Review Article

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Application of β-cyclodextrin drug inclusion complexes to improve solubility of poorly water soluble drugs

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Abstract

Solubility of new chemical entity was a major concern for formulation. Desired concentration of drugs was achieved through solubility in systemic circulation. A higher dose is required by feebly soluble drugs to reach therapeutic plasma concentration, Hence, to enhance the solubility, various methodologies are incorporated in which complexation is explained in detail in this review. Especially, types of complexation along with complexation agents are explained in this review. Various approaches used for making inclusion complexes are described.

Keywords: Solubility enhancement; β-Cyclodextrin; Inclusion complexes; Dissolution

1. Introduction

The formulation development to enhance drug solubility and dissolution properties are important. Solubility is the phenomenon of dissolution of solid in the liquid phase to give a homogeneous system. The important parameter of drug is solubility in systemic circulation for the pharmacological response to be shown. After oral administration, the weakly water soluble drugs require high doses to reach therapeutic plasma concentrations. Low aqueous solubility is the major problem of formulation development in new chemical entities. The techniques usually employed for solubilization of drug includes micronization, chemical modification, co-solvency, micellar solubilization, hydrotropy, pH adjustment, solid dispersion and complexation etc. In screening studies, solubilization of poorly soluble drugs is a frequently encountered challenge of new chemical entities as well as in formulation design and development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption [1, 2]. As solubility and permeability are the determining factors for the *in-vivo* absorption of the drug, these can be altered or modified by enhancement techniques [2]. Solubility is a term used to describe the amount of solute dissolved in a solvent at equilibrium stage. It can also be defined quantitatively as well as qualitatively. The term of quantitative solubility is defined as the concentration of the solute in a saturated solution at a certain temperature. The term of qualitative solubility is defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. The solubility of a drug is characterized by various concentration parameters such as percentage, molarity, molality, volume fraction and mole fraction [3, 4, 5].

Quantity of lipophilic drug molecules are increasing continuously by means of high throughput screening that is related to combinatorial chemistry and parallel synthesis. Most of these molecules are not able to be delivered at the site of action because of bioavailability problems as proposed [6]. To improve the formulation solubility by physical modification such as adding cyclodextrins, carbohydrates, hydrotropes, polyglycolized glycerides, and dendrimers are utilized. Around half of the drugs is in trial process due to unfavorable pharmacokinetics and approximately one-third in development process are soluble in water [7]. The improperly water soluble drugs are related with slow drug absorption contributing to inadequate bioavailability and gastrointestinal mucosal toxicity [8].

The cyclodextrins have been used to increase aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1, 4 - configuration to form rings of various diameters. The ring has a hydrophilic and lipophilic sides that are essential to organic molecules for non-covalent complexes resulting in increased aqueous solubility and chemical stability. Cyclodextrin complexes can enhance the stability, wettability and dissolution of the lipophilic repellent N, N-diethyl-m-toluamide (DEET) and the stability and photostability of sunscreens [9, 10, 11].

The molecular weights of cyclodextrin is greater than 1000Da. They enhance the complexation with cyclodextrin and decrease skin penetration [12, 13]. The important property of cyclodextrin is “entrapping” of hydrophobic molecules into their cavity in the aqueous phase.

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The main complex formation is the release of enthalpy-rich water from the cavity due to the entrapping of molecules of cyclodextrin. Weak Vander Waals forces, hydrogen bonds, and hydrophobic interactions form a complex. Therefore, the complexation process can be considered as a replacement of water molecules with drug molecules.

In this review, famotidine is used as a model drug. Famotidine is a highly selective H_2 receptor antagonist with properties of inhibiting gastric acid secretion and healing gastric and duodenal ulcers. The bioavailability of oral dose is 40 to 45 % and the aqueous solubility of the drug is 0.1% w/v at 20 °C i.e. practically insoluble in water. After oral administration, poorly water soluble drugs require high doses to reach therapeutic plasma concentrations. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities.

2. Complexation

Formation of a non-bonded entity with finely distinct stoichiometry leads to the process of association amidst of two or more molecules is known as complexation. Complexation depends upon weak forces such as London forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents and a partial list can be found in Table 1.

Table 1. Types of Complexing Agents

S. No.	Types	Examples
1	Inorganic	I_B^-
2	Coordination	Hexamine cobalt(III) chloride
3	Chelates	EDTA, EGTA
4	Metal-Olefin	Ferrocene
5	Inclusion	Cyclodextrins, Choleic acid
6	Molecular Complexes	Polymers

2.1. Factors Affecting Complexation

1. Steric effects
2. Electronic effects
   a. Effect of proximity of charge to CD cavity
   b. Effect of charges density
   c. Effect of charge state of CD and drug
3. Temperature, additives and co-solvent effects

2.2. Types of Complexation

1. Staching Complexation: The overlap of the planar regions of aromatic molecules leads to the formation of Staching Complexes. These complexes can be homogeneous or mixed. The earlier is known as self-association and later as complexation.

