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Significance of excipients to enhance the bioavailability of poorly water-soluble drugs in oral solid dosage forms: A Review

Manoj Kumar Vadlamudi^{1,2} and Sangeetha Dhanaraj¹

¹School of Advanced Sciences, VIT University, Vellore-632 014, Tamil Nadu, India

²Analytical Research and Development, Ashland India Private Limited, Hyderabad-500 078, Telangana, India

E-mail : manojvadlamudi2023@gmail.com

Abstract. Nowadays most of the drug substances are coming into the innovation pipeline with poor water solubility. Here, the influence of excipients will play a significant role to improve the dissolution of poorly aqueous soluble compounds. The drug substance needs to be dissolved in gastric fluids to get the better absorption and bioavailability of an orally administered drug. Dissolution is the rate-controlling stage for drugs which controls the rate and degree of absorption. Usually, poorly soluble oral administered drugs show a slower dissolution rate, inconsistent and incomplete absorption which can lead to lower bioavailability. The low aqueous solubility of BCS class II and IV drugs is a major challenge in the drug development and delivery process. Several technologies have been used in an attempt to progress the bioavailability of poorly water-soluble drug compounds which include solid dispersions, lipid-based formulations, micronization, solvent evaporation, co-precipitation, ordered mixing, liquid-solid compacts, solvent deposition inclusion complexation, and steam aided granulation. In fact, most of the technologies require excipient as a carrier which plays a significant role in improving the bioavailability using Hypromellose acetate succinate, Cyclodextrin, Povidone, Copovidone, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Crospovidone, Starch, Dimethylacetamide, Polyethylene glycol, Sodium lauryl sulfate, Polysorbate, Poloxamer, Mesoporous silica and so on. This review deliberates about the excipients significance on bioavailability enhancement of drug products in a single platform along with pragmatically proved applications so that user can able to select the right excipients as per the molecule.

1. Introduction

Near about 40% of presently endorsed drugs fall under the BCS class II and IV [1]. This solubility enhancement excipients trend will have the marketplace at a compound annual growth rate (CAGR) of approximately 13% from 2014 to 2024 [2]. In research and development, about 80% of drug compounds channel stated being a poorly soluble in aqueous media which can facilitate efficiency complications of pharmaceutical dosage forms and especially in oral solid dosage forms (OSDF) segment. As an outcome, the oral bioavailability is often quite small for poorly water-soluble active pharmaceutical ingredients (APIs). Therefore, several formulation approaches were established to improve the water solubility. For making an OSDF, excipients working as combined carriers [3]. Excipients are from a natural or synthetic or semisynthetic source plays a vital part in pharmacological formulations to improve the water solubility, bioavailability, and stability of low solubility drug



products [4]. So, solubilizing technologies along with excipients are building a sustainable growing market opportunity for solubility enhancement in particular APIs [5].

Traditionally, OSDF making scientists were addressed the most of the solubility challenges by reducing particle-size, converting salt forms and adding surfactants, but most of the people adopted solid dispersion technologies for solubility enrichment of BCS class II and IV compounds. In the process of drug absorption, dissolution place a significant role for lipophilic drugs [6]. Therefore, it is essential to improve the dissolution rate of these drug molecules to make the maximal therapeutic value. Before understanding different methods and technologies for the enrichment of dissolution rate, it is essential to know about dissolution. The process where the solute particles (drug) goes into a solution over a period called as dissolution. The drug rate of dissolution is proportionate to drug solubility [6]. Therefore solubility places a significant role which controls the speed of dissolution, and henceforward it's necessary to improve the absorption as well as the bioavailability of poorly water-soluble drugs by using various technologies along with excipients [7].

The global pharma excipient market has shown a significant growth in recent years because excipients are increasingly aiding APIs in achieving better functionality, overcoming solubility challenges by providing a product to competitive benefit [8].

Various technologies have been introduced to improve the solubility through Physical changes by Particle size reduction, Polymorphism, Co-solvency, Co-crystallization, Hydrotrophy, Micronization, pH alteration, Change in the dielectric constant of solvent, Changing into amorphous forms, and Slat formation. Chemical modifications using Surfactants, Complexation, Hydrates or solvates, Soluble pro-drugs, Selective adsorption on insoluble carriers, Functional polymer technology, Precipitation inhibitors, Solvent deposition, Ultrasonic waves, Spherical agglomeration, co-precipitation process, Lipid-based delivery system, Microemulsion, Micellar, Porous Microparticle, Floating drug delivery system, Solid dispersions, Vascular approaches and so on can be targeted to progress the bioavailability of poorly solvable molecules [7].

By doing all above ways to improve solubility, the ultimate goal is to have the sustainability of outcome in the form of stability and will be achieved using the various excipients and technologies as per the nature of APIs. Here in this review, we attempted to provide the wide-ranging of excipients which were pragmatically proved a substantial part in bioavailability enrichment of poorly water-soluble drug compounds.

2. The role of excipients in bioavailability

2.1. What is an excipient?

Pharmaceutical drug delivery systems consist of additional therapeutically inactive constituents other than APIs which required for the formulation to work in the biological system, called as excipients [9].

