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Abstract

The development of a new drug requires research and evaluation before the drug is approved to enter the market. One of the factors determining the efficacy of a drug is the aqueous solubility of the drug. A current problem in today's pharmaceutical industry is the low aqueous solubility of many useful drugs. A drug with a low aqueous solubility will not readily be absorbed by the body. The low aqueous solubility of a drug is often due to the drug's hydrophobic character. Drug enhancement methods are necessary to avoid the obstacle of drug insolubility and many methods have been developed. This paper focuses on the use of cyclodextrins and their derivatives as a drug carrier to increase the solubility of poorly soluble drugs. Cyclodextrins have both hydrophobic and hydrophilic character and are capable of encapsulating a hydrophobic drug molecule and forming guest-host complexes. The cyclodextrin's cylindrical shape allows the guest molecule, the drug, to be kept within the hydrophobic interior while the exterior of the cyclodextrin is hydrophilic and soluble in aqueous solution. This complex improves the drug solubility and ultimately the bioavailability of insoluble drugs. In this paper the complexation of four drugs with cyclodextrin was studied; ibuprofen, imatinib, praziquantel and camptothecin. In each case the aqueous solubility of the poorly soluble drug was increased with the use of cyclodextrins.

Introduction

The development of a drug is a process of converting a biologically active compound into a product that is safe and effective, it is a long and expensive process. The performance of a drug, the efficiency of the drug in carrying out the desired action, is dependent on the drug's properties. Chemical and physical properties of a drug determine the drug's ability to react with the necessary components along the path to achieving the desired effect. One of the factors determining a drug's performance and effectiveness is the aqueous solubility of the drug (Gareth, 2007).

Solubility of a Compound

IUPAC defines solubility as the composition of a saturated solution in terms of the amount of solute in proportion to solvent (McNaught, Wilkinson, 2006). Solubility is the term used to describe a solid, liquid, or a gas's ability to dissolve in a solvent. Aqueous solubility of a molecule changes depending on the electrostatic charge of the molecule and the degree of ionization. The dipoles in the water molecules are attracted to the charged molecules forming a shell around the molecule and solvating it (Trevor et.al. 2015).

Solubility of a compound depends also on its structure and polarity. Polar groups can hydrogen bond with water molecules and be solvated, nonpolar groups are insoluble in aqueous solution. Therefore, the aqueous solubility of a compound increases as the number of polar groups on the compound increases. In addition, if the polar groups on a compound have the ability to ionize in water, the compound will be further soluble. Lipid soluble compounds are those with more nonpolar groups and they may contain functional groups such as benzene rings, ethers and esters. Amphipathic compounds with polar and non-polar parts are soluble in both aqueous and lipid solvents (Gareth, 2007).

Drug Solubility

Solubility is a fundamental property that must be considered when evaluating a drug. The solubility of a drug can range from fully soluble, like ethanol in water, to poorly soluble, often referred to as insoluble (Clugston, Fleming, 2000). The Biopharmaceutics Classification System (BCS), is a guide from the U.S. Food and Drug Administration and is used to regulate and classify drugs based on aqueous solubility and membrane permeability. Class I drugs have high aqueous solubility and high membrane permeability, Class II drugs have low aqueous solubility and high membrane permeability, Class III have high aqueous solubility and low membrane permeability, and Class IV drugs have low aqueous solubility and low membrane permeability. Solubility of a drug is determined based on the drug's solubility over a pH range of 1 to 7.5 and is considered very soluble if the highest dose strength is soluble in <250 ml of water. The membrane permeability of a drug is measured by the extent of absorption and a drug is considered highly permeable when the absorption in humans is > 90% of an administered dose (FDA, BCS, 2016). Since cells typically contain 65% water, a drug must be water soluble to be effective. A drug must be absorbed before entering the bloodstream in order for the drug to be transported via the systemic circulation to its site of action. The more soluble the drug the greater amount of absorbed drug in the bloodstream. More drug in the bloodstream increases the gradient between the bloodstream and the extracellular fluid, in this way diffusion of the drug from the blood to the extracellular fluid will be facilitated (Trevor et. al. 2015). In addition, the more water soluble the drug the higher the bioavailability (Gareth, 2007). The amount of drug that is absorbed by the bloodstream, divided by the amount that was administered, is the bioavailability of that drug administered in that specific manner. Drug absorbed / drug administered = bioavailability of the drug (Trevor et. al. 2015).

