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Modified Hupu Gum: A Novel Application In Solid Dispersion Containing Pioglitazone HCl

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ABSTRACT

Pioglitazone HCl is an antidiabetic drug in thiazolidinediones group and it improves insulin sensitivity in insulin resistant patients. The drug has low solubility in biological fluid, lead to the poor bioavailability after oral administration. The present study aims at enhancement of dissolution profile of Pioglitazone HCl using Hupu gum (HG) and modified Hupu gum (MHG) as carriers by solid dispersion technique. MHG was prepared by heating at different temperature. The HG and MHG were characterized for viscosity, swelling index and water retention capacity. Solid dispersion was prepared by cogrinding method using HG and MHG in the ratio 1:1 and 1:2 respectively. The solubility data shows that solubility of Pioglitazone HCl is increases with HG and found high in MHG. The FTIR and XRD study was carried out. The X-Ray diffraction study shown crystalline nature of pure drug, which was converted into amorphous form in solid dispersion. The optimized formulation shows the higher in vitro drug release (93.49 %) within 120 min and also it shows higher absorption against pure Pioglitazone HCl. From this study it concludes that MHG could be novel approach useful as a carrier with in enhancing solubility in solid dispersion.

Keywords: Pioglitazone HCl, dissolution enhancement, hupu gum, modified hupu gum, X-Ray diffraction.

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INTRODUCTION

Pioglitazone HCl is poorly water soluble drug with high permeation rate. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the lipidic, muscular tissues and in the liver**.** Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water[1]. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction[2], crystal engineering[3], nano-suspension[4], salt formation[5], use of surfactant[6], complexation[7], and so forth. But most of these methods have several limitations. Improving the Solubility characteristics of poorly water soluble drugs is important to achieve better bioavailability and reduced side effects[1, 8]

The solid dispersion technique is one of best method in this direction[9]. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug[10].

Many carriers used in solid dispersions also cause problems due to their hygroscopic nature and high viscosity. Use of polymers with low viscosity and high swelling capacity offers better alternative for these types of polymers. The natural polymer is more beneficial because of their low cost, biocompatibility, and biodegradability[11, 12, 13]. It is reported that the swelling ability of the carrier improves dissolution rate of poorly water soluble drug. As the viscosity of the carrier reduces the dissolution rate, it is useful to modify the gum in such a way that its swelling ability remains same and viscosity reduced. This can be achieved by modifying the natural gums. Hupu gum also called as Gum Kondagogu is a natural gum exudates obtained from stems and branches of, *"Cochlospermum gossypium"* and belongs to Bixaceae family. Hupu gum is swellable in water and water binding capacity of hupu gum is 35.1mL/g. Hupu gum is mainly used as polymer and food additive[14].

The present work aimed on solubility enhancement of poorly water soluble drug Pioglitazone HCl using natural modified hupu gum (MHG) at various temperatures in comparison of hupu gum (HG).

MATERIALS AND METHODS:

Materials

Pioglitazone HCl and hupu gum were obtained as gift sample from Cadila Pharmaceuticals Ltd,

(Ankleshwar,India) and Nutriroma (Hyderabad, Andhra Pradesh, India) respectively. All other materials used were of analytical grade.

Preparation of Modified Hupu Gum

The MHG was prepared by heating hupu gum at 120^0C, 130^0C, 140^0C separately for 2 h in hot air oven. The prepared MHG was pass through 100 mesh sieve[15].

Characterization of HG and MHG as natural carrier:

The following characterization methods were performed for hupu gum and modified hupu gum.

Swelling Index

Swelling index of HG and MHG was determined as per the method described by Manjil Patel *et al*[11]. Swelling index was expressed as a percentage and calculated according to the following equation:

$$SI = [(Xt - Xo) / Xo] \times 100 \quad \text{---------- (1)}$$

Where X_o is the initial height of the powder in graduated cylinder and Xt denotes the hight occupied by swollen gum.

