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SYNERGISTIC EFFECT OF SOLID DISPERSION AND INCLUSION COMPLEX IN ENHANCING THE SOLUBILITY AND STABILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Majority of medications produced are known to be either weakly acidic or weakly basic with poor aqueous solubility properties. As a result, a variety of techniques utilized for the improvement of the solubility properties of poorly water-soluble medications which include micronization, pH adjustment, co-solvency, complexation, co-crystallization, hydrotrophy, etc. Poor bioavailability of drugs is a stumbling block in drug formulation in that active drug moiety does not get to the target site for pharmacological response to be elicited. Inclusion complexation and solid dispersion are among some techniques that can be used to curtail this problem. Before a particular solubility technique is chosen a few issues come to play; drug property, site of absorption, and required dosage form characteristics. By and large, both techniques thus solid dispersion and inclusion complex when used alone or in combination one way or the other enhances the solubility, dissolution rate and bioavailability of drugs. And this eventually improves wettability and results in decreased particle size, amorphous-structured particles, and higher porosity degree. This review highlights the need for this combination to enhance the solubility of poorly soluble drugs.

KEYWORDS: Solubility, Bioavailability, Stability, Dissolution, Solid dispersion, cyclodextrin.

INTRODUCTION

Villiers, a French scientist, discovered cyclodextrin (CD). CD formation is as a result of beautiful crystals observed after the production of dextrins from starch with mixed bacterial culture. And so Villiers decided to determine the chemical composition and properties the new crystals. Another scientist by name Schardinger also isolated the strain of bacteria known as Bacillus macerans, and this bacteria is responsible for the synthesis of the CD. Since he performed lots of experiments with CDs, he is known as the founder of CD chemistry.[1]

Cyclodextrins are made up of 6-8 glucopyranoside units; its regional anatomy can be to contain hydrophobic toroids in its interior with its exterior surface possessing having hydrophilic toroids for the interaction with less water-soluble compounds as shown in figure 1. These toroids are exposed to solvent secondary and primary hydroxyl groups in that they are made up of larger and smaller openings.[2]

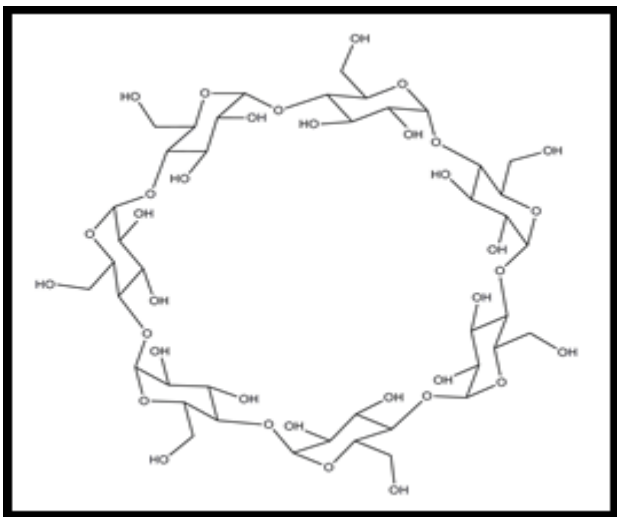

Figure 1: Chemical Structure of Cyclodextrin.

Most often than not, the formation of the inclusion compounds enhance the water solubility properties of the compound involved in this referred to as the guest molecule as shown in figure 2.[3,4] Both the physical and chemical properties of the mixture are significantly affected. Given this, it has gained more attention in many fields including pharmaceutical application because include compounds of CDs with hydrophobic molecules easily penetrate into body tissue to release active compounds under the required conditions.[5] The degradation process for such a complex is on a change in pH of the water solutions resulting in either a loss of hydrogen or ionic bonds between the host and the guest compounds.

