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A Study on the Dissolution Enhancement of Gliclazide Using Natural Polymers

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ABSTRACT

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Gliclazide (GLZ) BCS class II drug, is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus However, low aqueous solubility and poor dissolution of this molecule, delays its rate of absorption and finally the onset of action. Solid dispersion has been successfully utilized as dissolution enhancement technique using natural polymers for wide variety of poorly water-soluble drugs. The present study aims at enhancement of dissolution profile of Gliclazide using Xanthan gum, Guar gum and Hupu gum as carriers by solid dispersion technique. Solid dispersion containing GLZ was further investigated by Fourier transform infrared spectroscopy (FTIR). FTIR patterns suggest that there is no interaction between drug and excipients. From the study it concluded that the *in vitro* dissolution of Gliclazide can be enhanced by solid dispersion technique. Amongst the solid dispersions prepared. F6 formulation prepared by co-grinding method using Guar gum as carrier in 1:3 ratio shown the better release of Gliclazide (96.79 %) with in 60 min.

Key words: Solid dispersion techniques, Gliclazide, Natural polymers.

INTRODUCTION

Solubilization of poorly water-soluble drugs have gained much interest in the pharmaceutical industry (Riis T *et al*., 2007; Usui F *et al*., 1998). Many approaches have been developed to improve solubility and to enhance the dissolution rate of poorly soluble drugs, including both modifications to the drug substance itself and the creation of specific formulations. Physical modifications often aim to increase the surface area, solubility and wettability of the powder particles and therefore typically focus on particle size reduction or generation of amorphous states (Hancock BC *et al*., 1997; Grau MJ *et al*., 2000). Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs (Tanaka N *et al*., 2006; Streubel A *et al*., 2006; Leuner C *et al*., 2000).

Solid dispersions systems as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method (Chio WL *et al*., 1971). In general, solid dispersion (SD) is a molecular mixture of drug in various hydrophilic carriers used to enhance drug dissolution by changing drug crystallinity to an amorphous form and reducing particle size for better wettability (Heo MY *et al*., 2005; Tran TTD *et al*., 2009). The increase in dissolution rate from SDs can be attributed to one or a combination of the following factors: a reduction of particle size of the drug, a solubilizing effect on the drug by the water soluble carrier, enhancement of the wettability and dispersibility of the drug by the carrier material, and the possible formation of a metastable dispersion that has a greater solubility resulting in a faster dissolution rate (Shargel L, 1993; Swarbrick J, 1990).

Sekiguchi and obi were the first to report an improved dissolution of the drug from sulfamethazole-urea solid dispersion. Co-grinding is environmentally desirable as unlike other techniques it does not require toxic solvents and sophisticated equipment. In this research work an attempt was made to use the co-grinding technique as a promising technique to enhance the dissolution rate of a poorly water-soluble drug,

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gliclazide. Natural gums are safety, easyly available and freely water soluble.

Gliclazide(1-[(4-methylbenzene)sulfonyl]-3-{octahydrocyclopenta[c]pyrrolyl}urea),BCS class II drug, is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM).. Mean absolute bioavailability of gliclazide was 97% and ranged between 79 and 110% showing complete absorption. A similar moderate to low variability was observed after IV and oral administration showing the MR formulation did not add to the overall variability which is solely due to the disposition parameters, in particular metabolism of gliclazide (Delrat P *et al*., 2002). The peak plasma concentration is achieved after about 4-6 hrs following its oral administration. Thus, its availability seems to be dissolution rate limited.