Viscosity Measurement

The viscosity of 1% (w/v) HG and MHG solution was measured according to the US Pharmacopeia (USP XXII at 37^0 C) specification, using Brookfield Viscometer[16].

Angle of repose

The angle of repose was determined by the funnel method. The diameter of the powder heap was measured and angle of repose was calculated using equation 2.

$$\tan(Ø) = H / R \quad \text{---------- (2)}$$

where , H- Height of powder heap, R - Radius of powder heap

Density

The loose bulk density (LBD) and tapped bulk density (TBD) of HG and MHG powder were determined. Powdered gum (2 gm) was poured into calibrated measuring cylinder (10 ml capacity) and noted initial volume. The cylinder was tapped and continued until no further change in volume was found. LBD and TBD were calculated using the following equation:

LBD = Weight of the powder / Volume of the packing ---------- (3)

TBD = Weight of the powder / Tapped volume of the packing ---------- (4)

Compressibility (Carr's index)

Compressibility index (Carr's index) of HG and MHG was determined by using the following equation:

Carrs index (%) = [(TBD – LBD) × 100]/TBD

Water Retention Capacity:

The water retention capacity of HG and MHG was determined as per the method by Upendra Kulkarni *et al*. The difference between the original volume of the mucilage and the volume drained was taken as water retained by the sample referred as water retention capacity[12].

Method of preparation of solid dispersions

Solid dispersions of pioglitazone HCl were prepared by cogrinding method using natural hupu gum as carrier in ratio of 1:1 and 1:2. The hupu gum (HG) and modified hupu gum (MHG) were used separately. The dispersion were then sifted through sieve no. 100 and stored in desiccator till further use (Table. 1) [13].

Table 1: Composition of Pioglitazone HCl solid dispersion

Method	Carrier	Drug – carrier ratio	Formulations
Cogrinding	HG	1:1	SD 1
Method		1:2	SD 2
	MHG at 120^0 C	1:1	SD 3
		1:2	SD 4
	MHG at 130^0 C	1:1	SD 5
		1:2	SD 6
	MHG at 140^0 C	1:1	SD 7
		1:2	SD 8

CHARACTERIZATION OF SOLID DISPERSIONS

FT-IR Study

FTIR study (Shimadzu, Japan) using the KBr disk method with scanning range of 500 to 4,000 cm^{-1} at resolution 1 cm^{-1} of drug, carrier and solid dispersion was carried out.

X-Ray diffraction study:

One of desire property for preparation of solid dispersion is crystalline and amorphous nature of drug. The x-ray diffraction study of pioglitazone HCl, MHG and solid dispersion containing MHG was carried out using diffractometer Philips PW 3710, and Cu-Kα radiation. Diffractogram were run at scanning speed of 2 ^{o}/mm and chart speed of 2^o/2cm per 2θ.

Solubility study

A modified method of solubility determination was used to determine the solubility of pioglitazone HCl in different solid dispersion formulations. Pioglitazone HCl and formulations of solid dispersion each sample equivalent to 15 mg of pioglitazone HCl were separately introduced into in 15 ml stopper conical flasks containing 15 ml 0.3 M hydrochloric acid buffer (pH 2.0) and 15 ml of distilled water separately. The flasks were sealed and kept overnight on

mechanical shaker. Then solution was filtered and sample was analyzed by UV-Visible spectrophotometer at 218.5 nm triplicately[17].

In vitro dissolution study

The USP 23 type-I dissolution apparatus was used for the in vitro dissolution study of pioglitazone HCl and Solid dispersion formulations. The dissolution test was performed using 900 ml of 0.3M hydrochloric acid buffer (pH 2), at 37± 0.5^0C and 75 rpm. The sink condition was maintained throughout the study and the sample was filters through whatmann filter paper (no.45µm). Then samples were analyzed at 218.5 nm by UV Spectrophotometer in triplicate[18].

