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Review Article

Techniques and Carriers used in Solubility Enhancement of Drugs: An Extensive Review

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ABSTRACT

This review paper is written covering approaches techniques and hydrophilic carriers used in solubility hence dissolution rate enhancement of low soluble drugs (BSC Class 2). Solid dispersion is defined as the solid dispersion of one or more active pharmacological ingredients in a carrier, are useful approach for improving the dissolution of low water-soluble drug and therefore increasing their bioavailability. Low water solubility is one of the key issues with numerous types of drugs, and various approaches have been developed to improve their solubility. Water Solubility is a problem for more than 60 percent of potent medicinal formulations. Solid dispersions have gained a lot of attention as a way to improve the dissolution rate and thus the bioavailability of a variety of hydrophobic drugs. Pharmaceutical polymers are at the heart of drug formulations in both traditional and novel drug delivery systems.

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INTRODUCTION

One of the major qualities necessary for successful pharmaceutical formulation development is adequate water solubility of new chemical entities (NCEs). Solubility is defined as the concentration of a compound in a solution when it comes into contact with an excess of the solid compound and the concentration and solid form do not vary over time (Sugano et al., 2007) (1). Dissolution is a kinetic process that involves the detachment of drug molecules from the solid surface and subsequent diffusion across the diffusion layer surrounding the solid surface. Solubility is closely connected to dissolution. The Nernst–Brunner/Noyes–Whitney equation describes the link between solubility and dissolution rate:(2)

$$\mathbf{DM/dt = DAK_{W/O}(C_s - C_t)/Vh \ldots.Equ.1}$$

The development of NCEs has resulted in an increasing number of molecules with low water solubility due to the use of high-throughput screening and combinatorial chemistry (Lipinski 2000). Compounds with low solubility (Cs) will only produce a tiny concentration gradient (C_s-C_t), resulting in slow dissolving rates, according to the Nernst–Brunner/Noyes–Whitney equation. When low soluble drug is supplied by different modes of administration, this results in a slew of issues *in vivo*. Low bioavailability and substantial inter-subject variability are common side effects of low soluble drug given orally. Furthermore, low soluble drug has a higher proclivity for food interaction, resulting in substantial fast/fed variability (Gu et al., 2007) (3). In order to make low solubility drugs available for intravenous administration, they generally have to be solubilized employing large amounts of cosolvents and surfactants. Problems often arise from the fact that these excipients may not be well tolerated, potentially causing hemolysis and/or hypersensitivity reactions (Yalkowsky et al., 1998). In addition, there is the risk of drug precipitation upon injection due to the subsequent dilution of the solubilized formulation. Following oral administration of a solid dosage form, the drug must first dissolve in the GI fluids and then be absorbed across the intestinal mucosa to reach the systemic circulation and exert its pharmacological effects. (4)

Low-solubility drug must typically be solubilized with a considerable amount of cosolvents and surfactants before being administered intravenously. The fact that these excipients may not be well tolerated, resulting in hemolysis and/or hypersensitivity reactions, is a common source of problems (Yalkowsky et al., 1998). (5) Furthermore, due to the subsequent dilution of the solubilized formulation, there is a danger of drug precipitation during injection. Following

oral administration of a solid dosage form, the drug must first dissolve in GI fluids before being absorbed across the intestinal mucosa and exerting its pharmacological effect in the systemic circulation (6).

As a result, water solubility and intestinal permeability are two crucial qualities of potential therapeutic candidates that define the extent of oral bioavailability and are thus critical for effective oral product development. The Biopharmaceutics Classification System (BCS) assigns drugs to one of four categories based on these two critical parameters: high solubility, high permeability (BCS I); low solubility, high permeability (BSC II); high solubility, low permeability (BCS III); and low solubility and low permeability (BCS IV) (Amidon et al.,1995).(7). A NCE should ideally have high aqueous solubility and permeability (BCS I); however, only about 10% of NCEs meet this condition, with the remaining 90% being weakly soluble in combination with either high or low permeability (BCS II and IV) (Benet et al., 2006). BCS IV compounds are often challenging drug candidates due to their combination of low permeability and low solubility, and are thus rarely developed and sold. Because permeability across the GI mucosa is not an issue, BCS II compounds are usually more attractive options. However, intestinal absorption is limited by solubility and dissolution rate, resulting in low and unpredictable oral bioavailability.(8)

Challenges in oral delivery of Low Soluble Drug

The extent of oral bioavailability is influenced not only by pharmacological properties such as solubility and gastrointestinal permeability, but also by the susceptibility of a drug molecule to intestinal and hepatic metabolism, as well as active influx/efflux transporters. For many drugs oral bioavailability may be reduced by the presence of cytochrome P450 (CYP 450) metabolic enzymes in the endoplasmic reticulum of hepatocytes and intestinal enterocytes (Lee and Yang 2001; Paine et al., 2006) (9). First-pass metabolism refers to the pre-systemic metabolism of drug. This, according to Smith et al., will be especially true for drug that are lipophilic and hence easily traverse cell membranes, gaining access to CYP enzymes (Smith et al., 1996) (10).

Wu and Benet's research confirmed that highly permeable BCS I and BCS II drug are predominantly removed by metabolism, but low permeable BCS III and IV pharmaceuticals are mostly excreted unchanged into the urine and bile (Wu and Benet 2005; Benet 2010) (11). It should be noted, however, that the BCS definition of low/high permeability reflects differences in drug access to metabolic

enzymes within the cells, not necessarily differences in permeability into the cells (Custodio et al.,2008). Wu and Benet proposed the Biopharmaceutics Drug Disposition Classification System (BDDCS) based on their findings, in which drug are classified based on the amount of metabolism and solubility, rather than the permeability and solubility applied in the BCS (12).