According to the USP Classification, gliclazide is "practically insoluble" in water. For the drug that has a very poor aqueous solubility, the rate at which the drug dissolves in the GI fluids is often slowest step and therefore, exhibits a rate-limiting effect on the drug bioavailability. Improvement in the solubility characteristics of such a drug brings about faster dissolution in the GI fluids and hence faster absorption and ultimately faster onset of action. Among the various approaches to improve the dissolution of sparingly soluble drugs various techniques like pseudo-solid dispersion, solid dispersion and inclusion complexation have often proven to be very successful. Thus, in the present study these solid dispersion techniques are adopted to improve the dissolution of gliclazide. The aim of the present study was to formulate and evaluate the solid dispersions of gliclazide in natural polymers like xanthan gum, guar gum and hupu gum as carriers. Dispersions with carriers were prepared by co-grinding method.In order to characterize the prepared dispersions, Fourier–transform infrared spectroscopy, as well as dissolution and drug content studies were carried out.

MATERIALS

Gliclazide is procured by Cadila Pharmaceuticals Ltd., Ahmadabad, India, methanol is procured by S.D. Fine Chem. Ltd, Mumbai, India.

METHODS

FORMAULATION OF SOLID DISPERSIONS OF GLICLAZIDE BY CO-GRINDING METHOD

Method of Preparation of Solid Dispersion

Solid dispersions were prepared by co-grinding method using natural gums like xanthan gum, guar gum and hupu gum as carriers.

Co-grinding method

Solid dispersions were prepared by thoroughly grinding accurately weighed quantities of GLZ and each of the carriers (xanthan gum, guar gum and hupu gum) in various ratios (1:1, 1:2 and 1:3) for 20-30 minutes in glass mortar individually. The dispersions were then sifted through sieve no.80 and stored in desiccators till further use. Solid dispersions were prepared using compositions as given in Table.1.

EVALUATION PARAMETERS OF SOLID DISPERSION

Fourier Transform Infrared Spectroscopy (FT-IR)

The samples of GLZ, hupu gum, guar gum and xanthan gum and solid dispersion were prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FT-IR spectrophotometer.

Table.1 Composition of GLZ solid dispersions

Method	Carriers	Drug-Polymer ratio	Formulation Code
Co-grinding method	Hupu gum	1:1	F1
		1:2	F2
		1:3	F3
	Guar gum	1:1	F4
		1:2	F5
		1:3	F6
	Xanthan gum	1:1	F7
		1:2	F8
		1:3	F9

Drug Content

An accurately weighed quantity of solid dispersion equivalent to 10mg were transferred into 100ml standard flasks and volume was made up to 100ml with Methanol The content of GLZ was determined spectrophotometrically at 228 nm against suitable blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan).

In Vitro Dissolution Studies

The quantity of solid dispersion equivalent to 100 mg of GLZ was added to dissolution medium. The dissolution study of solid dispersions were conducted using dissolution testing USP apparatus II (paddle method) in 900 ml of HCL acid buffer of pH 1.2 at 37±0.5ºC and at a speed of 50 rpm. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 228 nm against suitable blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan).

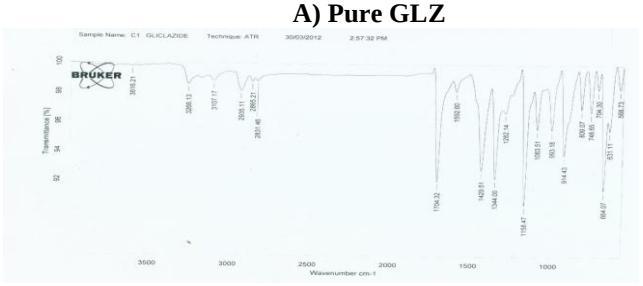
RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy

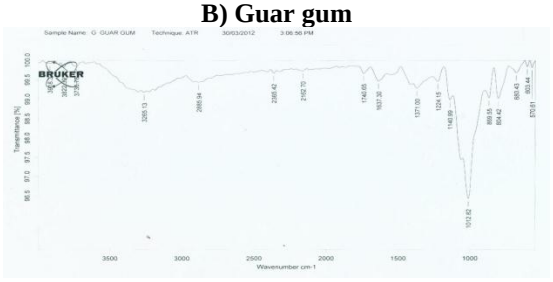
Fourier transform infrared spectroscopy has been used to assess the interaction between carrier and drug molecule. The FTIR spectrum of pure drug, xanthan gum, guar gum, hupu gum and solid dispersion prepared by co-grinding method were obtained which shows no chemical interaction between drug and polymers.

