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SOLUBILITY AND DISSOLUTION ENHANCEMENT OF GLIPIZIDE USING β CYCLODEXTRIN INCLUSION COMPLEX

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ABSTRACT

Keywords:

Glipizide, dissolution rate, β cyclodextrin, solubility

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Glipizide is second generation sulphonylurea that can acutely lower the blood glucose level in humans and is typically prescribed to treat non insulin dependent diabetes mellitus. It is practically insoluble in water. The purpose of the study was to enhance the solubility and dissolution rate of poorly water soluble glipizide drug with cyclodextrin complexation. The solid inclusion complexes of glipizide and β cyclodextrin were prepared by kneading method using different molar proportion of β cyclodextrin. The effect of β cyclodextrin on solubility and dissolution rate of glipizide was investigated by evaluating inclusion complex. The IR Spectroscopy, DSC and in vitro dissolution studies were used to characterized the inclusion complex. Complex prepared in this study was found to have higher dissolution rate compared to plain drug. It was observed that dissolution rate increases with increasing quantity of β cyclodextrin.

INTRODUCTION

Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidate has increased tremendously. The formulation of poorly soluble drugs for oral delivery present a challenge to the formulation scientists.⁽¹⁾ Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate.⁽²⁾ Various techniques have been used to improve the solubility and dissolution rate of poorly water soluble drugs. Among them solid dispersion and complexation with cyclodextrin are most frequently used.⁽³⁾ Complexation with cyclodextrin involves simple manufacturing steps, cost effective and industrial feasibility.⁽⁴⁾

Cyclodextrin are cyclic (α -1-4) linked oligosaccharides of α D glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. During the past two decade cyclodextrin and their derivatives have aroused considerable interest in the pharmaceutical field because of their potential to form complex with variety of drug molecule.⁽⁵⁾ Glipizide is second generation sulphonyl urea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat non insulin dependent diabetes mellitus ⁽⁶⁾ .It is oral hypoglycemic agent that is 100 times more potent than Tolbutamine, which is used for treatment of type II diabetes mellitus. As per BP it is practically insoluble in water (classification as BCS class II drug). Glipizide dosage form show poor solubility and dissolution and hence considered as rate determining step in its absorption from gastrointestinal tract.⁽⁷⁾

MATERIALS AND METHODS

Material

Glipizide was obtained as a gift sample from USV ltd Mumbai. β cyclodextrin was purchased from Merck India Ltd, Mumbai. All other chemicals used were of analytical reagent grade. Freshly prepared distilled water used throughout the study.

Preparation physical mixture:-

Physical mixture (PM) of Glipizide with β cyclodextrin in 1:1, 1:2, 1:3, 1:4, 1:5 molar ratio was prepared by thoroughly mixing the accurately weighed quantity of drug and carrier in glass mortar and pestle for 5 min.and stored in a dessicator for 24 hours.

Preparation of B-Cyclodextrin Complex ⁸

Mixture of Glipizide and β cyclodextrin in different Molar weight ratio wetted with water and kneaded thoroughly for 30 min in glass mortar. The dried paste formed was dried under vacuum for 24 hours. The dried powder was passed through sieve no. 100 and stored in desiccators until further evaluation. Formulations were named as B1, B2, B3, B4 and B5.

Determination of Drug content⁹

The percent drug content of each solid dispersion, was determined using powder equivalent to 50 mg Glipizide and was dissolved in minimum amount of methanol and volume was made up to mark 100ml using pH 7.4 phosphates buffer. The solution was then filtered through Whatman filter paper no. 42 and required dilution were being made and assayed for drug content using UV double beam spectrophotometer at 276 nm. Three replicates were prepared and average value was reported.

Solubility Study⁰⁸

Solubility study was assessed out according to the method of Higuchi and cannors. The solubility of Glipizide as pure drug and its solid dispersion were determined in distilled water and phosphate buffer pH 7.4. Glipizide and solid dispersion equivalent to 10mg of drug was taken and to this 10 ml of respective medium was being added in 100 ml stoppered volumetric flask and shaken for 25 hrs at RT on magnetic stirrer. The entire samples were protected from light by wrapping the flask by aluminum foil. After 24 hr samples were filtered through Whatman filter paper no. 42 and aliquots were suitably diluted and assayed spectroscopically at 276 nm.

Each solubility was determined in triplicate and average values were reported.

