinate monohydrate (FSM). The antioxidant properties were further investigated using the reducing power assay method with a typical antioxidant, ascorbic acid. TPGS-loaded FSM film was compared to FSM film without TPGS, pure drug, and ascorbic acid in terms of reducing power. According to the findings, FSM film formulations containing TPGS had a remarkable ability to exhibit antioxidant activity by transforming reactive free radicals into non-reactive free radicals, effectively breaking the free radical chain reaction (19).

Mechanism of TPGS in overcoming MDR

TPGS has been shown to target cancerous tumor cells with minimal harm to healthy cells. TPGS-based formulations assemble more in the cell and penetrate deeper to prevent metastasis. TPGS aids in overcoming MDR activity and accentuate the anticancer activity of drug aiding in cell death (20). In general, TPGS has been shown to improve drug entrapment efficiency, modulated drug release, and enhanced cellular uptake by inhibition of P-gp overexpression as well as cellular absorption via clathrin-mediated endocytosis (21). Using TPGS, Han SM et al. (2018) formulated PTX-loaded liposomes. In MCF-7/ADR cells, cellular absorption of PTX from the TPGS coated PTX-liposome was significantly higher than that of the PTX-liposome attributed to the rapid internalization of liposomes and drug release in the cellular environment. The inhibited P-gp expression confirmed by western blot assay was

ascribed to the higher cytotoxicity potential of the TPGS coated PTX-liposome (22). Post cellular uptake increases ROS output and converts ATP to ADP, reducing ATP supply and utilization and causing direct damage to mitochondrial function. Further, TPGS induces intracellular ROS which decreases mitochondrial membrane potential, resulting in mitochondrial dysfunction and induction of apoptotic process (23-25). Neophytou et al. (2014) demonstrated TPGS mediated selective inhibition of cancer cell growth inhibition in breast cancer cell lines (MCF-7 and MDA-MB-231) as compared to non-tumorigenic immortalized cells (MCF-10A and MCF-12F). Molecularly, TPGS induces G1/S phase cell cycle arrest via upregulation of P21 and P27Kip1 proteins. Further, it induces caspase -dependent and -independent apoptotic signalling pathways via inhibition of phospho-AKT and downregulation of the anti-apoptotic proteins, Survivin and Bcl-2 (26). The various formulations developed using TPGS have been documented in table 1.

Table 1: Representative examples of TPGS based nanocarriers overcoming MDR in cancer

FORMULATION	TYPE OF CANCER	BIOLOGICAL EFFECT	REF.
TPGS-doxorubicin (hybrid micelle)	Malignant melanoma cancer, breast cancer, hepatocellular carcinoma	• Enhanced cellular uptake and drug release • Increased blood circulation time and stability of doxorubicin • Enhanced translocation of a drug from the cytoplasm into resistant cancer cells	27
TPGS-Cis aconitic anhydride-modified doxorubicin nanoparticles	Lung cancer	• Improved cellular uptake of doxorubicin	28
TPGS-paclitaxel (PTX) prodrug	Ovarian cancer	• TPGS facilitated PTX aggregation in PTX-resistant ovarian cancer cells via P-gp inhibition. • IC50 of TPGS-PTX was enhanced by 55% than that of Taxol alone • Improved tumor growth inhibition with low systemic cytotoxicity	29
TPGS-cisplatin micelle	Hepatoma	• High drug loading up to 4.95% (w/w) and controlled release at low pH conditions. • IC50 value TPGS- cisplatin micelle was decreased from 0.19 to 0.08 g/mL.	30
TPGS/Tween 80-PTX loaded nanoemulsions	Breast cancer	• IC50 of nanoemulsion was reduced from 101.45 mg/ml to 5.39 mg/ml.	31
TPGS-5-fluorouracil-PTX nanoemulsion	Epidermal carcinoma	• Nanoemulsion was found to be stable with entrapment efficiency of 95%. • Reversal of MDR due to the synergy of 5-FU and PTX and P-gp inhibitory activity by TPGS.	32

Conclusion

We have provided a brief insight about the role of TPGS, a FDA approved pharmaceutical adjuvant to combat MDR in cancer. Prominently, TPGS has shown to overcome MDR via inhibition of P-gp efflux, prevent cancer cell metastasis and induce cell apoptosis. Through its multifactorial use, TPGS as an excipient offers new perspectives in designing dosage forms to administer anticancer therapeutics for management of cancer plagued with multidrug resistant issues.

Reference

1. Bukowski K, Kciuk M, Kontek R. Mechanisms of multidrug resistance in cancer chemotherapy.International journal of molecular sciences. 2020 Jan;21(9):3233.
2. Dong Y, Liao H, Yu J, Fu H, Zhao D, Gong K, Wang Q, Duan Y. Incorporation of drug efflux inhibitor and chemotherapeutic agent into an inorganic/organic platform for the effective treatment of multidrug-resistant breast cancer. Journal of nanobiotechnology. 2019 Dec;17(1):1-5.
3. Rose-James A, Sreelekha TT, George SK. Nanostrategies in the war against multidrug resistance in leukemia. Anticancer Drugs. 2013;1(1):3e-9e.
4. Zhang M, Liu E, Cui Y, Huang Y. Nanotechnology-based combination therapy for overcoming multidrug-resistant cancer. Cancer biology & medicine. 2017 Aug;14(3):212.
5. Guo Y, Luo J, Tan S, Otieno BO, Zhang Z. The applications of Vitamin E TPGS in drug delivery. European journal of pharmaceutical sciences. 2013 May 13;49(2):175-86.
6. Zhang Z, Tan S, Feng SS. Vitamin E TPGS as a molecular biomaterial for drug delivery. Biomaterials. 2012 Jun 1;33(19):4889-906.
7. Yang C, Jiang L, Bu S, Zhang L, Xie X, Zeng Q, Zhu D, Zheng Y. Intravitreal administration of dexamethasone-loaded PLGA-TPGS nanoparticles for the treatment of posterior segment diseases. Journal of biomedical nanotechnology. 2013 Jan 1;9(9):1617-23.
8. Alkholief M, Albasit H, Alhowyan A, Alshehri S, Raish M, Kalam MA, Alshamsan A. Employing a PLGA-TPGS based nanoparticle to improve the ocular delivery of Acyclovir. Saudi Pharmaceutical Journal. 2019 Feb 1;27(2):293-302
9. Aggarwal N, Goindi S, Mehta SD. Preparation and evaluation of dermal delivery system of griseofulvin containing vitamin E-TPGS as penetration enhancer. Aaps Pharmscitech. 2012 Mar;13(1):67-74.
10. Vijayakumar, M.R., Kumari, L., Patel, K.K., Vuddanda, P.R., Vajanthri, K.Y., Mahto, S.K. and Singh, S., 2016. Intravenous administration of trans-resveratrol-loaded TPGS-coated solid lipid nanoparticles for prolonged systemic circulation, passive brain targeting and improved in vitro cytotoxicity against C6 glioma cell lines. RSC advances, 6(55), pp.50336-50348.
11. Yusuf H, Ali AA, Orr N, Tunney MM, McCarthy HO, Kett VL. Novel freeze-dried DDA and TPGS liposomes are suitable for nasal delivery of vaccine. International journal of pharmaceutics. 2017 Nov 25;533(1):179-86.
12. Li H, Yan L, Tang EK, Zhang Z, Chen W, Liu G, Mo J. Synthesis of TPGS/curcumin nanoparticles by thin-film hydration and evaluation of their anti-colon cancer efficacy in vitro and in vivo. Frontiers in pharmacology. 2019 Jul 12;10:769
13. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=browseByLetter.page&Letter=T
14. European Food Safety Authority (EFSA). Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS) in use for food for particular nutritional purposes. EFSA Journal. 2007 May;5(5):490.
15. Rajebahadur M, Zia H, Nues A, Lee C. Mechanistic study of solubility enhancement of nifedipine using vitamin E TPGS or solutol HS-15. Drug delivery. 2006 Jan 1;13(3):201-6.
16. Sheu MT, Chen SY, Chen LC, Ho HO. Influence of micelle solubilization by tocopheryl polyethylene glycol succinate (TPGS) on solubility enhancement and percutaneous penetration of estradiol. Journal of controlled release. 2003 Mar 26;88(3):355-68.
17. Varma MV, Panchagnula R. Enhanced oral paclitaxel absorption with vitamin E-TPGS: effect on solubility and permeability in vitro, in situ and in vivo. European journal of pharmaceutical sciences. 2005 Jul 1;25(4-5):445-53.
18. Yan A, Von Dem Bussche A, Kane AB, Hurt RH. Tocopheryl polyethylene glycol succinate as a safe, antioxidant surfactant for processing carbon nanotubes and fullerenes. Carbon. 2007 Nov 1;45(13):2463-70
19. Singh H, Narang JK, Singla YP, Narang RS, Mishra V. TPGS stabilized sublingual films of frovatriptan for the management of menstrual migraine: Formulation, design and antioxidant activity. Journal of Drug Delivery Science and Technology. 2017 Oct 1;41:144-56
20. Su Z, Chen M, Xiao Y, Sun M, Zong L, Asghar S, Dong M, Li H, Ping Q, Zhang C. ROS-triggered and regenerating anticancer nanosystem: an effective strategy to subdue tumor's multidrug resistance. Journal of controlled release. 2014 Dec 28;196:370-83)16
21. Ramachandra M, Ambudkar SV, Chen D, Hrycyna CA, Dey S, Gottesman MM, Pastan I. Human P-glycoprotein exhibits reduced affinity for substrates during a catalytic transition state. Biochemistry. 1998 Apr 7;37(14):5010-9
22. Han SM, Baek JS, Kim MS, Hwang SJ, Cho CW. Surface modification of paclitaxel-loaded liposomes using d-α-tocopheryl polyethylene glycol 1000 succinate: Enhanced cellular uptake and cytotoxicity in multidrug resistant breast cancer cells. Chemistry and physics of lipids. 2018 Jul 1;213:39-47
23. Khurana RK, Gaspar BL, Welsby G, Katare OP, Singh KK, Singh B. Improving the biopharmaceutical attributes of mangiferin using vitamin E-TPGS co-loaded self-assembled phosholipidic nano-mixed micellar systems. Drug delivery and translational research. 2018 Jun;8(3):617-32
24. Gorain B, Choudhury H, Pandey M, Kesharwani P. Paclitaxel loaded vitamin E-TPGS nanoparticles for cancer therapy. Materials Science and Engineering: C. 2018 Oct 1;91: 868-80.
25. Fan Z, Jiang B, Shi D, Yang L, Yin W, Zheng K, Zhang X, Xin C, Su G, Hou Z. Selective antitumor activity of drug-free TPGS nanomicelles with ROS-induced mitochondrial cell death. International Journal of Pharmaceutics. 2021 Feb 1;594:120184
26. Neophytou CM, Constantinou C, Papageorgis P, Constantinou AI. D-alpha-tocopheryl polyethylene glycol succinate (TPGS) induces cell cycle arrest and apoptosis selectively in Survivin-overexpressing breast cancer cells. Biochemical pharmacology. 2014 May 1;89(1):31-42.
27. Bao Y, Yin M, Hu X, Zhuang X, Sun Y, Guo Y, Tan S, Zhang Z. A safe, simple and efficient doxorubicin prodrug hybrid micelle for overcoming tumor multidrug resistance and targeting delivery. Journal of Controlled Release. 2016 Aug 10;235:182-94.
28. Hou W, Zhao X, Qian X, Pan F, Zhang C, Yang Y, de La Fuente JM, Cui D. pH-Sensitive self-assembling nanoparticles for tumor near-infrared fluorescence imaging and chemo–photodynamic combination therapy. Nanoscale. 2016;8(1):104-16.
29. Bao Y, Guo Y, Zhuang X, Li D, Cheng B, Tan S, Zhang Z. D-α-tocopherol polyethylene glycol succinate-based redox-sensitive paclitaxel prodrug for overcoming multidrug resistance in cancer cells. Molecular pharmaceutics. 2014 Sep 2;11(9):3196-209.
30. Mi Y, Zhao J, Feng SS. Vitamin E TPGS prodrug micelles for hydrophilic drug delivery with neuroprotective effects. International journal of pharmaceutics. 2012 Nov 15;438(1-2):98-106.
31. Bu H, He X, Zhang Z, Yin Q, Yu H, Li Y. A TPGS-incorporating nanoemulsion of paclitaxel circumvents drug resistance in breast cancer. International journal of pharmaceutics. 2014 Aug 25;471(1-2):206-13.
32. Ma Y, Liu D, Wang D, Wang Y, Fu Q, Fallon JK, Yang X, He Z, Liu F. Combinational delivery of hydrophobic and hydrophilic anticancer drugs in single nanoemulsions to treat MDR in cancer. Molecular pharmaceutics. 2014 Aug 4;11(8):2623-30.

Nanocellulose – A sustainable, eco-friendly and versatile pharmaceutical excipient

Harsha Farenjiya Khatik &
Preeti K. Suresh*

University Institute of Pharmacy, Pandit Ravishankar Shukla University, Raipur, 492 010, Chhattisgarh, India.

suresh.preeti@gmail.com

Introduction

The interdisciplinary research work of nanotechnology and polymer science has proposed cellulose at nanostructural level with the advent of "Nanocellulose", possessing additional potential properties in terms of mechanical strength, high surface area, recyclability, renewability, as well as eco-friendly and non-toxic nature. For instance, it is proven advantageous over cellulose suspensions containing more than 90% water, which dramatically raises the cost of transport and increases the risk of degradation by bacteria or fungi. Thus, being the bearer of such unique properties, it offers a wide range of new opportunities that makes it a good candidate to replace petroleum-based surfactants and polymers (1,2,3).

