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Cyclodextrin Inclusion Complexes: Novel Techniques to Improve Solubility of Poorly Soluble Drugs: A Review

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Abstract

For a formulation scientist, the dilemma of solubility is a crucial test during the product development phase that can be resolved by opting various technological strategies. Some of the strategies that are usually applied for enhancing solubility of drugs with low aqueous solubility include micronization, solvent deposition and solid dispersion. With these approaches, some advantages as well as drawbacks, are affiliated. The strategy of complexation amid all techniques, has been applied more accurately for the improvement of dissolution profile, aqueous solubility, and bioavailability of poorly soluble drug candidates. Cyclodextrin are unique cyclic carbohydrates that have been exploited as successful complexing agents having capability of forming inclusion complexes with insoluble drugs. Numerous strategies have been considered to analyze the methods for preparation of inclusion complexes. In this review, we have pursued the discussion on different complexation techniques and in a nutshell, emphasized the applications and economical/technical limitations related to these techniques.

Key Words: Cyclodextrins, Solubility, Inclusion Complexes, Bioavailability

Introduction

Incorporation of non-polar molecule or the non-polar region of the molecule (known as guest) into the cavity of other polar molecule (host) results in the formation of inclusion complexes. Cyclodextrins(CDs) are most commonly used host molecules (Arun et al., 2008, Li et al., 2004). Cyclodextrins are oligosaccharides, cyclic in structure, that are produced by enzymatic degradation of starch by cyclodextrin glucosyl transferase. Cyclodextrins are composed of D-glucopyranose units linked by glycosidic (α-1, 4) linkage and arranged in a truncated cone-shaped structure (Sareen *et al.*, 2012, Zhou *et al.*, 2012). Hydroxyl group on the surface of cyclodextrin renders them aqueous solubility but the hydrophobic cavity impart a micro environment for non-polar molecules (Vyas et *al.*, 2008). Cyclodextrins have the ability of interacting with a huge variety of guest molecules by forming noncovalent inclusion complexes and this is due to their lipophilic inner cavities and hydrophilic outer surfaces. CDs exist in three natural forms, α-, β-, and γ-cyclodextrins (with 6, 7, or 8 glucose units respectively), that differ only in their ring size and solubility (Challa *et al.*, 2005, Loftsson and Brewster, 1996). Cyclodextrins remain intact in stomach and small intestine however; colonic microflora causes fermentation of cyclodextrin into small saccharides and increases drug release from inclusion complex in large intestine (Challa *et al.*, 2005).

This review is aimed to discuss the detailed information on use of cyclodextrins (CDs) as complexing agents. The use of different technologies for the formation of inclusion complexes of poorly water-soluble drugs with CDs as well as applications and limitations that are associated with these techniques are also the focused in this review.

Methods of Preparation of Cyclodextrin Inclusion Complexes

Various techniques are employed for the inclusion

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complex formation and some of them are discussed below (Patil and Jagadevappa 2010).

Physical Blending

By the method of mechanical trituration, solid physical mixture of drug and cyclodextrin is prepared. In laboratory, drug and cyclodextrin are triturated in a mortar and then passed through sieve of suitable size in order to get the desired particle size. While in industries, the drug and cyclodextrin are blended extensively in a rapid mass granulator usually for 30 minutes, to get physical mixtures. These powdered physical mixtures are then stored at controlled temperatures and humidity conditions (Patil and Jagadevappa 2010).

Kneading

This method involves the wetting of cyclodextrin with small amount of water just to change it into paste. The drug is added slowly into the paste and then kneaded in pestle and mortar for specific time period. After kneading, mixture is dried and passes through the sieve. On large scale, extruders and other equipment are used for kneading. This is most common and economical method for the preparation of inclusion complexes (Savjani, Gajjar et al. 2012).

Co-precipitation

Most commonly used method in the laboratory for the formation of inclusion complex is co-precipitation. In this method, firstly cyclodextrin is dissolved in water. After that, drug is added with continuous stirring of cyclodextrin solution. The precipitates are collected by the methods of centrifugation, filtration and decantation. The precipitates can be washed with water or water miscible liquid to remove drug particles attached on the surface of cyclodextrins (Del Valle 2004).

Lyophilization/Freeze Drying

When a porous and amorphous powder with high degree of interaction between drug and cyclodextrin is desired, lyophilization/freeze-drying technique is used. In this method, solvent is removed from solution through freeze drying followed by drying of complex at reduced temperature. This method is suitable for thermolabile materials. The drawback of this technique is that it is a time consuming process, it requires specialized equipment, and poor flow properties of powder (Cao, Guo et al. 2005).

Microwave Irradiation

This procedure is called microwave irradiation because reaction between cyclodextrin and drug takes place in microwave. In a mixture of water and organic solvent, drug and cyclodextrins are dissolved in specific portions and then the mixture is allowed to react at 60 ^{0}C for one to two minutes in microwave. Once the reaction is completed, a sufficient amount of solvent is added in order to remove the free drug and cyclodextrin from mixture. The precipitates are separated by filtration and then dried at 40 ^{0}C in a vacuum oven. This is best method for industrial scale due to higher yield and shorter reaction time (Wen, Tan et al. 2004).

Melting

Melted drug in excess is mixed with powdered cyclodextrin. The mixture is then allowed to cool. After that, uncomplexed drug is extracted by washing with suitable solvent. This technique is used for sublimable drug molecules like menthol.