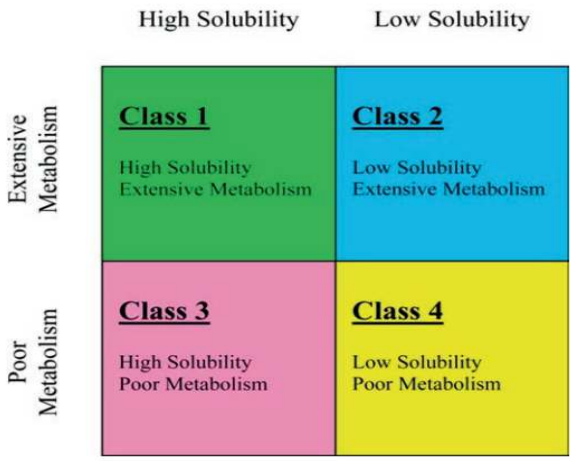


Figure 1: BCS classification

A significant number of NCEs with low aqueous solubility poses a number of obstacles for the development of effective drug delivery methods. Low soluble drug is frequently delivered orally, which results in limited bioavailability and an increased risk of food interactions. The hurdles may be overcome with developments in various solubilization and particle-size reduction technologies, allowing for successful oral delivery of a wide spectrum of drug. The restricted number of permitted excipients is one of the key obstacles in the administration of low soluble drug via the pulmonary, nasal, and parenteral routes (13).The discovery of new excipients may open up new possibilities for the delivery of low soluble drug. The time and money required to conduct a comprehensive toxicological examination of a novel excipient, as well as the risk of regulatory delays or rejection, may deter pharmaceutical companies from creating new excipients. In the formulation of low soluble drug, significant progress has already been made. Several techniques to improving solubility/dissolution, such as nanosuspensions or cyclodextrin inclusion complexes, have showed promise in terms of improved *in vivo* performance. Concerns about the safety of specific excipients or delivery systems persist. As a result, further research is needed in the future to make low soluble drug available via diverse delivery channels.

Determination of aqueous solubility (14)

Direct determination in aqueous suspension is the most extensively used experimental approach for determining solubility. Excess drug is placed in a specified volume of water and kept at a steady temperature in this approach. Periodically, samples are obtained, and the drug concentration is evaluated analytically (i.e., HPLC analysis). Seedher et al., for example, looked at the solubility of seven low soluble anti-diabetic drug.

Excess drug was placed in 5-mL of water in a sealed container in their study. The suspensions were kept at 25 °C and magnetically stirred for 24 h until they reached equilibrium. The suspensions were then centrifuged, filtered through a 0.45-m membrane, and drug measurement was done using UV absorbance (Seedher and Kanojia 2009).

The researchers were using the same procedure to test a variety of cosolvents for their ability to improve solubility. The centrifugation and filtration processes are important because they remove possible seeds for recrystallization and ensure that no particulate matter is dissolved during dilution for analysis, which might lead to incorrect results. Teijeiro used a direct aqueous suspension method to determine the solubility of AZT-Iso, a zidovudine derivative, employing excess drug in 4 mL of water and continual shaking. Following equilibration, filtration was used again, and the samples were evaluated using UV absorbance (Teijeiro and Brión 2006).

Allowing substances evaluated by direct determination in aqueous suspension to attain equilibrium is critical. The equilibration duration in the aforementioned investigations was only 24 h; nonetheless, for many low soluble drugs, this time is insufficient. At 25 °C, Venkatesh discovered that cosalane took 48 h to attain equilibrium. Shaw et al., on the other hand, discovered that reaching equilibrium for ibuprofen at 37 °C took 5 days (Shaw et al., 2005). For a new chemical entity, samples should be taken every 8 h for the first 24 h, then every 24 h for the next four days. The investigation may be extended for longer periods of time if the calculated concentration has not reached a plateau.

pH-Solubility Profiles

A low soluble drug's pH-solubility profile can be a determining aspect in its development. When compounds like itraconazole are exposed to neutral medium, their solubility drops dramatically, necessitating gastric absorption or intestinal super saturation to increase bioavailability (15).

The pH-solubility profiles can be obtained using the direct determination in aqueous suspension approach. Wang et al., for example, used 10 mL deionized water in numerous 15-mL bottles to dissolve surplus sildenafil citrate. Individual vial pH readings were then titrated to a pH range of 3–11. After that, the suspensions were kept at 37 °C for 48 h.

After confirming that there had been no change in pH, samples were filtered through recommended filters, diluted with mobile phase, and HPLC examined (Wang et al., 2008). The pH-solubility profile of haloperidol free base and the associated hydrochloride and mesylate salts was also

determined using the direct determination in aqueous suspension method to identify the more soluble species (Li et al., 2005). In this iteration, surplus solids were added to 5 mL of water to make a single vial of each chemical. The suspensions were then titrated to the appropriate pH with HCl or NaOH solutions and allowed to equilibrate at 37 °C for 24 h. The pH was verified after 24 h, and an aliquot was obtained for analysis (16).

D'Souza et al., (2009) adopted a modified version of the approach to test the solubility of a synthetic recombinant plague antigen. The researchers began by making buffers varying in pH from 3 to 10. After that, aliquots of a monomer stock solution were diluted with one of the buffers to a concentration of 360 g/mL. This solution was then dialyzed for 15 h under refrigeration against the appropriate diluting buffer in a dialysis cassette. The dialysate was then filtered and the solubilized component was determined using UV absorbance. The method of direct determination in aqueous suspension has some drawbacks. Many analytical techniques can't detect substances with extremely low solubilities since they're too small.

A brief review on the technologies along with a few reports is presented to emphasize their importance in enhancing the oral bioavailability of low soluble drugs.

METHODS FOR ENHANCEMENT OF THE SOLUBILITY (17)

As per the definition the drug candidate which has the following properties is one with low bioavailability, such as; low aqueous solubility and/ or slow dissolution rate in the biologic fluids, low stability of the dissolved drug at the physiologic pH, inadequate partition coefficient and thus low permeation through the biological membrane, extensive presystolic metabolism

There are three major approaches used to overcome the solubility problems.