Structure and Properties of Nanocellulose

Cellulose $(C_6H_{10}O_5)_n$ contains linear chain of homopolysaccharide containing repeating units of cellobiose ($C_{12}H_{22}O_{11}$). These units are formed from the two monomers of β-D-anhydroglucose, which are linked via β-1,4 glycosidic bond (Figure 1) (5)

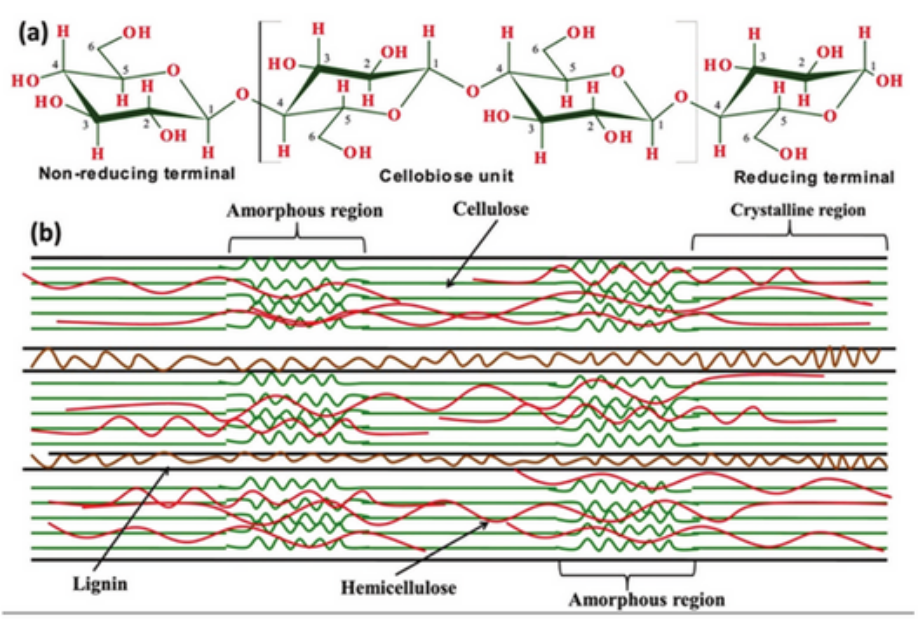


Figure 1: a) Super-molecular structure of cellulose having three (–OH) groups at the C2, C3 and C6 atoms of each β-D-glucopyranose unit, and (b) amorphous and crystalline regions present in the composite structure of the lignocellulosic biomass (5)

Due to the presence of extensive hydrogen bonding among the hydroxyl groups, it exhibits remarkable properties such as hydrophilicity, chirality, amenability to chemical functionalization, insolubility in most aqueous solvents, and infusibility. The characteristics of this biopolymer depends on the degree of polymerization and length of polymer chain. Native cellulose consists of two domains, one is ordered i.e. crystalline and other is disordered i.e. amorphous. Crystalline cellulose is tightly packed, stabilized by strong network of intra and intermolecular hydrogen bonds and thus unsusceptible to chemical, mechanical, and enzymatic treatments. While on the other hand, amorphous ones can easily react with other molecular groups (6).

Sources

i. Bacteria: E.g., Acetobacter, Agrobacterium, Azotobacter, Pseudomonas, Rhizobium, Rhodobacter, Salmonella, Sarcina, and Gluconacetobacter. The yield of nanocellulose can be increased via yeasts or by symbiotic co-cultivation with Medusomyces gisevii. It is chemically and structurally similar to plant cellulose but is free of by-products like lignin, pectin, and hemicelluloses (7,8).

ii. **Plants:** Nanocellulose from leaves (e.g., birch) is referred as hardwood-derived, while nanocellulose obtained from coniferous trees is softwood-derived (e.g., Pinus radiata). Cotton and hibiscus are the examples of shrub sources (7).

iii. Algae: Some algae as sources of nanocellulose are Cladophora (have been studied for its biomedical applications in terms of the presence of impurities, such as heavy metals, glucans, and endotoxins) and Cystoseria myrica (in combination with Fe3O4 has been tested for eliminating mercury ion pollution) (7).

i**v. Animals:** Marine invertebrates i.e., from phylum Chordata and sub-phylum Tunicata, such as Styela clava and Halocynthia roretzi Drasche. Lately, the researchers have majorly focused on class Ascidiacea (Sea squirts), which produce cellulose in the outer tissue, tunic, from which a fraction of pure cellulose, tunicin, can be extracted. Cellulose films derived from Styela clava tunics have been tested for wound dressings, and have found biomedical applications as stitching fibers, tissue engineering scaffolds, absorbable haemostats, and haemodialysis membranes, among others (7).

Types of Nanocellulose

Nanocellulose can be broadly divided into three types viz., cellulose nanocrystals (CNC), cellulose nanofibrils (CNF), and bacterial cellulose (BC). CNC are also referred as nanocrystalline cellulose, cellulose (nano) whiskers, rod-like cellulose microcrystals. CNF are also known as nanofibrillated cellulose, microfibrillated cellulose, or cellulose nanofibers while BC has the synonym microbial cellulose (9).

Nanocellulose-based nanocomposites

Being the bearer of such unique properties, nanocellulose is in great demand to be used as a filler for polymer composites. The biocompatibility of biomedical polymeric-based composites

can be influenced by copolymer ratio, chemical structure, functional groups, as well as morphologies and processing of fillers, which may further affect the cellular activity of the targeted host. Since human body is devoid of cellulolytic enzymes, cellulose cannot be degraded by it and this may lead to some incompatibility issues. The same can be expected with nanocellulose. To address this issue, a study was conducted to modify nanocellulose, particularly CNF to enhance biocompatibility. It was found that crosslinking of CNF with adipic acid dihydrazide (ADH) and oxidized konjac glucomannan (OKGM) was able to improve the biocompatibility of CNF. It also supported the growth of cells on the surface of the membrane (11).

Conclusion and Future Aspects

Novel forms of nanocellulose are generating substantial research activity nowadays. Various types of nanocelluloses have interesting properties, such as high modulus, hydrophilicity, possibility for chemical modification, lower density, anisotropy, high surface area, substantial strength, excellent biocompatibility, and the formation of self-organized and assembled morphologies. Owing to such remarkable properties, nanocelluloses are widely applied in drug delivery, medical implants, wound healing, leukocyte blood-free transfusions, tissue scaffolds, and also in healthcare treatments (table 1). Apart from the number of sources presented in this article, the strategies of its extraction from biomass waste are also in the trend. Its super-molecular structure, excellent properties, and biodegradable nature can take the waste management industry towards a new elevation and it will be a feasible candidate for replacing petroleum-based products. However, some research needs to be done, mainly the environment-friendly pretreatment/extraction methods at a lower cost with less consumption of energy so that up-scaling can be done effortlessly. This will head up for the broader acceptance of nanocellulose and thereby open the door for new applications and improvement of the existing ones.

Field	Key Findings	Ref
Drug Delivery	• As excipient, pure CNC used to bind water-soluble antibiotics (tetracycline and doxorubicin), while cationic-CNC allows binding with nonionized hydrophobic anticancer agents (docetaxel, paclitaxel and etoposide). It can also be employed as co-stabilizer to improve the physicochemical and flow properties of polymeric excipients. • BC demonstrated as drug carrier to extend the release duration of berberine hydrochloride and berberine sulfate in comparison with commercial tablet.	(9)
Tissue Engineering	• Using freeze-drying, incorporation of CNCs has been done in chitosan/alginate/hydroxyapatite scaffold, results in improvement of physical as well as chemical properties and also enhances proliferation and cell adherence. • Human cartilage made via 3D-printing through NC-alginate based hydrogels.	(6) (12)
Diagnostics	• Colorimetric based biosensor using NC employed for glucose determination with test strip of improved colour homogeneity.	(13)
Medical Devices	• In polyurethane, NC (from Pineapple leaf fibres) act as a reinforcing agent that has been employed for the manufacture of vascular prostheses. • SYNTHECEL® Dura Repair, a bacterial cellulose sheet product introduced to repair of duramater i.e., outer layer of brain.	(11) (14,15)
Haemodialysis	• The heparinized PPy-cellulose composite is consequently a promising haemodialysis material, concerning both potential-controlled extraction of small uraemic toxins and haemocompatibility.	(16)
Dental	• BNC membranes used in periodontal tissue recovery. • Modification of glass ionomer cement by NFC from eucalyptus pulp significantly improved the mechanical properties.	(11) (11)
Ophthalmic	• Addition of CNC within the PVA matrix enhances its mechanical properties and encourages the growth of human corneal epithelial cells that would be favourable for corneal implants, disposable contact lenses, and ophthalmic prostheses. • BNC is used as a substrate for the culture of retinal pigment epithelium.	(11) (17)
Wound Dressing	• AgNP/BNC composites exhibit remarkable activities to prevent wound infection. • Hyaluronic acid-CNC composite containing nanochitosan carrying granulocyte macrophage colony-stimulating factor demonstrated as a novel candidate for wound healing.	(11) (6)

Table 1: Biomedical Applications of Nanocellulose

References

1. Peng BL, Dhar N, Liu HL, Tam KC (2011). Chemistry and applications of nanocrystalline cellulose and its derivatives: A nanotechnology perspective. The Canadian Journal of Chemical Engineering. 89:1191.
2. Yun X. T. (2016). Catalytic Conversion of Cellulose into Nanocellulose in Ionic Liquid. Retrieved from https://pdfs.semanticscholar.org/51e3/c0f9e8804ee8ca13dd18d5fb54f3dc96b1e8.pdf.
3. Thakur V.K. (2015) Nanocellulose Polymer Nanocomposites: Fundamentals and Applications. NJ: John Wiley & Sons, Inc. and Scrivener Publishing LLC.
4. Lee K. Y. (Ed.) (2018) Nanocellulose and sustainability: Production, Properties, Applications and Case studies. NewYork: CRC Press.
5. Thakur V., Guleria A., Kumar S., Sharma S., and Singh K. (2021). Recent advances in nanocellulose processing, functionalization and applications: a review. Royal Society of Chemistry.
6. Trache D, Tarchoun AF, Derradji M, Hamidon TS, Masruchin N, Brosse N and Hussin MH (2020) Nanocellulose: From Fundamentals to Advanced Applications. Front. Chem. 8:392.
7. Bacakova L., Pajorova J., Bacakova M., Skogberg A., Kallio P., Kolarova K., and Svorcik V. (2019) Versatile Application of Nanocellulose: From Industry to Skin Tissue Engineering and Wound Healing. Nanomaterials. 9:2.
8. Kargaezadeh H., Ahmad I., Thomas S., and Dufresne A., (Eds.). (2017) Handbook of Nanocellulose and Cellulose Nanocomposites. Wiley VCH Verlag GmbH & Co.
9. Ning Lin N. and Dufresne A. (2014) Nanocellulose in biomedicine: Current status and future prospect. European Polymer Journal.59:302.
10. Sina Salimi S., Gharebagh R. S., Zarghami R., Chan S. Y. and Yuen K.H. (2019) Production of Nanocellulose and Its Applications in Drug Delivery: A Critical Review. ACS Sustainable Chem. Eng. 19:15800.
11. Sharip N. S., Yasim-Anuar T. A. T., Norrrahim N. F., Shazleen S. S., Nurazzi N. M., Sapuan S. M. and Ilyas R. A. (2020) A Review on Nanocellulose Composites in Biomedical Application, CRC Press, 1-30.
12. Curvello R., Raghuwanshi V. S. and Garnier G. (2019) Engineering nanocellulose hydrogels for biomedical applications. Advances in Colloid and Interface Science. 267:47.
13. Neubauerova K., Carneiro M. C., Rodrigues L. R., Moreira F.T. and Sales, M.G. (2020) Nanocellulose based biosensor for colorimetric detection of glucose. Sensing and Bio-Sensing Research. 29:100368.
14. Kharchenko A. V. and Stupak V. V. (2019) Bacterial nanocellulose as a plastic material for closure of defects of the duramater: literature review. Journal of Spine Surgery. 16:62.
15. https://www.exilva.com/blog/nanocellulose-future-of-medical-devices
16. Ferraz N., Carlsson D.O., Hong J., Larsson R., Fellstro B., Nyholm L., Strømme M. and Mihranyan A. (2012). Haemocompatibility and ion exchange capability of nanocellulose polypyrrole membranes intended for blood purification. J. R. Soc. Interface 9:1943.
17. Goncalves S., Padrao J., Silva J. P. and Patrico M.I. (2015) Bacterial Cellulose as a support for the growth of retinal pigment epithelium. Biomacromolecules. 16:1341.

Eyeing the Novel Polysachharide-Based Excipients for Ocular Formulations



Narayan Hemnani, Shweta Ramkar & Preeti K. Suresh*

University Institute of Pharmacy, Pandit Ravishankar Shukla University, Raipur, 492 010, Chhattisgarh, India.
suresh.preeti@gmail.com

Ocular products present a major challenge for formulation scientists primarily due to the extensive precorneal loss and the various physiological barriers that restrict the drug from reaching the posterior segment of the eye. Polysaccharides have been widely used to address these multiple issues. Polysaccharides are polymers comprising several monosaccharide molecules linked through glycosidic bonds. They can either be homopolysaccharides or heteropolysaccharides, and with the varying chemical composition, degree of polymerization, number of branches, and surface charge, polysaccharides display not only discrete structures but also unique physicochemical properties, which can be tailored to have different characteristics.