In-vitro dissolution studies⁰⁹

Dissolution study was carried out by using USP rotating basket (apparatus-I) (Electrolab) for 2 hr. the stirring rate was 100 rpm. Phosphate buffer pH 7.4 and distilled water was used as medium (900 ml) and was maintained at $37 \pm 5^{\circ}\text{C}$. samples equivalent to 5mg of Glipizide was filled in hard gelatin capsule used for dissolution studies. Samples were collected at regular interval of time and assayed for dissolution spectroscopically at 276 nm. Each dissolution rate test was repeated thrice and average values were reported.

FTIR studies

The FTIR spectra of the drug, β cyclodextrin and inclusion complex in different ratio were recorded with FTIR spectrophotometer (Jasco V-6001). The samples were prepared by using potassium bromide and scanned for the absorbance at 4000-400/cm

Differential scanning calorimetry

DSC pattern of Glipizide, β Cyclodextrin, physical mixture and inclusion complex with β Cyclodextrin (1:5) were recorded using Shimadzu D 60 thermal analyzer (Japan). Samples were sealed in aluminum pan, the lid was pierced and the DSC thermogram were recorded at heating rate of $20^{\circ}\text{C}/\text{min}$ from 60 to 240°C using nitrogen atmosphere.

RESULT AND DISCUSSION

Drug content

The content of Glipizide in each preparation was assayed by UV spectroscopy. The assay values were between 97% to 99% of the theoretical value.

Solubility studies

Solubility profile of Glipizide with β cyclodextrin is shown in Table 1. The solubility of Glipizide in water and in phosphate buffer, without β cyclodextrin was found to be 0.0365 mg ml⁻¹. The solubility of Glipizide increased as a linear function of carrier concentration. All the inclusion complex shows enhanced solubility but higher in case of complex prepared by β cyclodextrin (1:5 ratio).

Dissolution Studies

In vitro dissolution study was carried out for pure drug and all formulation in distilled water as well as in phosphate buffer pH 7.4. The release rate profile were plotted as the percentage glipizide dissolved from the solid dispersion and pure Glipizide verses time. Figure 1 showed the dissolution profile of Glipizide with β cyclodextrin at different drug carrier ratio. In case of pure drug only 34.35% was dissolved at the end of 2 hours in phosphate buffer pH 7.4 while in case of inclusion complex (1:5 ratio) 96.98% dissolved at the end of 2 hours. The kneading method prepared complexes at the molar ratio of 1:1 the dissolution rate was slightly increased as compared to physical mixture and drug alone, but at the ratio of 1:4 and 1:5 the dissolution rate was dramatically increased. From the dissolution data concluded that dissolution rate was greatly improved by kneading method. This is because of higher hydrophilicity and wetting property of β cyclodextrin. The dissolution of the drug was increased with increase in the carrier ratio in the formulations.

FTIR study

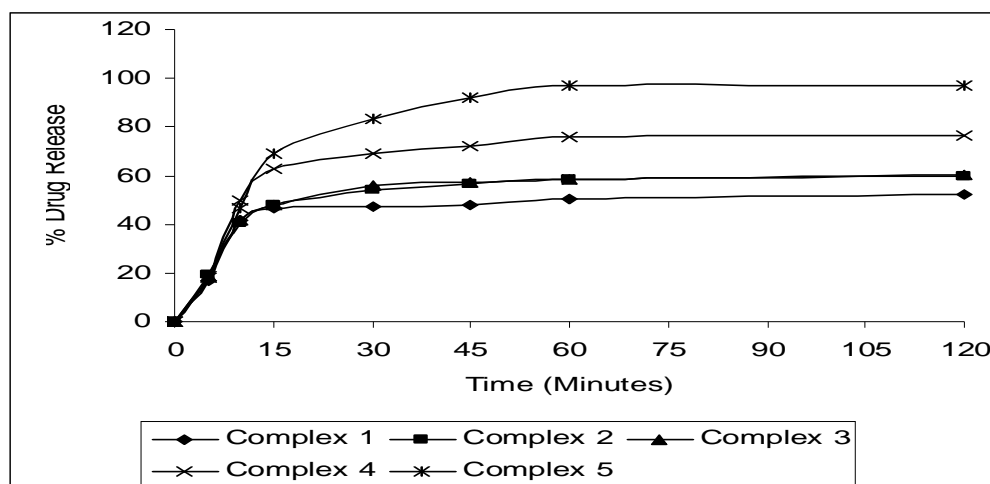
FTIR was performed on Glipizide, β cyclodextrin and inclusion complex of Glipizide with all carriers. The IR spectra of solid dispersion (figure 2) showed all the principal IR absorption peak of Glipizide 3324 cm⁻¹, 3051 cm⁻¹, 1648 cm⁻¹, 1395 cm⁻¹. FTIR of inclusion complex of drug and all carriers shows that all the peaks of drug and carrier as it is and drug is present in free form. This indicates that there is no interaction in between Glipizide and the entire carrier employed in complex.

