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A Study of Hydroxypropyl A-Cyclodextrin and A-Cyclodextrin Inclusion Complexity

Pashupati Nath Sharma*

Research Scholar, Department of Chemistry, SSSUTMS, Sehore.

Abstract - Cyclodextrins are generated with a range of readily available enzymes for the treatment of ordinary starch. Along with amylase, cyclodextrin glycosylotransferase is commonly used. The first is to liquify starch by thermal treatment or amylase and add CGTase to the enzyme conversion. The synthesis of all three types of cyclodextrins is possible at ratios that depend strictly on the enzyme used. Each CGTase has an independent synthesis relationship. Cyclodextrins are filtered according to their different water solubility: CDs that are very poorly water-soluble can be easily crystallised while the more soluble - and -CDs (145 and 232 g/l) normally cleaned using chromatographic techniques. Alternatively, during the enzymatic conversion, a "complexing agent" may be added to form a complex with the desired cyclodextrin (usually organic solvents such as toluene, acetone or ethenol). The complex formation contributes to the conversion of starch to a precipitate cyclodextrin's synthesis and hence increases the content of the final product mix. Cyclodextrins Extracting amylase starch from Bacillus macerans results in a crude cyclodextrin mixture. There were some other linear and ramified dextrins in the mix along with small quantities of proteins and other impurities. Dramatic changes to their efficiency were attributed to biotechnological advancement in the 1970s. Various forms of CGTases made by evolution have been used to produce cyclodextrins more active and precise than previously used enzymes. Along with other technical advances, these enzymes developed highly purified cyclodextrin which can be used as drugs.

Keywords - Hydroxypropyl, α-Cyclodextrin, Inclusion Complexity, cyclodextrin glycosyltransferase, Cyclodextrins Extracting

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INTRODUCTION

For several formulations of drug delivery, reduced solubility of therapeutic systems is a great challenge. The majority of new chemicals and existing pharmaceutical molecules display poor solubility which means less effective dissolution and low bioavailability. Scientists have built a mystery of conventional and modern methods, such as salt formation, solid scattering, euthetic mixtures, micro-ionisation, lipid drug delivery systems, colloid delivery systems and hot melt extrusion to increase the aqueous solubility of lipophilic moieties formulation. Only few of the techniques described above proved successful and resulted in the formulation of the actions of desired dissolution. In practise, the formation of integration complexes through molecular encapsulation in a hydrophobical cavity of cyclodextrins is a well-known strategy for cyclodextrins (CD). This technology is used for a wide variety of products in the pharmaceutical market[6].

Glipizide (GPZ) is a frequently used antidiabetessulphonylurea agent that is used to treat patients with type II diabetes with a wide level of applications. Glipizide induces the secretion of insulin from the β cells of the tissue of pancreatic islets, raises the concentration and can raise insulin receptor levels in the pancreatic vein. Glipizide, in the biopharmaceutical classification scheme, is a weak acid (pKa =5.9) that essentially is insoluble in water, acidity and extremely permeable (classII) drugs (BCS). Gliclazide (GLC) is a hypoglycemic hypoglycemicsulfonyl urea used in the treatment of diabetes mellitus that is not insulin-dependent. The treatment demonstrates high tolerability, low hypoglycemic occurrence and a low secondary failure. Gliclazide is a highly insoluble white crystalline water powder. Gliclazide'spKa is 5.8200. The name of the IUPAC glipizide is: 1-cyclohexyl-3 urea, Gliclazide (GLC), IUPAC is classified as 1-1-[4-methylbenzene) sulfonyl]-3-octahydrocyclopenta[C] pyrrole-2-yl] urea.

The increase in solubility and dissolution of these drugs can lead to oral bioavailability, further enhancing therapeutic effectiveness and patient observance. Different techniques have been employed to enhance the solubility and dissolution of poorly soluble products, and the cyclodextrin complexation phenomenon gained much interest in recent years among alternative medicines. Cyclodextrins consist of cyclic oligosaccharides composed from glucopyrannose units and may be represented with a hydrophobic cavity as a truncated cone structure. Inclusion of compounds with different

guest molecules is the hydrophobic cavity. Inclusion complex formation can alter the physiochemical properties of poorly water-soluble medicines such as solubility, stability and bioavailability.