Oral drugs are the most common form of drug administration. They are easy to administer, are less specific in their sterility requirements, they are most cost effective, have a high patient compliance, and there is flexibility in the dosage form. For this reason many pharmaceutical companies prefer to produce bioequivalent oral drugs. The difficulty with oral bioequivalent drugs is their low aqueous solubility and therefore low bioavailability. Oral drugs must first dissolve in the aqueous gastric fluid in order to be transported to the site of action. Therefore, solubility of a drug is an important factor in determining the concentration of a drug

that is required to achieve a desired response. More than 40% of pharmaceutical developments are poorly soluble in water. Low solubility of a drug slows the absorption rate, decreasing the bioavailability. Thus, solubility enhancement methods are necessary. Increasing a drug's solubility is a challenge faced by the drug development industry, especially the solubility of oral drugs (Savjani et. al. 2012). Increasing the solubility of Class II drugs that have low solubility and high permeability would be very productive. The rate limiting step for Class II drugs, according to the BCS, is the insolubility of the drug, therefore increasing the solubility will increase the bioavailability of those drugs.

There are many methods that are currently used to increase the solubility of new chemical entities (NCE's). There are physical and chemical modifications that can be made to a drug to increase its solubility. Particle size reduction can be employed, as well as solid dispersion, nanosuspension, colloidal particles, and changes to the crystal form. Additionally, chemical changes to pH as well as complexation and salt formation affect the solubility (Savjani et. al. 2012).

Other methods include the use of surfactants, micelles, liposomes and inclusion complexes (Gareth, 2007). These methods utilize the hydrophobic effect in increasing the solubility of a molecule. Cyclodextrins and cyclodextrin derivatives form inclusion complexes with insoluble drugs. Inclusion complexes apply guest-host chemistry in the formation of the complex. This paper will focus on cyclodextrins and cyclodextrin derivatives as a method to increase the solubility of a poorly soluble drug.

Methods

This study was completed by analyzing various articles collected from databases including Touro Library and PubMed. The research collected mainly explored cyclodextrins and their ability to form guest-host complexes.

Discussion:

Cyclodextrin and Cyclodextrin Derivatives

Cyclodextrins (CD's), and their derivatives are amphipathic molecules capable of forming guest-host complexes with drug molecules. The complex improves the drug solubility and ultimately the bioavailability of insoluble drugs. Cyclodextrins are used as a drug delivery system because of their potential to change physical, chemical and biological properties of a drug by forming a guest-host complex (Gareth, 2007). From a microscopial point of view, each guest molecule is micro-encapsulated leading to changes in the chemical and physical properties of the molecule. Cyclodextrins and their derivatives can improve the solubility of a molecule, modify a liquid substance to a powder, and mask a bad taste, smell or color of a drug (Chaudhary, Patel, 2013).

Cyclodextrin Structure

Cyclodextrins are cylindrical oligosaccharides typically made up of six, seven, or eight glucose units. The cyclodextrin ring form is composed of α-D-glucopyranoside units with 1→4 linkage like in amylose (Gareth, 2007). When glucose is degraded by the enzyme glucosyltransferase, a product of the chain splitting can undergo an intramolecular reaction to form cyclic molecules, cyclodextrins. Each glucose molecule in the cyclodextrin contains two secondary alcohols and a primary alcohol. Alpha (α), beta (β), or gamma (γ) cyclodextrins, depending on whether they contain six, seven, or eight glycosyl units respectively, are classified as natural cyclodextrins. Chemically derived cyclodextrins are hydroxypropyl-β-cyclodextrin, randomly methylated-β-cyclodextrin, and sulfobutylether-β-cyclodextrin. These derivatives are often preferred due to their enhanced physiochemical and biopharmaceutical properties (Gidwani, Vyas, 2015).

Cyclodextrin Synthesis

B. macerans is the microbe responsible for the formation of cyclodextrins. A method to synthesize cyclodextrins is to treat starch with amylase from Bacillus macerans. A crude product of cyclodextrin is then obtained with about 60% αCD, 20% βCD, and 20% γCD. The product also contains small amounts of other materials including proteins. To purify the different

cyclodextrin derivatives, various forms of glucosyltransferases are genetically engineered. These glucosyltransferases are active towards the production of specific cyclodextrin derivatives. The glucosyltransferase enzymes distinguish the six, seven, or eight glucopyranose units from the non-reducing end of an amylose and alter the linkage to produce a specific cyclodextrin derivative (Brewster, Loftsson, 2007).