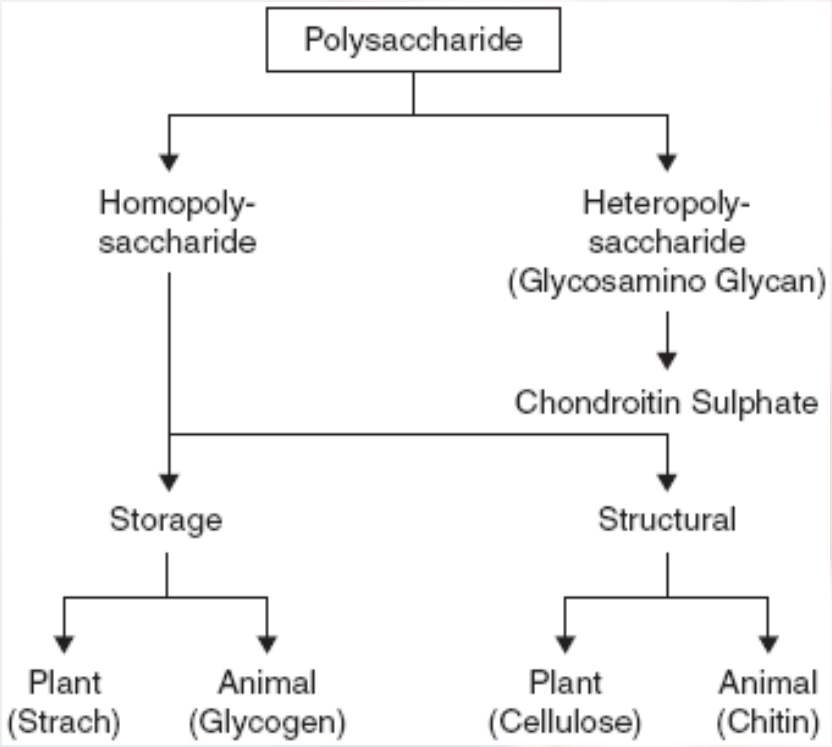


Figure 1: Classification of Polysaccharides

Advantages of Polysaccharides in Ophthalmic Products

Natural polysaccharides have emerged as versatile excipients for fabrication of ocular products due to attractive features like ready availability, low cost, non-toxic profile, biodegradability, biocompatibility, and their amenability for chemical modifications. The chemical modifications have assisted in preparing derivatives having better rheological, mucoadhesive, ocular retentive, and drug solubility profile. In the current scenario, these polysaccharides are predominantly present in the commercial products as inert thickening agents. It is anticipated that more polysaccharides may be added to this list of acceptable excipients for ophthalmic formulations. The combination of polysaccharides with other polymers or additives is an elegant strategy to tune and control the formulation characteristics towards a desired goal, which are not available in each material by itself. Some of the promising polysaccharides and their combinations are discussed in the following section.

Sodium Alginate

Sodium alginate is a water-soluble, derivative of alginic acid having 1,4-β-d-mannuronic and α-l-guluronic acids. It is used as a gelling agent in combination with HPMC. It also blends with many synthetic and natural polymers to increase its mechanical strength with better adhesion properties. It can be used to make blends, hydrogels, micelles, nano-carriers, nano-gels, nano-composites, nanoparticles, tubes, cationic systems, aerogels, among others with wide applications. Sodium alginate coating is remarkable by adding different antimicrobial agents (1). The problem of initial burst or fast release of drug encapsulated in alginate polymer can be addressed by coating with polycations or increasing the polymer hydrophobicity by grafting polymers (2).

Guar Gum

Guar gum, a natural water-soluble nonionic galactomannan polysaccharide is harvested from the ground endosperm of Indian cluster bean, Cyamposis tetragonolobus. Even in small concentrations, it forms extremely viscous, pseudoplastic solutions due to its high molecular weight and presence of extended repeating units formed by hydrogen bonding. This feature allows guar gum to be soluble and gel even in cold conditions and in water. Guar gum with borax cross-linking can serve as a polymer in ocular inserts. Blends of chitosan and guar gum form smart ternary systems, with the possibility of incorporating a combination of these two polysaccharides into a thermosensitive pluronic water solution (3, 4).

Methylcellulose

Methylcellulose (MC), a water-soluble non-ionic cellulose ether dissolves due to its weak physical cross-links, and undergoes inverse thermal gelling to form a physically cross-linked hydrogel at physiological temperatures. The presence of hydroxyl groups in MC makes it water-soluble and the solution shows thermoreversible sol–gel phase transition at about 60°C. Gelation temperature of MC can be further reduced by adding salts or other additives affecting the hydrogen bonding interactions between hydroxyl groups of MC and water molecules (5). The semi-interpenetrating hydrogels of MC are thermosensitive. The addition of MC to polyacrylic acid films showed sustained drug release due to hydrogen bond network formation and reduced irritant effects. MC and ι-carrageenan dispersions have also been explored for transscleral delivery of macromolecules (6).

Hydroxypropyl Methylcellulose

Hydroxypropyl methylcellulose (HPMC) has also found wide applications in ophthalmologic products (7, 8). HPMC does not alter the pH of tear and ocular fluids, which are buffered at pH 7.65, since HPMC chains carry no ionizable groups. In eye drops, HPMC is frequently used as a viscosity enhancer, stabilizer and mucoadhesive. The derivatization of cellulose into HPMC reduces considerably the crystallinity and provides thermoplastic behavior. Porous micrometric sponges produced by crosslinking HPMC chains with citric acid or oxalic acid and nontoxic crosslinkers can work as reservoirs for subconjuctival drug delivery. Low molecular weight HPMC samples have higher entropy of dissolution than high molecular weight HPMC samples and therefore, the drug release is faster from a low molecular weight HPMC matrix than from a high molecular weight HPMC matrix.

Xanthan Gum

Xanthan gum (XG) is a polysaccharide extracted by culture fermentation from Xanthomonas campestris, consisting of d-glucosyl, d-mannosyl, and d-glucuronyl acid residues (2:2:1 molar ratio) with variable ratios of O-acetyl and pyruvyl residues. XG is a highly viscous molecule, even at low polymer concentrations. From the rheological point of view, it is similar to normal tears and it shows a pseudoplastic behavior, with viscosity decreasing with increasing shear rate. XG is a molecule characterized by the presence of many OH– residues, which confer a good antioxidant activity. Loaded with these properties, XG can reduce the friction, lowering the ocular surface nerve stimulation and the inflammation due to oxidative stress of the ocular surface in elderly subjects (9).

Carboxymethylcellulose

Carboxymethylcellulose (CMC) is also widely used in artificial tears for the treatment of dry eye symptoms, ocular surface staining and epithelial suffering or after laser in situ keratomileusis. CMC can also effectively reduce the incidence of epithelial defects through stimulating epithelial cell migration by its binding to matrix proteins (9, 10). It binds to ocular surface cells and accelerate wound healing in animal model systems. Potential synergistic effects of combining CMC and HA in a single formulation have been demonstrated in iridocorneal endothelial syndrome (ICES)-induced dry eye and may be an important addition to treatment options available for patients with dry eye disease (11).

Hyaluronate Sodium

Hyaluronic acid (HA), a naturally occurring glycosaminoglycan of the extracellular matrix plays an important role in wound healing, and inflammation. Its lubricative and viscoelastic properties make it ideal for use in ophthalmic practice to protect the corneal endothelium and to maintain the anterior chamber depth during intraocular surgery. Studies indicate that sodium hyaluronate promotes migration on human corneal epithelial cells (HCECs) in vitro and has beneficial effect in corneal wound healing by rapid migration of cells leading to rapid wound closure.Italso enhances the spread of the tear film lipid layer (10, 12). Sodium hyaluronate, a derivative of HA, shares many of its beneficial properties. It is a humectant, lubricant, and hypo-osmotic and is naturally produced in the eye as a response to ocular surface damage.It has extreme water holding capacity and viscoelastic properties and is used in the formulations for treating dry eye disease.

Ophthalmic viscosurgical devices (OVD) used for complicated cataract, corneal lamellar and glaucoma surgeries. OVD are viscoelastic systems consisting of sodium hyaluronate and/or HPMC. During the surgical procedures, they are used to fill the intraocular space, reduce the damage to the cornea, protect the intraocular structures, protect the corneal cells against temperature increase and against hydroxyl free radicals (HO•) generation (8).

Chitosan

Chitosan (CH) is a natural, linear and cationic polysaccharide of randomly distributed D-glucosamine and N-acetyl-D-glucosamine units linked with β-linkage. Apart from its biocompatibility, biodegradability and nontoxicity, it is also known for its antibacterial activity, and bioadhesion to the corneal surface. It also has penetration-enhancing property due to the opening of the tight junctions located in epithelial cells (13, 14). CH chemically modified with succinic anhydride and 2-carboxybenzaldehyde has been used for the preparation of nanoparticles. The water-soluble CH oligosaccharide lactate has been used as coating for nanostructured lipid carriers. PLGA, alginate, cyclodextrin, dextran sulfate, lecithin and acrylic acid are well-known carriers and have been tested in combination with CH for ophthalmic application (15).

Conclusion and Future Aspects

Polysaccharides clearly have significant advantages as excipients for ophthalmic products. But some concerns and poorly explored aspects remain to be resolved. For instance, biodegradation of polysaccharides in vivo is difficult to evaluate, and the most enzymes involved in their degradation are still to be characterized in ocular tissues, making the polymer degradation and the rationale for polymer design nonoptimal. Another point of concern is the polymer degradation that may effect material removal from the eye. A polymer that has slower degradation than drug release rate may lead to unwarranted polymer “ghosts”. Thus, it is crucial to coordinate polymer degradation and elimination with the anticipated period of drug release. The biodegradation profile of polysaccharide-based nanoscale carriers in the ocular milieu too is much below acceptable levels, inspite of the fact that they degrade rather easily in vivo. There are also some serious concerns as to the fate of nanocarriers based on polysaccharide regarding their decomposition, metabolism, and excretion; nature of metabolites produced and the probable physiological impacts on the eye, specifically for hybrid and composite nanomaterials.

Table 1: List of FDA-Approved Polysaccharides used as Excipients for Ophthalmological Drugs

Polysaccharide	Administration	Drug Dosage Form	Max Potency	Brand Names
Sodium alginate	Topical	insert	1 mg	-
Guar gum	Topical	Suspension	0.2%	-
Methylcellulose	Topical	Solution, suspension	0.05-05%	Murocel
Hydroxypropyl methylcellulose (HPMC)	Topical	Solution, suspension and gel	0.1-0.6% 2.25% (gel)	Genteal, Nature's Tears, Tearisol
Xanthan gum	Topical	Solution, suspension	0.6%	I-Dew Ultra
Carboxymethylcellulose (CMC)	Intravitreal, Topical	Solution, suspension, injections	0.5%	Refresh Tears
Hyaluronate sodium	Intravitreal	Solution	2.3%	Healon, Amvisc, Provisc, AMO Vitrax
Hydroxyethyl cellulose	Topical	Solution, suspension	0.25 -1.6%	Rohto Hydra

References

1. Ahmad A., Mubarak N. M., Jannat F. T., Ashfaq T., Santulli C., Rizwan M., and Ali S. (2021). A Critical Review on the Synthesis of Natural Sodium Alginate Based Composite ``Materials: An Innovative Biological Polymer for Biomedical Delivery Applications. Processes, 9(1), 137.
2. Mohammad Sadeghi A., Farjadian F. and Alipour S. (2021). Sustained release of linezolid in ocular insert based on lipophilic modified structure of sodium alginate. Iranian Journal of Basic Medical Sciences.
3. Kumar S., Issarani R., Nagori B. P. and Ahuja, M. (2012). Design and evaluation of guar gum-based ofloxacin sustained release ocular insert. Asian Journal of Pharmaceutics, 6(3), 198-203
4. Branca C., Conti Nibali V., Khouzami K., Wanderlingh U. and D'Angelo G. (2020). Comparative study of pluronic-chitosan and pluronic-guar gum composite. International Journal of Polymer Analysis and Characterization, 26(2), 179-188
5. Bhowmick B., Sarkar G., Rana D., Roy I., Saha N. R., Ghosh S. and Chattopadhyay D. (2015). Effect of carrageenan and potassium chloride on an in situ gelling ophthalmic drug delivery system based on methylcellulose. RSC Advances, 5(74), 60386-91.
6. Dubashynskaya N., Poshina D., Raik S., Urtti A. and Skorik Y. A. (2020). Polysaccharides in ocular drug delivery. Pharmaceutics, 12(1), 22.
7. Liu D., Wu Q., Chen W., Lin H., Zhu Y., Liu Y. and Zhu, F. (2019). A novel FK506 loaded nanomicelles consisting of amino-terminated poly (ethylene glycol)-block-poly (D, L)-lactic acid and hydroxypropyl methylcellulose for ocular drug delivery. International Journal of Pharmaceutics, 562, 1-10.
8. Tundisi L. L., Mostaço G. B., Carricondo P. C. and Petri D. F. S. (2021). Hydroxypropyl methylcellulose: Physicochemical properties and ocular drug delivery formulations. European Journal of Pharmaceutical Sciences, 159, 105736.
9. Postorino E. I., Aragona P., Rania L., Spinella R., Puzzolo D., Micali A. and Papa V. (2020). Changes in conjunctival epithelial cells after treatment with 0.2% xanthan gum eye drops in mild-moderate dry eye. European Journal of Ophthalmology, 30(3), 439-445.

10. Lee J. S., Lee S. U., Che C. Y. and Lee J. E. (2015). Comparison of cytotoxicity and wound healing effect of carboxymethylcellulose and hyaluronic acid on human corneal epithelial cells. International Journal of Ophthalmology, 8(2), 215.
11.She Y., Li J., Xiao B., Lu H., Liu H., Simmons P. A., and Chen W. (2015). Evaluation of a novel artificial tear in the prevention and treatment of dry eye in an animal model. Journal of Ocular Pharmacology and Therapeutics, 31(9), 525-530.
12.Chun T., MacCalman T., Dinu V., Phillips-Jones S.O.M.K. and Harding S.E., 2020. Hydrodynamic Compatibility of Hyaluronic Acid and Tamarind Seed Polysaccharide as Ocular Mucin Supplements. Polymers, 12(10), 2272.
13. Tan G., Yu S., Pan H., Li J., Liu D., Yuan K. and Pan W. (2017). Bioadhesive chitosan-loaded liposomes: a more efficient and higher permeable ocular delivery platform for timolol maleate. International Journal of Biological Macromolecules, 94, 355-363.
14.Rong X.; Yang J.; Ji Y.; Zhu X.; Lu Y. and Mo X. Biocompatibility and safety of insulin-loaded chitosan nanoparticles/PLGA-PEG-PLGA hydrogel (ICNPH) delivered by subconjunctival injection in rats. J. Drug Deliv. Sci. Technol. 2019, 49, 556–562.
15.Pontillo A. R. N. and Detsi A. (2019). Nanoparticles for ocular drug delivery: modified and non-modified chitosan as a promising biocompatible carrier. Nanomedicine, 14(14), 1889-1909.