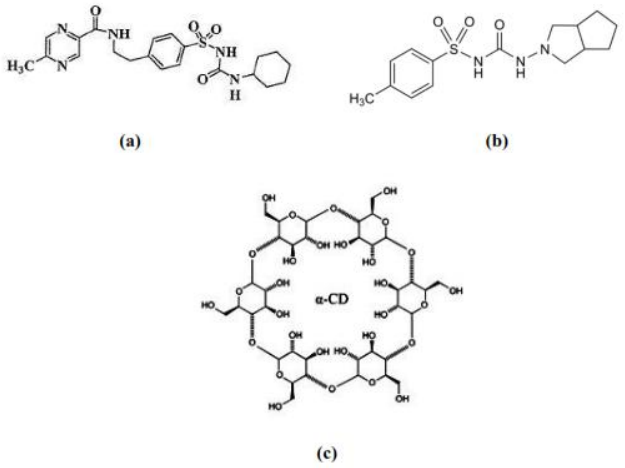

Figure 1: Structure of (a) Glipizide (b) Gliclazide and (c) α-Cyclodextrin

The pH of the medium is also considered to be an important factor for the solubility of the drugs203. The current research will therefore study the effects of pH on the solubility of glipizide and glyclazides in selected compounds of cyclodextrines i.e., α-cyclodextrin (α-CD) and hydroxypropylα-cyclodextrin (HPα-CD). The solubility analysis is performed in various media. I mean, I mean. pH2, and pH~7 to detect the physiological pH with the highest solubility of drugs and also to enhance the solubility of glipizid and gliclazide through α-cyclodextrin complexation.

Preparation of pH solutions

With the addition of phosphate buffer (NaOH – H3PO4), the pHs of the solution within the range 2.0-12,0 is adjustable. This buffer quenched the sample fluorescence and did not change the prototropiceqbilibrium tested. Sufficient amounts of sodium hydroxide and acid were applied to preserve the total analytical concentration of buffers for the pH solution. The acidity scale of Hammett (H0) is used to calculate the strength of very weak foundations for solutions with a pH below 2.0. Hamett has used a range of highly acidic solvents such as hydrochloric acid, nitric acid, perchloric and sulfuric acids with water and has built the scale H0. Paul et al. have checked this scale, and later on it have been altered with a strong set of indicators for sulfuric acid water mixtures by Jorgenson and Hatter. This analysis uses the modified H0 scale. Similarly, Yagil developed a H_ scale for aqueous sodium, potassium lithium hydrate with the Hammett indicator concept, using indole derivatives as indicator.

Preparation of liquid inclusion complex of Glipizide: HP α-CD

Approximately 0.0089 g of Glipizide was weighed and dissolved with 10 ml of the pH~2 buffer solution. In the beaker of 250 ml approximately 0.354 g of the HP α-CD was distilled in 30 ml water. Glipizide:HP alpha-CD inclusion complexes were made from 2x10-3 M to 1x10-2 M Glipizide by varying concentrations of HP alpha-CD. Like pH~7, glipizide has been dissolved in the pH~7 buffer and inclusion complexes have been formed.

Preparation of liquid inclusion complex of Gliclazide: HP α-CD

Around 10 ml buffer solution retained at pH~2 was precisely wown and dissolved by around 0.0064g of gliclazide. In the beaker of 250 ml approximately 0.354 g of the HP α-CD was distilled in 30 ml water. A varied concentration of HP α-CD from 2x10-3M to 1x10-2M with Gliclazide in the inclusive complexes of Gliclazide:HP α-CD was prepared. Gliclazide has also dissolved in pH~7 buffer and inclusion complexes have been formed in pH~7 for pH~7.

Preparation of liquid inclusion complex of Glipizide: α-CD

Around 0,0089 g of Glipizide was carefully weighed using a 10 ml buffer solution maintained at pH~2 with the electronicalbalance.Around 0,2918 g α-cyclodextrine was weighed precisely into a beaker and dissolved into 30 ml distillated water. Differentiated the α-CD concentration from 2x10-3 M to 1x10-2 M with Glipizide in the inclusion complexes. Application of the Glipizide integration complex: α-CD at pH~7 is also followed.