Co-Evaporation/Solvent Evaporation

Co-evaporation/solvent evaporation involves the dissolution of drug in organic solvent and of cyclodextrin in water. Drug solution is added into cyclodextrin solution on stirring for 24 hrs and evaporation of solvent to get solid powdered inclusion complex. The dried powder is pulverized and passed through 60 mesh sieves. This is very simple and economical method, both on laboratory and industrial scale.

Milling/Co-Grinding

Inclusion complexation is achieved by milling/co-grinding of drug and cyclodextrin with the assistance of mechanical device. Mixture of drug and cyclodextrin is brought into the mill and grinded for adequate time to attain final product. Solid powder is then passed through a sieve of 60 mesh size. This technique is safe when compared with other methods for the formation of inclusion complex because it does not require toxic organic solvents.

Spray Drying

This is the most commonly used method for the preparation of inclusion complex from solution. This method produces the inclusion complex with sufficient and efficient interaction between drug and cyclodextrin which in turn increase the complexation efficiency and dissolution of drug. Vozone et al prepared the inclusion complex of budesonide with

cyclodextrin by using spray drying method for inhalation (Kanaka Durga Devi, Prameela Rani et al. 2010).

Conclusion

Most of newly discovered drug substances have low aqueous solubility which in turn affects their bioavailability and efficacy. In order to improve the dissolution profile of such poorly soluble drug candidates, solubility augmentation techniques have played a significant part. The favorable advancement in the dissolution profile of poorly aqueous soluble drug entities, depends predominantly on the technique that we select to enhance this property. The topmost enticing technique to improve the water solubility of poorly soluble drug molecules is the formation of inclusion complexes with cyclodextrin. CDs that serve as promising solubilizing agent for both oral and parenteral dosage forms. The duplex of drug and CDs have the ability of fabricating highly aqueous soluble amorphous forms by altering physicochemical characteristics of drugs namely particle size, solubility, thermal conduct and crystalline structure. Because of their paramount aqueous solubility, CDs have become promising new candidates for enhancement of bioavailability and dissolution rate of drugs with low solubility in water. Additionally, the inclusion complex of the drug with CDs also has the capability to augment the permeability of drug molecules through different biological membranes.

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Appendix

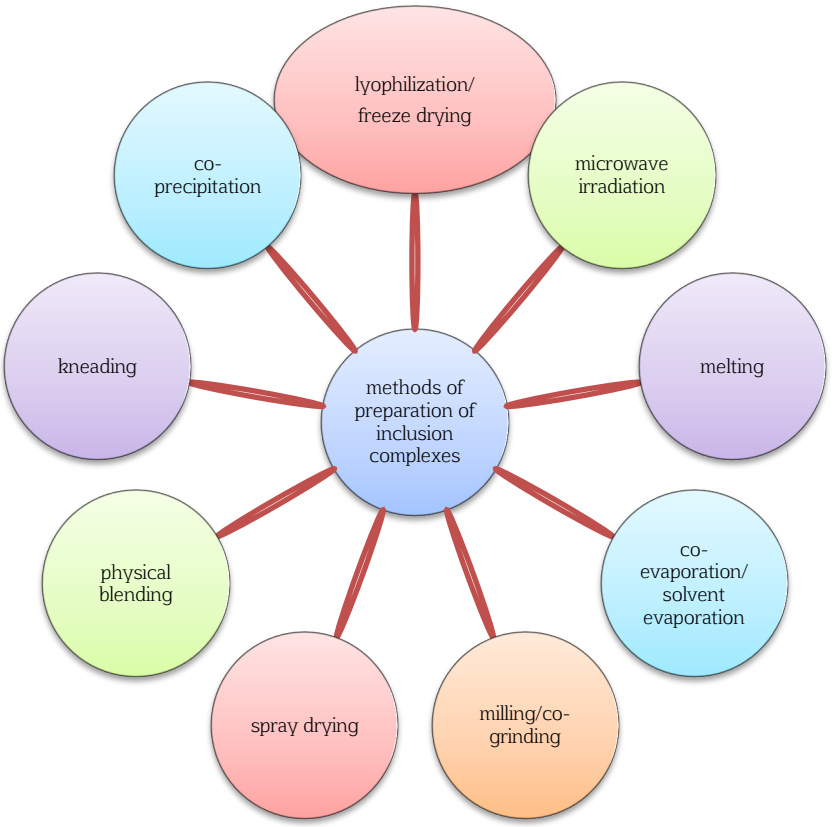

Figure 1: Methods of preparation of inclusion complex

Table 1. Examples of Cyclodextrin Inclusion Complexes

Drug	Complexing agent	Method of preparation	Reference
Piroxicam	Beta cyclodextrin	Kneading method, steam granulation	(Cavallari, Abertini et al. 2002)
Ibuprofen	Beta cyclodextrin	Wet granulation	(Ghorab and Adeyeye 2001)
Nimesulide	Beta cyclodextrin	Kneading, co evaporation method	(Chowdary and Nalluri 2000)

Itraconazole	Beta cyclodextrin and HP beta cyclodextrin	Solvent evaporation method	(El-Barghouthi, Masoud et al. 2006)
Lorazepam	Beta cyclodextrin	Coprecipitation method	(Sanghavi, Choudhari et al. 1993)
Celecoxib	Beta cyclodextrin	Kneading method	(Rawat and Jain 2004)
Pioglitazone	Beta cyclodextrin, methyl beta cyclodextrin and ϒ-CD	Kneading method	(Pandit, Gorantla et al. 2011)