Heating and enzymatic action can alternatively be another means of degradation, and it takes place at the α-1,4 linkages between glucose monomers. CDs are used to enhance the solubility of poorly water-soluble compounds, improve the bioavailability of drugs, enhance stability, mask an unpleasant taste, odor, reduce irritation and prevent drug incompatibility in the pharmaceutical field.[6]

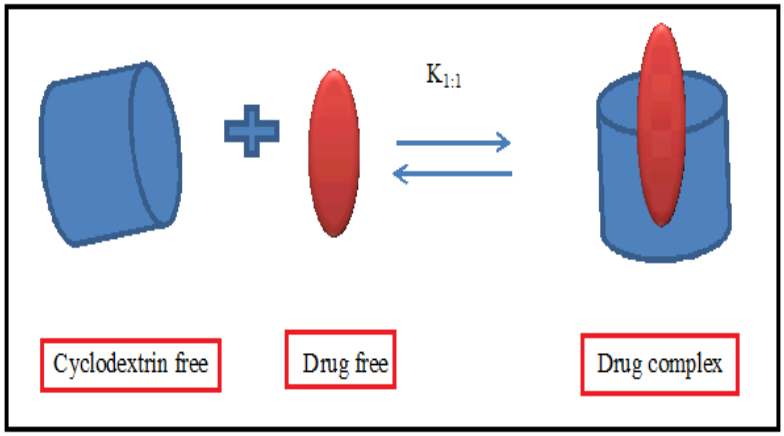

Figure 2: Schematic Representation of Drug-cyclodextrin complex formation.

2. Cyclodextrin toxicity

It is a fact the saccharide nature of CDs makes non-toxic to humans. However, β-cyclodextrin can be toxic to humans when is used for parenteral purposes; it can lead to nephrotoxicity.[7] Apart from β-cyclodextrin, other chemically modified CDs used for parenteral purposes with strict conditions regarding tolerance by humans. To improve the safety profile of chemically modified β-cyclodextrins have been identified, i.e. SBE- β-CD and HP- β-CD of which is commercially produced by Janssen. Currently, these compounds are used us approved product by the Food and Drug Administration (FDA).

No irreversible adverse effects are associated with i.v. Doses of hydroxypropyl β-cyclodextrin up to 400 mg/kg, and safe, high oral doses.[7] On the other hand, sulfobutylether derivatives of β-cyclodextrin are less hemolytic than the parent compound β-cyclodextrin. It is worth noting SBE7- β-CD shows no hemolysis to human erythrocytes whereas β-CD> SBE1- β-CD>> SBE4- β-CD.[8]

3. Solubility and dissolution improvement by cyclodextrin complexation

Chaturvedi et al. enhanced the solubility and stability properties of domperidone. In this article, the kneading method used in preparing the DOM-complex thus using 2-hydroxypropyl-ß-cyclodextrin; the complexation prepared was further formulated into MDT

by direct compression using disintegrants such as Kyron-T314, sodium starch glycolate, and Plantago ovata husk in different ratios. Saturation solubility was higher in the case of DOM-complex as compared to domperidone alone.[9]

According to Kale Mohana et al., d-a-tocopheryl polyethylene glycol, 1000 succinate (TPGS) and l-ascorbic acid-2-glucoside (AA2G) were attached to hydroxypropyl-ß-cyclodextrin (HPBCD) to improve the solubility properties of hypocholesterolemic drug ezetimibe. Binary and ternary cyclodextrin complexes were prepared using freeze-drying. Aqueous solubility, dissolution, and antihypercholesterolemic activity used to analyze log P values. Even though both complexes lead to a reduction in the log P values, aqueous solubility, dissolution, and antihypercholesterolemic activity, the ternary cyclodextrin component was markedly reduced.[10]

Agustina Garcia et al. improved the solubility and dissolution rate of albendazole using a citrate derivative of ß-cyclodextrin. Magnetic resonance experiment indicated both the tail and aromatic ring of albendazole were inside the cavity of the cyclodextrin derivative. Spraying drying method used in preparing the inclusion complex. The drug dissolution rate of albendazole showed a 100% drug release after 20 minutes.[11]

2-Hydroxypropyl-b-cyclodextrin (HPbCD) is approved for IT administration in humans and therefore can be used to improve the solubility of a drug such as D9-Tetrahydrocannabinol (THC). THC has a potent antinociceptive effect in animals after intrathecal (IT) or intracerebroventricular (ICV) administration however due to its lack of appropriate solvent it inhibits, IT administration in humans. In this article, two formulations prepared from the inclusion complex i.e.30 µg and 135 µg, and then tested on Wistar rat. The antinociceptive effect (using the tail flick test) locomotor activity and body temperature monitored. The results showed that the ICV injection of 135 µg leads to an increase in tail flick latency reduced locomotor activity and a dual effect on body temperature. Concerning the 30 µg formulation, a hyperthermic effect observed. Even after the administration of the drugs, both groups of animals appeared healthy. This result suggests that HPbCD is a carrier in the administration of THC.[12]