A) Pharmaceutics approaches: It is done by modifying of formulation, manufacturing processes or physiochemical properties of the drug are done.

B) Pharmacokinetic approaches: Alteration of pharmacokinetic parameters by modifying its chemical structure.

C) Biological approaches: The route of administration is changed in this method. Solubility and rate of dissolution are very important factors in third approach (18).

Cosolvency (19)

Cosolvents, which are water miscible solvents in which the drug has high solubility, can boost the solubility of a low water-soluble drug. Co-solvents are solutions made up of water and one or

more water miscible solvents that improve the solubility of low soluble substances. Because of its simplicity, this is one of the most widely utilized procedures. Cosolvents are simple to make and assess. PEGS 300, propylene glycol, ethanol, methanol, acetone, DMA, DMF, DMSO etc. are examples of solvents used in co-solvent combinations. Low soluble drug can be delivered orally and parentally using co-solvent formulations.

Since solubilization of nonpolar drugs is one of the most important tasks in the formulation design of liquid dosage forms, Amit et al investigated and compared the Cosolvency using three different cosolvents: PEGS 400, Propylene glycol, and glycerin on the aqueous solubility enhancement of a low aqueous soluble drug, etoricoxib when cosolvents such as PEGS 400, Propylene glycol, and glycerin were added. According to the findings, less polar solvents enhanced aqueous solubility more, emphasizing the hydrophobic interaction mechanism. Water-PEGS 400 had the best solubilization potential of all the solvent cosolvent mixes tested. As a result, the research yielded a valuable set of data that could be used to compare the effects of various cosolvents on aqueous solubility of etoricoxib.

Particle size reduction (20)

The solubility is related to drug particle size. By reducing particle size, effective surface area increases which in turn improves the dissolution properties. Particle size reduction is done by milling techniques using jet mill, rotor stator colloid mills etc. Size reduction is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Currently Particle size reduction can also be achieved by micronisation and nanosuspension. Each technique utilizes different equipment for reduction of the particle size. In micronisation the solubility of drug is often intrinsically related to drug particle size. By reducing particle size, surface area increases which in turn improves the dissolution properties. Micronisation of drugs is done by milling techniques using jet mill, rotor stator colloid mills. Bansal et al studied that the dissolution rate is one of the limiting factors for achieving good bioavailability. In various formulations, the particle size of drugs and components may affect the processing and bioavailability. Many compounds that are investigated in pharmaceutical field have low aqueous solubility and fall in class II and IV of the biopharmaceutical classification system. (21-22). Particle size reduction, leading to increase in surface area, is a leading tool to increase dissolution rate and in turn the

bioavailability of low water-soluble compound (23).

Hydrotrophy (24)

Currently number of techniques addressed the enhancement of solubility and dissolution rate of low soluble drugs. Hydrotropic solubilization is one of them. Hydrotrophy is a solubilisation technique in which a large amount of second solute is added which results in an increase in the aqueous solubility of another solute. Solute which is used consists of alkali metal salts of various organic acids. A hydrotrope is a compound that solubilizes hydrophobic drugs in aqueous solution. Hydrotropes are having the ability to increase the solubility of low water-soluble drug and this tendency is greatest when concentration of hydrotropes is sufficiently enough to form the associated structures. Hydrotropic agents are ionic organic salts. The additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism" (25).

Hydrotropic solutions do not exhibit colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy leads to increase in solubility in water due to the presence of large number of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the low soluble drugs (26).

Mixed Hydrotropy

It is a solubilization technique to increase the water solubility of low water-soluble drugs by using different ratio of blends of hydrotropic agents which gives synergistic enhancement effect. The main advantage of this technique is that it reduces the concentration of individual hydrotropic agents which directly reduces the side effects of individual hydrotropic agent (27).

Solid Dispersions (28)

The effective surface area is one of the important factors which govern the dissolution rate of low soluble drugs. Apart from micronisation and nanosizing technologies, solid dispersion is the promising of enhancing the effective surface area available for dissolution. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix (carrier) and a hydrophobic drug. The matrix can be

either crystalline or amorphous. As per biopharmaceutical classification system class II drugs are with low solubility and high permeability and are the promising candidates for improvement of bioavailability by preparing solid dispersions.

To be used as carrier in should meet the following criteria of preparation of solid dispersions it should freely water-soluble with intrinsic rapid dissolution properties, non-toxic and pharmacologically inert, heat stable with a low melting point for the melt method, soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method, able to preferably increase the aqueous solubility of the drug.

The probable mechanisms for may be due to; reduction in particle size, improvement in wettability and dispersibility, changing crystalline form of drug to amorphous form, reduction in aggregation and agglomeration of drug particles.

The development of a compound or complex between the drug and the carrier occurs when the drug forms a solid-state complex with an inert soluble carrier. The solubility and stability constant of the molecule or complex determine the drug's bioavailability. The creation of a water-soluble compound with a high dissociation constant has been shown to improve dissolution rate and oral absorption. Cyclodextrins are a type of complex carrier that is widely employed. These cyclic oligosaccharides are made up of glucopyranose units and have the ability to build a cavity with a hydrophobic inner and a very hydrophilic exterior (29).

Solvent Evaporation Method (30)

Tachibana and Nakamura were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water-soluble carrier povidone. Many investigators studied solid dispersion of meloxicam, naproxen, and nimesulide using solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of low water-soluble drugs.

Hot-Melt Extrusion (31)

Hot-melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of the drug and the matrix could be a problem. High-shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of

continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

Lyophilization/Freeze-Drying Technique (32)

In order to get a porous, amorphous powder with high degree of interaction between drug and Cyclodextrin, lyophilization/freeze drying technique is considered suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are the use of specialized equipment, time consuming process. Lyophilization/freeze drying technique is considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent.

