PREPARATION AND EVALUATION OF CO-GRINDING MIXTURE AND SOLID DISPERSION OF PROPAFENONE HYDROCHLORIDE USING NATURAL POLYMER

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ABSTRACT
The aim of the present study was to enhance the dissolution rate of Propafenone Hydrochloride (PHC), a poorly water soluble antiarrhythmic drug, by preparation of solid dispersion using modified guar gum (MGG). Formulations were prepared by physical mixture, ground mixture and solvent evaporation method using different PHC – MGG ratio. Prepared formulations were characterized by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), Powder X-ray diffraction (XRD) and evaluated for in-vitro release study. XRD data indicated that PHC is crystalline in nature. In physical mixture, it remains crystalline but in ground mixture & solid dispersion, drug lost its crystallinity. The result obtained from in-vitro dissolution study indicated that the solubility of drug from PHC solid dispersions was improved as compared to pure drug. Among various methods employed, solvent evaporation method showed better results compared to physical mixture, ground mixture. Solid dispersion exhibits better solubility of PHC.

Key words: Co-ground Mixture, Solubility, Dissolution rate, Hydrophilic Carrier.

INTRODUCTION
The oral route is most common and preferable route of drug administration because of convenience and ease of ingestion (Dhirendra et al., 2009). However, for a drug substance to be absorbed, it needs to be solubilized. According to Biopharmaceutical Classification System (BCS), drugs can be divided into four classes, depend upon their solubility and permeability (Mariarosa Moneghini et al., 2008). Drugs which belong to class II are characterized by low solubility and high permeability. The low dissolution profile of relative insoluble drugs is the rate limiting step in the absorption of a drug from a solid dosage form.

Several methods are used to enhance the drug solubility and the dissolution of the drug like Solid Dispersion (SD), Complexation, Salt Formation and Micronization². SD is widely used method to improve solubility of drug. SD is defined as the dispersion one or more active ingredients in inert carriers at solid state. SD can be prepared by various methods such as solvent evaporation, kneading and hot melt extrusion method (Festo Damian et al., 2000; Chiou WL, 1971; Ford JL, 1986).

Propafenone Hydrochloride (PHC) is chemically 2’-[2-Hydroxy-3-(propylamino)-propoxy]-3-Phenyl propiophenone hydrochloride (MJO Neil, 2006). PHC is a Class 1C antiarrhythmic drug (Yeung et al., 2010). PHC is used for the treatment of frequent ventricular ectopic depolarizations (Siddoway et al., 1987), sustained ventricular tachyarrhythmias (Heger et al., 1984) and arrhythmias related to accessory atioventricular pathways (Breithardt et al., 1984). The starting dose of
PHC is 450 mg/day orally. It is practically insoluble in water, having only < 10% oral bioavailability.

Guar gum (GG) is a natural nonionic polysaccharide derived from the ground endosperm of Cyamopsis tetragonolobus (L) Taub. (Family: Leguminaceae). It consists of a high-molecular weight hydrocolloidal polysaccharide, composed of galactan and mannate units combined through glycosidic linkages, which may be described chemically as galactomannan (Raymond et al., 2009). Guar gum is hydrophilic and swells in cold water, forming viscous colloidal dispersions or sols. This gelling property retards release of the drug from the dosage form, making it more likely that degradation will occur in the colon. Guar gum was found to be a colon-specific drug carrier in the form of matrix and compression-coated tablets as well as microspheres. The aim of the present study is to improve solubility of PHC by preparing physical mixture, ground mixture and solid dispersion using modified guar gum (MGG).

MATERIALS AND METHODS

Materials
Propafenone Hydrochloride was purchased from Sigma-Aldrich (USA). Guar Gum (GG) was purchased from Loba Chemie Pvt Ltd (Mumbai). All the chemicals were of reagent grade, and all materials were used as received.

Methods

Modification of Guar Gum
Preparation of MGG was done by heating method. Briefly, powdered gum was taken in a porcelain bowl and subjected to heating using sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity studies revealed that the modified forms possessed swelling property similar to GG, but viscosity was decreased as a function of temperature and time period of heating. However, it was observed that GG samples were charred, when heated at and above 150 °C. In the preparation of modified form of GG, no further change in viscosity of GG was observed by heating it at 125°C for more than 2 h. Hence, the conditions of heating at 125 °C for 2 h were selected to prepare modified form of GG. The prepared modified form of GG was finally re-sieved (100 mesh) and stored in airtight container at 25 °C (Murli Mohan Babu et al., 2002).