2.2. What is the significance of excipients?

Excipients have a broad range of functionalities in making formulations in the form of bulking agents, binders, disintegrants, flavors, glidants, lubricants, preservatives, permeation enhancers, solubility enhancers, preservatives and sweeteners [10].

2.3. What is the significance of solubility?

The oral route of drug direction is the maximum favored process of drug delivery system, but for the case of BCS class II and IV drugs can be tough way due to its poor solubility and thus will lead to less absorption. Therapeutic efficiency of a drug is contingent on the solubility and bioavailability [7]. Typically, the solubility of a drug substance fundamentally depends on the solvent, temperature, and pressure [11]. However, the solubility of the pharmaceutical product directly related to the dissolution rate as per Noyes-Whitney equation, and hence dissolution rate step will play a major role in bioavailability improvement of aqueous solubility.

3. What is the significance of bioavailability?

It is the portion of a stable directed dose of medicine that goes to the systemic circulation. If the medication directed intravenously, its bioavailability is 100%. But, bioavailability tends to decrease when it administrated through other routes such as oral, rectal, transdermal, and subcutaneous due to its incomplete absorption at the site of action. Moreover, the bioavailability is one of the necessary tools in pharmacokinetics to determine dosages for non-intravenous routes of the administration [7,12] so here, the enhancement of bioavailability place a vital role in drug delivery systems of OSDF. In some cases, excipients will contribute to achieving the improvement of the bioavailability by using some conventional formulation technologies and methods.

4. How to select right excipients?

Nowadays, most of the people are working towards a pragmatic approach to the selection of polymers for solubility enhancement which consequences in formulators using polymers based on their traditional and reported applications. However, to select the polymers, the following approaches can be beneficial [13].

1. Physicochemical properties of conventional polymers, copolymers, blocks polymers including safety need to study.
2. Compatibility and miscibility studies need to perform between poorly soluble drugs and polymers.

Solid dispersion technologies have commonly used for enhancement of drug bioavailability by using suitable excipients for conversion of amorphous form. Here, the polymer role is to stabilize amorphous form against crystallization and also to progress the dissolution rate by preventing the re-crystallization process [14].

5. Categories of excipients

Solubility increasing excipients are comparatively new to the functionalities mentioned above. However, the need of excipients on growing part due to an increase in the growth rate of poorly soluble compounds in OSDF submissions. Solubility enhancing excipients mainly categorized into three sections called as a polymer, surfactant, and lipid based. However, polymer based excipients widely used for solubility enrichment process [15].

5.1. Polymer based excipients

Foremost function of polymeric excipients was used to stabilize the amorphous APIs and then maintains its supersaturation in an aqueous medium. TechNavio analysts forecast the growth of 16.8% CAGR over the period of 2014–2019 for OSDF in Global polymer based solubility enhancement excipients market [15].

5.2. Surfactant based excipients

APIs with high lipophilicity nature can have the poor wetting properties so; surfactants can facilitate their solubilization. Further, surfactants can solubilize the poorly soluble drug molecules by micelle formation or by acting as cosolvents. Non-ionic surfactants extensively used in pharmaceutical applications [16].

5.3. Lipid based excipients

The combination of lipophilic surfactants, hydrophilic surfactants, water-soluble co-solvents, triglyceride oils, co-surfactants can be able to build the efficient and stable self-emulsifying drug delivery system which can able to improve drug solubility and oral absorption called as lipid based excipients. So, lipid based excipient formulations can enable to improve the oral absorption of complex molecules, mainly on lipophilic drugs.

6. List of excipients

The following excipients played a major role pragmatically in improving the solubility and bioavailability of poorly solvable compounds.

6.1. *Hypromellose acetate succinate*

6.2. *Cyclodextrin*

6.3. *Povidone and Copovidone*

6.4. *Hydroxypropyl cellulose*

6.5. *Hydroxypropyl methylcellulose*

6.6. *Crospovidone*

6.7. *Starch*

6.8. *Dimethylacetamide*

6.9. *Polyethylene glycol*

6.10. *Sodium Lauryl Sulfate*

6.11. *Polysorbate*

6.12. *Poloxamer*

6.13. *LoxOral*

6.14. *Polyvinyl caprolactam- Polyvinyl acetate-Polyethylene glycol*

6.15. *Mesoporous silica*

6.1. Hypromellose acetate succinate

Hypromellose acetate succinate is a hydroxypropyl methylcellulose acetate succinate (HPMC-AS) polymer contains four types of semi-randomly substituted 12-28% of methoxy groups (-OCH₃), 4-23 % of hydroxypropoxy groups (-OCH₂CHOHCH₃), 2-16% of acetyl groups (-COCH₃) and 4-28% succinoyl groups (-COC₂H₄COOH) [17]. For structure refer to figure 1.

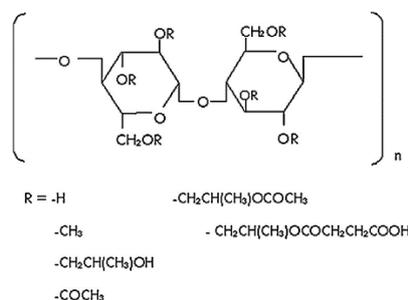


Figure 1. Structure of HPMC-AS.

