Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2014, Volume 2, Issue 7
ISSN:2321–3647(online)

Modification and Physical Characterization of Hupu Gum As A Carrier In Solid Dispersion Containing Clopidogrel Bisulphate

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ABSTRACT

The objective behind this study was to enhance the solubility of clopidogrel bisulphate by solid dispersion technique and also to modify, evaluate and compare desired properties of carriers for solid dispersion. The melting point, swelling index, viscosity, bulk density, tapped density, angle of repose, water retention capacity were evaluated for plain and modified Hupu gum (MHG). The plain and modified Hupu gum was also characterized by differential scanning calorimetry and X-ray diffraction technique for physical interaction and crystallinity respectively, the comparative evaluation of plain and modified Hupu gum highlighted that the modified Hupu gum shows more desirable properties for preparation of solid dispersion. It concludes that modification of natural gums by heating at different temperature is one of the best techniques to acquire desired properties of carrier. Solid dispersion was prepared by Gel entrapment technique using and MHG in the ratio 1:1, 1:2 and 1:3 respectively. Solubility of pure Clopidogrel bisulphate was determined and compared the same with solid dispersion. Finally it was observed that enhancement in solubility of Clopidogrel bisulphate was obtained using MHG and drug in 1:2 ratio.

Keywords: Hupu gum, Modified Hupu gum, Clopidogrel bisulphate, Solid dispersion.

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Received 30 June 2014, Accepted 05 July 2014

Please cite this article in press as: Amar S *et al.*, Modification and Physical Characterization of Hupu Gum As A Carrier In Solid Dispersion Containing Clopidogrel Bisulphate. American Journal of Pharmacy & Health Research 2014.

INTRODUCTION

Solubility is The important aspect which may greatly affect the performance of the drug especially aqueous solubility is an important physico - chemical property of drug. The drug must be in solution state to exert better therapeutic efficacy or better bio-availability and to have drug in the solution state, it must have high dissolution rate and high solubility. Unfortunately more than 90% of drugs approved since 1995 have poor solubility. Also More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water.[1]

The solid dispersion is one of the most important and desirable technique of solubility enhancement. As per Chiou and Riegelman, the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" 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. The matrix can be either crystalline or amorphous.[2, 3] The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles, the use of natural carrier in solid dispersion gives prominent and ecofriendly results. Many carriers have limitations in enhancing solubility of poorly water soluble drugs due to their high hygroscopic nature and viscosity, modifying natural gum at different temperature provides carrier which have low viscosity and high swelling capacity offers better alternative for natural carriers. Modification of natural gums also changes physical characteristics like swelling index, viscosity, water retention capacity and crystalline nature of powder into amorphous.[3, 4, 5]

MATERIALS AND METHODS:

Clopidogrel bisulphate and Hupu gum were obtained as gift sample from Cipla Pharmaceuticals Ltd, (Mumbai, India) and Nutriroma (Hyderabad, Andhra Pradesh, India) respectively. And methanol as a solvent used was of analytical grade.

Preparation of Modified Hupu Gum to change its physical characters (MHG):

The MHG was prepared by the method reported by Murali Mohan Babu et al. Generally modification in done by Heating at different temperature, but temperature mut be below its charring temperature. Powdered gum was placed in a porcelain bowl and subjected to heating in hot air oven for 140^0C for 2 hr. The prepared MHG was finally resieved (100 mesh) and stored in airtight container at 25°C. it must be identified that there was no any kind decoloration and charring. This indicates that the gum was stable physically as well as chemically at high temperature. Temperature for modification was finalized on the basis of desired properties.[6,7]

Characterization of Hupu Gum and Modified Hupu Gum:

The following characterization methods were performed for both Hupu gum and modified Hupu gum at temperature 140^0C.

Melting point

The melting point of drug was determined using capillary method. The small amount of Hupu Gum (HG) was taken in a capillary tube closed at one end and it was placed in melting point apparatus and the temperature at which the drug melts was noted.

Density

The loose bulk density (LBD) and tapped bulk density (TBD) of Hupu Gum (HG) and Modified Hupu Gum (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 i.e. taps (~100) until the powder bed volume has reached a minimum.LBD and TBD were calculated using the following equation:

LBD = Weight of the powder / Volume of the packing ----------(1)

TBD =Weight of the powder / Tapped volume of the packing----------(2)

Viscosity Measurement

The viscosity of 1% (w/v) HG and MHG solution was measured according to the US Pharmacopoeia (USP XXII) specification, using Brookfield Viscometer.