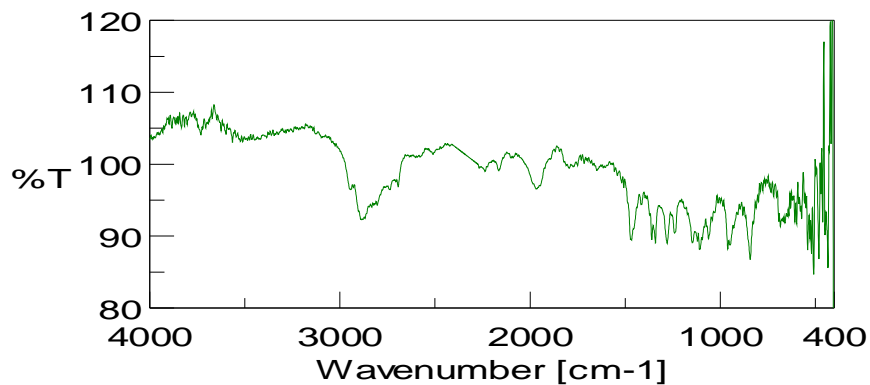
Table 1: Solubility of Glipizide from various complexes

Sr No.	Solid dispersion	Solubility distilled water (mg/1000ml)	Solubility (phosphate buffer) (mg/1000ml)
1	Plain Drug	36.5	55.86
2	B1	82.31	158.57
3	B2	121.73	219.49
4	B3	154.02	272.09
5	B4	183.26	314.02
6	B5	198.96	356.98

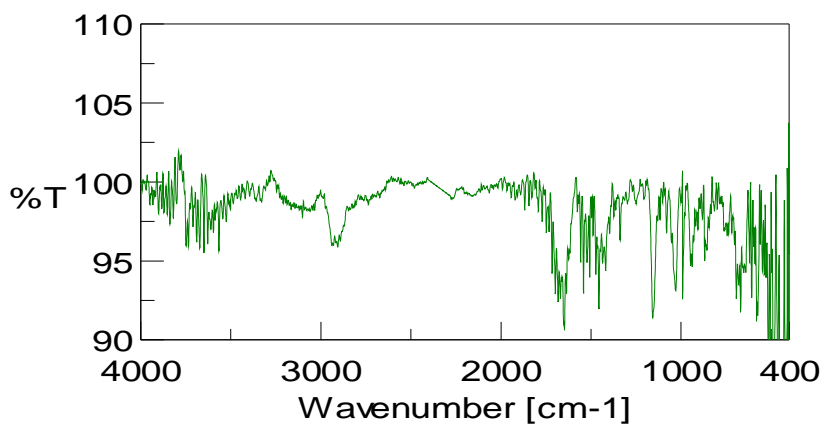
Table 2: Cumulative % drug dissolved from inclusion complex prepared using β cyclodextrin in phosphate buffer 7.4 pH

Time (min)	Batch code*				
	B1	B 2	B 3	B 4	B 5
0	0	0	0	0	0
5	17.02	19.07	18.56	18.48	18.30
10	41.70	40.35	41.66	49.61	46.70
15	46.79	47.76	48.14	62.67	69.00
30	47.35	54.03	55.85	69.00	83.10
45	48.00	56.33	57.46	72.30	92.00
60	50.26	58.22	58.54	75.91	96.75
120	52.47	59.44	60.11	76.72	96.98

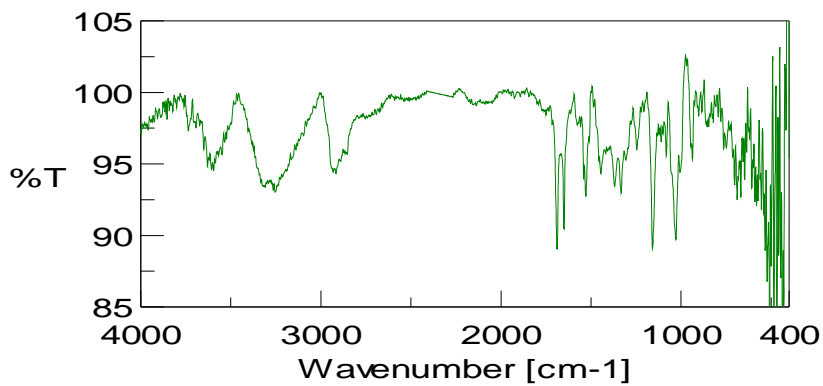
**Figure 1: *In vitro* drug release profile from complex prepared using β cyclodextrin in phosphate buffer 7.4 pH**