6.1.1. Mode of function

It plays a crucial part in converting to amorphous form from crystalline either by spray dried and or by hot melt extrusion (HME) methods. HPMC-AS proved as an efficient way of producing some stable amorphous solid dispersions for poorly soluble APIs due to the following properties [18, 19].

1. Due to its swelling nature in gastric fluids, it dissolves rapidly in the upper small intestine and thus HPMC-AS solid dispersions carrier act as bioavailability enhancer for poorly water-soluble drugs.
2. It has a high glass transition temperature (T_g) at un-ionized state can be able to associate with kind of molecules having less mobility and forms an exceptional physical stability through spray-dried dispersions (SDDs).
3. It is having high solvable in volatile diluents like acetone, methanol, ethanol, and thus permits for cost-effective and controlled processes to form SDDs.
4. It permits unsolvable drug molecules to interact with the hydrophobic areas of polymer to form stable colloids in aqueous media due to its amphiphilic nature.
5. HPMC-AS is a unique polymer in making amorphous solid phase dispersions [18, 20].

6.1.2. Application 1

Physically stable formulations made for two-year shelf-life under the standard storage conditions by HPMC-AS based SDDs [18].

6.1.3. Application 2

HPMC-AS employed as a bioavailability enhancer excipient for Nimodipine delayed-release tablets using spray dried technology [21].

6.1.4. Application 3

HPMC-AS was found to be more efficient than poly vinyl pyrrolidone at maintaining the supersaturation of Felodipine during dissolution [22].

6.1.5. Application 4

HPMC-AS based SDDs of Nifedipine drug molecule showed an increase in dissolution pattern as compared to plane Nifedipine [23].

6.1.6. Application 5

Nifedipine dissolution was improved using HPMC-AS along with a higher succinyl substituent by solid dispersion technology [24].

6.2. Cyclodextrin

Cyclodextrins (CDs) belongs to the group of carbohydrates and are cyclic oligosaccharides. Cellulose first discovered by A. Villiers in 1891, after that F. Schardinger identified these naturally occurring as α -, β - and γ -CDs, also referred as Schrodinger Sugars [25, 26].

Typical CDs contains glucose monomers ranging from 6 to 8 units in a ring as shown in figure 2 [25, 27, 28]. α -, β - and γ -CDs contain 6, 7 and 8 membered sugar ring molecules respectively.

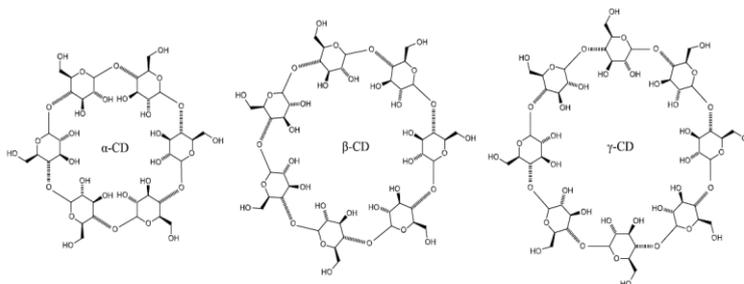


Figure 2. Structure of α -, β - and γ -CD.

6.2.1. Mode of action

CDs can form inclusion complexations in aqueous media which can able to improve the solubility of poorly-soluble drug compounds. It reduces the hydrophobicity nature of drugs by complexations, also improves their rectal absorption.

6.2.2. Application 1

An increase in aqueous solubility observed for Anandamide using hydroxypropyl β -CDs complexation [29].

6.2.3. Application 2

Pilocarpine drug oral bioavailability enhancement was found to be with β -CDs complexation [30].

6.2.4. Application 3

Practical solubility enhancement detected in complexation of Acyclovir with β -CDs [31].

6.3. Povidone and Copovidone

Povidone made up synthetically with multiple units of 1-vinyl-2-pyrrolidinone [32]. Copovidone made up with three parts of 1-vinyl-2-pyrrolidinone and two parts of vinyl acetate [33]. For individual structures refer to figure 3 and 4.

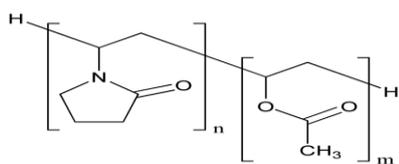


Figure 3. Structure of Copovidone.

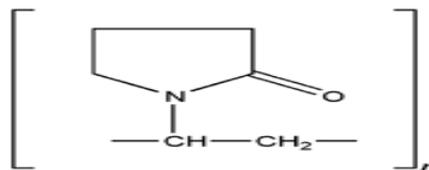


Figure 4. Structure of Povidone.

6.3.1. Mode of action

Widely used Povidone and Copovidone polymers in making solid dispersions because of having following properties.

1. Chemically inert to most of the molecules.
2. It has hydrogen bond acceptor which will enhance the thermodynamic and kinetic stability of solid dispersions in HME.
3. Non-pH dependent dissolution.
4. It has a solubility, stability and low viscosity in a wide range of solvents used in spray-dried dispersion technologies.
5. It improves the thermodynamic and kinetic stability of solid dispersions.