Table no. 1 Example of Different Drugs, Polymers and Methods of solubility Enhancement

Sl.No.	Drug	Polymer used	Methods of Solubility Enhancement
1	Raloxifene HCl	HPMC E5 LV	Microwave-induced fusion method
2	Loratadine	Poloxamer 188, poloxamer 407	Solid dispersions (Kneading method)
3	Amlodipine	Polyvinylpyrrolidone (PVP)	Solvent evaporation method
4	cefdinir anhydrous	Hydroxypropyl-methylcellulose (HPMC) Polyvinyl pyrrolidone K30 (PVP K30), CMC	Spray-drying method
5	Cyclosporine A	Polyvinyl pyrrolidone (PVP)	Super saturable Self-Emulsifying Drug Delivery System
6	Clonazepam	polyethylene glycol 6000 (PEG- 6000), Kollidon VA 64 and Poloxomer	Solvent evaporation method
7	Atorvastatin	Neem Gum	Solvent Evaporation Method, Kneading Method

8	Allopurinol	Polyvinylpyrrolidone (PVP), polyethylene glycol 6000(PEG 6000)	Solvent evaporation method, Kneading method, Closed Melting method, Co-precipitation method (CP)
9	Tacrolimus (Orally Disintegrating Tablets)	PVP VA64 (Kollidon VA 64) and Soluplus®, Hydroxypropyl Cellulose (HPC, LF grade)	Hot Melt Extrusion
10	Tamoxifen citrate	polyethylene glycol (PEG 6000), beta-Cyclodextrin (β-CD), Hydroxyl propyl -β -Cyclodextrin (HP- β-CD)	Solvent evaporation method

Evaluation parameter of solid dispersion

Phase solubility study

For this study excess amount of drug is added to aqueous solution of carrier in specific dissolution media containing increasing concentration of carrier. Then flask is sealed and shaken at 37°C in thermostatically controlled water bath. Then sample is filtered, filtrate is suitably diluted, and analyzed spectrophotometrically at suitable wavelength (33).

Drug content

In this defined amount of solid dispersion is dissolved in suitable solvent then after appropriate dilution concentration is measured by UV spectrophotometry. HPLC is also a useful tool for drug content measurement. Calibration graph is constructed by peak area verses concentration of drug (34).

Powder X-ray diffraction studies

Powder X-ray diffraction (PXRD) can be obtained by employing X-ray diffractometer. It is a method of determination of arrangement of atom within the crystal, in which a beam of X-ray strikes a crystal and diffracts into various specific directions. From the angles and intensities of these diffracted beams, X-ray diffractometer can produce a three-dimensional picture of the densities of the electrons within the crystal. From this electron density, the mean position of atoms in the crystal can be determined, as well as their chemical bonds and various other information.

Thermal data analyses

In differential thermal analysis (DTA), the temperature difference that develops between a sample and an inert reference material is measured, when both are subjected to identical heat under nitrogen

atmosphere on an aluminum pan at the rate of 10°C/min. The related technique of differential scanning calorimetry (DSC) relies in differences in energy required to maintain the sample and reference at an identical temperature. Thermal data analysis of the DSC thermograms is obtained (35).

Fourier transform infrared spectroscopy

FTIR can be employed to characterize the possible interaction between the drug and the carrier in solid state by conventional KBr method. In this method about 10 mg of sample is mixed with dried KBr of equal weight and sample is scanned over a frequency range 4000-500 cm^{-1} and FTIR spectra of the sample are obtained using FTIR spectrophotometer.

Dissolution studies

Dissolution study of given solid dispersion can be performed using recommended dissolution test apparatus, media, sampling intervals, temperature and rpm in the pharmacopoeia or official guidelines (36).

Polymers (37)

"Polymer" word is derived from Greek roots "Poly" meaning many and "Meros" meaning parts. Polymers have very large molecular weights made up of repeating units (or monomers) throughout their chains. Polymers are considered to be a subset of macromolecules. A monomer is a small molecule that combines with other molecules of the same or different types to form a polymer. If two, three, four, or five monomers are attached to each other, the product is known as a dimer, trimer, tetramer, or pentamer, respectively. An oligomer contains from 30 to 100 monomeric units. Products containing more than 200 monomers are simply called a polymer. From the structural perspective, monomers are generally classified as functional (containing reactive functional groups) and olefinic (containing double bond). Polymers can have different chemical structures, physical properties, mechanical behavior, and thermal characteristics. The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Polymers can be used as film coatings to disguise/mask the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. Pharmaceutical polymers are widely used to achieve taste masking; controlled release (e.g., extended, pulsatile and targeted) enhanced stability and improved bioavailability. Monolithic delivery devices are systems in which a drug is dispersed within a polymer matrix and released by diffusion. The rate of the drug release from a matrix product depends on the initial drug concentration and

relaxation of the polymer chains which overall displays a sustained release characteristic (38).

Classification of Polymers

Polymers can have different chemical structures, physical properties, mechanical behavior, thermal characteristics and can be classified in different ways by following below are,

1. Based on the origin (39)

i) Natural Polymers

Protein-based

Polysaccharides.

ii) Synthetic Polymers

Biodegradable

Polyesters

Polyanhydrides.