4. Bioavailability

The limitation primarily associated with oral drug administration is due to first-pass metabolism.[13,14] The bioavailability principle was first recognized by Oser et al. in 1945.[15]

The U.S. Food and Drug Administration defines it as the rate and extent to which an active drug moiety is absorbed from the drug product and made available to the target site.[16] Levy defines bioavailability as a ratio between the quantity of investigated drug and blood concentration using standard dosage forms.[17] Since the absorption of intravenously administered drugs is instantaneous and complete is of this reason most drugs are formulated into oral dosage forms usually capsules or tablets for purposes of convenience and stability. For this kind of dosage forms absorption is affected by some factors like a drug, dosage form, and patient. Regarding bioavailability in respect to orally administered drugs is defined as the absorption of medication from the gastrointestinal tract (GIT) and dosage form and it may be a solution, suspension, tablet, capsules, etc. Other dosage forms are its intra-muscular injections, ointments, and other topical preparations, transdermal patches and implants also require an absorption step before systemic circulation can take place. Intravenous injection is the only route that a drug can achieve 100% bioavailability.[18]

5. Classification of drugs based on solubility and intestinal permeability

Biopharmaceutics classification system (BCS) is a scientific classification of medications is premised on both the solubility and permeability of the drug that corresponds to in vitro dissolution and in vivo bioavailability of drug products.[19,20] USP and BP classify the solubility regardless of the solvent used, just only regarding quantification and have defined the criteria as given in Table 1.[21,22] All drugs fall under four main categories: class I— high soluble and high permeable, type II—low soluble and high permeable, type III—low soluble and high permeable and class IV—low soluble and low permeable. For BCS class II drugs bioavailability is limited due to poor dissolution even though permeability does not seem to be a problem. Given this, various solubility enhancement techniques have been explored to improve upon their bioavailability.[23,25] In the case of BCS class, III drugs bioavailability is limited due to poor permeability in as much as dissolution might occur quickly. To curtail this problem formulation scientist formulate IR solid dosage forms with absorption enhancers to improve permeability.[26] The bioavailability of BCS class IV drug compounds is limited as result of poor dissolution as well as poor permeability. This class of drugs is weak candidates for drug development because of its low membrane permeability, and solubility enhancers alone cannot improve the bioavailability of such a drug.

Table 1: Solubility approximations according to the USP and BP.

Term	Part of the solvent which dissolves one (1) part of the solute
Very Soluble	Less than 1 part
Freely Soluble	From 1 to 10 parts
Soluble	From 10 to 30 parts
Sparingly Soluble	From 30 to 100 parts
Slightly Soluble	From 100 to 1,000 parts
Very Slightly Soluble	From 1000 to 10,000 parts
Practically insoluble	More than 10,000 parts

6. Solid dispersions

Solubility is one of the most significant hurdles for formulation scientist all over the world. Over 60% of new drugs produced in the pharmaceutical industry are most often than not insoluble in water.[27] Various formulation strategies, such as particle size reduction[28,29], solid dispersions(SDs)[30], co-crystal formation,[31,32] complexation employing cyclodextrins[33], cosolvents[34] and lipid formulations[35] have been useful in improving drug solubility. SDs technique has been in operation since 1960 for the enhancement of poorly soluble drugs.[36]

SDs are classified into three categories based on one principle, i.e. how a hydrophobic drug compound dispersed in a hydrophilic carrier. Based on the above the law, SDs can be described us eutectic mixture, solid solution and microfine crystalline dispersion. Figure 2 complements the above classification.[37] A eutectic system deals with the melting points of compounds. This system involves compounds aggregating to form one composite mixture whereby the melting point of the composite mixture is smaller than individual compounds. A solid solution is into three central systems which are substitutional crystalline solid, interstitial solid and amorphous solid solutions. In substitutional crystalline solid solutions, the interstitial solid solution forms due to solute atoms occupying interstices within the carrier matrix. With the amorphous solid solutions unlike the substitutional, the drug molecules dispersed within the carrier. When a crystalline drug intersperses within a carrier matrix, this process is microfine crystalline dispersion.