6.3.2. Application 1

Dissolution rate enhanced by taking a mixture of 2% w/w of mannitol and PVP K 25 in Indomethacin and Naproxen [34].

6.3.3. Application 2

As a polymeric blend, Copovidone and Hydroxypropyl methylcellulose combination was successfully demonstrated in higher and longer time of supersaturation and also increased the dissolution performance of the Oxeglitazar extruder by HME technology compared to the physical mixture [35].

6.3.4. Application 3

HME of Oleanolic acid using copovidone was found to be improved in oral bioavailability [36].

6.3.5. Application 4

The solubility enhancement was achieved by solid dispersions of Pizotifen malate with Povidone [37].

6.3.6. Application 5

Povidone/Copovidone combination excipients were used for Desloratadine to form SDDs and also maintained amorphous form by contributing steric hindrance for nucleation and crystal growing [38].

6.4. Hydroxypropyl cellulose

Hydroxypropyl cellulose (HPC) is a derivative of cellulose family having both aqueous and organic solubility. For structure refer to figure 5.

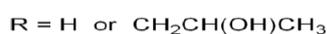
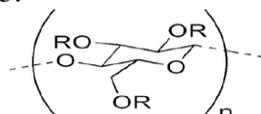


Figure 5. Structure of HPC.

6.4.1. Mode of function

HPC enhances the HME processability to improve the solubility due to its thermoplastic nature.

6.4.2. Application 1

Co-grinding technique was employed using a water-soluble HPC polymer for improvement of the dissolution rate in Benzo furoquinoline derivative molecule [39].

6.4.3. Application 2

Oral absorption improved for Insulin by using medium viscosity HPC polymer [40].

6.4.4. Application 3

Oral bioavailability has been enhanced using HPC solid dispersions of Indomethacin [41].

6.5. Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose (HPMC) is a combination of methyl and hydroxypropyl ether. It is semisynthetic, inert, and viscoelastic cellulose molecule. For structure refer to figure 6.

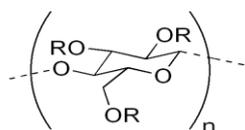


Figure 6. Structure of HPMC.

6.5.1. Mode of function

HPMC used as a solid dispersion solubilizer in spray-dried or/and HME formulations.

1. It acts as a hydrogen bond acceptor, donor, superior stabilizer, supersaturation inhibitor, chemically inert to most of the molecules in solid dispersion formulations.
2. pH independent dissolution in solid dispersions.
3. The low-viscosity grade of HPMC acts as a surfactant which can enhance the wetting properties of the drug and thus improves the solubility [42].

6.5.2. Application 1

A co-grounded mixture of Nifedipine, polyethylene glycol 6000 and HPMC with a small amount of water showed a remarkable effect on Nifedipine dissolution and its apparent solubility [43].

6.5.3. Applications 2

HPMC had a profound effect on solubility enhancement of Carbamazepine form III in both physical mixture and solid dispersions [44].

6.5.4. Application 3

Simvastatin apparent solubility was enhanced using low viscous hydrophilic HPMC polymer by co-solvent evaporation methodology [42].

6.6. Crospovidone

It is a form of cross-linked homopolymer made up synthetically with *N*-vinyl-2-pyrrolidinone [45].

6.6.1. Mode of function

It is a unique superdisintegrant with high interfacial action which can able to improve the dissolution rate of low solvable compounds [46]. It can act as an amorphous form stabilizer for few drugs by inhibition of drug re-crystallization [47]. It improves the wettability of hydrophobic drugs and thus improves the solubility. For structure refer to figure 7.

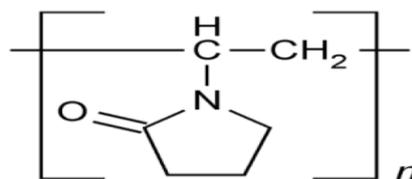


Figure 7. Structure of Crospovidone.

6.6.2. Application

Dissolution rate has been improved in Furosemide using Crospovidone by both kneading and co-precipitation methods [48].

6.7. Starch

It is the most abundant carbohydrate which reserves in trees, leaves, flowers, fruits, seeds, stems and roots. It consists of more number of glucose units joined by glycosidic bonds.

6.7.1. Mode of function

Here, Amylose exhibits as a higher tendency towards the crystallization resulting in insoluble adducts, while amylopectin shows slow jellification and finally forming highly translucent and opaque systems over the period which will tend to enhance the solubility of APIs [49]. For structure refer to figure 8.

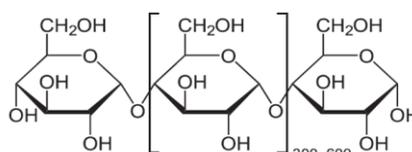


Figure 8. Structure of Starch.

6.7.2. Application 1

Solubility enhancement of Griseofulvin was observed using corn starch by solid dispersions technology [50].

6.7.3. Application 2

Aceclofenac solid dispersions exhibited dissolution enhancement by using corn starch as a carrier [51].