Hydropathy of Cyclodextrin

Cyclodextrins are amphipathic molecules. They have hydrophobic and hydrophilic character. Cyclodextrins have a hydrophobic interior and hydrophilic exterior. The polar exterior of the cyclodextrin forms hydrogen bonds with the aqueous solution. The hydrophobic effect drives the non-polar portion of the cyclodextrin inwards, away from the aqueous solution, forming a hydrophobic cavity. This property enables the cyclodextrin to form guest-host inclusion complexes with hydrophobic molecules (Chaudhary, Patel, 2013).

Cyclodextrins can encapsulate many molecules. The nonpolar hydrophobic molecule interacts with the nonpolar groups in the interior of the cyclodextrin, while the polar hydroxyl groups on the exterior surface of the cyclodextrin are hydrophilic. Hydrophobic molecules the size of one or two benzene rings can fit into the cyclodextrin cavity. The cyclodextrins in the complex increase the aqueous solubility of the guest molecule, often a drug. The interactions between the cyclodextrin and the drug form the inclusion complex, the cyclodextrin host molecule with the guest drug (Tiwari et. al. 2010).

Cyclodextrin-Drug Complex

A number of forces are responsible for the complex formation; hydrogen bonding, van der Waals interactions, release of conformational strain, and exclusion of high energy water bonds in the cyclodextrin cavity. Thermodynamic interactions are the main drive in the formation of the cyclodextrin-guest complex. Thermodynamically, the interaction between the cyclodextrin host, the guest molecule, and the solvent, must overall be favorable in order for the reaction to proceed (Chaudhary, Patel, 2013). The cyclodextrin complex formation is usually enthalpy driven. In an aqueous solution the cyclodextrin cavity contains polar water molecules that are readily exchanged for non-polar hydrophobic guest molecules. The water molecules situated inside the non-polar environment of the cyclodextrin cavity do not have a full complement of hydrogen bonds and are higher in energy than the water molecules outside the cyclodextrin. Liberating the water molecules that are enthalpy-rich, high in energy, is a driving force for the complexation. Sterically, the size and certain functional groups of the guest molecule determine the ability of the guest to fit into the cyclodextrin cavity. Additionally, the complex formation is dependent on the chemical properties of the guest molecule (Brewster, Loftsson, 2007).

The formation of the cyclodextrin-drug complex can be achieved through several methods. The kneading method is a simple and inexpensive method and is therefore the most commonly used method for preparing the complex (Savjani et. al. 2012). This method converts the cyclodextrin into a paste by saturating the cyclodextrin or cyclodextrin derivative with water or hydroalcoholic solution. The drug is then added to the paste and the mixture is kneaded. The kneading can be done either in the laboratory or using machines for large scale achievement of the complex. An additional method, the lyophilization/freeze-drying technique, works with a solution of cyclodextrin and drug. The solvent in the solution is removed by freezing the solution and then drying it by rapidly reducing the pressure, generating a powder. The increased surface area of the powder enables considerable interactions between the cyclodextrin and the drug (Savjani et. al. 2012).

Cyclodextrins can increase the solubility of the guest molecule in three patterns when graphed with cyclodextrin concentration and drug solubility. AL profiles indicate a linear increase in drug solubility as the concentration of cyclodextrin is increased. AP systems have a curve that deviates in a positive direction from the linearity indicating that the cyclodextrin is proportionally more effective at higher concentrations. AN relationships have a negative deviation from the linearity indicating that at higher concentrations cyclodextrin's effectiveness decreases (Brewster, Loftsson, 2007).

Complex Dissociation

Once a product of drug-cyclodextrin is obtained, the complex must dissociate to release free drug upon reaching the site of action. When drug is encapsulated within the cyclodextrin there are factors that cause the complex to dissociate and release free drug. The drug and cyclodextrin interactions are non-covalent interactions that are in dynamic equilibrium, constantly associating and dissociating. There are two important factors concerning the complex's non-covalent interactions; firstly the complexation strength, defined by K, and secondly the complex lifetime. In a 1:1 complex ratio of drug to cyclodextrin the complexation strength, the K constant, is defined by the equation: $K = kf / kt = [DCyD] / [Df] [CyDf]$ where kf and kt are the forward and reverse rate constants, [DCyD] is the complex concentration and [Df] and [CyDf] are free drug and free cyclodextrin respectively.