Figure.1 FT-IR spectra

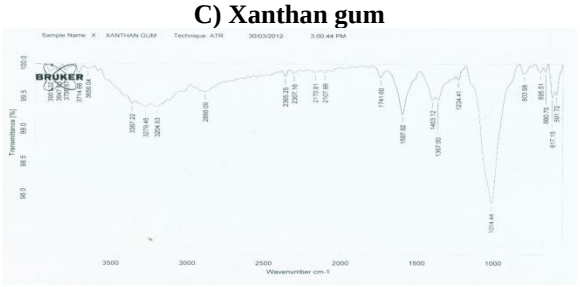
A) Pure GLZ



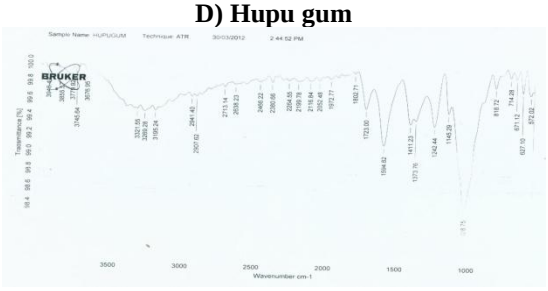
B) Guar gum



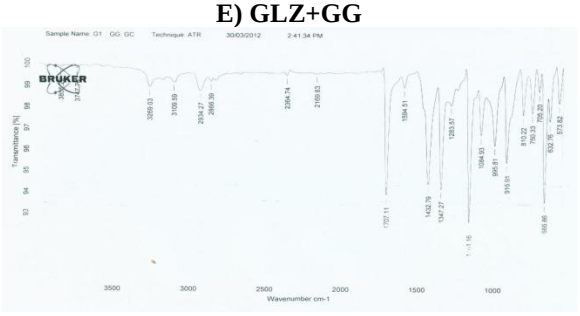
C) Xanthan gum



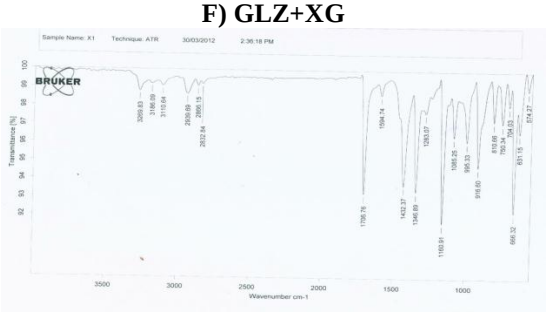
D) Hupu gum



E) GLZ+GG



F) GLZ+XG



G) GLZ+HG

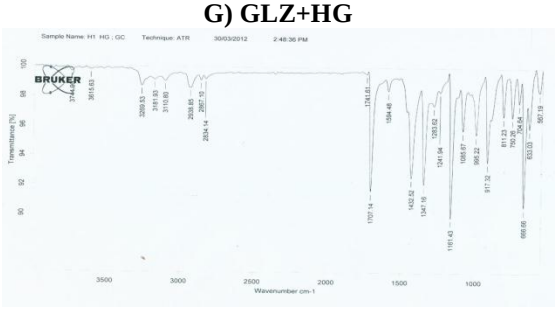


Table.2 Comparison of *in vitro* dissolution profile data of GLZ in pure form and its solid dispersions with hupu gum

S.No	Time (Min)	% Drug Release Of Pure Drug	Percentage drug release (GLZ:HG)		
			1:1 (F1)	1:2 (F2)	1:3 (F3)
1	15	20.99	53.91	47.15	40.92
2	30	22.77	54.62	63.16	52.31
3	45	26.69	57.29	62.63	61.20
4	60	40.39	61.38	65.83	76.33