Fun & frolic

Unscramble the words below

1. RSDTTNIGIENA _____
2. ENPOITMERA _____
3. VOONETSLC _____
4. EPCDSORCSEO _____
5. RBIVAESA _____
6. CIARNTBLU _____
7. NTELTRCTOPAOY _____
8. ARAINPFF _____
9. TALSECO _____
10. MONEILTLE _____

Solution on Page 53

Penetration Enhancers for Ocular Drug Delivery






Pooja Bagul, Pallavi Bhagwat, Aishwarya Pawar, Nilesh Shelke, Deepa Warrier & Ujwala Shinde*

Department of Pharmaceutics, IPA-MSB's Bombay College of Pharmacy, Kalina, Santacruz, Mumbai, Maharashtra, India

ujwala29@gmail.com

Introduction

The eye is a unique organ, both anatomically and physiologically, containing several widely varied structures with independent physiological functions that render the organ highly impervious to foreign substances. Ophthalmic drug delivery is one of the most interesting and challenging endeavours faced by pharmaceutical scientist due to the presence of blood-retinal, blood-aqueous humour and blood-vitreous humour barriers. The most commonly used dosage form in treating ocular diseases is locally administered eye drops. Topical administration of drugs is beneficial for delivery to the anterior (cornea, conjunctiva, sclera, anterior chamber) as well as posterior (vitreous humor, retina, choroid) segments of the eye (1). Permeation of a compound via the conventional mode of ocular drug administration, the topical drop, is opposed by precorneal and corneal barriers. Pre-corneal barriers include formulation drainage; blinking; tear film; tear turn-over; and formulation-induced lacrimation. The corneal pathway is considered a major pathway for drug entry into the anterior and posterior segment of the eye. The poor corneal penetration is attributed to the presence of tight junctions between juxtaposed corneal epithelial cells, which prevent drug molecules from moving between them. The diversity of the corneal layer polarity further hampers the penetration of drug across the cornea. The corneal epithelial layer is lipophilic, preventing hydrophilic drugs from penetrating, while the stoma is hydrophilic, preventing lipophilic drugs from penetrating. As a result, to pass through the cornea, the drug molecule must have a certain degree of hydrophilic and lipophilic character. Owing to the physiological and anatomical barriers, only a small fraction of the applied dose is absorbed and reaches its target, i.e., anterior or posterior segments. Two key criteria for improving ocular bioavailability of topically applied formulation - the first, to increase the formulations corneal contact time, and the second, to use penetration enhancers to improve drug molecules corneal penetration (2). Ocular penetration enhancers are compounds that help to increase the permeability of active pharmaceutical ingredients across the ocular membranes including the cornea. Permeation enriching substances to be used in eye preparations must preferably be non-toxic yet non-irritating, efficient at a lower level, rapid action, as well as with reversible results (3).

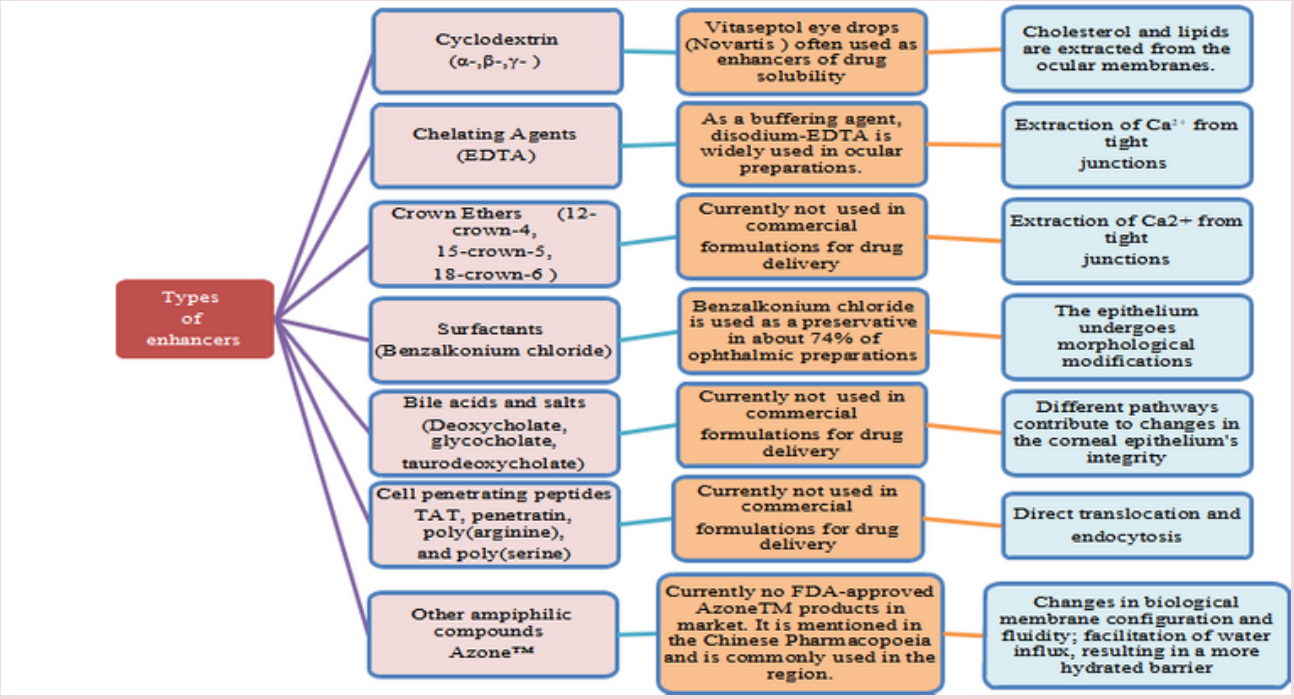
Different types of penetration enhancer and their mechanism for ocular drug delivery

Permeation enhancers used in ocular formulations facilitate drug delivery via three main mechanisms (4-6):

- Changing the balance of the tear film on the eye's layer
- Altering corresponding epithelial cells' surface elements, like lipid bilayers
- Relaxing rigid epithelial joints

Although penetration enhancers cause a temporary structural alteration of the corneal epithelium, enhancers should be harmless, causing no long-term damage and initiate with a minor irritant effect.

The classification of ocular penetration enhancers is as follows (7):



Listed below are the most commonly used ocular penetration enhancers.

Cyclodextrins: These are truncated cone-shaped cyclic oligosaccharides and have aqueous solubility (8). These form inclusion complexes with the hydrophilic or lipophilic drugs. Cyclodextrin molecules have lipophilic cavities- which enclose lipophilic drug molecules and the external surface has a hydroxyl functional group that helps to bind hydrophilic drug molecules. These molecules are unable to penetrate lipophilic membranes and the corneal epithelium, but they do allow drug interaction with the ocular epithelial surface. The enhanced ocular permeation of drug with cyclodextrin inclusion complex is attributed to the disruption of corneal the membrane, either by or by extracting some lipophilic components, such as cholesterol and phospholipids, from the membrane (9).

Crown ethers: These are a class of synthetic macrocyclic polyether molecules. They have a hydrophobic molecular ring structure with an electron-rich hydrophilic cavity. Crown ethers can form complexes with metal ions, neutral as well as ionic organic molecules, yet these complexes can cross biological membranes (10,11).

Their unique structural feature imparts flexibility to crown ethers to structurally adapt itself to the surrounding biological environment. In an aqueous milieu, these can interact with water by exposing hydrophilic oxygen atom to external surrounding whereas in lipophilic medium crown ethers interact by exposing their ethylenic groups (12). The mechanism by which crown ethers work as a penetration enhancing agent is the same as cyclodextrin that is by modifying lipid bilayers(13).

Surfactants: Surfactants are amphiphilic molecules and serve the purpose of permeation enhancer for a drug by disrupting the epithelial layer that is by loosening tight junctions between the epithelial cells. There are four main types of surfactants- cationic surfactants, anionic surfactants, zwitterionic surfactants and non-ionic surfactants.

Non-ionic surface-active agents like tween-20, Brij-35 are the most commonly used surface-active agents as permeation enhancers in case of ocular drug delivery followed by cationic surfactants like benzalkonium chloride (BAC). Some plant-based surfactants like amphiphilic glycosides, e.g. saponins have also been tested and reported to be effective for improved ophthalmic delivery of a drug (14)(7). Sasaki et al. reported the use of penetration promoters for ocular beta-blockers with varying lipophilic features. The permeation enhancer taurocholic acid, saponin, EDTA and capric acid were compared for their permeation enhancing properties. The study was also designed to compare corneal and conjunctival permeation in albino rabbits. The use of permeation enhancer markedly showed an increase in corneal permeability (15).

Transcutol® P is a topical solubilizer used as a permeation promoter for transdermal drug delivery systems. Liu et al. demonstrated that the use of Transcutol P in the concentration range of 0.005-0.03 % did not exert any irritation and showed slight irritation at a concentration of 0.05% (16).

Digitonin has some surface-active characteristics which seem to have the potential as penetration enhancer. Digitonin selectively solubilize cholesterol membranes and exfoliate the epithelial layer of cornea. (9).

Labrasol® is a non-ionic surface-active agent, is a PEG derivative of a medium-chain fatty acid triglyceride of capric and caprylic acid and has the potential to be used as a corneal permeation promoter. Liu et al illustrated an increase in baicalin penetration through the cornea of the rabbit by 1.69, 3.14 and 2.23 folds at 1.5, 2.0 and 3.5% Labrasol concentrations, respectively. Another potential corneal permeability enhancer is Azone™ (1-dodecylazacycloheptan} and amphiphilic surfactant, Gelucires (17).

Lysophospholipids are amphiphilic surface-active agents formed by the phospholipases in a naturally occurring manner. As an enhancer, their mode of action is not fully known. It is thought that phospholipases interact with intracellular proteins or even polar phospholipid groups in intercellular areas of corneal epithelium like other surfactants. This may favor the formation of channels that permit the water permeation and dissolved substances (6).

Bile Acids and Bile Salts: Bile acids /bile salt derivatives such as deoxycholate, glycocholate, and taurodeoxycholate naturally produced in the human digestive system. Bile salts alter the protective mucus barrier of ocular tissue by virtue of their mucolytic properties, thus allowing enhanced drug transit into ocular tissue (7)

Cell-Penetrating Peptides (CPPs): These are short sequences of amino acids joined via peptide bonds and derived from various combinations of amino acids. The possible mechanism of penetration enhancement is direct translocation and endocytosis (18).

Liu et al. performed ex vivo permeation studies of a variety of fluorophone-labelled cell-penetrating peptides, including TAT, penetratin, poly (arginine), low molecular weight protamine, and poly (serine), using a rabbit model (19).

Studies conducted by Pescina et al. centered on the functionalization of new CPPs for future use as permeation promoter for metabolically sensitive ocular drugs like aminoglycoside antibiotics, cysteamine and antiviral agents. The studies showed that CPPs can give a great amount of advantage in carrying these drugs across ocular barriers and has great potential to carry drugs to the anterior as well as the posterior segment of the eye (20).

Bioadhesive Polymers:
Polymers viz. Carbopol®, Pemulen™ and Noveon® are versatile and efficient in complex topical mucosal formulations. These monograph-compliant, mucoadhesive excipients are compatible with most active pharmaceutical ingredients (APIs) and offer several advantages for effective ocular formulation development, including:

- Bioadhesion / Mucoadhesion – maximize drug absorption by prolonging contact time with the eye, which can increase bioavailability, reduce dosing frequency, and subsequently improve patient compliance
- Versatility – compatible with a wide variety of acidic, basic, and neutral APIs across a broad pH range while providing customizable rheology and viscosity for your product
- Emulsification – ability to suspend oils in solution and suitable salt tolerance, which are important qualities for many topical products such as eye drops

Non-irritating and non-toxic – enhances patient comfort and safety

Sperminated pullulans: The charge density is a significant feature of cationic polymer for improved penetration. In the case of cationized polymers, spermine, a polyamine with four amino groups can be beneficial to enhance charge density. Pullulan has a number of hydroxylic groups that can react with spermine. Sperminated pullulans are modified form of pullulan to make the enhancer more powerful.

The impact of sperminated pullulans on corneal permeation was investigated on hydrophilic and lipophilic drugs. The findings indicate that sperminated pullulans greatly enhanced the transcorneal penetration of three hydrophilic drugs (Ofloxacin, Tobramycin as well as sodium fluorescence), however, the transcorneal penetration of a lipophilic drug was not greatly enhanced (dexamethasone). Drugs enter the cornea, either by flowing across or moving between the cells (transcellular) (paracellular) (21).

Miscellaneous compounds: Fatty acids enhance ocular drug permeation by changing the properties of cell membranes and loosening tight junctions. Fatty acid-like caprylic acid and capric acid can form ion-pair complexes with cationic drugs. Capric acid disturbs both proteins and lipid components of cellular membranes, while caprylic acid interacts with proteins. Capric acid has been shown to improve ocular penetration of β-blockers, with mild improvements for hydrophilic β-blockers and only minor improvements for lipophilic β-blockers (17).

Borneol is a terpene derivative that can be used to improve ocular penetration. According to Yang et al, the ability of borneol to promote indomethacin and dexamethasone corneal permeability may be due to changes in the arrangement of lipid molecules in the cell membrane of corneal epitheliocytes, improving the orderliness of the molecular chains of lecithin (22).

Colloidal carrier systems have been extensively investigated for ocular bioavailability improvement. The mechanism of enhancement is generally believed to be related to the ability of carriers to penetrate into the epithelial cells of the cornea without causing damage to the cell membrane (23).

These are some of the commercial products in which cyclodextrins are used as penetration enhancers: chloramphenicol (Clorocil ®: Edol), diclofenac (Voltaren Ophthalmic ®: Novartis), and indomethacin (Indocid ®: Merck Sharp & Dohme-Chibret) (24).

Conclusion

Ocular topical delivery systems are popular due to the non-invasive nature of this route of administration along with ease of application. However, due to complexity in the chemical composition and structure of the eye, delivery of therapeutics is challenging for the formulator. These challenges can be addressed with the help of ocular penetration enhancers. Though, a plethora of research is available in the field of ocular penetration enhancers, it is critical to identify the properties of the various novel excipients and understand how they help in increasing the drug penetration from the ocular drug delivery systems. This review is an attempt to summarize in brief the various advancements in the field of ocular penetration enhancers.