Amorphous forms of drugs are highly unstable given this it is, therefore, necessary to stabilize these forms of drugs.[38] In light of this, some polymers, as well as surfactants, have developed and used as excipients for amorphous solid dispersions (ASD). Larger molecules like lipids, carbohydrates, and proteins used as stabilizing agents.[39] On the other, smaller molecules which include meglumine,[40] urea,[41] sugars,[42] amino acids[40] and organic

acids[43] are also useful as stabilizing agents. Studies have shown polymeric SDs (PSDs) increase the solubility and dissolution rate of drugs. Some techniques used be in SDs Solvent Evaporation Method,[44,45] Hot-Melt Extrusion,[46] fusion method,[47,48] Lyophilization techniques,[49] melt agglomeration[50,52], spray drying[53,54], use of surfactant.[55-58]

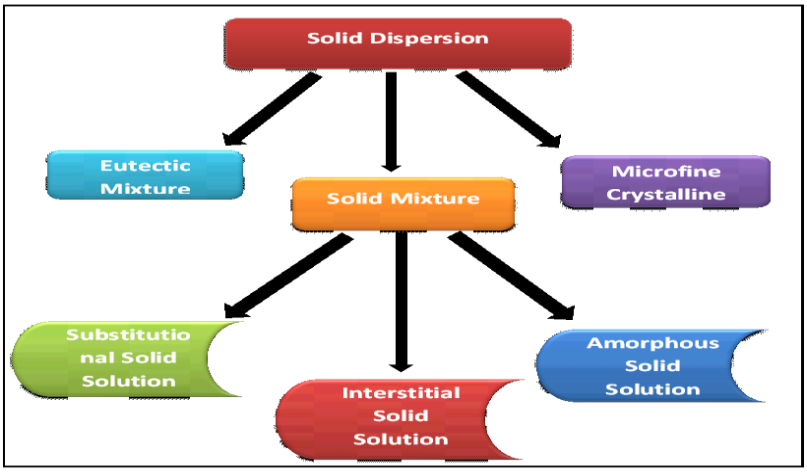

Figure 3: Classification of solid dispersions.

7. How drugs are characterized using solid dispersions

After drug formulation, it is, therefore, the need to know the amount of drug in the crystalline state. Table 2 gives some strategies that can be used for this determination and also at what condition one strategy is preferred over the other.[59]

Table 2: Summary of solid dispersion Characterization.

Drug –carrier miscibility	Drug carrier interactions	Physical Structure	Amorphous content	Stability	Dissolution enhancement
Hot stage microscopy	FT-IR spectroscopy	Scanning electron microscopy	Polarised light optical microscopy	Humidity studies	Dissolution
Differential scanning calorimetry	Raman spectroscopy	Surface area analysis	Hot stage microscopy	Isothermal Calorimetry	Intrinsic dissolution
Powder X-ray diffraction	Solid-state NMR	Surface properties	Humidity stage microscopy	DSC (Tg, Temperature recrystallization)	Dynamic solubility
NMR 1H Spin-lattice relaxation time		Dynamic vapor sorption	DSC (MTDSC)	Dynamic vapor sorption	Dissolution in bio-relevant media
		Inverse gas chromatography	ITC	Saturated solubility studies	
		Atomic force microscopy	Powder X-ray diffraction		
		Raman microscopy			

The solubility of clotrimazole which is a BCS class II drug was prepared by A. Madgulkar et al. using a different weight ratio of D-mannitol, D-fructose, D-dextrose, and D-maltose by fusion method. The solubility of these sugars as solid dispersion carriers compared to raw clotrimazole drug. Moreover, the dissolution of the solid dispersion tablets, compressed clotrimazole tablet, and plain were tested using U.S. Pharmacopeia standards. With Mannitol solution an 806-fold increase in solubility compared to plain clotrimazole. Again mannitol solid dispersion improved the dissolution profile of clotrimazole. The zone of inhibition for mannitol solid dispersion was 54mm suggesting an enhanced antifungal activity against Candida albicans as compared with plain clotrimazole which was 6.6mm.[60]