Preparation of liquid inclusion complex of Gliclazide: α-CD

Glass was correctly measured at approximately 0.0064 g and dissolved in 10 ml pH~2 buffer solution. Approximately 0.2918 g of a CD-α has been precisely weighed and dissolved in 30 ml of distilled water. Differentiating concentrations of α-CD between 2x10-3 M and 1x10-2 M with gliclazide were used to build inclusion complexes. Gliclazide uses the same procedure: α-CD complexes at pH~7.

Preparation of solid inclusion complex of Glipizide: HP α-CD

Around 0.0267 g Glipizide has been precisely weighed and dissolved in approximately 30 ml of methanol approximately 0.354 g HP α-CD in a 250 ml beaker with 30 ml of distilled water. Both solutions were combined in a beaker and then stirred constantly at room temperature for 48 hours. The precipitation was dried and used for characterisation following evaporation.

Preparation of solid inclusion complex of Gliclazide: HP α-CD

Gliclazide has been precisely weighed and dissolved in approximately 0.0192 g in 30 ml of methanol. In the beaker of 250 ml approximately 0.354 g of the HP α-CD was distilled in 30 ml water. Both solutions were combined in a beaker and then stirred constantly at room temperature for 48 hours. The rainfall was dried and used for characterization after evaporation.

Preparation of solid inclusion complex of Glipizide: α-CD

About 0.0267 g of 30 ml of methanol, glipizide was measured correctly and dissolved. The precise weighing and dissolution was approximately 0,2918 g of α-CD in 30 ml of distilled water. Both solutions were combined in a beaker and then stirred constantly at room temperature for 48 hours. The precipitation was dried and used for characterisation following evaporation.

Preparation of solid inclusion complex of Gliclazide: α-CD

About 0.0192 g of 30 ml of methanol, gliclazide was precisely weighed and dissolved. The precise weighing and dissolution was approximately 0,2918 g of α-CD in 30 ml of distilled water. Both solutions were combined in a beaker and then stirred constantly at room temperature for 48 hours. The rainfall was dried and used for characterization after evaporation.

Determination of the stoichiometry of the inclusion complex

To determine the stoichiometry of the inclusion complex, a Job's method is used from the absorption and fluorescence values of 1:2 complex. A plot of $\frac{1}{A-A_0}$ versus $\frac{1}{[\alpha\text{-CD}]^2}$ - for absorption and $\frac{1}{I-I_0}$ VS $\frac{1}{[\alpha\text{-CD}]^2}$ - gives a good linear correlation indicating the stoichiometry for the formation of 1:1 and 1:2 guest host inclusion complex can be obtained by using the modified Benesi Hildebrand equation209 for the 1:1 and 1:2 complexes between Glipizide with α-CD as shown below.

$$\frac{1}{A-A_0} = \frac{1}{A'-A_0} + \frac{1}{K\ A'-A_0\ [\alpha\text{-CD}]} \quad \text{----- (1)}$$

$$\frac{1}{I-I_0} = \frac{1}{I'-I_0} + \frac{1}{K\ I'-I_0\ [\alpha\text{-CD}]} \quad \text{----- (2)}$$

$$\frac{1}{A-A_0} = \frac{1}{A'-A_0} + \frac{1}{K\ A'-A_0\ [\alpha\text{-CD}]^2} \quad \text{----- (3)}$$

$$\frac{1}{I-I_0} = \frac{1}{I'-I_0} + \frac{1}{K\ I'-I_0\ [\alpha\text{-CD}]^2} \quad \text{----- (4)}$$

Where K is the binding constant, A0/I0 the initial absorption/fluorescence intensity of free Glipizide, A'/I' the absorption/fluorescence intensity of α-CD complex, A, I is the observed absorption or fluorescence intensity.

ELECTROANALYTICAL TECHNIQUES

Electro analytical methods for characterising the stability constants for integration complexes were considered as requirements for evaluating solution. Polarography and voltammetry are the most commonly used approaches.

1. Polarography and Voltammetry

Polarography and volta metering are powerful instruments for the study of cyclodextrin'scomplexation with electrical molecules to learn about the existence of such inclusion complexes as necessary techniques. They are also particularly useful to test complexes of interaction constants at very low concentrations. The polarography can be seen as a consequence of the electronic redistribution in the presence of cyclodextrins, changes in potential of a half-wave molecule of the visitors. Furthermore, cyclodextrins are complicated and minimise the volume of current, which then decreases the diffusion of the guest molecules when they are complicated with cyclodextrins. The results of the DPP studies have also found that the portion of the guest molecule integrated in the CD cavity is the aromatic nitro group of nifedipine and thesis scientists, according to the results of DPP and UV spectrophotometry, for measurement of Stability Constant of Inclusion Compounds with Nifedipine and Nicardipine Cyclodextrins.