***In vivo* study:**

An in vivo evaluation study was performed on normal healthy Swiss albino mice. The experimental design was approved by Institutional Animal Ethical Committee. Four groups of albino mice of either sex weighing 25 to 30 g each (4 in each group) that were fasted (with water) at 24 hours before the experiment. Diabetes was induced in the mice by administering alloxan monohydrate (150 mg / kg) intraperitoneally into the 24 hours fasted mice (except control group). The mice had free access to standard laboratory feed and water and keeping under standard laboratory conditions. Blood samples were collected after 48 hours and blood glucose levels were estimated. Albino mice which have shown more than 200 mg/dl blood glucose levels were considered as diabetic[19,20]. The blood glucose level for the control and test samples was determined by Auto Biochemical analyzer (Om Sai Clinical Lab).

RESULTS AND DISCUSSION:

The prepared physical characterization of HG and MHG shows slight changes at different temperature (Table 2). The swelling index and viscosity of modified hupu gum decreases with increasing temperature than hupu gum. The viscosity of MHG was markedly lower than HG but its swelling index is decreased and water retention capacity were increased. It may be due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution. The viscosity of 1% w/v solution of MHG at 28°C is lower than that of HG. Thus, the dissolution rate of pioglitazone HCl from the MHG solid dispersion is higher than that of HG. It was observed that the HG which is more viscous than MHG resulted in formation of lumps of drug-carrier particles during dissolution, whereas pioglitazone HCl-MHG particles dispersed rapidly. The modified hupu gum at different temperature gives tremendous changes in structural bonding, cohesive and adhesive forces of attraction, crystallinity of drug etc. These changes are modified changes that help to lower the viscosity and swelling index. This change also increases water

holding capacity which improves the wettability of drug and helps to dissolve the poorly water soluble drug.

Table 2: Characterization of HG and MHG

Parameters	HG	MHG (120^0C)	MHG (130^0C)	MHG (140^0C)
Swelling index(%)	1328	1233	837.5	794.7
Viscosity (cps)	1350	850	650	Not found
Water retention capacity (ml)	15	30	35	43
Loose bulk density (g/ml)	0.90	1	1	0.95
Tapped density (g/ml)	1.10	1.14	1.22	1.20
Angle of repose (Ø)	29.68	31.79	32.61	30.11
Carrs index (%)	18.18	12.28	18.03	20.83
Hausners ratio	1.22	1.14	1.22	1.26

Solubility study

The result of solubility study data of all formulation are given in Table 3. The solubility data indicated that the HG and MHG enhance the solubility of pioglitazone HCl using co-grinding method. It was observed that, as the concentration of gum increases, solubility of Pioglitazone HCl increased. Solid dispersion of Pioglitazone HCl with MHG 1:2 (SD 8) (Modified at 140^0C) significantly enhances the solubility than other solid dispersions. The solubility of solid dispersion containing pioglitazone HCl of 1:2 ratio prepared by using MHG at 140 ^{0}C increases water holding capacity, which might be due to the cohesive and adhesive forces of attraction and decreasing viscosity, form dispersion with good wettability.

Table 3: Solubility study in distilled water and 0.3 M HCl buffer

Sr. no.	Formulations	Solubility in water (mg/ml)*	Solubility in 0.3M HCL (mg/ml)*
1	Pioglitazone HCl	0.650±0.01	2.58±0.034
2	SD 1	3.91± 0.65	8.41±.096
3	SD 2	4.57±0.56	10.08±0.86
4	SD 3	5.33±0.96	12.79±0.47
5	SD 4	9.58±0.07	14.04±0.05
6	SD 5	5.25±0.86	14.25±0.78
7	SD 6	8.66±0.59	16.75±0.49
8	SD 7	10.33±0.65	17.83±0.36
9	SD 8	12.16±0.09	18.79±0.62