Polyamides

Non-biodegradable

Cellulose derivatives: hydroxypropyl methylcellulose (HPMC), HPC, CMC

Silicones

Others: Polyvinyl pyrrolidone (PVP), poloxamers, poloxamines etc.

iii) Semi-synthetic Polymer

2. BASED ON BACKBONE

Polymers with carbon chain backbone

Polymers with hetero chain backbone

3. Based on the presence of carbon (organic and inorganic) [40]

Organic Polymers

Inorganic Polymers

4. Based on the types of monomers [41]

On this basis, polymers can be classified into two classes

Homoplymer: A polymer containing a single type of repeat units is called a homopolymer,

Copolymer: If a polymer is made up of two different monomers, then it is called copolymer,

5. Based on interaction with water [42]

Non-biodegradable hydrophobic Polymers: e.g., Polyvinyl chloride

Soluble Polymers: HPMC, PEGS

Insoluble polymers

Hydro gels: Polyvinyl pyrrolidone

Hydrophilic carrier

Some commonly used hydrophilic carriers are: polyethylene glycols PEGs or Macrogols) of different grades PEG 1500-40000; polyvinyl pyrrolidones (PVPs) of different grades PVP K 30-90; poly (oxyethylene–co-oxypropylene) i.e., poloxamers of different grades 188, 407; fatty acid macrogol glycerides, Gelucires of different grades 44/14- 50/13 (The numerator indicates the melting point and denominator indicates the HLB value); poly(vinyl acetate-co-vinyl caprolactameco-ethylene glycol) i.e., Soluplus® etc.

Poloxamers and poloxamines are examples of biocompatible ABCs that were introduced in the 1950s by BASF (NJ, USA) when they started being used for detergent development, but also in other

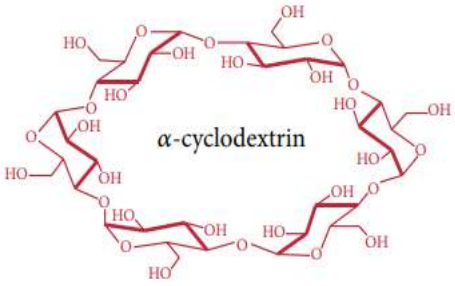
areas, like agriculture, food, and paints. In this sense, the potentiality of these surfactants it was not neglected, on the contrary, it promoted the beginning of an interest for their use in the biomedical and pharmaceutical area. Increasingly, the majority of researchers in the field of medical sciences have been working in the search for new treatments that are safer, less invasive, faster and with a large percentage of efficacy using lower doses, however, the delivery of highly effective therapeutic agents to a target cell remains a concern and challenge for researchers. Furthermore, poloxamers and poloxamines arise as a good alternative to surpass this problem, being known as "smart" polymers, due to their stimuli-sensitive properties (43).

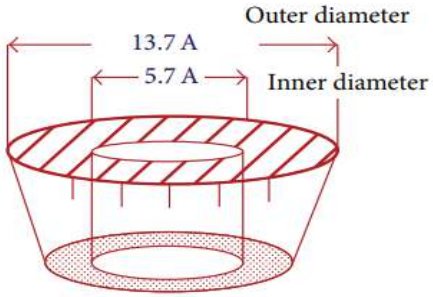
Cyclodextrin (44)

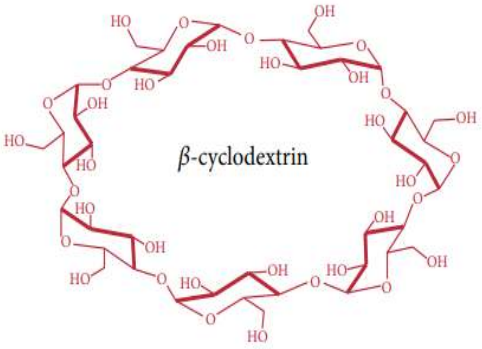
Cyclodextrins are cyclic oligosaccharides containing at least six d-(+)-glucopyranose units attached by α (1→4) glucoside bonds. The three natural cyclodextrins, α, β, and γ, differ in their ring size and solubility. They contain 6, 7, or 8 glucose units, respectively.

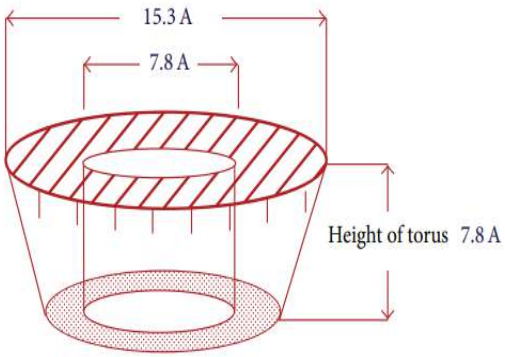
Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

β-Cyclodextrin (betadex) is the only cyclodextrin to be currently described in a pharmacopeia. Alfa dextrin is the rINN for α-cyclodextrin.









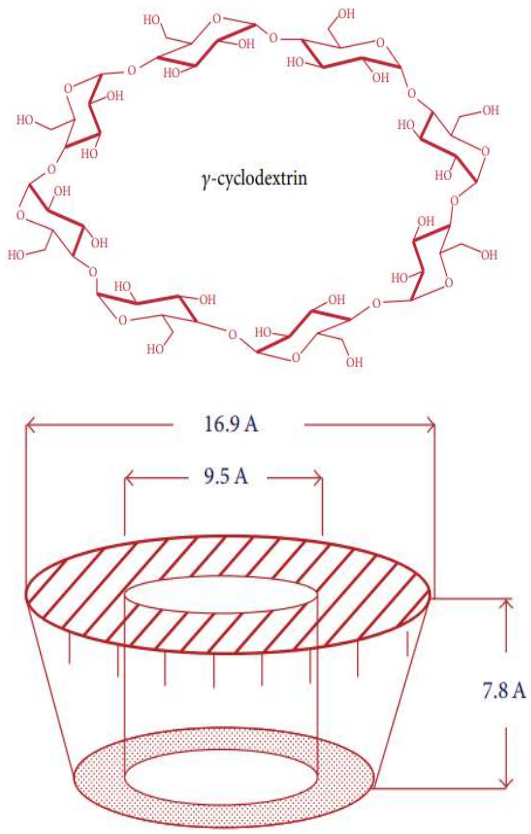


Figure2: Structure of different types of Cyclodextrin

Solubility

α- cyclodextrin: soluble 1 in 7 parts of water at 20 ˚C, 1 in 3 at 50 ˚C.