2. pH-Potentiometry Titration

Potentiometric tests are typically used to assess the interaction complex (CD/drug) constants. Thus, by means of potentialometric pH calculation at different temperatures, interaction constancy values of inclusion complexes made of equimolarhydroxypropyl-DC and the ionised forms of drug flurbiprofen and ibuprofen were calculated. In complexation modes, potential measurements are also used. Various methods including potentiometric titration have been used to analyse neutral and protonated forms of benzimidazole with β-CD. The potential measurements were used with a glass electrode to compute the stabilising constant of β-CD and Ʈ-CD in various local anesthesias (tetracaine, lidocaine, and prilocaine). The findings for tetracain were well in line with fluorescence spectroscopy results, whereas complex prilocain and lidocaine are not detectable. Different inclusion complexes were characterised by different analysis methods, such as potentiometric titration, supporting the inclusion phenomenon.

3. Electrical Conductivity

In order to establish the equilibrium constants of complexes between the CDs and different

surfactants, the electrical conductivities were calculated with other amphiphilic molecules.

E. Junquera et al., used for the assessment of CD complex electrical conductivity. The mixture of the counterion surfactant, with the inclusion and variation of the ionic molar concentration of the complex conductivity, is used to measure the binding constants β-cyclodextrin or hydroxypropyl-beta-tyclodextrine in the aqueous solution with dodecyltrimethyl bromide. The conduct of three tricyclic antidepressants (imipramine, desipramine, and hydrochloride amitriptyline) in the absence of and presence of β-CD was assessed in order to study the actions. It has also been studied, using the conductivity to vary stability constant, in various acidity conditions, the development of integration complexes in the aqueous solutions between the β-CD and local anaestheticnovocaines. Conductometric tests have shown that through introducing β -CD to the drug solution, the apparent vital micelle concentration of the drug has been shifted to higher concentre, as monomers participate in the complexing CD and the inclusion process is verified.

PHARMACEUTICAL APPLICATIONS OF CYCLODEXTRINS

1. Enhancement of Bioavailability of Drugs

Generally, low water solubility and crystalline pharmaceuticals with limited biomass availability. Cyclodextrins are water-soluble and able to form water-insoluble compounds for inclusion. The resulting complexes mask the majority of functional hydrophobic groups in the cyclodextrin cavity, while hydroxyl groups are exposed. Methylated molar substitution CDs tend to be the most effective solubilizersof various commercially available CDs. Reducing drug crystalline content with complex or solid CD dispersion also leads to increasing the CD's apparent solubility and dissolution rate. CDs can improve drug dissolution even without any problems in their solid state because their ability to form insitution complexes in dissolution medium is. For many medicines, SBE-β-CD was demonstrated to be an excellent solubilizer and to be more effective than β-CD, but not as effective as DM-β-CD.

2. Active Stabilisation

The highly active molecules are prone to heat, oxygen or water degradation and chemical reactions. In the cavity, the reacting element cannot diffuse into the cavity and react with the covered client if these molecules are integrated. CDs can improve dehydration, hydrolysis, oxidative treatment and photodecomposition stability of many labile drugs and thus improve the shelf life and drug stability of drugs. Inhibition of drug interaction with vehicles and/or inhibitance of drug bioconversion at the absorption point was recorded as a result of CD-induced increase in drug stability. CD complexation encapsulates molecular drug molecules and thereby isolates them from different degradation processes by supplying a molecular shield. CD complexationIn many chemically unstable products, SBE-β-CD showed greater improvement in stability than other CDs. The stabilising effect of CDs depends on the type and impact of the functional group included on drug stability and on the nature of the car. Catalyzing effects on the photodegradation of 1, 4-dihydropyrimidine derivatives were reduced by complexation with CDs, as was the stabilising effect of halogen and cyanogen groups. The photographing of 2–ethyl hexyl p–dimethyl aminobenzoate was greatly reduced by HPβ-CD in solution rather than by the emulsion vehicle. CDs have enhanced trimeprazinephotostability (with decreased solution pH) and promethazine. CDs have increased stabilisation of the solid state and drug shelf life. CDs have been reported to improve the physical stability of gene therapy virus vectors, with sucrose and CD formulations being stable at 20°C for 2 years. The stability of the drug/ CD-complex, namely the magnitude of the complex stability constants, plays a significant role in deciding the level of safety because the hydrolysis of drugs encapsulated in the CD is slower than that of free drugs.