Angle of repose (Flowability)

The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The diameter of the powder heap was measured and angle of repose was calculated using equation 3.

$$\text{Tan } (Ø) = H / R \quad \text{---------- (3)}$$

Where, H is High of powder heap, R is Radius of powder heap

Swelling Index

About 1 gm of HG and MHG was accurately weighed and transferred to a 100-ml Stoppard measuring cylinder. Initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100 ml mark with distilled water. The volume occupied by the gum sediment was shaken gently and set aside for 24 hr at room temperature. The volume occupied by the gum sediment was noted after 24 hr.[8] swelling index was expressed as a percentage and calculated according to the following equation:

$$SI = [(Xt - X_o) / X_o] \times 100 \quad \text{---------- (4)}$$

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

Water Retention Capacity:

The water retention capacity of HG and MHG was determined as per the method by Upendra Kulkarni *et al* [9]. briefly, the contents from the measuring cylinder used for swelling index test were filtered through a muslin cloth and the water was allow to drain completely into a dry 100 ml graduated cylinder. The volume of water was noted 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 or water absorption capacity of gum.

Fourier transforms Infrared spectroscopy (FT-IR):

The FT-IR (Agilent Cary 630 - ATR FTIR spectrophotometer) study was carried out for MHG and HG. The sample preparation involved ATR sampling technique, the spectrum was scanned over the frequency range between 4000 and 600 cm^{-1} and at 4 cm resolution.

Differential Scanning Calorimetry:

The DSC study of MHG and HG was carried out at scan rate 10^oC/min at temperature 30 – 300^oC (Make SII Nanotechnology-SEIKO model/series/DSC 6220) for purity of drug sample.

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 MHG and HG was carried out using measurement program wide range, owner nandini and Cu-Kα radiation. The ratio of K Alpha 2/ K Alpha 1= 0.5, Diversion slite 1.52, Scan axis = Gonio and scan range was 4.997-50.00045.

Preparation of Solid Dispersion of Clopidogrel bisulphate:

Solid dispersion of Clopidogrel bisulphate with modified hupu gum was prepared by Gel Entrapment technique. The composition is shown in table 1.

In this method, weighed quantity of polymer (MHG) Carrier is dissolved in organic solvent (Methanol) to form a clear and transparent gel. Then drug is dissolved in gel by sonication for few minutes. Organic solvent (Methanol) is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved.[10, 11]

Table 1: Composition of Clopidogrel bisulphate in solid dispersion

Formulation Code	Clopidogrel bisulphate : MHG
SD1	1:1
SD2	1:2
SD3	1:3

Solubility Determination:

The Solubility of the Clopidogrel Bisulphate was determined in distilled water and phosphate buffer pH 6.8. Excess amount of drug was taken and dissolved in a measured amount of each (distilled water, phosphate buffer 6.8) solvent in a glass beaker to get a saturated solution. The solution was shaken for 1 hr or sonicate for 30 min intermittently to assist the attainment of equilibrium with the un-dissolved drug particles. Then measured quantity of the filtered drug solution was withdrawn after 1 hr and successively diluted with respective solvent and concentration was measured by UV Spectrophotometer at 218.2 nm. Same procedure of solubility determination was repeated for solid dispersion and compared with the solubility of pure clopidogrel bisulphate. [12]

RESULTS AND DISCUSSION:

The prepared MHG were identified as free from discoloration and charring. This indicates that, the MHG was stable physically as well as chemically at high temperature. The 140^0C temperature was finalized on the basis of desired properties. The result of characterization of HG and MHG are given in Table 2. The swelling index and viscosity of modified MHG gum decreases with increasing temperature than HG. The viscosity of MHG was marked lower, but its swelling index is decreased and water retention capacity was increased. It may be due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution. At higher temperature (140^0C) MHG loose its structural arrangement and reduces adhesive and cohesive force of attraction which helps to retain water and decease viscosity. Increase in density and angle of repose is noted in case of modified Hupu gum. In case of melting point determination it was observed that the gum gets charred at 174^0C.

Table 2: Characterization of HG and MHG

Parameters	HG	MHG(140^0C)
Swelling index (%)	1400	990.90
Viscosity (cps)	2538.75	2040
Water retention capacity (ml)	12	25
Loose bulk density(g/ml)	0.86	0.90
Tapped density (g/ml)	1.05	1.17
Angle of repose(Ø)	29.79	31.61
Melting point(^{0}C)	Charred at 174^0C	Charred at 174^0C

Infrared Spectroscopic Study:

Infrared spectra of Hupu gum (A) and Modified Hupu gum (B) are presented in figure 1. FT-IR spectroscopy shows various vibrations between the functional groups at different bond. The

corresponding table (table 3) shows clear stretching vibration due to varying functional groups and indicating no overlapping found over the peaks.