β- cyclodextrin: soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20 °C, 1 in 20 at 50°C; practically insoluble in acetone, ethanol (95 %), and methylene chloride.

γ- cyclodextrin: soluble 1 in 4.4 parts of water at 20 °C, 1 in 2 at 45 °C.

Applications in Pharmaceutical Formulation or Technology (45)

Cyclodextrins are cyclic oligosaccharides derived from starch that are crystalline and non-hygroscopic. The most common forms are and -cyclodextrin, which have 6, 7, and 8 glucose units, respectively. There are also substituted cyclodextrin derivatives available. Cyclodextrins are toroid molecules with a rigid structure and a central cavity, the size of which varies depending on the cyclodextrin type. Because of the arrangement of hydroxyl groups within the molecule, the internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic. This arrangement allows the cyclodextrin to accommodate a guest molecule within the cavity, resulting in the formation of an inclusion complex.

Cyclodextrins can be used to form inclusion complexes with a wide range of drug molecules, resulting in improved dissolution and bioavailability due to increased solubility and chemical and physical stability. Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active ingredients and to convert liquids to solids.

Although it is the least soluble, cyclodextrin is the most commonly used cyclodextrin. It is the least expensive cyclodextrin, is commercially available from a variety of sources, and can form inclusion complexes with a variety of pharmaceutically relevant molecules. - cyclodextrin, on the other hand, is nephrotoxic and should not be used in parenteral formulations. - When given orally, cyclodextrin is regarded nontoxic

and is primarily used in tablet and capsule formulations. β-cyclodextrin derivatives tend to be nontoxic when used either orally or parenterally, and the derivatives 2-hydroxypropyl-β-cyclodextrin and 3-hydroxypropyl-β-cyclodextrin are becoming increasingly important in pharmaceutical formulations.

α- Cyclodextrin is primarily used in parenteral formulations. However, because it has the smallest cavity of the cyclodextrins, it can form inclusion complexes with a small number of molecules. -cyclodextrin, on the other hand, has the largest cavity and can be used to form inclusion complexes with large molecules; it is low in toxicity and has increased water solubility (46).

β-cyclodextrin can be used in both wet-granulation and direct-compression processes in oral tablet formulations. -cyclodextrin's physical properties differ depending on the manufacturer. When directly compressed, however, -cyclodextrin has low flow properties and requires a lubricant, such as 0.1 percent w/w magnesium stearate. Cyclodextrins have been used in parenteral formulations to create stable and soluble preparations of drugs that would otherwise have been formulated using a nonaqueous medium. In eye drop formulations, cyclodextrins form water-soluble complexes with lipophilic drugs such as corticosteroids. They have been shown to increase the water solubility of the drug; to enhance drug absorption into the eye; to improve aqueous stability; and to reduce local irritation. Cyclodextrins have also been used in the formulation of solutions, suppositories, and cosmetics.

2-Hydroxypropyl-β-cyclodextrin (2-HP-β-CD) (47)

Synonym: *Kleptose HPB*.

Appearance: White crystalline powder.

Solubility: Greater than 1 in 2 parts of water at 25°C.

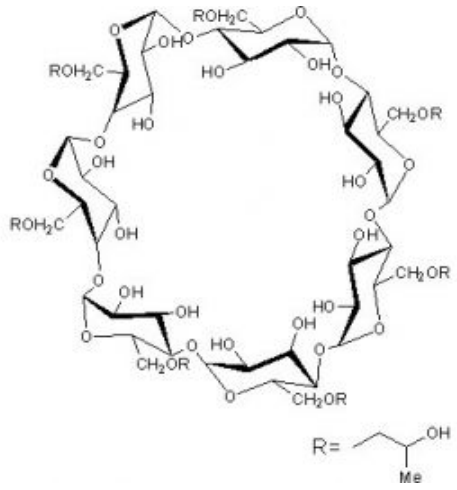


Figure 3: Structure of 2-HP-β-cyclodextrin

Comments: β- cyclodextrin is used in applications similar to those of -cyclodextrin. It has, however, been suggested for use in parenteral formulations because it is not nephrotoxic. Included in oral and parenteral pharmaceutical formulations approved for use in Europe and the United States. The degree to which hydroxypropyl groups are

substituted can vary. The polymer could be recycled and reused without a significant loss in ibuprofen adsorption. These findings provided critical information for the development of novel adsorbents capable of removing ibuprofen efficiently.

POLOXAMER

Poloxamers generally occur as white, waxy, free-flowing granules, or as cast solids. They are practically odorless and tasteless. At room temperature, poloxamer 124 occurs as a colorless liquid Poloxamers are triblock copolymers, available under the trade name of Pluronic (BASF) Lutrol (BASF), Kolliphor (BASF), Synperonic (Croda) and Antarox (Rhodia) (48). They are formed by two hydrophilic PEO blocks, which are linked to a hydrophobic PPO block being arranged according to the chemical structure PEOxPPOyPEOx, in which x and y represent the number of units of PEO and PPO blocks, respectively. In this sense, poloxamers are synthesized through the sequential addition of PO and EO monomers in the presence of an alkaline catalyst, such as sodium or potassium hydroxide, producing various poloxamers with a different number of hydrophilic EO and hydrophobic PO units, which are also characterized by their distinct hydrophilic-lipophilic balance (HLB) value. Furthermore, it also exists an inverted substructure composed by PPO–PEO–PPO sequence, known as reverse poloxamers and they are commercially available by the trade name of Pluronic R and Antarox R, being used as wetting and defoaming agents in industrial processes. The hydrophobicity of PPO at temperatures exceeding the cloud point (>15 °C) and the high hydrophilicity of PEO in temperatures between the 0–100 °C explain the fact that these block copolymers present amphiphilic features accompanied by surface-active properties.

An example of a commercial product is the poloxamer 188, which is sold like poloxamer P188 but also like Pluronic F68 and Kolliphor P188, which is used in cell culture (mammalian, insect and plant) because it can control shear forces and confer cryoprotection in suspension cultures (49-50).