(a)



(b)



(c)

Figure 2: FTIR Spectra of a) Pure drug b) β cyclodextrin and c) inclusion complex

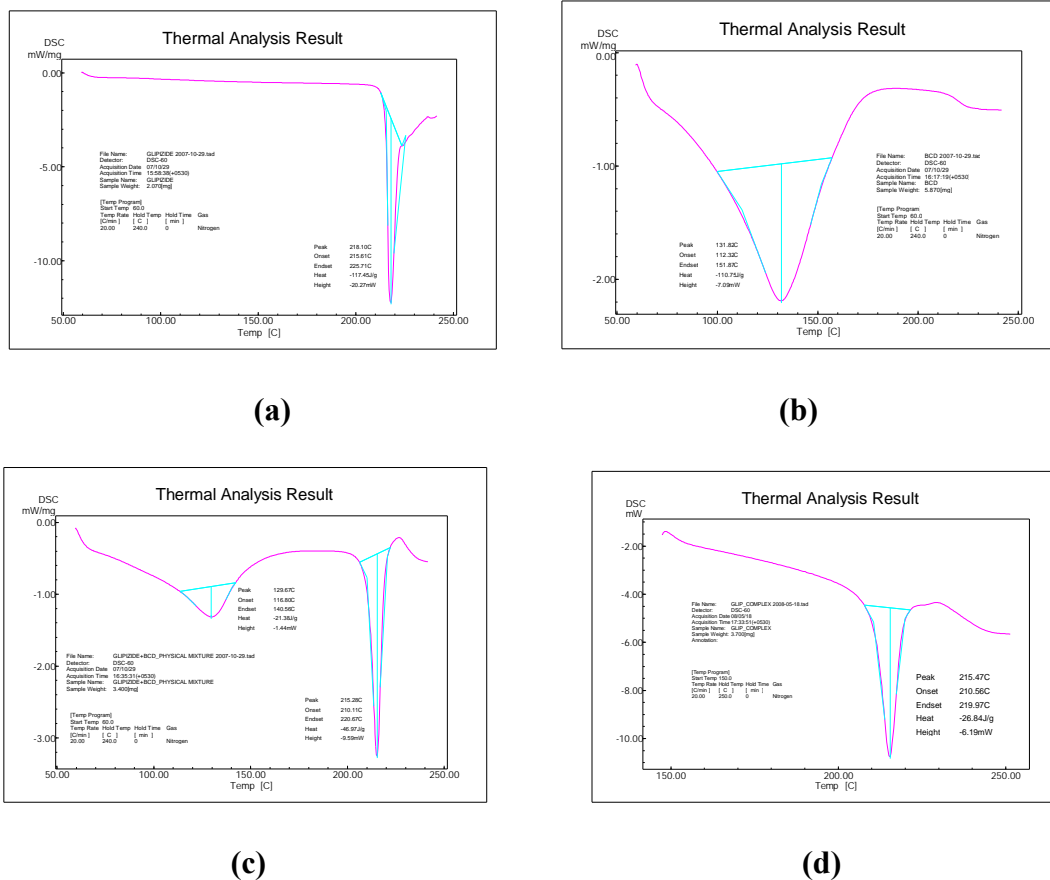


Figure 3: DSC Curve of a) pure drug b) β cyclodextrin c) physical mixture and d) inclusion complex of glipizide.

DSC Study

The thermal behavior of Glipizide- β cyclodextrin complex was studied using DSC in order to confirm the formation of solid complex. DSC thermograms of Glipizide complex are shown in figure 3. DSC thermograms of glipizide exhibited an endothermic peak at 210.11 °C corresponding to its melting point. DSC curves revealed that both beta cyclodextrin and Glipizide exhibited an endothermic peak with onset temperature of 116.80 and 210.11 °C respectively. These melting peaks indicated the crystalline nature of both components. The thermograms of physical mixture and complex are different from the pure drug, which gives clear evidence that there is formation of the complexes.

CONCLUSION

Inclusion complex of glipizide and β cyclodextrin prepared by kneading method exhibited higher rate of dissolution as compared to physical mixture and plain drug. Analytical method of IR spectrum showed there was no degradation of drug. The solubility and dissolution studies

showed there is possibilities of improved solubility and dissolution of glipizide through inclusion complex with β cyclodextrin. A maximum increase in dissolution rate was found with glipizide: β cyclodextrin complex with a molar ration 1:5. Though β cyclodextrin complex by kneading method showed faster dissolution rate when compared with plain drug.

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