In Vitro Dissolution Rate Study

The dissolution profile of pure drug and solid dispersion formulations shown in figure no.1 and 2. The amount of pure drug dissolved during 120 min was 37.19 %. The dissolution rate of Pioglitazone HCl was gradually increasing in formulation SD1, SD2 and SD3. The release of drug during first 5 minute was high in formulation SD4, SD5, SD7 and SD8. The dissolution rate

of drug from solid dispersion was more than pure drug. Also the decline concentration of drug after 60 minute was found in SD3, SD7and SD8. The optimal release of drug was found in SD4 and SD8, 93.49 and 92.49 % respectively. As concentration of drug decline during 105 minute in SD8 and the concentration of drug gradually increasing during 120 minute in SD4, the optimized batch on the basis of solubility and release pattern was found SD4. In vitro dissolution, (figure. 1-2) the gradually increasing concentration of drug up to 120 minute due to drug: carrier interaction, which enhance slowly wettability of drug particles. While sudden release of drug after 5 minute might be due to the heating at various temperatures. This looses certain force of attraction and viscosity of carriers.

When an drug-carrier particle come in contact with dissolution fluid, seeping of dissolution medium into the drug-carrier particles takes place, which initiates the formation of a stagnant gel layer of carrier around the particles. It was proved that as the viscosity of the carrier decreased, the dissolution rate of drug increased.

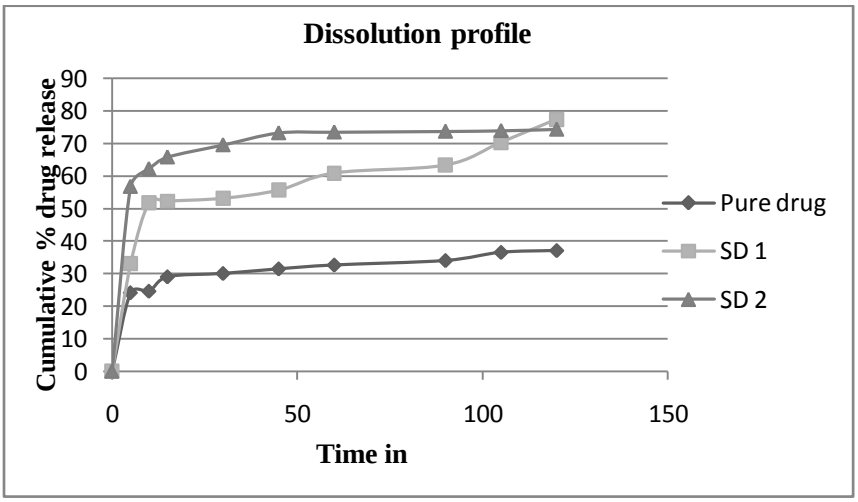

Figure 1. Drug release profile of pure drug and SD1 to SD2.

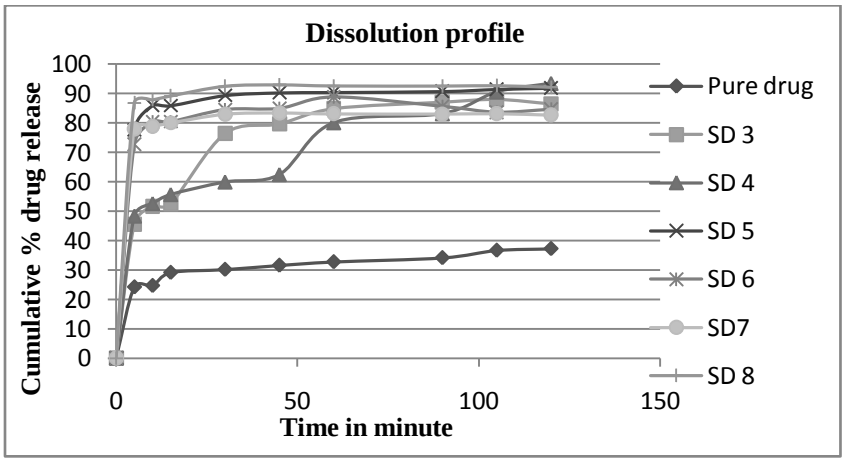

Figure 2. Drug release profile of pure drug and SD3 to SD8.