Empirical Formula and Molecular Weight

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_a$. The grades included in the European Pharmacopoeia 2005 and USPNF 23. The European Pharmacopoeia 2005 states that a suitable antioxidant may be added (51).

Table No.2: Typical poloxamer grades

Poloxamer	Physical form	*a*	*B*	Average molecular weight
124	Liquid	12	20	2090–2360
188	Solid	80	27	7680–9510
237	Solid	64	37	6840–8830
338	Solid	141	44	12700–17400
407	Solid	101	56	9840–14600

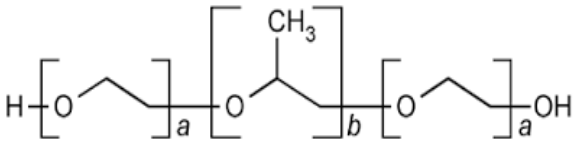


Figure 4: Structure of Poloxamer

Applications in Pharmaceutical Formulation or Technology

Poloxamers are nonionic polyoxymethylene–polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. The polyoxymethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range and a number of different types are commercially available (52).

Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings. Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes and in the preparation of solid-dispersion systems. More recently, poloxamers have found use in drug-delivery systems. Therapeutically, poloxamer 188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation; it is usually used in combination with a laxative such as danthron. Poloxamers may also be used therapeutically as wetting agents in eye-drop formulations, in the treatment of kidney stones, and as skin-wound cleansers. Poloxamer 338 and 407 are used in solutions for contact lens care (53).

Hydrocolloid

Hydrocolloids refer to a range of polysaccharides and proteins that are nowadays widely used to perform a number of functions in the pharmaceutical and biomedical sector. The specific application of plant-derived hydrocolloids in pharmaceutical formulations include

their use in the manufacture of solid monolithic matrix systems, implants, films, beads, microparticles, nanoparticles, inhalable and injectable systems, as well as viscous liquid formulations. The hydrocolloids are available in a wide range and variety, which can be modified depending upon research requirement (54).

Sodium carboxymethyl cellulose

It is a low-cost commercial soluble and polyanionic polysaccharide derivative of cellulose that has been used in medicine, as an emulsifying agent in pharmaceuticals, and also used in cosmetics (55). Carboxymethyl cellulose (CMC) is one of the important cellulose derivatives in industries, which is widely used as an anti-caking agent, emulsifier, stabilizer, dispersing agent, thickener, and gelling agent. Sodium carboxymethyl cellulose is used in both therapeutic and excipient. Therapeutic uses include bulk-forming laxatives in which it may be the primary ingredient. Excipient uses include those of suspending, tablet binding, or viscosity increasing (56).

Hydroxypropylcellulose

Hydroxypropylcellulose (HPC)-SL and low-viscosity HPC polymers are versatile pharmaceutical excipients. It is widely used in pharmaceutical formulations like in oral products, as a tablet binder, in film-coating, and as a controlled-release matrix. All of the cellulosic polymers described in the previous section have been used as binders for solid dosage forms in wet granulation and dry- or direct-compression tableting processes (57).

HYDROXYPROPYL METHYLCELLULOSE (HPMC) (58)

Hypromellose is a solid, slightly off- white or cream- white fibrous or granular odorless and tasteless powder. The compound forms colloid when dissolved in water. Hypromellose solution is a non-Newtonian solution and exhibits pseudoplastic, more specifically hypromellose in an aqueous solution, unlike methyl cellulose, exhibits a thermal gelation property [shown at a critical (congealing) temperature].

Functionally HPMC is very similar to HEMC (hydroxyl ethyl methyl cellulose) trade names include ethocel and Walocel. The global leading producer is Dow Wolff Cellulosic GmbH.

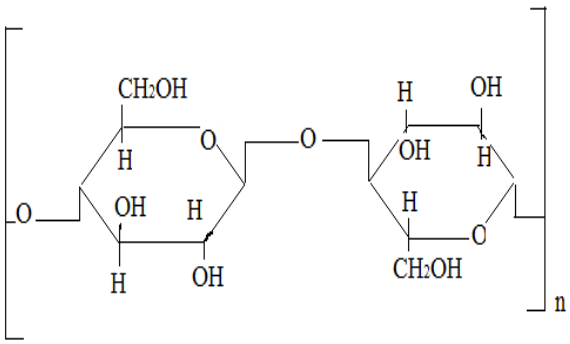


Figure 5: Structure of HPMC

Applications in pharmaceutical formulation or technology:

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. It is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. Hypromellose solutions were patented as a semi-synthetic substitute for tear-film.

PEGS

PEGS-containing vehicles for drug delivery such as liposomes, dendrimers, nanoparticles, or micelles are valid alternatives to direct PEGylation of drugs. Mei et al., developed a multistage liposome drug delivery system co-modified with RGD, TAT, a specific ligand and a penetrating peptide, containing a cleavable PEGS that increased the stability and circulation time of the liposomes. Liposomes undergo passive extravasation to tumor tissues, where the dual ligands become exposed through controlled exogenous administration of reducing l-cysteine. Subsequently, RGD recognize integrins, commonly overexpressed on malignant tumors, and mediate the internalization in a synergistic effect with TAT, penetrating deep into avascular tumor spheroids (59).

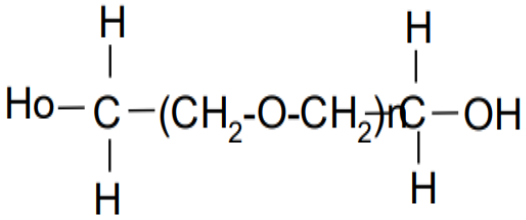


Figure 6: Structure of Polyethylene glycol

Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGSs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases. Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats. For example, the melting point of the

suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble drug decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats (60).