Characterization OF GG AND MGG (Patel et al., 2008)

Viscosity Measurement
The viscosity of 1% (w/v) GG/MGG solution was measured at 37°C using a Brookfield, DV-II Pro Viscometer and Spindle 62 (LV2).

Angle of Repose
The angle of repose was determined by the funnel method. The powder was allowed to flow through funnel freely on to the surface. The diameter of the powder heap was measured and angle of repose (θ) was calculated using the following equation:

\[
\theta = \tan^{-1} \left( \frac{H}{R} \right)
\]

Where, H = Height of powder heap, R = Radius of powder heap

Density
The loose bulk density (LBD) and tapped bulk density (TBD) of LBG/MLBG powder were determined. Powdered gum (2 gm) was poured into calibrated measuring cylinder (10 ml capacity) and noted initial volume. Then, the cylinder was allowed to fall under its own weight onto the hard surface from the height of 2.5 cm at 2-s intervals. The tapping was then continued until no further change in volume was noted. LBD and TBD were calculated using the following equation:

\[
LBD = \text{Weight of the powder/Volume of the packing}
\]

\[
TBD = \text{Weight of the powder/Tapped volume of the packing}
\]

Compressibility
Compressibility index (Carr’s index) was determined by using the following equation:

\[
\text{Carr’s index} (%) = \left( \frac{TBD - LBD}{TBD} \right) \times 100 \times \text{TBD}
\]

Preparation of Physical Mixture
The physical mixtures of PHC and MGG were obtained by simple blending of the PHC and MGG in different ratios (Table 1) with a spatula. PM is used to represent the physical mixtures of PHC-MGG.

Preparation of Ground Mixture
Ground mixtures of PHC and MGG were obtained by grinding a physical mixture of PHC and MGG in different ratios for 20 minutes in a ceramic mortar and sifted through 100 mesh. GM is used to represent the ground mixture of PHC and MGG. To ascertain the effect of method, carrier, or both on the dissolution rate of PHC. All the samples were stored in a desiccator at room temperature.

Preparation of Solid Dispersion by Solvent Evaporation Method (Sethia et al., 2008)
The drug and the polymer were dissolved in sufficient volume of dichloromethane with continuous stirring. The solvent was then completely evaporated at room temperature with continuous stirring to obtain dry granules. The resulting solid dispersion was stored in airtight container till further use.

Evaluation of Prepared Solid Dispersion

Percentage Yield

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation:

\[
\text{Practical Mass} = \frac{\text{Theoretical Mass (Drug + Carrier)}}{X 100}
\]

**Drug Content**

The physical mixture and solid dispersion equivalent to 50 mg of drug were taken and dissolved separately in 100 mL of methanol. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 304 nm by UV-visible spectrophotometer. The actual drug content was calculated using the following equation as follows:

\[
\text{Practical Drug Content} = \frac{\text{Theoretical Drug Content}}{X 100}
\]

**Fourier Transform Infra red spectroscopy (FTIR)**

FTIR spectra of pure drug, PM, GM and solid dispersion were obtained using KBr pellet method (applying 6000 kg/cm²). Spectral measurements were obtained by powder diffuse reflectance on a FTIR spectrophotometer (Shimadzu, Model 8033, USA) in the wave number region 400-4000 cm⁻¹

**Differential scanning calorimetry (DSC)**

All dynamic DSC studies were carried out on DuPont thermal analyzer with 2010 DSC module. Calorimetric measurements were made with the help of an empty cell (high purity alpha alumina discs of DuPont Company) as the reference. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°C/minute. The runs were made in triplicate.

**Powder X-ray diffraction studies (pXRD)**

Powder X-ray diffraction (pXRD) patterns were obtained using an X-ray diffractometer using (Phillips PW 1710, Tokyo, Japan) X-ray diffractometer with a copper target, voltage 40 Kv, current 30 mA at a scanning speed of 0.30°C/min.

**In-vitro Dissolution Studies**

In-vitro dissolution studies were done in USP dissolution apparatus containing dissolution medium (phosphate buffer pH 7.4). Pure drug and SDs powder was put in 900 mL of the dissolution media (equivalent to 50 mg of drug), temperature maintained at 37 ± 2°C and speed was set at 50 rpm (USP XXVI). The samples (5.0 mL) were withdrawn at various time intervals, filtered through Whatman filter paper and analyzed by UV spectrophotometrically at 304 nm.

As a model-independent approach, Dissolution Efficiency (DE) was employed to evaluate the dissolution rate from different solid mixtures (Paulo Costa and Jose’ Manuel Sousa Lobo, 2001). DE₁₀ and DE₃₀ values were calculated from the dissolution data and used for comparison.