***In vivo* study:**

The in-vivo study of the optimized SD4 formulation of pioglitazone HCl was performed on Swiss albino mice by measuring the hypoglycemic effect. The optimized formulation of Pioglitazone HCl was administered by preparing a suspension. A rapid decreasing in blood glucose level was observed within the two hour after oral administration as compared to the Pioglitazone HCl. In-vivo study proved relative bioavailability of Pioglitazone HCl from the solid dispersion, which was higher than that of pure pioglitazone HCl. These partially contrary results of bioavailability of solid dispersion formulations shown that still more in-vivo data is needed to confirm the superiority of solid dispersion (figure 3).

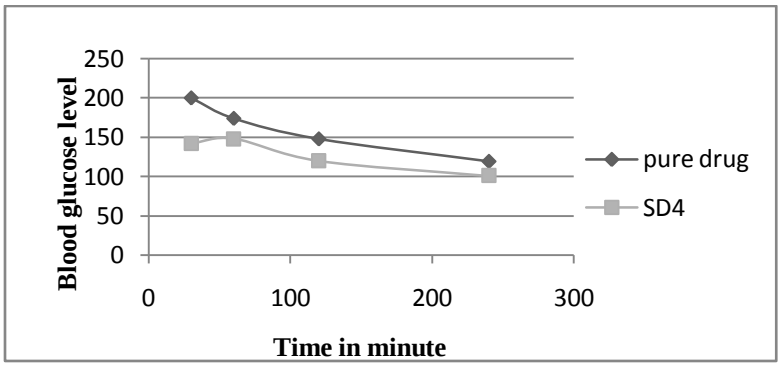

Figure 3: Reduction in blood glucose level in Swiss albino mice.

Infrared Spectroscopic Study

Infrared spectra of pioglitazone HCl & binary system with HG and MHG are presented in figure 4 and 5. Pure pioglitazone HCl spectra showed sharp characteristic peaks at 711.73, 1039.63, 1431.18, 1460, 1516.05, 1550.71, 1610.56, 1705- 1707, 2900- 2800, 3440.71cm^{-1}. HG and MHG spectra showed characteristic peaks at 1020.34, 2885.51, 2947.23, 2989.66, 3464.15 cm^{-1}.

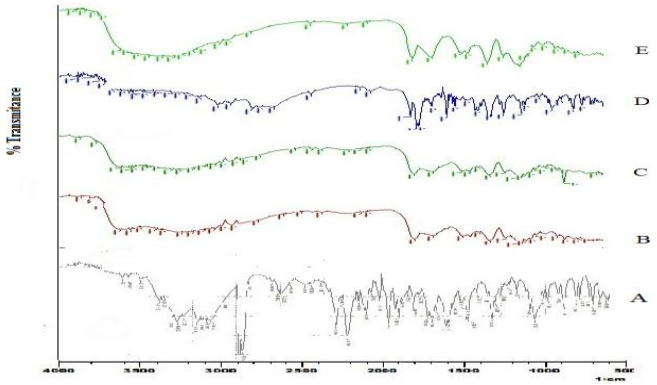

Figure 4: FTIR spectra of (A) Pioglitazone HCl, (B) HG, (C) MHG (120^{0}C), (D) MHG (130^{0}C), (E) MHG (140^{0}C).

The characteristic FTIR peaks are preserved in the spectra of solid dispersion systems at almost same wave number. This indicates that there is no interaction between drug and carrier.