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers. Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEGS 300 and PEGS 400 have been used as the vehicle for parenteral dosage forms. In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules (61).

POLYDIMETHYLAMINOETHYLMETHACRYLATE

A poly[2-dimethylamino)ethyl - methacrylate] (PD), biocompatible, water-soluble polymer finds extensive applications as membranes, efficient non-viral gene-delivery vectors, antimicrobial agents, and biosensors. N-hydroxypropyl trimethylammonium polydimethyl aminoethyl methacrylate (PDG) prepared by the quaternization reaction of PD was conducted using N-hydroxypropyl trimethylammonium chloride as the quaternizing agent. Swelling of polymers or drug-polymer matrices in the dissolution test media have been reported according to significant effects on ordinary dosage forms and controlled drug release systems (62).

PDG having high positive charge displayed a calcium binding property, which helped in the loosening of epithelial tight junctions by actin filament dislocation and binding to ZO-1 proteins. The PDG polymer is mucoadhesive thereby making it a suitable carrier for the mucosal delivery of proteins (63).

Soluplus

Soluplus is a polyvinyl caprolactam – polyvinyl acetate - polyethylene glycol graft copolymer. It has an amphiphilic structure and can be regarded as a

polymeric solubilizer. This innovative excipient was launched in 2009 and was designed to be used in hotmelt extrusion and to solubilize low soluble actives (64).

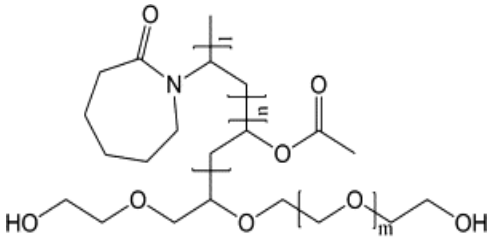


Figure 7: Structure of Soluplus

Soluplus acts as a matrix polymer for solid solutions prepared for instance by spray drying or evaporation techniques. It can also be used as a wet or dry binder, film former in oral strips, solubilizer, emulsion stabilizer and protective colloid. In most of these applications, it improves formulation characteristics by its outstanding solubilizing effect. Furthermore. Soluplus can increase the bioavailability of low soluble drugs (65).

GELUCIRE 44/14 (66)

Gelucire 44/14: Lauroyl polyoxyl-32 glycerides NF, From Gattefossé

Gelucire 44/14 is an inert semi-solid waxy material, which is amphiphilic in nature.

The suffixes 44 and 14 refer to its nominal melting point and HLB value respectively.

Gelucire 44/14 comprises about 20% mono-, di- and triglycerides, 72% mono- and di- fatty acid esters of PEGS 1500 and 8% of free PEGS1500.

Gelucire 44/14 is derived from the reaction of hydrogenated palm kernel oil with PEGS 1500 and conforms to the requirements of the European Pharmacopoeia 4th Edition (2002) under the "lauroyl macrogolglycerides" monograph. Gelucire 44/14 comprises about 20% mono-, di- and triglycerides, 72% mono- and di- fatty acid esters of PEGS 1500 and 8% of free PEGS1500.

Application: Capsule Filling, Dry Granulation, Granulation, Melt Congealing, Melt Spraying, Roller Compaction, SMEDDS, Solubilization, Spheronization, Spray Drying, Spray Congealing, Solid Lipid Nanoparticles, Nano Lipid Carrier

Functionality: Bioavailability Enhancer, Carrier, Emulsifier, Gastrointestinal Dispersion, Multifunctional, Rapid Release Agent, Solubilizer, Surfactant, Penetration Enhancer, Modified Release (67).

Crospovidone (68)

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

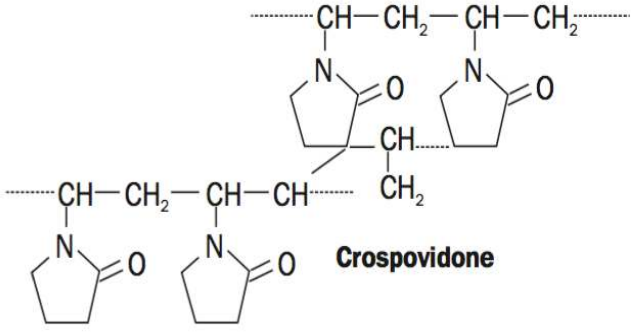


Figure 8: Structure of Crospovidone

Table No. 3: Density values of commercial grades of crospovidone.

Commercial grade	Density (bulk) g/cm^3	Density (tapped) g/cm^3
Kollidon CL	0.3–0.4	0.4–0.5
Kollidon CL-M	0.15–0.25	0.3–0.5
Polyplasdone XL	0.213	0.273
Polyplasdone XL-10	0.323	0.461

Conclusions

Solid dispersions constructed of polymers were used to improve drug solubility. Solid dispersion has been proven to improve the solubility of low soluble pharmaceuticals such BSC II therapies. In all cases where the polymeric component of the solid dispersions was increased, there was an increase in drug release from the created solid dispersions. The researchers discovered that utilizing the proper combination of hydrophilic carriers and hydrophilic porous adsorbents ensures that solid dispersions dissolve fast and thoroughly, allowing them to be used in oral pharmaceutical formulations. Polymeric compounds come into touch with pharmaceuticals not only as ingredients in final dosage forms, but also as processing aids or packaging materials. As a result of a long record of pharmaceutical marketing, the bulk of polymers used as additives in traditional dosage forms are natural polymers. The most common materials used in pharmaceutical packaging are polyethylene, polypropylene, and PVC. However, more eco-friendly, biodegradable polymers are increasingly being used to replace them. Progress in the field of controlled drug distribution has only been possible because to the combination of polymer science and pharmaceutics. The development of sophisticated pharmaceutical goods necessitates multidisciplinary efforts. This involves the development of intelligent polymeric systems capable of detecting and responding to physiological and pathological events. Polymers will continue to be significant in the development of new drug.

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