3. Masking of Odour and Taste

The encapsulation inside the cyclodextrin cavity masks moles or particular functional groups that cause an unpleasant odour or taste. There is no bad taste or scent in the resulting formulations, so they are very patient compliant.

4. Enhancement of Compatibility

In a single formulation, typically several ingredients are combined to achieve a single dose. This can often contribute to a reactive effect among the ingredients that can annul the effect of the ingredients. When embedded in the cyclodextrin cavity, it can lead to a physical separation of the ingredients so that there is no chemical contact. Many irritating ingredients in cyclodextrin cavity minimise their irritating nature to the stomach, the eyes or the skin. CDs is used for the improvement of drug discomfort. The improvement in the quality and strength of the drug (i.e. the reduction of the dose needed for optimum therapy), caused by improved CD solubility, will decrease the toxicity of the drug with a lower dosage efficiency. The β-CD improved the efficacy of ganciclovir on clinical strains of human cytomegalo viruses and reduced the drug toxicity as a result of the increase in drug strength.

5. Beneficial in Material Handling

Oils, volatile fluids are active ingredients that can be handled and shaped into solid types of dosage. The forming of cyclodextrin inclusions allows for good powder form with excellent flow properties and by

traditional manufacturing processes and equipment they can be formed into a tablet.

CONCLUSION

The NMR spectrum shows an upfield difference of H-3 and H-5% with the magnitude of protons less in H-3 than H-5 for Pioglitazone hydrochlorides. This means that Pioglitazone hydrochloride is used as part of the HP α-CD cavity. When the Pioglitazone:α-CD NMR spectrum is measured, it is noted that H-3 is subjected to downfield shifts with H-5 being subjected to upfield shift alone. It has been shown that Pioglitazone hydrochloride has been partially incorporated into the α-CD cavity. Glimepiride:HPα-NMR CD's spectra revealed that both protons H-3 and H-5 had a shift in the elevation. Compared to H-5 protons, the change for H-3 is smaller. A complete integration into the HPα-CD cavity therefore took place. In Glimepiride:α-CD, a magnitude higher than H-5 proton for upfield shift is observed, suggesting that only part of the glimepiride is included in the cavity α-CD. Comparing HPα-CD and α-CD for the three narcotics, stable compounds consist more of α-CD than HPα-CD, with Metformin and Glimepiride hydrochloride. The HPα-CD is more stable than α-CCD pioglitazone hydrochloride. Of the 3 medications, hydrochloride metformin was more stable than hydrochloride and glimepiride with α-CD and HPα-CD inclusion complexes. Thus, HPα-CD and α-CD complication will improve the solubility of the three medications. In contrast to other drugs the higher binding constant value and consequently the stable inclusion complex of metformin hydrochloride with α-CD, which fits in the cavity of α-CD and HPα-CD, is due to smaller scale.

Two antidiabetic medications, glipizide and gliclazide, are used in the treatment and management of human Type II diabetes. The effect of pH is investigated on these two medicines. For research on the inclusion complexes, acid and neutral medium are selected. The glipizide and gliclazide absorption spectra are both HPα-CD and α-CD bathochromatically shifted to pH ~2. For pH~7, both the glipizide and the α-CD absorption spectrums are hypsochromic. For both glipizide and gliclazide HPα-CD and α-CD complexes the fluorescent spectra are hypsochromically moved at pH~2 and PH~7. Spectral changes confirm that HPα-CD and α-CD form integrative drug complexes. The chemical changes of the Glipizide:HPα-CD NMR spectrum are noted. The upfield change in H-5 can be found to be higher than that of H-3. This indicates the inclusion of Glipizide:HPα-CD in complex formation. In Glipizide:α-CD, the magnitude of the H-3 change was greater than that of H-5, suggesting that Glipizide is embedded inside the α-CD cavity.

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Corresponding Author

Pashupati Nath Sharma*

Research Scholar, Department of Chemistry, SSSUTMS, Sehore