Dilution is a major factor assumed to play a role in the dissociation of the complex. 1000-fold dilution of a drug with a low binding constant to cyclodextrin decreased the complexation percentage from 98% to 5.7%. The fraction of complexed drug decreased from 99.5% to 47.5% in the presence of 1000-fold dilution of a drug with a high binding constant to cyclodextrin.

Therapeutically, the complexed drug is diluted either in the plasma or in the aqueous extracellular fluid. A 1mL

drug-cyclodextrin complex administered via intravenous injection is diluted in the plasma by a factor of 1:3,500, in the extracellular fluid the factor is 1:21,000. Dilution alone is not sufficient in orally administered drugs because the complex resides in the gastrointestinal tract before reaching the site of action.

Drug binding to plasma protein is another factor responsible for complex dissociation. If a drug has the ability to bind to plasma protein the complex would dissociate further to release more free drug according to Le Chatelier's principle. Drugs with a high binding constant to cyclodextrin that have the ability to bind moderately to proteins, in 1000-fold dilution, are further dissociated and only 31.9% complexed drug remains. If the drug binds more tightly to proteins the factor of complexed drug decreases to 8.9%.

Furthermore, if a drug is lipophilic and can be taken up by tissue more drug would be released from the complex. The cyclodextrin would remain in the aqueous solution and drug would be taken up by tissue. This mechanism is especially useful in drug administered at a site that has insignificant dilution (Stella et. al. 1999).

The dissociation process is driven mainly by an increase of water molecules in the surrounding environment and happens relatively fast. In a dilute environment there is a concentration gradient which shifts the equilibrium to the left, dissociating the cyclodextrin and the drug, thereby releasing free drug to be absorbed. In the body's dynamic environment, it is not likely that the drug will encounter another cyclodextrin with which to form a complex and in this way it remains free in the solution (Chaudhary, Patel, 2013).

Complexed Drug Pharmacokinetics

The effect of cyclodextrins on the pharmacokinetics of complexed drug must be considered before cyclodextrin complexation can be applied. Kurkov et. al. studied the effect of complexation on the pharmacokinetics of close to 200 drugs. The results concluded that the hydroxypropyl-β-cyclodextrin does not have a significant effect on the pharmacokinetics of the drugs. However, although not altered, some drug is lost due to the complexation. The hydrophilic cyclodextrins are excreted unchanged by the kidneys and any drug still encapsulated is excreted too. This is especially true when the drug has a high binding constant to cyclodextrin (Kurkov et. al. 2012).

Toxicological Considerations

Orally administered cyclodextrins are not significantly absorbed in their intact form from the gastrointestinal tract. The Cyclodextrins range from 1000 Da to over 2000 Da in molecular weight and are hydrophilic with significant hydrogen bonding donors and acceptors, therefore they cannot be absorbed in their original form. Natural α-cyclodextrin and β-cyclodextrin cannot be hydrolyzed by human salivary and pancreatic amylases and in general oral administration is not associated with significant adverse effects and is well tolerated. After IV injection α-cyclodextrin is mainly excreted unchanged in the urine. β-cyclodextrin is nephrotoxic when administered parenterally but non-toxic in the topical, buccal, rectal or oral form and can be found in numerous marketed drugs. The metabolism of γ-cyclodextrin is similar to that of starch and linear dextrins and only small amounts are absorbed intact. After iv injection the γ-cyclodextrin is mainly excreted unchanged in the urine (Brewster, Loftsson, 2007).

Ibuprofen-Cyclodextrin

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used to treat mild to moderate pain and fever. Ibuprofen works by inhibiting cyclooxygenase, an enzyme that converts arachidonic acid to cyclic endoperoxides. Cyclic endoperoxides are precursors to prostaglandins responsible for inflammation (PubChem, 2004).