References

1. Mun EA, Morrison PWJ, Williams AC, Khutoryanskiy V V. On the barrier properties of the cornea: A microscopy study of the penetration of fluorescently labeled nanoparticles, polymers, and sodium fluorescein. Mol Pharm. 2014;11(10):3556–64.
2. Ibrahim MM, Maria DN, Di Wang X, Simpson RN, Hollingsworth TJ, Jablonski MM. Enhanced corneal penetration of a poorly permeable drug using bioadhesive multiple microemulsion technology. Pharmaceutics. 2020;12(8):1–19.
3. Loch C, Zakelj S, Kristl A, Nagel S, Guthoff R, Weitschies W, et al. Determination of permeability coefficients of ophthalmic drugs through different layers of porcine, rabbit and bovine eyes. Eur J Pharm Sci [Internet]. 2012;47(1):131–8. Available from: http://dx.doi.org/10.1016/j.ejps.2012.05.007
4. Morrison PWJ, Khutoryanskiy V V. Enhancement in corneal permeability of riboflavin using calcium sequestering compounds. Int J Pharm [Internet]. 2014;472(1–2):56–64. Available from: http://dx.doi.org/10.1016/j.ijpharm.2014.06.007
5. Burgalassi S, Chetoni P, Monti D, Saettone MF. Cytotoxicity of potential ocular permeation enhancers evaluated on rabbit and human corneal epithelial cell lines. Toxicol Lett. 2001;122(1):1–8.
6. Kaur IP, Smitha R. Penetration enhancers and ocular bioadhesives: Two new avenues for ophthalmic drug delivery. Drug Dev Ind Pharm. 2002;28(4):353–69.
7. Moiseev R V., Morrison PWJ, Steele F, Khutoryanskiy V V. Penetration enhancers in ocular drug delivery. Pharmaceutics. 2019;11(7).
8. Loftsson T, Stefánsson E. Cyclodextrins in eye drop formulations: Enhanced topical delivery of corticosteroids to the eye. Acta Ophthalmol Scand. 2002;80(2):144–50.
9. Loftssona T, Järvinen T. Cyclodextrins in ophthalmic drug delivery. Adv Drug Deliv Rev. 1999;36(1):59–79.
10. Boojar MMA, Goodarzi F. Cytotoxicity and the levels of oxidative stress parameters in WI38 cells following 2 macrocyclic crown ethers treatment. Clin Chim Acta. 2006;364(1–2):321–7.
11. Capel-Cuevas S, de Orbe-Payá I, Santoyo-González F, Capitán-Vallvey LF. Double-armed crown ethers for calcium optical sensors. Talanta. 2009;78(4–5):1484–8.
12. Steed JW. First- and second-sphere coordination chemistry of alkali metal crown ether complexes. Coord Chem Rev. 2001;215(1):171–221.
13. Song MZ, Zhu LY, Gao XK, Dou JM, Sun DZ. Microcalorimetric study on host-guest complexation of naphtho-15-crown-5 with four ions of alkaline earth metal. J Zhejiang Univ Sci. 2005;6 B(1):69–73.
14. Shih RL, Lee VHL. Rate Limiting Barrier to the Penetration of Ocular Hypotensive Beta Blockers Across the Corneal Epithelium in the Pigmented Rabbit. J Ocul Pharmacol. 1990;6(4):329–36.
15. Sasaki H, Igarashi Y, Nagano T, Nishida K, Nakamura J. Different Effects of Absorption Promoters on Corneal and Conjunctival Penetration of Ophthalmic Beta-Blockers. Vol. 12, Pharmaceutical Research: An Official Journal of the American Association of Pharmaceutical Scientists. 1995. p. 1146–50.
16. Liu Z, Nie S, Guo H, Pan W, Li J. Effects of Transcutol P on the corneal permeability of drugs and evaluation of its ocular irritation of rabbit eyes. J Pharm Pharmacol. 2006;58(1):45–50.
17. Liu Z, Zhang X, Li J, Liu R, Shu L, Jin J. Effects of Labrasol on the corneal drug delivery of baicalin. Drug Deliv. 2009;16(7):399–404.
18. Pescina S, Ostacolo C, Gomez-Monterrey IM, Sala M, Bertamino A, Sonvico F, et al. Cell penetrating peptides in ocular drug delivery: State of the art. J Control Release [Internet]. 2018;284:84–102. Available from: https://doi.org/10.1016/j.jconrel.2018.06.023
19. Liu C, Tai L, Zhang W, Wei G, Pan W, Lu W. Penetratin, a potentially powerful absorption enhancer for noninvasive intraocular drug delivery. Mol Pharm. 2014;11(4):1218–27.
20. Pescina S, Sala M, Padula C, Scala MC, Spensiero A, Belletti S, et al. Design and synthesis of new cell penetrating peptides: Diffusion and distribution inside the cornea. Mol Pharm. 2016;13(11):3876–83.
21. Yu N, Xun Y, Jin D, Yang H, Hang T, Cui H. Effect of sperminated pullulans on drug permeation through isolated rabbit cornea and determination of ocular irritation. J Int Med Res. 2010;38(2):526–35.
22. Yang H, Xun Y, Li Z, Hang T, Zhang X, Cui H. Influence of borneol on in vitro corneal permeability and on in vivo and in vitro corneal toxicity. J Int Med Res. 2009;37(3):791–802.
23. Fraunfelder FT, Hanna C. Ophthalmic drug delivery systems. Vol. 18, Survey of Ophthalmology. 1974. 292–298 p.
24. Prasad D, Chauhan H. Nano-Biomaterials For Ophthalmic Drug Delivery. Nano-Biomaterials Ophthalmic Drug Deliv. 2016

Regulatory Requirements for Novel Excipients



Bhagya V Rao*, Deepa PB &Anusuya Patil

KLE College of Pharmacy, KAHER, Bengaluru

bhagyapkumar@gmail.com

Novel excipient is an excipient that is being used for the first time in a drug product, or by a new route of administration. It may be a new chemical substance or a well-established one which has not yet been used for human administration and /or for a particular human administration pathway. Novel excipients play a vital role in bringing new, better and safer drugs to the pharmaceutical field. The lack of universal regulatory rules brings substantial challenges in the development of novel excipients (1).

Excipients are the main ingredients of any pharma formulation and are critical for its safe and effective use. The rationale of excipients is very varied and diverse: they can act as fillers, lubricants, colouring agents, antioxidants, preservatives, adjuvants, stabilizers, emulsifiers, solubilizers, permeation enhancers, etc. The use of novel excipients is necessary for the formulation of various advanced products and the majority of approved products are traditional, well-studied excipients. New excipients play an important role in the formulation development and this strategy helps in advanced drug delivery systems designed to improve the therapeutic profile of drug substances and for more suitable routes of administration (2).

Regulatory Setting

Under the current regulatory structure, novel excipients are not assessed separately, but as part of a submitted investigational new drug application (IND) or the investigational medicinal product dossier (IMPD). Therefore, applicable guidelines should be taken into account early in the development of drug products containing novel excipients (Figure 1) (3).

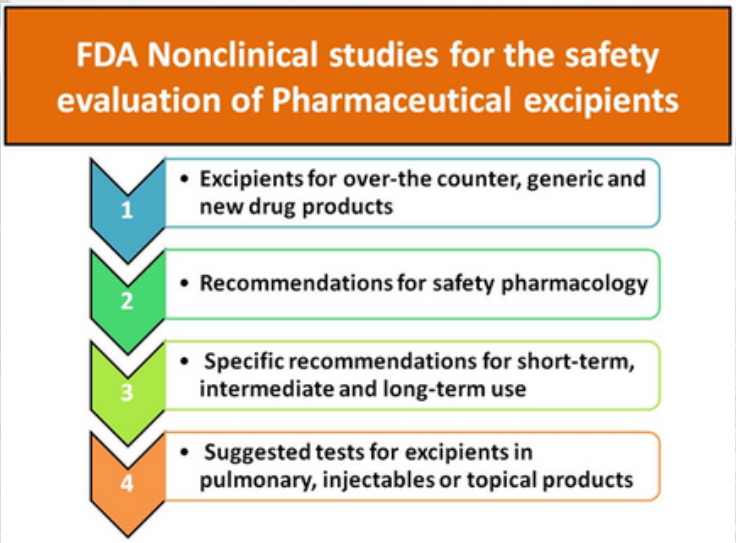


Figure 1: FDA Guidelines: The development of novel excipients, adapted from (7)

Novel excipients are essential for the improvement of advanced drug delivery systems. Even though several novel excipients are developed for pharmaceutical use, they are not often seen in drug products due to the stringent regulatory needs. The complex evaluation procedure results in the delay in the approval process of new products. Regulatory authorities consider novel excipients as new drug entities or substances and they require complete systematic evaluation similar to new drug substances. Consequently, regulatory approval for marketing of new drug products with novel excipient requires complete evaluation information that is much more complex and comprehensive than that for already known excipients.

Difficulties and challenges in the development of novel excipients

Pharmaceutical companies are generally reluctant to launch novel excipients in their formulations due to the amount of extra information necessary to support regulatory approval. Definitely, complete facts on the novel excipient´s manufacture, characterization and controls, with back references to supporting non-clinical and clinical safety data must be provided (4). Data should be presented in a format similar to the active substance format with significant quantity of detail. A consequence of this is the increased costs and time required for the development of the final drug product. Also, specific regulatory requirements do not yet exist for novel excipients and expectations are not aligned worldwide (5). Finally, significant parts of developed data on novel excipients consist of commercially sensitive and proprietary information and therefore, the intellectual property rights come into the picture. To guard this delicate information, the Excipient Drug Master File are used in the USA, but there are no equivalent procedures available in Europe (Figure 2).

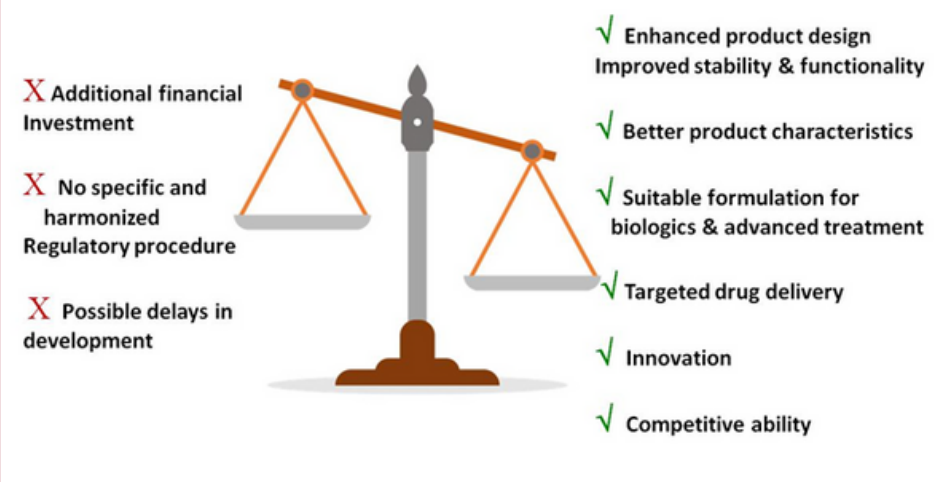


Figure 2: Challenges and benefits of using novel excipients in new product development adapted from (7)

Strategic approaches for novel excipient research

The systematic approach to a novel excipient strategy starts with a comprehensive literature search, which should determine all available chemical and toxicological data for the excipient of interest. Particular attention should be paid to monographs of the major international compendia (Pharmacopeia of Europe, USP and JP), the international specifications like FAO,WHO, JECFA, FDA Inactive Ingredient Database, Handbook of Pharmaceutical Excipients, historical usage as a food additive or cosmetic product, and Food Chemicals Codex. Next step, the important product specific parameters which include compatibility and performance

associated aspects will be determined and consigned as per diverse guidelines (6). This approach helps in the development of new and efficacious excipient which considers existing regulatory guidelines and targets reduced resources with high-quality end product (Figure 3).