6.7.4. Application 3

The porous starch functioned as solubility enhancement carrier for Carbamazepine [49].

6.7.5. Applications 4

Efavirenz tablets formulated by solid dispersion technology using starch phosphate excipient worked as a rapid and higher dissolution rate than pure and commercial tablets [52].

6.7.6. Application 5

Efavirenz solid dispersions offered a fast and tertiary dissolution rate than pure and commercial tablets using starch citrate as a carrier [53].

6.7.7. Application 6

Dissolution enhancement of Irbesartan tablets was found to be more than pure drug using starch phosphate by solid dispersions technology [54].

6.8. Dimethylacetamide

Dimethylacetamide (DMA) is a colorless water-miscible organic compound having high boiling liquid and is miscible with most of the solvents.

6.8.1. Mode of function

DMA used as a solvent and co-solvent in pharmaceutical formulations for increasing the bioavailability of APIs [55, 56]. For structure refer to figure 9.

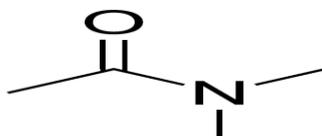


Figure 9. Structure of DMA.

6.8.2. Application

DMA used as co-solvent for the production of nanoparticles by which incremental dissolution was observed in Norfloxacin [57].

6.9. Polyethylene glycol

Polyethylene glycol (PEG) is a form of polyether compound [58].

6.9.1. Mode of function

The solid dispersion formulation together with PEG and Polysorbate 80 will place a vital role in the bioavailability enhancement of poorly water-soluble drugs [59]. For structure refer to figure 10.

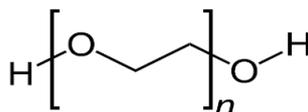


Figure 10. Structure of PEG.

6.9.2. Application 1

Enrichment of dissolution release rate and oral-absorption of Griseofulvin was observed using PEG 4000 and 6000 by pulverized solid sides ions process [60].

6.9.3. Application 2

The combination of PEG 4000, PEG 6000 and urea were used as carriers in solid dispersion technology for Ketoconazole by solvent evaporation method which led to substantial change in solubility [61].

6.10. Sodium Lauryl Sulfate

6.10.1. Mode of action

Sodium Lauryl Sulfate (SLS) is an anionic surfactant and act as a solubilizer in greater than critical micelle concentration [62]. For structure refer to figure 11.

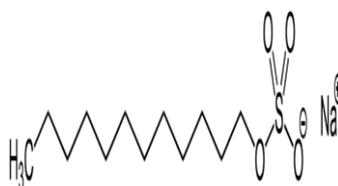


Figure 11. Structure of SLS.

6.10.2. Application 1

Diazepam and Fenofibrate tablets manufactured by solid dispersion technology using SLS as a carrier which resulted in solubility enhancement [63].

6.10.3. Application 2

An incremental solubility observed in Rofecoxib using SLS in water at all the temperature [64].

6.11. Polysorbate

Polysorbates are from Polyoxyethylene Sorbitan Fatty Acid Esters, and it acts as a solubilizing agent [62]. Polysorbates played a significant role in solubilizing the essential oils into water-based compounds. Polysorbate 80 and 20 are widely used as solubilizers. For structure refer to figure 12.

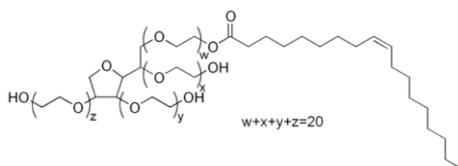


Figure 12. Structure of Polysorbate 20.

6.11.1. Mode of function

Polysorbate 80 and 20 are nonionic surfactants, emulsifiers often used in food as well as in cosmetics [65,66]. Polysorbate 80 frequently used as a constituent in medicating vehicles for pre-clinical *in-vivo* studies [67].

6.11.2. Application

Polysorbate 80 improved the absorption of P-glycoprotein substrate, digoxin, in rats [67].

6.12. Poloxamer

6.12.1. Mode of function

These are nonionic triblock copolymers consists of a central hydrophobic chain of polyoxypropylene allied by two hydrophilic chains of polyoxyethylene [68]. For structure refer to figure 13.

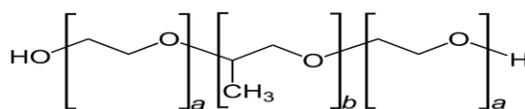


Figure 13. Structure of Poloxamer,
(a = 2–130 and b = 15–67).

6.12.2. Application 1

The significant improvement observed in the solubility enhancement of recoveries without modulating transporter-mediated efflux in Human Colon carcinoma (Caco-2) system by using a mixture of 2.5% w/v of Poloxamer 188 and 4% w/v of BSA (Bovine serum albumin) to HBSS (Hanks balanced salt solution) [69].

6.12.3. Application 2

Poloxamer 407 has the better solubility enhancement nature over Pioglitazone Hydrochloride and Glimperide using wet granulation technique [70].

6.12.4. Application 3

Dissolution enhancement resulted in Rofecoxib molecule by preparing its SDDs using Poloxamer 188 by melting method [71].