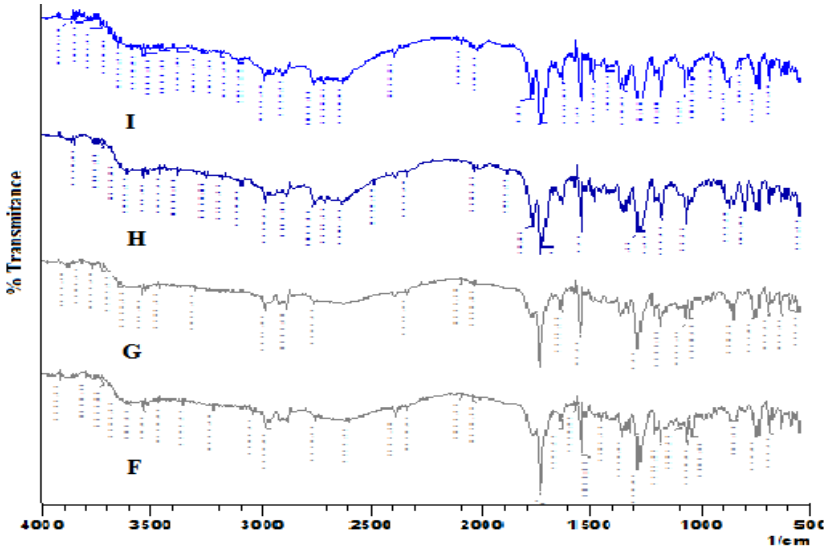

Figure.5: FTIR spectra of pioglitazone HCl SD with (F) HG, (G) MHG (120^{0}C), (H) MHG (130^{0}C), (I) MHG (140^{0}C).

X-Ray Diffraction Study:

XRD spectra of Pioglitazone HCl, MHG and solid dispersion containing MHG are shown in fig.6. The sharp, intense representative peak of pioglitazone HCl notably at (2Ø) 9, 13, 17.5, 19, 20, and 23 were observed.

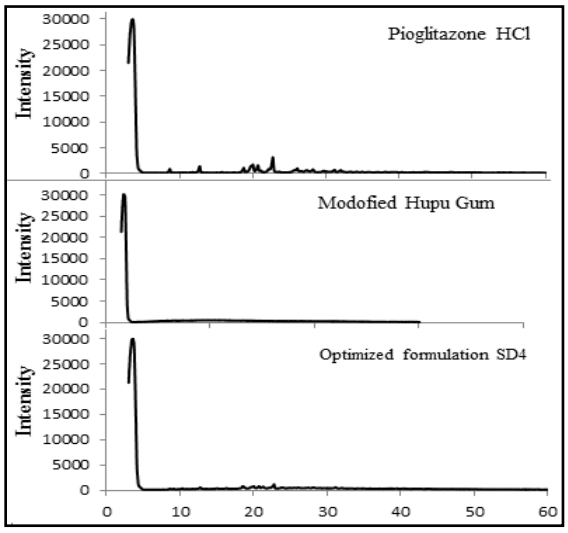

Figure 6 : Powdered X-ray diffraction study.

The MHG was found amorphous in nature as there were few peaks with very weak intensities. In XRD (figure. 6), the series of sharp and intense diffraction peak indicated that, the crystalline nature of pure pioglitazone HCl. The crystalline peaks of optimized batches were found on low / negligible intensity at the same wavelength. It indicates that the crystallinity of pure drug was converted into amorphous form in solid dispersion. This happened might be due to use of amorphous MHG as carrier, which form high surface area dispersion.

CONCLUSION:

From the present study, it can be concluded that MHG could be used as a potential carrier in the solubility and dissolution rate enhancement of poorly water soluble drug. Increased wettability, dispersibility, surface area and solubilization effect of HG and MHG enhance the solubility of poorly water soluble drug. The MHG at various temperatures is ideal carrier for the preparation of solid dispersion. These novel applications with desired properties are fruitful for poorly water soluble drug.

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