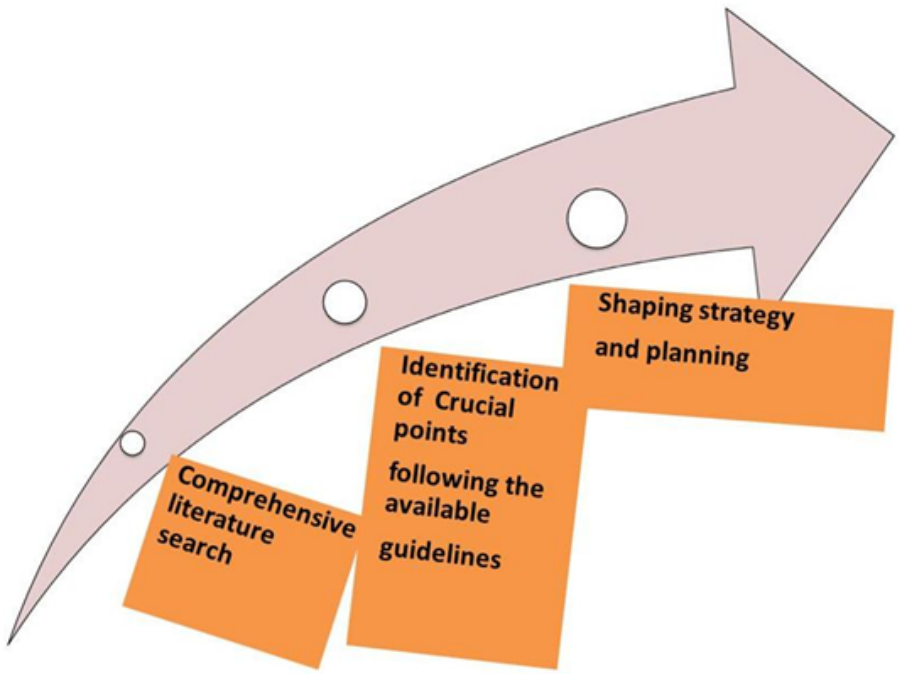


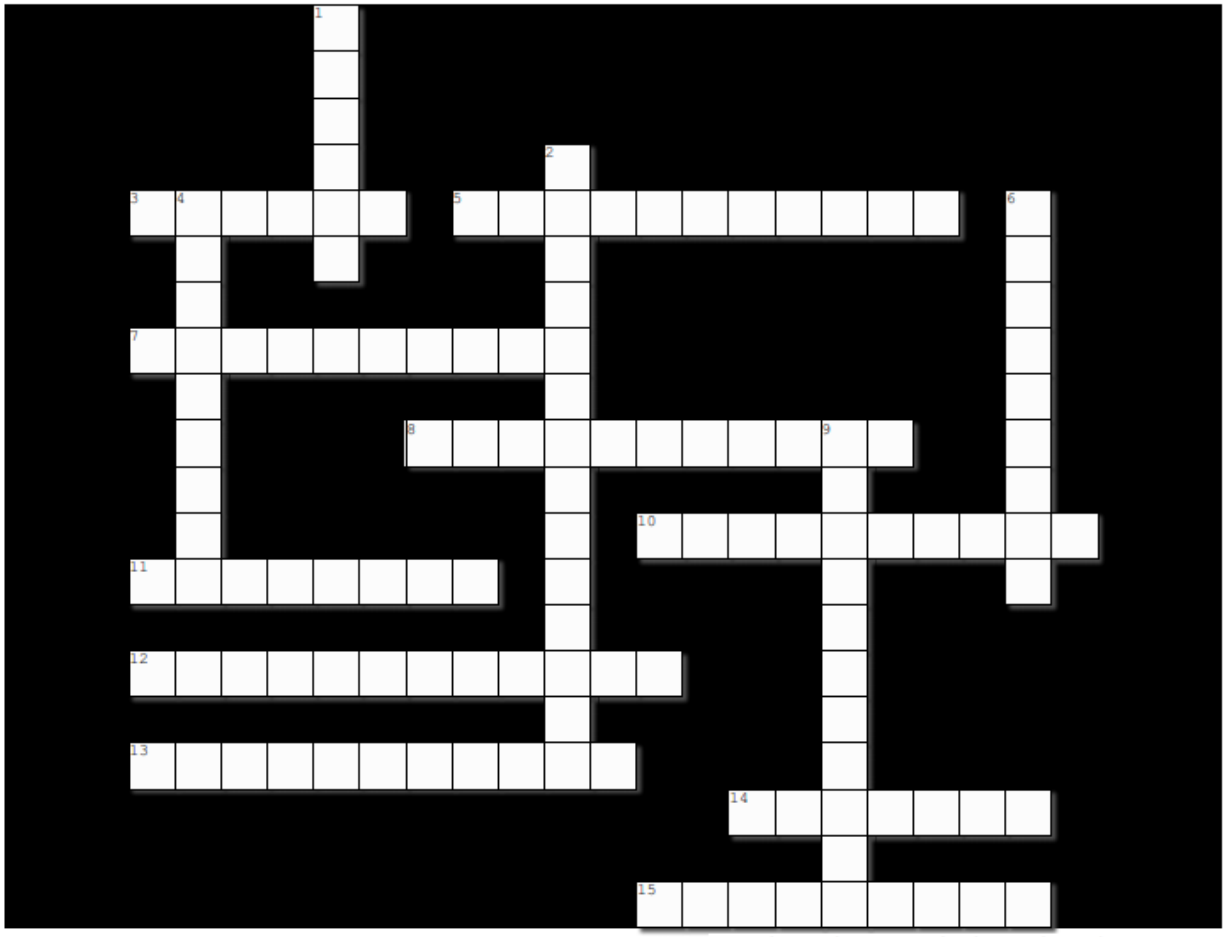
Figure 3: Strategy to approach a novel excipient research adapted from (7)

References

1. DeMerilis C., Goldring J., Schnoeker D: Inside IPEC: New Excipient Evaluation Procedure, Pharmaceutical Technology 2008;32
2. DeMerilis C., Goldring J., Velagaleti R., Brock W., Osterberg R: Regulatory Update: The IPEC Novel Excipient Safety Evaluation Procedure, 2009;33
3. FDA, 1989. Guideline on Drug Master Files (DMF). https://www.fda.gov/ Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ DrugMasterFilesDMFs/ucm073164.htm. FDA, USA (accessed 07.01.18).
4. Katdare, A., Chaubal, V.M., 2006. Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery. Informa Healthcare, New York.
5. Kolter, K., 2011. Novel excipients: a rare species. Pharm. Technol. Eur. 23, 10.
6. Kozarewicz, P., 2014. Regulatory perspectives on acceptability testing of dosage forms in children. Int. J. Pharm. 469, 245–248.
7. Best Practices in Dealing with Novel Excipients [Internet]. Biopharma Excellence. [cited 2021 Mar 28]. Available from: https://www.biopharmaexcellence.com/news/2019/12/13/best-practices-in-dealing-with-novel-excipients

Fun & frolic

Crossword



Created using the Crossword Maker on TheTeachersCorner.net

Across

3. Sweetening agent
5. Ascorbyl palmitate
7. Preservative
8. Antifoaming
10. Sorbitan monolaurate
11. Solubilizing agent
12. Superdisintegrant
13. Makes the polymer pliable and soft
14. Improves the flow of powder
15. Hyperosmotic laxative

Down

1. Suspending agent
2. Sustained release coating
4. Bulking agent
6. Regulates the moisture content of cream
9. Stabilizer

Solution on Page 55

Fun & frolic

Wordsearch Solution on page 54

N M F Z D S F Q I M X D A W F Q V Z T M
X W S S E R P I D U L V X B S J F L S K
B R O S O E N E X P L O T A B S P O J Z
P P B C U D A R O S I H T K T V E S I Z
K A R A F G N W M N X R A A W M L I L N
Q P E P C R M W K E A J R L C Z O D Y P
F A S T F L O M L N E T Z O P X S C E G
V K V E Z I H R S J A J M B Q H A A B P
A O O X H Y Z C T B P P E M U G R C G R
P D Z L Q V U O F Z R R S K H L B O R I
J X Y L L T X E Q E I I H I I Y A H D M
Y S O O O I J B S F Y M R T P H L Z A O
Q J Y L U E D S N P Y E O Q M V V P C J
Y A Z T V M L O H V T L B D X F S O L E
Q G J R G D P W N Z F L A J C A P M U L
L B F I F E K X R L W O B U D A R V A C
H J T X S X D C A E N S W Z K O L V N O
J T H B Y U P S P X F E G S A N N P X Z
D H E Q X N H Z F I Y U K A Y L W G Q B
P C U F Q W A V I C E L F C Y Q Z X I T

ACDISOL
TRANSCUTOL
EXPLOTAB
KOLLIDON
PEARLITOLFLASH
EMDEX
PRIMOJEL
CAPMUL
HISORAD
PRIMELLOSE
LUDIPRESS
FASTFLO
LABRASOL
CAPTEX
AVICEL
STARTAB
EMCOMPRESS
NEOSORB

Industry Roundup

02nd February, 2021: Lupin Pharmaceuticals, Inc, has entered into partnership with Phil, Inc, to deliver Solosec® (secnidazole), the only single 2g oral dose therapy, 2g oral granules for the treatment of bacterial vaginosis (BV), the most common vaginal infection in the US among adult women.

04th February, 2021: Enzene Biosciences Ltd has procured marketing authorisation from the Drug Controller General of India (DCGI) for teriparatide, a bioactive part of human parathyroid hormone (PTH). This peptide will provide an anabolic approach to the treatment of osteoporosis unlike the anti-resorptive therapies such as bisphosphates. The approved product will be marketed through their holding company Alkem Laboratories Ltd and currently they are also exploring other potential partnering opportunities.

08th February, 2021: AstraZeneca India (AstraZeneca Pharma India Limited), has received marketing authorisation for their anti-diabetic SGLT-2i class drug dapagliflozin, in India for the treatment of patients of chronic kidney disease (CKD) up to Stage III. The DAPA-CKD study concluded globally on March 30, 2020 demonstrated significant benefits in reducing CKD progression in patients with and without type-2 diabetes.

09th February, 2021: Umralisib sold under the brand name UKONIQTM is a product invented by Rhizen Pharmaceuticals, a clinical-stage oncology-focused biopharmaceutical company based in Switzerland, where Vadodara based Alembic Pharma has a 50% ownership. Umbralisib, a novel, next-generation, oral, once-daily, inhibitor of phosphoinositide 3 kinase delta and casein kinase 1 epsilon, was licensed to TG Therapeutics at an IND stage (TGR 1202) in 2012. It has recently secured US Food and Drug Administration (USFDA) accelerated approval for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20 based regimen, and adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy. Accelerated approval was granted for these indications, under a priority review (MZL), based on the results of Phase 2 UNITY-NHL Trial (NCT02793583).

09th February, 2021: USFDA has granted approval to market generic product, Tavaborole Topical solution, an antifungal medication by Lupin. This product is a generic of Anacor Pharmaceuticals' Kerydin Topical Solution indicated for the topical treatment of onychomycosis of the toenails due to Trichophyton mentagrophytes.

10th February, 2021: USFDA has granted Emergency Use Authorization (EUA) for the coadministration of Bamlanivimab (LY-CoV555) 700 mg, a human antibody (discovered by AbCellera and developed with Eli Lilly and Company) and Etesevimab (LY-CoV016) 1400 mg (a Eli Lilly antibody) for the treatment of mild to moderate COVID-19 in high risk patients aged 12 and above.

10th February, 2021: LupinLife has launched a Be One, ayurvedic health and wellness supplement which contains 100 per cent ayurvedic natural ingredients including ashwagandha, shatavari and shilajit. It is specially developed for men to boost energy levels and improve immunity.

11th February, 2021: Jubilant Biosys and Yale University have entered into a research collaboration for multiple small molecule research programmes in areas of medicinal chemistry, structural biology, in vitro and in vivo pharmacology among others. In this partnership, Jubilant Biosys will extend their research services to investigators at Yale University working on novel therapeutic targets.

12th February, 2021: Kixelle, a fast-acting biosimilar insulin analog co-developed by Biocon Biologics, a subsidiary of Biocon, Viatris, has received marketing authorisation approval as a 100 units/ml solution for injection in vial and pre-filled pen presentations from the European Commission. The biosimilar is indicated for the treatment of diabetes mellitus in adults, adolescents, and children aged 1 year and above.

12th February, 2021: USFDA has granted approval to generic Treprostinil injection, 20 mg/20 ml (1 mg/ml), 50 mg/20 ml (2.5 mg/ml), 100 mg/20 ml (5 mg/ml), and 200 mg/20 ml (10 mg/ml), multiple-dose vials by Alembic Global Holding SA. Treprostinil injection, used for the treatment of pulmonary arterial hypertension, is a generic of United Therapeutics Corp Remodulin injection in the same strengths. The injection is indicated for the treatment of pulmonary arterial hypertension to reduce symptoms associated with exercise and curb the rate of clinical deterioration.

13th February, 2021: USFDA has approved supplemental Biologics License Application (sBLA) for intravenous PANZYGA (Immune Globulin Intravenous [Human] – ifas 10% Liquid Preparation). This therapy is recommended for the treatment of adult patients with a rare neurological disease of the peripheral nerves called chronic inflammatory demyelinating polyneuropathy (CIDP). Pfizer and Octapharma AG are parties to a license agreement which grants marketing and commercialization rights of PANZYGA in the US to Pfizer, while Octapharma retains exclusive rights to commercialise the product globally outside of the US.

16th February, 2021: Glenmark Pharma launched SUTIB, the generic version of Sunitinib oral capsules to treat kidney cancer in India. The product is priced 96 per cent lower compared to the innovator brand.

16th February, 2021: Beta Drugs, a leading manufacturer of oncology products, launched Adsunib branded generic of Sunitinib in dosage strength of 12.5/25/50 mg capsules, used for the treatment of Renal Cell Carcinoma, Gastro-Intestinal Tumor & Pancreatic Neuroendocrine Tumor.

17th February, 2021: Lupin launched Posaconazole delayed-release tablets, a generic equivalent of Noxafil delayed-release tablet of Merck Sharp & Dohme Corp. This product is indicated for prevention of invasive aspergillus and candida infections in high-risk, low level immunity patients.

18th February, 2021: Dr Reddy's Laboratories launched Fluphenazine Hydrochloride tablets, a therapeutic equivalent of Prolixin tablets approved by the USFDA. The product is indicated for management of manifestations of psychotic disorders, in the US market.

19th February, 2021: USFDA granted approval to Zydus Cadila to market Droxidopa capsules in the strength of 100 mg, 200 mg, and 300 mg, used to treat low blood pressure. The product is indicated for treatment of hypotension in patients suffering from Parkinson's disease, multiple system atrophy, autonomic failure, and others.

19th February, 2021: USFDA also granted approval to Aurobindo Pharma to manufacture and market Droxidopa capsules in the strengths of 100 mg, 200 mg and 300 mg, a generic of Northera capsules manufactured by Lundbeck NA.