Ibuprofen is a poorly water soluble drug. Although it contains a carboxylic acid functional group which can hydrogen bond with water and be solvated, the alkyl groups and the benzene ring are non-polar and make the drug poorly soluble. Ibuprofen is complexed with cyclodextrin derivatives to increase its solubility (Hussein et. al. 2007).

Khaled Hussein, et al. conducted a study on the ibuprofen-β-cyclodextrin complex (Hussein et. al. 2007). A solid complex of ibuprofen, MW 206.3 g/mol, and β-cyclodextrin, MW 1,135.0 g/mol, was prepared. Using controlled Particle Deposition (CPD) with supercritical carbon dioxide the ibuprofen-β-cyclodextrin complex was formed. The CPD method dissolves the desired solution in supercritical carbon dioxide which then enters the pores of the carrier at extremely high pressure and precipitates following a rapid pressure drop.

The "n-hexane wash" method determined whether the complex was formed. β-cyclodextrin and its complexes are insoluble in n-hexane but the free drug is soluble. The supernatant liquid that was insoluble was separated, dried and then analyzed by high-performance liquid chromatography (HPLC). HPLC determined the product yield as well as the content of ibuprofen in the complex. The inclusion yield of the complex was determined using the following equation:

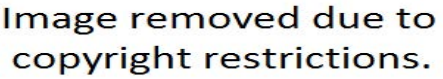
Percent of included ibuprofen= [complexed amount of ibuprofen/free amount + complexed amount] x 100 49.83±3.65 inclusion yield % was calculated.

Infrared spectroscopy of pure ibuprofen showed all the characteristic peaks including the carbonyl peak at 1,706 cm-1. The complexed drug's infrared spectroscopy had a very week carbonyl peak indicating that the drug molecule was encapsulated inside the β-cyclodextrin. Morphological changes were also observed. Pure ibuprofen is rough needle-shaped crystals and β-cyclodextrin is parallelogram shaped. The shape of the complexed particles appeared smaller in size and different than pure drug or pure β-cyclodextrin. This observation adds to the evidence of the ibuprofen-β-cyclodextrin complex formation.

The complex was tested for drug release using a flow system with a dissolution vessel at pH 5 and 37°C. A sample of pure ibuprofen and a sample of complexed ibuprofen, each containing 3mg ibuprofen, were added to the vessel. Samples were taken from the dissolution fluid at set intervals and were studied spectrophotometrically. Kw, the dissolution coefficient, was calculated. Kw corresponds to the time when 63.2% of the drug is dissolved.

The dissolution of pure ibuprofen in vitro at pH 5 showed poor dissolution after 15 minutes and after 75 minutes. The complexed drug had a significantly higher dissolution rate and amount, due to the presence of the β-cyclodextrin. The dissolution rate of the complexed product was 0.086±0.002 min^{-1}, the rate of pure ibuprofen was excluded from analysis since it did not reach 63.2% within 72 minutes. The dissolved amount of drug after 15 minutes was determined to be 71.9±3.62% for the complexed prepared using the CPD method, and 22.0±3.56% for pure drug. After 72 minutes, 93.5±2.89% of drug dissolved from the ibuprofen-β-cyclodextrin complex and from pure ibuprofen sample only 59.5±4.86% of drug dissolved. The complexed drug had a significant increase in aqueous solubility.

Imatinib-Cyclodextrin



Imatinib, known as Gleevec, is an oral tablet or a capsule used for the treatment of Philadelphia chromosome positive chronic myeloid leukemia (CML) or gastrointestinal stromal tumors. Imatinib works by inhibiting protein tyrosine kinase, the growth factor receptor that causes unregulated cell growth of cancer cells (PubChem, 2005).

Aqueous solubility of imatinib is charge dependent and varies depending on the pH. The active compound, imatinib, can be mono, di, tri and tetra protonated. The more protonated the compound the greater the overall charge of the compound. Increased charge increases the aqueous solubility. At a pH below 5.5 the formation of different protonated species of imatinib results in a charged drug that is water soluble. However, the free base form of imatinib is neutral, uncharged, and therefore poorly soluble. To increase the aqueous solubility of the free base form of imatinib, the drug was complexed with β-cyclodextrin and with randomly methylated β-cyclodextrin (RAMEB). Szabolcs Beni, et al. performed a study determining the effectiveness of cyclodextrin and cyclodextrin derivatives in increasing the solubility of the neutral drug form (Beni et. al. 2007).