Table.3 Comparison of *in vitro* dissolution profile data of GLZ in pure form and its solid dispersions with guar gum

S.No	Time(Min)	% Drug Release Of Pure Drug	Percentage drug release (GLZ:GG)		
			1:1 (F4)	1:2 (F5)	1:3(F6)
1	15	20.99	38.43	64.94	70.28
2	30	22.77	42.88	74.19	75.66
3	45	26.69	55.16	88.53	86.12
4	60	40.39	84.69	91.99	96.79

Table.4 Comparison of *in vitro* dissolution profile data of GLZ in pure form and its solid dispersions with xanthan gum

S.No	Time(Min)	% Drug Release Of Pure Drug	Percentage drug release (GLZ:XG)		
			1:1 (F7)	1:2 (F8)	1:3 (F9)
1	15	20.99	45.72	50.35	46.08
2	30	22.77	49.11	52.66	56.58
3	45	26.69	57.29	57.65	70.81
4	60	40.39	60.49	62.80	73.84

Figure.2 Comparison of *in vitro* dissolution profile of GLZ in pure form and its solid dispersion with HUPU GUM prepared by co-grinding method

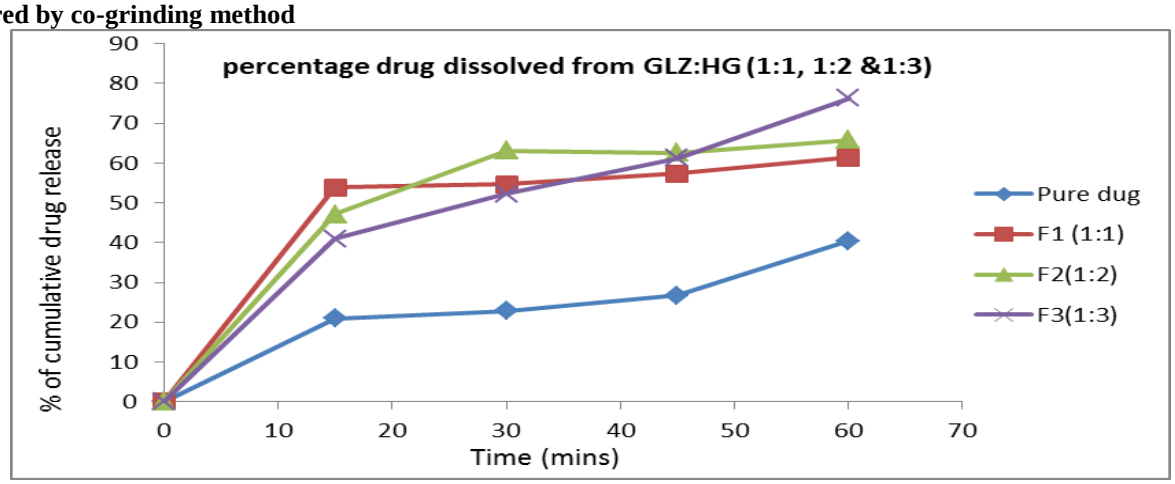


Figure.3 Comparison of *in vitro* dissolution profile of GLZ in pure form and its solid dispersion with GUAR GUM prepared by co-grinding method