Source

1. https://www.biospectrumindia.com/category/segments/pharma-biopharma
2. www.expresspharma.in
3. https://health.economictimes.indiatimes.com/news/pharma/5

Contributor for this section:

Dr. Clara Fernandes

Associate Professor, Department of Pharmaceutics, Bombay College of Pharmacy, Mumbai

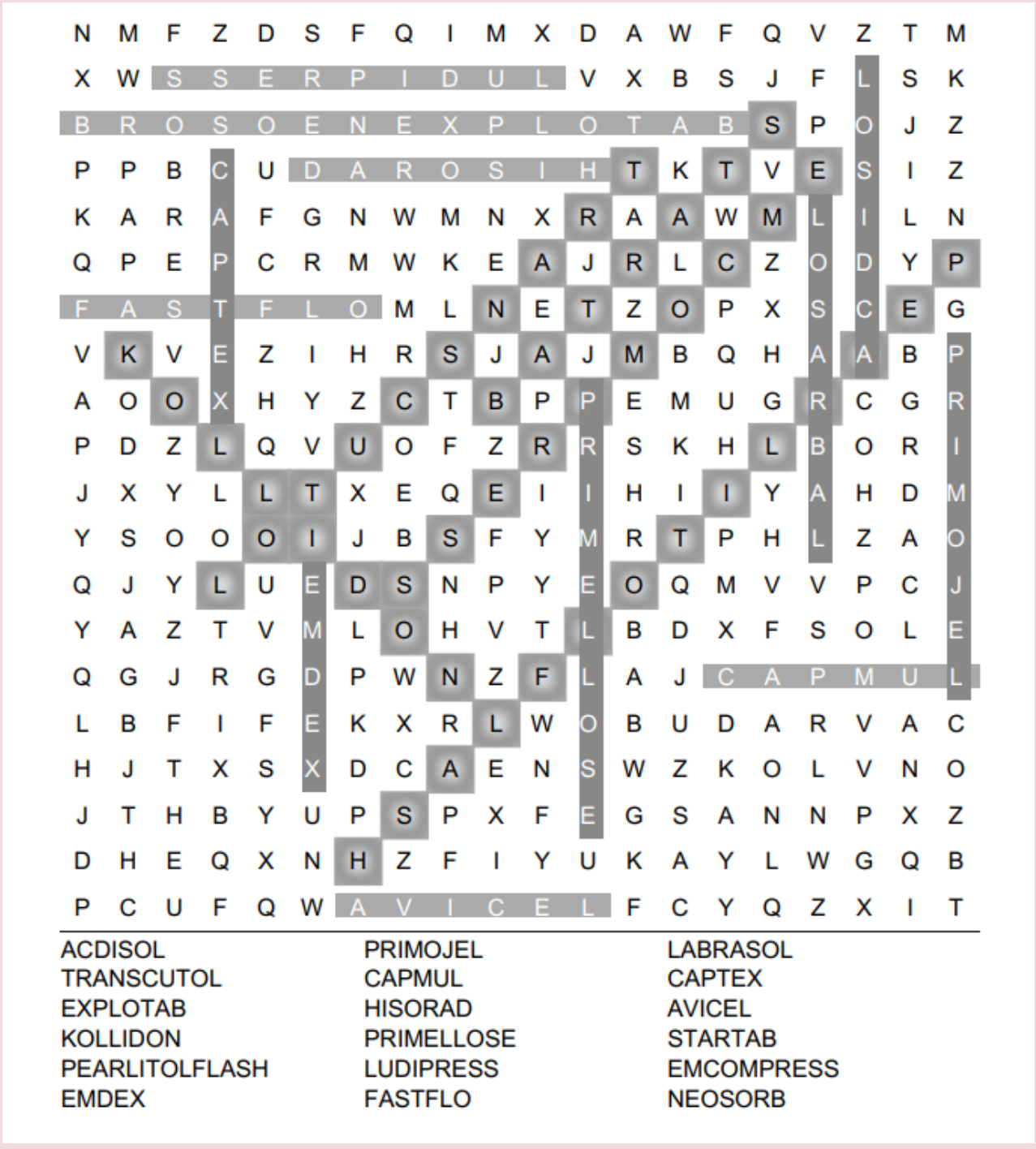
Fun & frolic

Unscramble from page 38

1. RSDTTNIGIENA	DISINTEGRANT
2. ENPOITMERA	PERMEATION
3. VOONETSLC	COSOLVENT
4. EPCDSORCSEO	COPROCESSED
5. RBIVAESA	ABRASIVE
6. CIARNTBLU	LUBRICANT
7. NTELTRCTOPAOY	LYOPROTECTANT
8. ARAINPFF	PARAFFIN
9. TALSECO	LACTOSE
10. MONEILTLE	EMOLLIENT

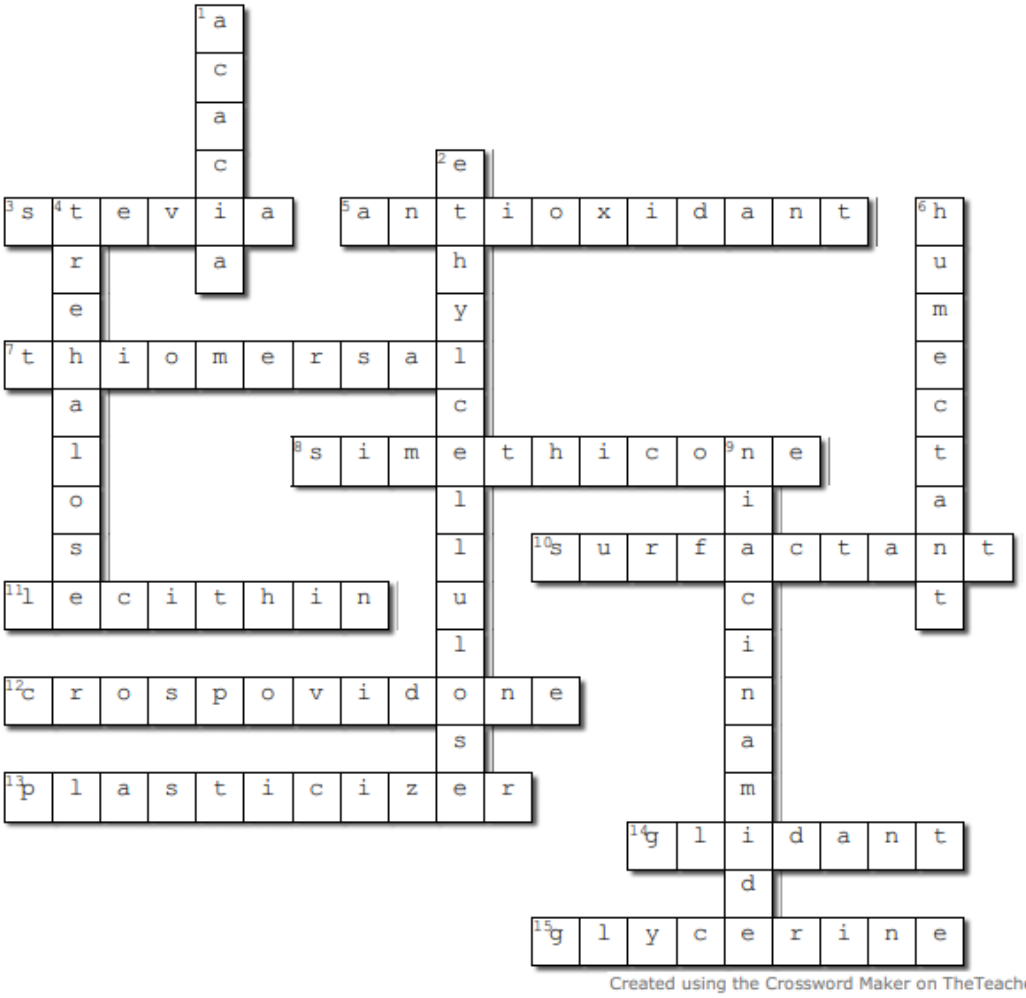
Fun & frolic

Wordsearch from page 48



Fun & frolic

Crossword from page 49



Across

3. Sweetening agent (**stevia**)
5. Ascorbyl palmitate (**antioxidant**)
7. Preservative (**thiomersal**)
8. Antifoaming (**simethicone**)
10. Sorbitan monolaurate (**surfactant**)
11. Solubilizing agent (**lecithin**)
12. Superdisintegrant (**crospovidone**)
13. Makes the polymer pliable and soft (**plasticizer**)
14. Improves the flow of powder (**glidant**)
15. Hyperosmotic laxative (**glycerine**)

Down

1. Suspending agent (**acacia**)
2. Sustained release coating (**ethylcellulose**)
4. Bulking agent (**trehalose**)
6. Regulates the moisture content of cream (**humectant**)
9. Stabilizer (**niacinamide**)

News & Events

International Women's Day 2021

International Women's Day 2021 was organized and celebrated by APTI Women's Forum on 8th March, 2021 through online platform. It was aimed to celebrate and salute the tremendous efforts put forward by women and girls worldwide in shaping a more equal future and recovery from the COVID-19 pandemic. The program was lead with the theme of "Women in leadership: Achieving an equal future in a COVID-19 world" and sub theme of "Womanhood divinities: an inherent source of vitality and dynamism (WDVD 2021)". The program was graced by Prof. P.D. Chaudhary APTI President; Prof. Swarnlata Saraf, APTI Vice President (CZ), Prof. Raman Dang, Secretary APTI and APTI officials and members from different states. The program started with the welcome address by Dr. Manju Singh, Co-convener APTI Women's Forum. Prof. Vandana Patravale, Convener APTI Women's Forum, introduced the entire team of APTI Women's Forum. The eminent guests and speakers were invited and program was well-coordinated by Mrs. Pragya Baghel as Moderator. First speaker was Ms. Divya Rathod, Silverynanos Innovations LLP who shared her professional and entrepreneurial experiences with everyone. Subsequently, second speaker Ms. Pracchi Parihar Saxenna, Curatio Healthcare Pvt Ltd shared her entrepreneurial and success story. Concluding remarks and vote of thanks was given by Prof. Purnima Ashok, Co-convener APTI Women's Forum. The program was successfully organized and celebrated with invited guest along with more than 90 participants online. The program was aimed at providing a platform where highly ambitious minds will get an opportunity to show their abilities. This event provided a platform to express and exchange the work done by young women experts in the field of pharmacy and health education to inspire the young budding scholars.

Contributed by:
Dr. Manju Rawat Singh
DHR-ICMR International Fellow, School of Pharmacy, Univ. of MS, Oxford, MS Assistant Professor,
Pt. Ravishankar Shukla University, Raipur (C.G.), India.

IWD celebration at IPGA

Central Executive Council of Indian Pharmacy Graduates Association – Women Forum celebrated an International Women's Day on 7th March, 2021. The theme for the webinar was "*Celebrating Sheroes of Pharmaceutical Research*". Following speakers graced the occasion.

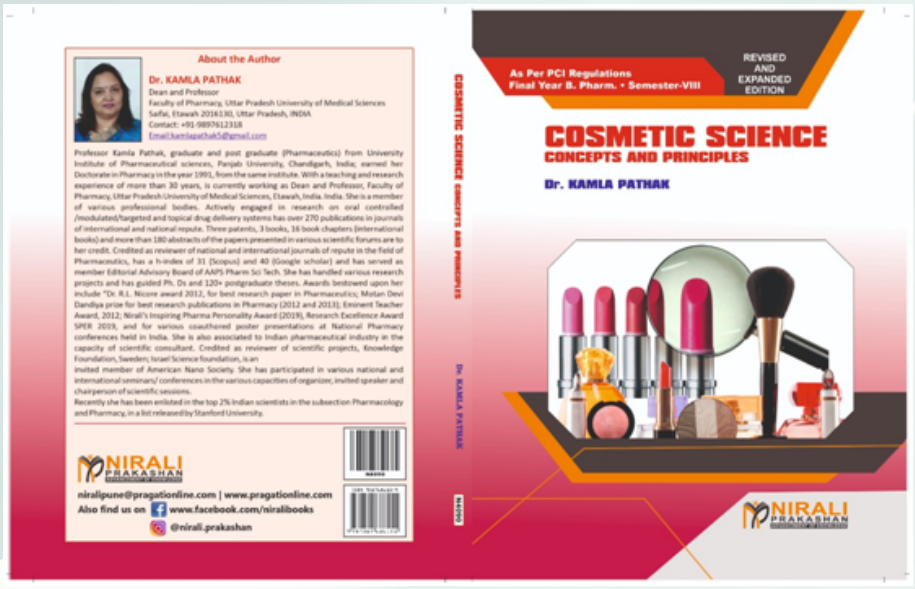
1. Dr. Kanchan Kohli, Former Professor and Head, Department of Pharmaceutics, Jamia Hamdard and currently Director, Lloyd Institute of Management & Technology, Greater Noida, UP;
2. Dr. Harvinder Popli, Director, School of Pharmaceutical Studies, DPSRU, New Delhi;
3. Dr. Vandana Patravale, Professor, Pharmaceutics, Institute of Chemical Technology, Mumbai and
4. Dr. Harsha Kharakwal, Director & Associate Professor, Amity Institute of Phytochemistry & Phytomedicine, Amity University, Noida.

Dr. Kanchan Kohli stressed on how to balance between the work life and family life as a female and also keep on achieving small goals to reach any milestones. Dr. Popli mentioned that how to enroll any work you do with your family members, which would help you in getting complete support and motivation from the family. Dr. Patravale talked about importance of the setting the priorities, how to remain always positive in your life and also talked about how to give time for yourself. She also emphasized on how we can inculcate good research habits in the students. Dr. Harsha gave a wonderful presentation on her innovations done for the benefits of the society. She talked about the self-defense spray, novel biopolymers as antidiarrheal, herbal hair dyes, herbal shampoo, lipsticks, herbal colors for food and cosmetics and overall, the biodegradable plastics and vegetarian capsules. She also talked about the different projects where she along with her team had empowered the women after the Kedarnath tragedy. The program was coordinated by Dr. Arti R. Thakkar, Associate Professor and Dr. Neerupma Dhiman, Associate Professor, Amity University, Noida

Contributed by:
Dr. Arti Thakkar
Associate Professor, Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India.

Book Review

Cosmetic Science



Inclusion of "Cosmetic Science" as an individual elective subject in B. Pharmacy Curriculum by the Pharmacy Council of India is laudable. It prepares students for careers in the consumer products industry, researching, developing, and testing new cosmetics, perfumes, toiletries, household products, and more.

The second edition of the book by Dr. Kamla Pathak, Dean and Professor, Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, has chapters that have been carefully revised and expanded to include newer concepts in the subject. Notably, the contents of the book are in accordance with the syllabus content of the elective subject Cosmetic Science, by Pharmacy Council of India. The revised version has separate section of Multiple choice questions, short questions and long answer question to help students in understanding the chapter and inculcating answer writing ability. Utmost care has been taken to incorporate all the elements described in the syllabus. Additional topics that might be useful for a student gearing up for cosmetic industry have also been included. The language is kept as simple as possible and illustrations have been used for easy grasping. In order to directly correlate the product description examples of marketed products have been included. This however does not imply that the author is in any way promoting the exemplified product.

This book will be a valuable guide for not only getting success in the examinations but also for those pursuing career in cosmetic industry.
Priced at Rs 360/-

Contributed by:
Prof. Shubhini A. Saraf
Professor and Dean (School of Pharmaceutical Sciences), Former Head,
Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University (A Central University)
Vidya Vihar, Raebareli Road, Lucknow, India.

.

Achievements

Dr. Sujata Sawarkar

Department of Pharmaceutics, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, India

Dr. Sujata was granted an Indian Patent (4230/MUM/2015), entitled "Pharmaceutical Hair Gel".