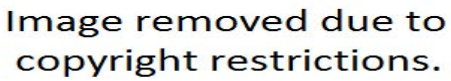
In a solution of Na2CO3 at a pH of 10.5, 2 mg of imatinib was added to a 1 ml solution of varying concentrations of β-cyclodextrin, 0-13 mM. The mixture was shaken for two days at 25.0 ± 0.5°C and a complexed product of 1:1 stoichiometry was formed.

The aqueous solubility of the free base form of imatinib was enhanced by complexing it with β-cyclodextrin. At a pH of 10 the linear AL phase solubility diagram indicated the improvement in the solubility of the drug. With increased cyclodextrin concentration, the solubility of the drug increased linearly, complexation increased the drug solubility tenfold.

Titration of pure imatinib with KOH precipitated above a pH of 6.5. Titration of 1mM imatinib in the presence of fourfold β-cyclodextrin or randomly methylated β-cyclodextrin (RAMEB) did not precipitate due to the complex's effect on the solubility. The most stable form of the imatinib-cyclodextrin complex formed with the neutral form of imatinib. This is because the neutral imatinib is most hydrophobic and interacts most with the hydrophobic interior of the cyclodextrin. The affinity of imatinib towards cyclodextrin decreased as the charge on the drug increased.

^{1}H NMR chemical shift titration method quantified the non-covalent molecular interactions. At a titration of pH 3.5 the predominant imatinib species was the deprotonated form. The mono and tri protonated forms were present in smaller quantities. Interactions between the imatinib forms and the β-cyclodextrin was evident. The data collected suggests that the benzamide fragment of imatinib is involved in the inclusion complex.

2D ROESY NMR spectra was recorded at the same pH to verify the data. The evidence suggested that the imatinib inclusion proceeds through the narrower part of the cyclodextrin host. For steric reasons the inclusion proceeds in an unusual way, through the narrower part of the cyclodextrin. The result

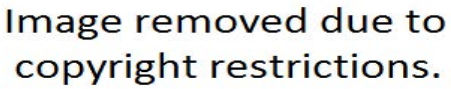


of the study concluded that a tenfold increase in the imatinib solubility was achieved with 12mM β-cyclodextrin complexation. The increased aqueous solubility of imatinib greatly increases the effectiveness of the anti-cancer drug.

Praziquantel-Cyclodextrin

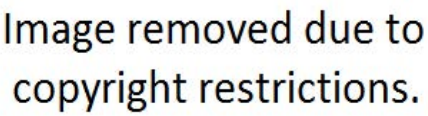
Praziquantel (PZQ) is a Class II drug, according to the BCS, used for the treatment of schistosomiasis. The drug works by causing severe spasm and paralysis to the worms' muscles and the worms are then destroyed in the intestines or passed in the stool. It is classified as a Class II drug due to its high membrane permeability but low aqueous solubility. The low aqueous solubility is due to its lipophilic character (PubChem, 2005).

As a Class II drug, a high dose of praziquantel is necessary in order for it to be effective. Improving the aqueous solubility of praziquantel can potentially result in the classification of the drug as a BCS-Class I compound. To increase the aqueous solubility



of praziquantel the drug was complexed with β-cyclodextrin and hydroxypropyl-β-cyclodextrin. A study was conducted to determine whether this Class II drug can be complexed with cyclodextrin and behave like a Class I drug (Maragos et. al. 2009).

The praziquantel-cyclodextrin complexes were formed via the kneading method. 0.080 grams of praziquantel was mixed with cyclodextrin in varying ratios; 1:1, 1:2, and 1:4 molar ratios. The complexed praziquantel-β-cyclodextrin reached equilibration within 12 hours and the praziquantel-hydroxypropyl-β-cyclodextrin complex reached equilibration after a 24 hour period. Heating the samples at 70°C for an hour prior to the experiment accelerated the reaction and also increased the formation of the praziquantel-cyclodextrin complex. The concentration of praziquantel in the binary system remained constant while it was in a shaking bath at 25°C for 72 hours.