Examples are purine, anthracene, pyrene, methylene blue, nicotinamide, salicylic acid, ferulic acid, gentisic acid, theobromine, benzoic acid, caffeine, and napthalene etc.

2. Inclusion Complexation: Inserting a nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules leads to the formation of inclusion complexes (known as host). Examples are cyclodextrins. Aqueous solubility and drug stability can be enhanced by the complexation of drugs with cyclodextrins. 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1, 4 – configuration are present in cyclodextrins of pharmaceutical relevance to form rings of various diameters. Formation of appropriately sized organic molecules takes place in hydrophilic exterior and lipophilic core from which non-covalent inclusion complexes can be formed resulting in enhanced aqueous solubility and chemical stability. Most commonly used in pharmaceutical formulations are derivatives of β-cyclodextrin with increased water solubility (e.g. hydroxypropyl-β-cyclodextrin HP-β-CD). Cyclodextrin complexes have been shown to increase the stability, wettability and dissolution of the lipophilic insect repellent N, N-diethyl-m-toluamide (DEET)) and the stability and photostability of sunscreens [14, 15, 16].

Cyclodextrins are large molecules, with molecular weights greater than 1000Da, therefore it would be expected that they would not readily permeate the skin.

Complexation with cyclodextrins has been variously reported to both increase and decrease the skin penetration. Some methods that can be applied to enhance the complexation efficiency are shown in Table 2.

Table 2. Various drugs and methods used for complexation

S. No.	Drug	Molecular weight	Mechanism of action	Method	Indication	Reference
1.	Pioglitazone	356.44 g/mol	Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α	Physical mixture, kneading and spray drying	Antibiotic	[17]
2.	Aspirin	180.157 g/mol	aspirin suppressed the production of prostaglandins and thromboxanes	Physical mixture, kneading method, Precipitation method, solid dispersion method	NSAIDs	[18]
3.	Nimodipine	418.44 g/mol	Nimodipine binds specifically to L-type voltage-gated calcium channels	Physical Mixture	Calcium channel blocker	[19]
4.	Rizatriptan benzoate	269.345 g/mol	Rizatriptan acts as an agonist at serotonin 5-HT_{1B} and 5-HT_{1D} receptors	kneading method	Antimigraine	[20]
5.	Domperidone	425.911 g/mol	Domperidone is a peripherally selective dopamine D_2 and D_3 receptor antagonist.	Kneading method	Proton-Pump inhibitors	[21]
6.	Acyclovir	225.21 g/mol	Competitively inhibits and inactivates HSV-specified DNA polymerases preventing further viral DNA synthesis without affecting the normal cellular processes.	Solid dispersion and kneading method	Antiviral	[22]
7.	Ketoprofen	254.281 g/mol	Ketoprofen undergoes metabolism in the liver via conjugation with glucuronic acid, CYP3A4 and CYP2C9 hydroxylation of the benzoyl ring, and reduction of its keto function	Physical Mixture, kneading Co-ppt	NSAIDs	[23]
8.	Carvedilol	406.474 g/mol	Carvedilol is both a non-selective beta adrenergic receptor blocker (β1, β2) and an alpha adrenergic receptor blocker (α1)	Kneading method	β-Antiadrenergic	[24]
9.	Cilostzol	369.46 g/mol	Cilostazol is a selective inhibitor of phosphodiesterase type 3 (PDE_3) with therapeutic focus on increasing cAMP	Kneadin, Spray drying and physical mixture mthod	Phosphodiesterase inhibitor	[25]
10.	Tiagabine	375.55 g/mol	Tiagabine increases the level of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, by blocking the GABA transporter 1 (GAT-1), and hence is classified as a GABA reuptake inhibitor (GRI)	Freeze-drying method	Anti-convulsive	[26]
11.	Albendazole	265.333 g/mol	Albendazole causes degenerative alterations in the intestinal cells of the worm by binding to the colchicine-sensitive site of β-tubulin, thus inhibiting its polymerization or assembly into microtubules	By dissolution of ABZ in HP- β-CD	Anthelmintic	[27]
12.	Gemfibrozil	250.333 g/mol	Gemfibrozil is a potent lipid regulating drug whose major effects are to increase plasma high density lipoproteins (HDL) and to decrease plasma triglycerides (TG) in a wide variety of primary and secondary dyslipoproteinemias	Kneading co-ppt, co-evaporation, freeze drying	Lipid regulating agent	[2]
13.	Cabamazepine	236.269 g/mol	Carbamazepine is a sodium channel blocker	Kneading method	Antiepileptic	[28]

3. Conclusion

It can be concluded from the above review that solubility of the drug was the most important factor that controls the formulation of the drug as well as the therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug was the rate determining step for oral absorption of the poorly water soluble drugs. So, the aqueous solubility and dissolution rate of famotidine can be increased by inclusion complexation. Beta-cyclodextrin would be an interesting candidate for improvement of solubility of molecules and improve the dissolution profile of the drug used.

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