Dr. Sujata served as the Editor and also co-authored chapters in a book: "*Immunotherapy – Immunotherapy – A Novel Facet of Modern Therapeutics*" ISBN978-981-15-9038-2, published by Springer Nature Singapore Pvt. Ltd. https://link.springer.com/book/10.1007/978-981-15-9038-2

Dr. Mital Patel

Shobhaben Pratapbhai Patel School Of Pharmacy & Technology Management, NMIMS, Mumbai, India

Dr. Mital received First Prize in the event for Innovative Idea and received 3,500 INR as cash prize in a Challenge in the 1st STUDENT RESEARCH CONGRESS under the theme "Innovations for Better Health", organized online by SVKM's Dr. Bhanuben Nanavati College of Pharmacy and Co-hosted by the University of Mumbai on 28-30 September, 2020.

Dr. Babita A. Agarwal

Associate Professor in Pharmaceutical Chemistry & Central Instrumentation Facility Incharge, Marathwada Mitra Mandal's College of Pharmacy, Pune, India

Mrs. Babita has been awarded with Doctor of Philosophy by Savitribai Phule Pune University, Pune on 31st July 2020 for her research entitled "Development and Validation of Stability Indicating Method for Pharmaceuticals and Analysis of its Degradants " under the guidance of Dr. Santosh V. Gandhi, Professor at A.I.S.S.M.S College of Pharmacy, Pune.

Dr. Madhuri Deshmukh

Head of Department, Department of Pharmaceutics, R.D,College of Pharmacy Bhor, Pune, India

Dr. Deshmukh published an Indian Patent (Application No. 202121005110) entitled "Formulation, Optimization And Charactrization Of Gastroretentive Olanzepine Microsphere Using Factorial Design".

She was awarded with Doctor of Philosophy by Shivaji University, Kolhapur for her thesis entitled "Preparation and Evaluation of Mucoadhesive Microsphere of Anti-depressant Drugs" under the guidance of Dr. S. K. Mohite, Rajaramprabhu College of Pharmacy, Kasegaon.

Dr. Varsha Pradhan

Visiting Associate Professor, Delhi Pharmaceutical Sciences & Research University, New Delhi & currently pursuing her MS (Regulatory Science) at the University of Maryland, Baltimore

Dr. Varsha was part of the team which won 1st place in the 9th Annual Center of Excellence in Regulatory Science and Innovation (M-CERSI) 'America's Got Regulatory Science Talent Competition' held on 15 January 2021. The team presented its idea for "PrescripChain," a user-friendly mobile application for adverse event reporting that utilizes blockchain technology to provide automatic, bench-to-bedside tracing of the entirety of a drug's lifespan.
https://www.umaryland.edu/news/archived-news/january-2021/pharmacy-students-win-regulatory-science-contest.php

Dr. Sarasija Suresh

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, NIPER Mohali, India

Dr. Sarasija was granted a patent (No. 359071) entitled "Novel Curcumin-Drug conjugates"; (Inventors: Sandeep Kumar Jain, Sarasija Suresh and Manjinder Singh Gill); Patentee- NIPER, Mohali; on 22nd February, 2021.

Another patent (No. 390922) entitled "Process for preparation of Monosubstituted Ureas"; (Inventors: Dinesh K.T., Pinninti D.P., Bharani D, Rohini P.B., Sarasija S, Manjinder S.G.); Patentee: NIPER, Mohali; was also granted on 5th November, 2020.

Dr. Rajashree Sunil Chavan

Principal, Pune District Education Association's Seth Govind, Raghunath Sable College of Pharmacy, Saswad, Pune, India

Dr. Rajashree received a grant under the MODROB (Modernization and Removal of Obsolescence) scheme under AICTE, New Delhi for purchase of HPTLC (High Performance Thin Layer Chromatography); the amount of grant was INR 16,66,667/-

Dr. Krutika Sawant

Professor and Head, Department of Pharmacy, Dean, Faculty of Pharmacy, Kalabhavan Campus The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India.

Dr. Sawant received Indian Patent (347985; Application No.: 1625/MUM/2014), entitled "Oral Compositions And Processes For Preparing Different Dosage Forms Comprising Of Controlled Release Multi Unit Particulate System"; (Inventors: Mr. Mundada Piyush Kishor, Mrs. Mundada Veenu Piyush and Dr. (Mrs.) Sawant Krutika Khanderao); granted on 28th September, 2020.

Dr. Monica Gulati

Registrar, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India.

Dr. Gulati was granted Indian Patent (Publication no.: 09/2015), entitled “Media for In Vitro Dissolution Testing of Polysaccharide Based Colon Targeted Formulations and Method Thereof”; (Inventors: Goud Niranjan Kotla, Gulati Monica, Singh Sachin Kumar, Basotra Mohit, ChaudharyYashwant).

Dr. Aarti V. Belgamwar

Assistant Professor, Department of Pharmaceutics, Shri Vile Parle Kelvani Mandal's Institute of Pharmacy, Dhule, Maharashtra, India

Dr. Belgamwar was granted an Indian Patent (359346) entitled “Synthesis Of Chitosan-Grafthpßcd Copolymer By One Pot Synthesis Technique For Solubility Enhancement Ofefavirenz”; (Inventors: Ms. Aarti V. Belgamwar, Dr. Shagufta A. Khan and Dr. Pramod G. Yeole) on 24th February, 2021.

Dr. Aarti Abhishek Shah

Assistant Professor, Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM’s NMIMS, V.L. Mehta Road, Vile Parle (W), Mumbai, India.

Dr. Aarti was awarded Doctor of Philosophy on her Ph.D. Thesis entitled “*Development of nanoformulation of Resveratrol and its assessment on Postmenopausal Osteoporosis*”, in February 2020 from Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, formerly Manipal University, Manipal, Karnataka.

She was the Principal Investigator for the Project entitled, “D*evelopment of bone-targeted Resveratrol loaded nanoparticles for Postmenopausal Osteoporosis*” (Ref ID: SR/WOS-A/LS-444/2016) by Department of Science and Technology under Women Scientist Scheme- A (WOS-A) program worth of ₹21, 50, 000/- (Rupees Twenty-One Lakhs Fifty Thousand Only) for three years. (July 2017-July 2020).

Dr. Vaishali M. Gambhire

Assistant Professor, Department of Pharmaceutics, SND College of Pharmacy, affiliated to Savitribai Phule Pune University, Pune, India.

Mrs. Vaishali was awarded Doctor of Philosophy for her research work entitled "*Design, development and evaluation of solid lipid nanoparticles for enhancement of oral bioavailability*" from Savitribai Phule Pune University, Pune. The research work was carried out under the guidance of Supervisor Dr. (Mrs.) Nisharani S. Ranpise, Professor and Head of Department of Pharmaceutics, Sinhgad College of Pharmacy, Pune. She has developed solid lipid nanoparticles of dronedarone HCl and asenapine maleate for oral delivery to enhance intestinal uptake with improvement in bioavailability. During her Ph.D tenure, she had published 2 research papers in reputed International journals and also presented research posters in various Conferences including State level research Competition Avishkar 2017.

Dr. Santosh S. Bhujbal

Professor and Head Dept. of Pharmacognosy, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, India

Dr. S. S. Bhujbal has been conferred the “Best Teacher Award” (Professional Colleges- URBAN)- 2020-2021, by Savitribai Phule Pune University, Pune. Dr. Bhujbal was evaluated by the panel of experts on many aspects like, Research Projects, Teaching Paedogogy /Experiential Learning, Research Paper Publications, Books Published, Patents granted, Awards/Prizes, etc. The Award was given on the occasion of 72nd Foundation Day Programme of Savitribai Phule Pune University, Pune and by the hands of Prof. Dr. Nitin Karmalkar, Vice Chancellor and Dr. N. S. Umarani, Pro-Vice Chancellor, SPPU, Pune. The “Best Teacher Award” is considered as one of the most prestigious awards in the growing pharmacy field, which is awarded every year by SPPU to the fellow teachers, researchers and scientists for their exemplary contribution towards pharmacy profession. Dr. D. Y. Patil Unitech society’s Chairman Hon. Dr. P. D. Patil, Secretary Dr. Somnath Patil and Principal Dr. Sohan Chitlange congratulated Dr. Bhujbal for this prestigious achievement.

Dr. Yogesh Baban Zambare

Assistant Professor , Dr. D. Y. Patil Institute of Pharmaceutical Sciences & Research Pimpri, Pune, India

Yogesh B. Zambare has been awarded with Doctor of Philosophy in Pharmaceutical Chemistry for his research work entitled “*Design and Synthesis of Some New Heterocyclic Compounds As PPAR-'Y Receptor Agonist and Their Evaluation of Antidiabetic and Anticancer Activity*” from Savitribai Phule Pune University, Pune in Pharmaceutical Chemistry Savitribai Phule Pune University, Pune. The research work was carried out at Dr. D. Y. Patil Institute of Pharmaceutical Sciences & Research Pimpri, Pune and under the guidance of Dr. Sohan S. Chitlange, Principal, DPU Pharmacy. During his Ph.D. tenure, he has published research papers in reputed National and International Journals and also presented research work in National and International conferences. He sincerely acknowledges Dr. D. Y. Patil Unitech Society Chairman Hon. Dr. P. D. Patil, Secretary Hon. Dr. Somnath Patil, Principal Dr. Sohan Chitlange, for providing excellent infrastructure facilities for undertaking this research work.

Dr. Rakesh Kumar Mishra

Assistant Professor in Dr. D. Y. Patil Institute of Pharmaceutical Sciences & Research Pimpri, Pune, India.

Mishra Rakesh Kumar has been awarded the Degree of Doctor of Philosophy in Pharmaceutics for his research work entitled "*Development and Evaluation of Multiunit Drug Delivery System for the Treatment of Metabolic Syndrome*" from Savitribai Phule Pune University, Pune. in Pharmaceutical Chemistry Savitribai Phule Pune University, Pune. The research work was carried out at Dr. D. Y. Patil Institute of Pharmaceutical Sciences & Research Pimpri, Pune, under the guidance of Professor Dr. S. N. Dhole. During his Ph.D. tenure, he has published research papers in reputed National and International Journals and also presented research work in National and International conferences. This research work reached in State Level Avishkar competition held at Mumbai University. He sincerely acknowledges Dr. D. Y. Patil Unitech Society Chairman Hon. Dr. P. D. Patil, Secretary Hon. Dr. Somnath Patil, Principal Dr. Sohan Chitlange, for providing excellent infrastructure facilities for undertaking this research work.

Dr. Aditi Shrinivas Kulkarni

Assistant Professor , Dr. D. Y. Patil Institute of Pharmaceutical Sciences & Research Pimpri, Pune, India

Kulkarni Aditi Shrinivas, has been awarded with the Degree of Doctor of Philosophy (Ph.D.) in Pharmacognosy for his research work entitled "*Development and Evaluation of Herbal formulation using micro particulate drug delivery system in the management of Diabetes Mellitus*" from Savitribai Phule Pune University, Pune. The research work was carried out at Dr. D. Y. Patil Institute of Pharmaceutical Sciences & Research Pimpri, Pune and under the guidance of Dr. S. S. Bhujbal, Professor DPU Pharmacy. During her Ph.D. tenure, she has published research papers in reputed National and International Journals and also presented research work in National and International conferences. She sincerely acknowledges Dr. D. Y. Patil Unitech Society Chairman Hon. Dr. P. D. Patil, Secretary Hon. Dr. Somnath Patil, Principal Dr. Sohan Chitlange, for providing excellent infrastructure facilities for undertaking this research work.

Dr. Hetal Thakkar

Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda, Vadodara, India

1. Patent No. 358732 entitled “Liposomal dry powder inhaler (LDPI) of Azithromycin”(Name of the inventor(s):Hetal Paresh Thakkar, Thakore Sunil Pratapsinh, Shrivastave Praveen Kumar); granted on 17th February, 2021.
2. Patent No. 352012 entitled “Intravaginal ring(IVR) bearing Dehydrated Rehydrated vesicles (DRV) loaded with Raloxifene Hydrochloride and Leuprolide acetate” (Name of the inventor(s): Dr. Hetal Paresh Thakkar, Patel Arpita Ashokbhai); granted on 23rd November, 2020.
3. Patent No. 344646 entitled “PEGlyted spherulites of anticancer active ingredients” (Name of the inventor(s): Dr. Hetal Paresh Thakkar, Dhande Rahul Devidas); granted on 20th August, 2020.

Dr. Sonali Paresh Mahaparale

Associate Professor and Head Department of Pharmaceutical Chemistry at Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, India.

Dr. Sonali Paresh Mahaparale has received grant of Rs. 10 Lakh under MODROB scheme from AICTE, New Delhi. The college will procure different instruments under this MODROB grant which are useful for B. Pharm., M. Pharm. and Ph.D. students to conduct research activities.

Prof. Vandana B. Patravale

Professor of Pharmaceutics, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology (Deemed University under section 3 of UGC act 1956), Mumbai, Maharashtra, India

1. Dr. Vandana Patravale was granted an Indian patent (Patent No. 341894) entitled “Highly Porous Tablet”; (Inventors: Dr. Vandana Patravale, Mr. Ammar M Arsiwala, Dr. Dalapathi B Gugulothu, and Ms. Rashmi H Prabhu) on 17th July, 2020.
2. Another patent (Application No: 201921019828 a) entitled “Topical Composition”; (Inventors: Dr. Vandana Patravale, Mehul Shah, Lalatendu Pani Grahi and Pratik Kakade) was published on 27th November, 2020.
3. She was also granted a patent (Patent No: 358722) entitled “Vaccine delivery system for non-invasive immunization against brucellosis using green technology” on 17th February, 2021.

ASSOCIATION OF PHARMACEUTICAL TEACHERS OF INDIA (APTI)

APTI SECRETARIAT: K L E College of Pharmacy 2nd Block, Rajaji Nagar, Bengaluru, KA - 560 010. Phone : 080 23325611

LOTUS LOGO STORY

As a lotus is able to emerge from muddy waters un-spoilt and pure it is considered to represent a wise and spiritually enlightened quality in a person; it is representative of woman who carries out her tasks with little concern for any reward and with a full liberation from attachment. Lotus-woman in the modern sense of women's qualities: she is superbly intelligent, highly educated, and totally committed to individualism. She is politically astute and works incessantly for a better and more humane society. She is exquisite in her taste for music, art and culture, abounds in social graces and performs brilliantly in communication.