6.13. LoxOral

6.13.1. Mode of function

LoxOral act as a base, exceptional flow properties and reduces static which will improve the dissolution rate. It is gluten, free from dye, magnesium stearate, SLS, lactose, soy and also called as isomalt which has the potential prebiotic effects [72].

6.13.2. Application

LoxOral was found to be critical excipient for accelerating the dissolution and oral bioavailability of Ketoconazole.

6.14. Polyvinyl caprolactam- Polyvinyl Acetate-Polyethylene glycol (PVC-PVA-PEG)

6.14.1. Mode of function

PVC-PVA-PEG is a combination of 13% PEG 6000, 57% polyvinyl caprolactam and 30% polyvinyl acetate. It offers solubilizing assets for poorly water-soluble drugs by amorphous solid dispersions using HME technology [73]. For structure refer to figure 14.

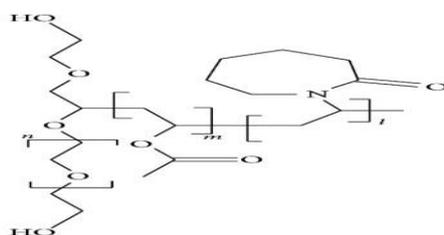


Figure 14. Structure of PVC-PVA-PEG.

6.14.2. Application 1

Eplerenone dissolution enhancement and stabilization significantly accomplished by solid dispersion technology using PVC-PVA-PEG as a carrier [74].

6.14.3. Application 2

Carvedilol solid dispersion preparation was studied using freeze drying method with PVC-PVA-PEG by which highest saturation solubility achieved [75].

6.14.4. Application 3

Atorvastatin spray-dried solid dispersions using PVC-PVA-PEG polymer enhanced the bioavailability in the ratio of 2:8 [76].

6.14.5. Application 4

Homogeneous solid dispersions of felodipine increased the solubility with PVC-PVA-PEG polymer [77].

6.15. Mesoporous silica

Mesoporous silica (MPS) shows exceptional properties to progress the oral bioavailability of low water-soluble molecules due to its uniform porosity, biocompatibility, and biodegradability. Some of the *in-vitro* studies showing improved dissolution by changing crystalline state to physically protecting amorphous form [78].

6.15.1. Mode of function

The use of mesoporous (Pore size from 2 to 50 nm range) silica for stable amorphous solid dispersions gained the attention of formulators due to its adjustable porosity, more surface area, inertness, and biocompatible [79].

In lipid-based drug delivery systems, MPS are used to absorb the liquid lipid/oil inside their confined pores [80]. In solvent based approach, the drug solution can be sprayed onto the silica carrier to load the drug molecule inside its pore structure. Because of its restricted orifice area and H-bonding, there are very fewer chances for re-crystallization of the drug. Another approach is co-milling/co-grinding with highly hydrophilic carriers like MPS. Since hydrophilic carriers possess a high density of silanol(Si-OH) groups on its surface, can generate H-bonding mechanism between drug and carrier, which can consequence the improvement of drug release in biological fluids [81]. For structure refer to figure 15.



Figure 15. Structure of MPS.

6.15.2. Application 1

Bioavailability of Atorvastatin drug improved using MPS materials like SBA-15 and Mesocellular siliceous foam [82].

6.15.3. Application 2

Studied the effect of spherical MPS nanoparticles for improving the oral bioavailability of Telmisartan [83].

7. Conclusion

By nature, most of the excipients might be inert. It is essential to know that the excipients are not only for bulking up the formulation but also place a vital part in the bioavailability enhancement of BCS class II and IV drug molecules through a pragmatic way of experimentations. In this review, consolidated the wide range of excipients portfolio along with the applications used for the

bioavailability improvement of poorly water-soluble compounds so that the user can able to identify and select the suitable excipients as per the nature of the drug molecule.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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References:

- [1] Javadzadeh Y, Siahi-Shadbad M R, Barzegar J M and Nokhodchi A 2005 *Il Farmaco* **60** 361-65.
- [2] www.klinegroup.com/reports/solubility_enhancement_pharmaceutical_oral_solid_dosage_for_ms.asp
- [3] Paus R, Prudic A and Ji Y 2015 *Int. J. Pharm.* **485** 277-87.
- [4] Widanapathirana L, Tale S and Reineke T M 2015 *Mol. Pharm.* **12** 2537-43.
- [5] Kanaujia P, Poovizhi P, Ng W K and Tan R B H 2015 *Powder Technol.* **285** 2-15.
- [6] Panchagnula R and Thomas N S 2000 *Int. J. Pharm.* **201** 131-50.
- [7] Vadlamudi M K, Dhanaraj S 2016 *J. Chem. Pharm. Res.* **8** 208-35.
- [8] <http://www.americanpharmaceuticalreview.com/Featured-Articles/174388-Trends-in-Demand-for-Variou-Excipients/>
- [9] Rowe C R, Sheskey P J and Quinn M E 2009 *A Handbook of Pharmaceutical Excipients (6th Edition)* London Pharmaceutical Press.
- [10] Walsh J, Cram A, Woertz K, Breikreutz J, Winzenburg G, Turner R and Tuleu C 2014 *Adv. Drug Deliv. Rev.* **73** 14-33.
- [11] Parve B, Shinde P, Rawat S, Rathod S and Waghmode G 2014 *World J. Pharm. Pharm. Sci.* **3** 400-22.
- [12] Hetal T, Bindesh P and Sneha T 2010 *Int. J. Pharm. Sci. Rev. Res.* **4** 203-23.
- [13] Chauhan H 2006 *J. Develop. Drugs* **4** 2329-6631.
- [14] Utracki L A 1998 *Commercial polymer blends* Springer 117-136.
- [15] <http://www.prnewswire.com/news-releases/global-polymer-based-solubility-enhancement-excipients-market-for-osdf-2015-2019-300181217.html>
- [16] <http://www.americanpharmaceuticalreview.com/Featured-Articles/179228-Solubility-Concerns-API-and-Excipient-Solutions/>
- [17] Official Monograph for Hypromellose Acetate Succinate USP40–NF35, 7704
- [18] Friesen D T, Shanker R, Crew M, Smithy D T, Curatolo W J and Nightingale J A S 2008 *Mol. Pharm.* **5** 1003-19.
- [19] Dong Z and Choi D S 2008 *AAPS PharmSciTech* **9** 991-7.
- [20] Curatolo W, Nightingale J A and Herbig S M 2009 *Pharm. Res.* **26** 1419-31.
- [21] Zhao Y, Xin T, Ye T, Yang X and Pan W 2014 *Asian J. Pharmacol.* **9** 35-41.

- [22] Konno H, Handa T, Alonzo D E and Taylor L S 2008 *Eur. J. Pharm. Biopharm.* **70** 493-9.
- [23] Tanno F, Nishiyama Y, Kokubo H and Obara S 2004 *Drug Dev. Ind. Pharm.* **30** 9-17.
- [24] Ueda K, Higashi K, Yamamoto K and Moribe K 2014 *Int. J. Pharm.* **464** 205-13.
- [25] Devi N K D, Rani A P, Javed M M, Kumar K S, Kaushik J and Sowjanya V 2010 *Pharmacophore* **1** 155-65.
- [26] Del Valle E M 2004 *Process Biochem.* **39** 1033-46.
- [27] Loftsson T and Brewster M E 1996 *J. Pharm. Sci.* **85** 1017-25.
- [28] Rajewski R A and Stella V J 1996 *J. Pharm. Sci.* **85** 1142-69.
- [29] Jarho P, Urtti A, Pate D W, Suhonen P and Järvinen T 1996 *Int. J. Pharm.* **137** 209-16.
- [30] Freedman K A, Klein J W and Crosson C E 1993 *Curr. Eye Res.* **12** 641-7.
- [31] Rossel C V P, Sepúlveda Carreño J, Rodríguez-Baeza M and Alderete J B 2000 *Quimica Nova* **23** 749-52.
- [32] Pera I 1988 *Oral hygiene formulation containing sodium alginate* US Patent US4775525 A.
- [33] Pattanayak D, et al. 2012 *Stable pharmaceutical compositions of olanzapine and process for their preparation* U.S. Patent US20120058185 A1.
- [34] Paus R, Prudic A and Ji Y 2015 *Int. J. Pharm.* **485** 277-87.
- [35] Kalivoda A, Fischbach M and Kleinebudde P 2012 *Int. J. Pharm.* **429** 58-68.
- [36] Gao N, Guo M, Fu Q and He Z 2017 *Asian J. Pharmacol.* **12** 66-72.
- [37] Margarit M V, Marin M T and Contreras M D 2001 *Drug Dev. Ind. Pharm.* **27** 517-22.
- [38] Kolašinac N, Kachrimanis K, Djuriš J, Homšek I, Grujić B and Ibrić S 2013 *Drug Dev. Ind. Pharm.* **39** 1020-27.
- [39] Yamada T, SAITO N, Imai T and OTAGIRI M 1999 *Chem. Pharm. Bull.* **47** 1311-13.
- [40] Mesiha M and Sidhom M 1995 *Int. J. Pharm.* **114** 137-40.
- [41] Chowdary K P R and Suresh Babu K V V 1994 *Drug Dev. Ind. Pharm.* **20** 799-813.
- [42] Pandya P, Gattani S, Jain P, Khirwal L and Surana S 2008 *AAPS PharmSciTech* **9** 1247-52.
- [43] Sugimoto M, Okagaki T, Narisawa S, Koida Y and Nakajima K 1998 *Int. J. Pharm.* **160** 11-9.
- [44] Bhise S and Rajkumar M 2008 *Asian J. Pharmacol.* **2** 38.
- [45] Sangekar S A, Lee P I and Vadino W A 1999 *Solid solution of an antifungal agent with enhanced bioavailability* U.S. Patent US5972381 A.
- [46] Kaur T, Gill B, Kumar S and Gupta G D 2011 *Int. J. Curr. Pharm. Res.* **3** 1-7.
- [47] Mohamed M B, Talari M K, Tripathy M and Majeed A B A 2012 *Int. J. Drug Form. Res.* **3** 13-28.
- [48] Shin S C, Oh I J, Lee Y B, Choi H K and Choi J S 1998 *Int. J. Pharm.* **175** 17-24.
- [49] Ali M T, Fule R, Sav A and Amin P 2013 *AAPS PharmSciTech.* **14** 919-26.