Table 3: Characteristic peaks of Hupu Gum (HG) and Modified Hupu gum (MHG)

Hupu gum (HG)		Modified Hupu gum (MHG)	
Functional group	**Peak (cm^{-1})**	**Functional group**	**Peak (cm^{-1})**
C-H stretching(alkane)	3057.17 cm^{-1}	C-H stretching(aromatic)	3115.04, 31088.95 cm^{-1}
C=C stretching.(aromatic)	1421.54 cm^{-1}	C-H stretching(alkane)	2945.30 cm^{-1}
C-Cl stretching	773.46 cm^{-1}	C=C stretching.(aromatic)	1415.75cm^{-1}
C-N stretching	1020.34 cm^{-1}	C-Cl stretching	7789.24 cm^{-1}
C=O stretching. (ester)	1724.35 cm^{-1}	C-N stretching	1148.57 cm^{-1}
C-O stretching (ester)	1147.85,1246.02 cm^{-1}	C=O stretching. (ester)	1724.33cm^{-1}
C-S stretching	711.73 cm^{-1}	C-O stretching (ester)	1358.45cm^{-1}
So4 stretching	1313.02 cm^{-1}	So4 stretching	1248.87cm^{-1}

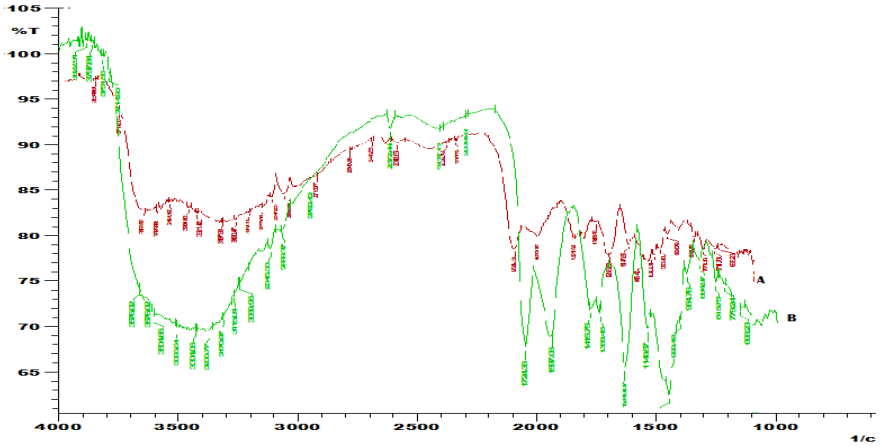

Figure 1: FTIR spectra of Hupu Gum (A) and Modified Hupu gum (B)

Differential Scanning Calorimetry:

The thermal profile of modified Hupu gum revealed a melting phenomenon at around 89.79 - 151.38^{0}C, that is endothermic peak observed for modified Hupu gum at 117.65^{0}C. hence the modified Hupu gum was obtained with thermal degradation (figure 2).

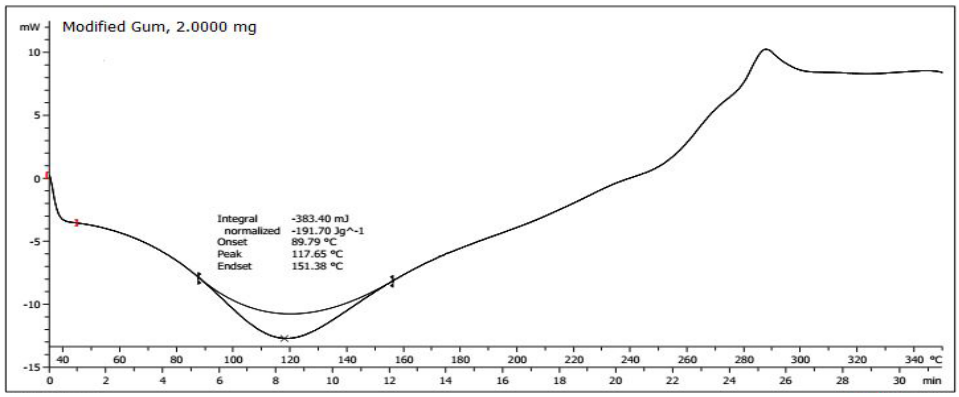

Figure 2: DSC thermogram of Modified Hupu Gum

X-Ray Diffraction Study:

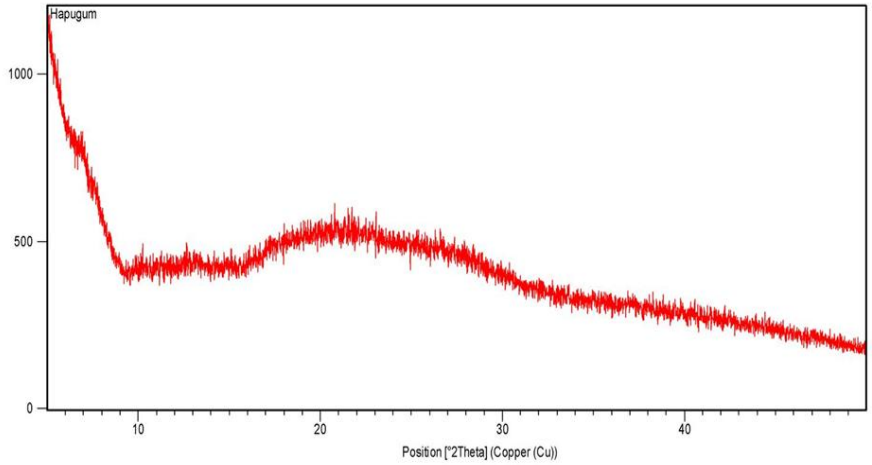

Figure 3: PXRD of Hupu gum.

The HG and MHG were found amorphous in nature as there were few peak with very weak intensities, and it was observed that the there was no any change in amorphous behavior of Hupu gum after modification (figure 3 & 4).

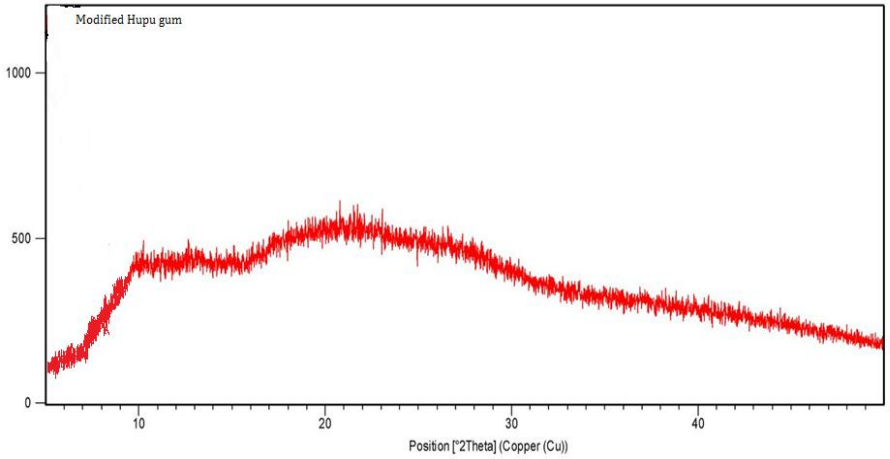

Figure 4: PXRD of Modified Hupu gum.

Solubility Determination:

The solubility data of Clopidogrel bisulphate in distilled water and 6.8 phosphate buffer is mentioned in table 4. It is observed that Clopidogrel bisulphate has lowest solubility in distilled water. Solubility of Clopidogrel bisulphate was considerably increased in 6.8 phosphate buffer.

Table 4: Solubility of Plain Clopidogrel bisulphate in distilled water and 6.8 phosphate buffer

Sr No.	Solubility in distilled water (mg /ml)	Solubility in 6.8 phosphate buffer (mg/ml)
1	6.32	9.06

Solubility Determination of solid dispersion in distilled water and 6.8 phosphate buffer:

The solubility of Clopidogrel bisulphate in different solid dispersion formulation in distilled water and 6.8 phosphate buffer was determined. The solubility data shown that the MHG enhanced the solubility of Clopidogrel bisulphate using Gel entrappement technique of solid dispersion. It was observed that, as the concentration of gum increases, solubility of Clopidogrel bisulphate decreased. Solid dispersion of Clopidogrel bisulphate with MHG 1:2 (SD2) significantly enhances the solubility than other solid dispersions. (Table 5)

Table 5: Solubility Study of solid dispersion in distilled water and 6.8 phosphate buffer

Formulation Code	Solubility distilled water(mg/ml)	Solubility 6.8 phosphate buffer(mg/ml)
SD1	8.38	10.71
SD2	10.43	15.43
SD3	8.24	14.61

CONCLUSION:

Modification in natural Hupu gum, gives novel application to the solid dispersion dosage form. The modification by heating at different temperature helps to improve ideal / desired properties of carriers without affecting the physical and chemical stability, and can be implemented in another dosage form if containing carriers. Solid dispersion containing natural carriers which is low toxicity in nature, biocompatible and easy available is an alternative and best choice for improving solubility of poorly water soluble drug (BCS-II) by using Gel entrapment technique.

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