According to Sriamornsak et al. Solid, ternary phase diagram was constructed to improve the stability of manidipine (MDP) with polyethylene glycol 4000/copovidone. The solid ternary phase diagram was made to locate similar solid dispersion sections after melting and solidifying had taken place at low temperature. The pulverized powder was characterized. The results indicated that MDP was dispersed in both PEG4000 and copovidone. Strong hydrogen bonding was seen between MDP and copovidone from the FTIR results thereby increasing the solubility and dissolution of MDP. The appearance and solubility of tSD were not affected after storage at accelerated condition (40°C/75%RH) for six months.[61]

Barzegar-Jalali et al. used different carriers to improve the solubility of piroxicam. The results confirmed an increase in dissolution rate of piroxicam plus polymer prepared by the cogrinding method. As part of the results, IR analysis showed no physicochemical interaction between drug and polymer.[62]

Barea S.A et al. developed thalidomide solid dispersion using solvent method was dispersed in various emulsifying carriers. Among the polymers used were lauroyl macrogol-32 glycerides and α-tocopherol polyethylene glycol succinate, in the presence or absence of the precipitation inhibitor polyvinylpyrrolidone K30. A semicrystalline solid dispersion formed as per the physicochemical analysis. The results confirmed an increased solubility of about two to three times as compared to the pure drug. For the dissolution studies, 80% of the drug was dissolved within 120mins while the pure drug recorded 40%.[63]

8. Combinatorial effect of both cyclodextrin and solid dispersion

By and large, both techniques thus solid dispersion and inclusion complex when used alone or in combination one way or the other enhances the solubility, dissolution rate and

bioavailability of drugs.[64-66] Eventually, it improves wettability and results in decreased particle size, amorphous-structured particles, and higher porosity degree.[38,40,67] The crystalline form of a drug has high purity and physical/chemical stability compared to amorphous forms. Thus pure amorphous drug compounds are not used alone in medicinal products due to its unstable nature.[68] However, due to the higher free energy and the disordered structure of the amorphous forms of drugs, it enables solute molecules to be dissolved more readily as compared to the crystalline forms of drugs. Leading to an increase in solubility, dissolution rate and oral bioavailability.[69]

According to Zoghbi et al., different polymers (i.e., Poloxamer 188 (PLX) and Polyvinylpyrrolidone K-30 (PVP) and hydroxypropyl-β-cyclodextrin were used together to improve both the solubility and stability properties of carvedilol. What was found out in this experiment was that the solubility and the stability properties of carvedilol (CV) significantly increased compared to individual techniques.[70]

Yuvaraja et al., cyclodextrin (CD), hydroxypropyl--cyclodextrin (HPCD), tartaric acid (TA), polyvinylpyrrolidone K-30 (PVP K-30) and poloxamer-407 (PLX-407) were used to enhance the solubility of carvedilol. When in vitro studies were conducted, CV with the solid dispersion had a lesser dissolution time than the pure drug. The conclusion that arose was because first of all the crystalline form of the medicine had compromised the wettability and the dispersing ability of the drug improved.[71]

Here again, Jatinderpal Singh et al. prepared and evaluated disintegrating tablets of lamotrigine using β-cyclodextrin and PVP-30 using kneading methods. Other drug excipients were used such as sodium starch glycolate (SSG) and crospovidone as a super disintegrating agent to reduce disintegration time. The ratio used was 1:1 (thus between β-cyclodextrin and PVP-30). Eventually, the formulation prepared had a disintegration time of 15s, wetting time of 24s and friability of 55%.[72]

9. Drawbacks

One primary set with both techniques is the fact that aging of the drug can affect the stability of the drug. It happens due to the amorphous state converting back to the crystalline state. Most notably temperature and moisture can affect both systems, and this can eventually lead to tackiness thus tricky to handle.[40]

10. Limitations

Problems of both techniques include a method of preparation and reproducibility of physicochemical properties, formulation into dosage forms, the physical and chemical stability of drugs and vehicle and scale-up manufacturing processes.[73]

11. CONCLUSION

Poor bioavailability of drugs is a stumbling block in drug formulation. Inclusion complexation and solid dispersion are among some techniques that can be used to curtail this problem. Drug solubility irrespective of the temperatures and pH is invariably affected because of these two approaches. No individual approach is more stable than the combined procedures. Other combinatorial techniques should be explored in this area to enhance the solubility of poorly soluble drugs. Shortly more and more combinatorial approaches should be looked at in this regard to improve the solubility and stability of drug molecules.

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Competing interest

The authors declare there is no competing interest.

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