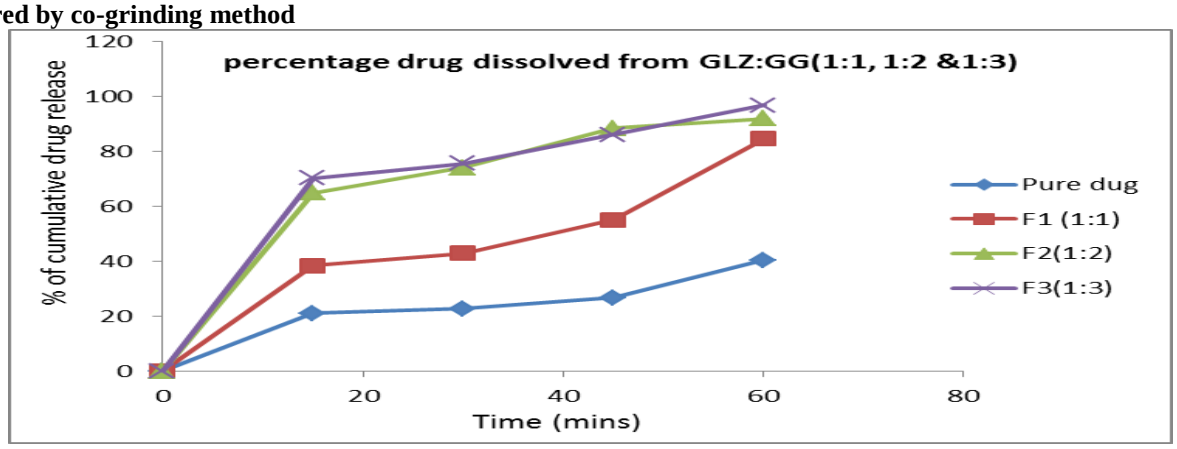
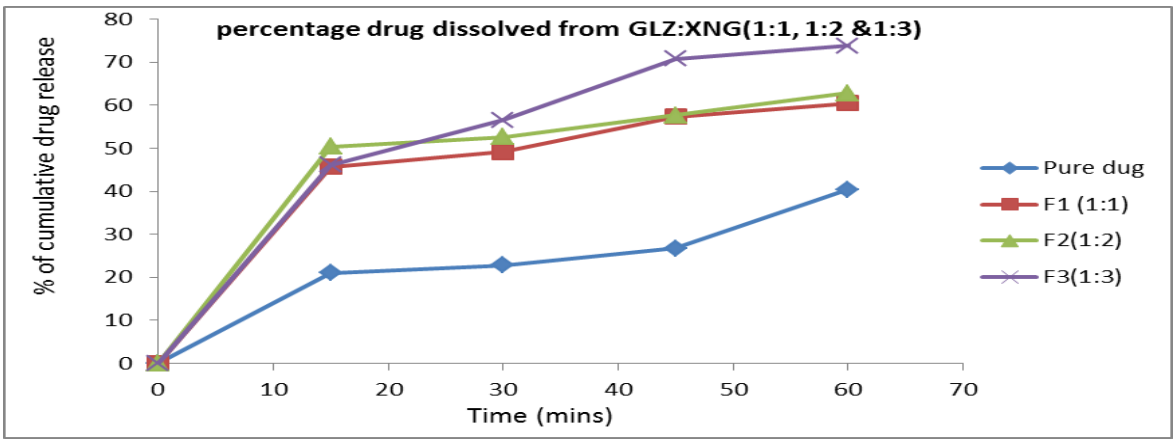


Figure.4 Comparison of *in vitro* dissolution profile of GLZ in pure form and its solid dispersion with XANTHAN GUM prepared by co-grinding method



In vitro Dissolution Studies of GLZ and Its Solid Dispersion

In vitro dissolution test results indicate complete dissolution of drug from all its solid dispersion within 60 min which is depicted in figures 5, 6, 7. Among the various formulations of preparation of solid dispersion, GLZ with guar gum (1:3) was found to be most effective. The formulation F6 showed faster dissolution rate (60 min). The enhanced dissolution may be due to enhanced wettability and dispersibility of drug in dissolution medium.

CONCLUSION

A systemic study involving dissolution enhancement of poor water soluble drug Gliclazide was made by preparation of solid dispersion using natural polymer (Hupu gum, Guar gum & Xanthan gum) by co-grinding method. . Amongst the solid dispersions prepared. F6 formulation prepared by co-grinding method using Guar gum as carrier in 1:3 ratio shown the better release of Gliclazide (96.79 %) with in 60 min.

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