The aqueous solubility of the lipophilic drug had a 4-5-fold increase upon complexation with cyclodextrin. Calculations of the praziquantel solubility in 0.01 M cyclodextrin versus the solubility of praziquantel without cyclodextrin calculated a solubility enhancement factor of 4.5. Preheating the samples at 70°C for one hour prior to the experiment increased the solubility enhancement factor; a factor of 5.5 was calculated for the praziquantel-β-cyclodextrin complex and 6.0 for the praziquantel-hydroxypropyl-β-cyclodextrin complex. Preheating the sample before complexation enhanced the drug complexation by increasing the dissolved amount of praziquantel that interacted with the cyclodextrin to form inclusion complexes.

The content of praziquantel in the product was determined spectrometrically. The isoquinoline ring of the praziquantel inserted in the cyclodextrin cavity. The phase solubility diagrams were linear. The praziquantel complexation was stronger with β-cyclodextrin than with the hydroxypropyl-β-cyclodextrin derivative as revealed by the complexation constants, K values,

obtained from the diagram. Furthermore, the complexation enhancement as a result of preheating the sample was more significant in the hydroxypropyl-β-cyclodextrin complex as reflected in the K values.

Praziquantel complexation with different molar ratios of cyclodextrin was studied. The praziquantel complex with β-cyclodextrin had the highest drug concentration in a 1:2 praziquantel-cyclodextrin ratio. The optimum praziquantel-hydroxypropyl-β-cyclodextrin complex molar ratio was 1:4. The different behaviors of the cyclodextrin derivatives are a result of hydrogen bond formation between the drug and cyclodextrin.

After complexation with β-cyclodextrin and hydroxypropyl-β-cyclodextrin the drug was reevaluated in terms of the BCS. The solubility/dose ratio, in relation to the dose and intestinal content, was calculated using solubility values of praziquantel in the presence and absence of β-cyclodextrin and hydroxypropyl-β-cyclodextrin. At a low dose of 150 mg the praziquantel complexed with β-cyclodextrin or hydroxypropyl-β-cyclodextrin had a higher solubility/dose ratio than pure drug. The solubility was increased while the dose decreased. The low dose form of praziquantel, 150 mg, thus classified as a BCS-Class I drug.

Camptothecin-Cyclodextrin

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Camptothecin is an antineoplastic agent that displays broad spectrum activity in the treatment of various cancers. Camptothecin is used against human lung cancer, prostate, breast, colon, stomach, and ovarian carcinomas and in the treatment of melanoma, lymphomas, and sarcomas. An alkaloid isolated from the bark of the Chinese tree Camptotheca acuminata, camptothecin works by inhibiting the enzyme topoisomerase I. Inhibition of topoisomerase I prevents DNA relegation leading to DNA damage and apoptosis (PubChem, 2005). Camptothecin is practically insoluble in aqueous solution at a pH above 7 the drug is converted to a water soluble but less active carboxylate form. Jichao Kang, et al. performed a study complexing camptothecin with cyclodextrin in attempt to increase the solubility of the pharmaceutically important drug (Kang et. al. 2002).

The solubility of the drug complexed with cyclodextrin was determined by placing 5 mg of camptothecin in 1.0 ml of a 0.02 M HCl solution containing different amounts of cyclodextrin. Analysis of the results gave a linear graph, the solubility of camptothecin increased linearly with the increasing concentrations of various cyclodextrins. Camptothecin in the β-cyclodextrin complex had the highest increase in solubility, increasing by about six-fold. α-cyclodextrin increased the camptothecin solubility three-fold and γ-cyclodextrin increased the drug's solubility five-fold. Of the modified cyclodextrin, RDM-β-CD exhibited the greatest increase in camptothecin's solubility. At 25% weight / volume concentration of RDM-β-CD, the solubility of camptothecin increased by a factor of 170. The methyl groups significantly increase the solubilizing effect of this cyclodextrin derivative by disrupting the intramolecular hydrogen bonding and enlarging the cyclodextrin cavity.

Conclusion

Drug solubility is an important factor in determining the efficacy of a drug. The low aqueous solubility of many pharmaceutical developments is an area of constant research. This paper studied the effect of cyclodextrins on the solubility of poorly soluble drugs. Cyclodextrins and their derivatives, by forming guest-host complexes, encapsulate an insoluble drug and increase its aqueous solubility. The cyclodextrin carries the drug through the aqueous solution and the complex dissociates upon reaching the site of action. The cyclodextrin drug carrier transports the insoluble drugs without altering the drug or causing significant harm to the patient.

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