- [50] Saito M, Ugajin T, Nozawa Y, Sadzuka Y, Miyagishima A and Sonobe T 2002 *Int. J. Pharm.* **249** 71-9.
- [51] Kumar S and Gupta S K 2014 *Arch. Pharm. Res.* **37** 340-51.
- [52] Chowdary K P R, Enturi Veeraiah 2013 *Int. J. Pharm. Sci. Drug. Res.* **3** 89-92
- [53] Chowdary K P R and Enturi V 2011 *J. Appl. Pharm. Sci.* **1** 119-23.
- [54] Enturi V, Chowdary B Y and Chowdary K P R 2014 *Asian J. Pharm.* **8** 171-7.
- [55] Strickley R G 2004 *Pharm. Res.* **21** 201-30.
- [56] Kawakami K, Oda N, Miyoshi K, Funaki T and Ida Y 2006 *Eur. J. Pharm. Sci.* **28** 7-14.
- [57] Jeon H J, Jeong Y I, Jang M K, Park Y H and Nah J W 2000 *Int. J. Pharm.* **207** 99-108.
- [58] Pedersen C J 1967 *J. Am. Chem. Soc.* **89** 7017-36.
- [59] Dannenfelser R M, He H, Joshi Y, Bateman S and Serajuddin A 2004 *J. Pharm.Sci.* **93** 1165-75.
- [60] Chiou W L 1977 *J. Pharm. Sci.* **66** 989-91.
- [61] Sonawane T D and Mujoriya R Z 2016 *Research Journal of Pharmaceutical Dosage Forms and Technology* **8** 173-6.
- [62] Patel N K and Kostenbauder H B 1958 *J. Pharm. Sci.* **47** 289-93.
- [63] De Waard H, Hinrichs W L J, Visser M R, Bologna C and Frijlink H W 2008 *Int. J. Pharm.* **349** 66-73.
- [64] Desai K G H, Kulkarni A R and Aminabhavi T M 2003 *J. Chem. Eng. Data.* **48** 942-45.
- [65] Singh A, Van Hamme J D and Ward O P 2007 *Biotechnol. Adv.* **25** 99-121.
- [66] Spornath A, Yaghmur A, Aserin A, Hoffman R E and Garti N 2002 *J. Agric. Food Chem.* **50** 6917-22.
- [67] Zhang H, Yao M, Morrison R A and Chong S 2003 *Arch. Pharm. Res.* **26** 768-72.
- [68] Moghimi S M and Hunter A C 2000 *Trends Biotechnol.* **18** 412-20.
- [69] Shah, Devang, et al. 2014 *Drug Metab. Lett.* **8** 109-18.
- [70] GRACE X F, Latha S, Shanthi S and REDDY C U 2012 *Int. J. Pharm. Pharm. Sci.* **4** 377-9.
- [71] Shah T J, Amin A F, Parikh J R and Parikh R H 2007 *AAPS PharmSciTec* **8** E18-E24.
- [72] Gibson Glenn R et al. 2010 *Food Sci. Technol. Bull. Funct. Foods* **7** 1-19.
- [73] Linn M, Collnot E M, Djuric D, Hempel K, Fabian E, Kolter K and Lehr C M 2012 *Eur. J. Pharm. Sci.* **45** 336-43.
- [74] Kendre P N and Chaudhari P D 2017 *Drug. Dev. Ind. Pharm.* **43** 751-61.
- [75] Shamma R N and Basha M 2013 *Powder. Tech.* **237** 406-14.
- [76] Ha E S, Baek I H, Cho W, Hwang S J and Kim M S 2014 *Chem. Pharm. Bull.* **62** 545-51.

- [77] Lu J, Cuellar K, Hammer N I, Jo S, Gryczke A, Kolter K, Langley N and Repka M A 2016 *Drug. Dev. Ind. Pharm.* **42** 485-96.
- [78] McCarthy C A, Ahern R J, Dontireddy R, Ryan K B and Crean A M 2016 *Expert Opin. Drug. Deliv.* **13** 93-108.
- [79] Choudhari Y, Hoefler H, Libanati C, Monsuur F and McCarthy W 2014 *In Amorphous Solid Dispersions* 665-93.
- [80] Choudhari Y, Reddy U, Monsuur F, Pauly T, Hoefler H and McCarthy W 2014 *Mesoporous Biomaterials* **1** 61-74.
- [81] Monsuur F, Choudhari Y, Reddy U, McCarthy W, Sadek I, Grohgan H, Rades T and Löbmann K 2016 *Int. J. Pharm.* **511** 1135-36.
- [82] Maleki A and Hamidi M 2016 *Expert Opin. Drug. Deliv.* **13** 171-81.
- [83] Zhang Y, Wang J, Bai X, Jiang T, Zhang Q and Wang S 2012 *Mol. Pharm.* **9** 505-13.