**RESULTS AND DISCUSSIONS**

Physical mixture, ground mixture and solid dispersions of the PHC with modified guar gum were prepared in various ratios. The prepared solid dispersions of PHC were evaluated for percentage yield, drug content and in-vitro dissolution studies. The results of the characterization of the GG and MGG are given in Table 2.

The results indicated that the viscosity of MGG was markedly lower when compared to GG. Due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution, and the dissolution rate of deposited drug is markedly enhanced. The percentage yield and the drug content of physical mixture, ground mixture and solid dispersion are given in Table 3.

The percentage yield was least in formulation SD₁₀ (91.22 %) and high for formulation SD₃ (94.71 %). The drug content of the prepared solid dispersions was found to be in the range of 94.13–97.75 %.

DSC studies were performed on PHC, MGG, physical mixture, ground mixture and solid dispersion. PHC exhibits a sharp endothermic peak at 173.12 °C presented in Fig. 1.

The peak intensity corresponding to the melting of PHC decreased in the thermograms of physical mixture, ground mixture and solid dispersion. The DSC thermograms of physical mixture, ground mixture and solid dispersion showed peak, which corresponding to the melting of pure PHC. It indicated the absence of chemical interaction between drug and modified guar gum.

From the FTIR studies (Fig.2), the characteristic bands for important functional group of PHC, physical mixture, ground mixture and solid dispersion were identical. It was observed that 3425 cm⁻¹ due to OH stretching, 3325 cm⁻¹ due to NH stretching, 2947 cm⁻¹ due to aliphatic C-H stretching, 1033 cm⁻¹ due to C-O stretching. FT-IR spectra also indicated the absence of interaction between drug and modified guar gum.

The XRD patterns of the PHC, MGG are compared with those of physical mixture, ground mixture and solid dispersion as shown in Fig. 3.
Physical mixture possessed the diffraction peaks of PHC crystals, indicating that PHC was in the crystalline state. Though ground mixture and solid dispersion showed no diffraction peaks of PHC crystals, indicating that PHC lost its crystallinity. This indicated that PHC was converted to an amorphous form. This finding is compatible with the enhanced dissolution rate of PHC from ground mixture and solid dispersion.

Fig. 4 shows the \textit{in vitro} dissolution profiles of the physical mixtures, ground mixtures, and solid dispersions in comparison with pure PHC. The values of DE$_{10}$ and DE$_{30}$ are given in Table 4.

It is evident that the rate of dissolution of PHC is very low compared with those of all mixtures tested. The physical mixtures had slightly improved dissolution patterns compared with the pure drug. PM, however, showed more improvement in PHC dissolution, when compared with pure drug. The increase in dissolution rate of PHC from GM was found to be greater. The rate of dissolution of PHC from SD was found to be greater, compared with PM and GM. The rank order according to DE values is PHC < PM < GM < SD. These results confirmed that the improvement in dissolution rate of PHC was due to the presence of MGG and not due to the decrease in particle size of PHC during grinding.

Ground mixture and solid dispersion of PHC with MGG resulted in transformation of large crystals of PHC to smaller crystals, as indicated by XRD studies, leading to increased surface area available for dissolution. Moreover, the hydrodynamic microenvironment around the particles was changed because of the hydrophilic nature of the carrier. From the results obtained, it appears decreased crystallinity resulting in increased solubility of drug particles contributed to the improvement of dissolution rate of PHC from the solid dispersion. The slight increase in the dissolution rate of PHC from physical mixtures as compared with the pure drug is likely due to the ability of the polymer to enhance the wettability of the hydrophobic PHC particles.

The results of dissolution studies also revealed the importance of the viscosity of the hydrophilic polymer. During the process of drug dissolution from ordered mixtures of drug and the hydrophilic carrier, when a drug-carrier particle comes in contact with the dissolution fluid, seeping of dissolution medium into the drug-carrier particle takes place, which initiates the formation of a stagnant gel layer of carrier around the particle. Therefore, the diffusion of dissolved drug through the gel layer is a determining factor in the enhancement of dissolution rate. During the dissolution process, the drug particles that are not agglomerated but disperse rapidly throughout the dissolution medium expose a greater surface area, resulting in rapid drug release.

<table>
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<th>Table 1. Formulation of Solid Dispersion</th>
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<td>PM$_3$</td>
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| Table 2. Characterization of Guar Gum (GG) and Modified Guar Gum (MGG) |
|--------------------------|----------------|-------------------|
| **Parameters** | **Guar Gum** | **Modified Guar Gum** |
| Viscosity (cps) | $4860 \pm 62.86$ | $1511 \pm 48.82$ |
| Angle of Repose ($\theta$) | $30.94 \pm 0.6$ | $37.42 \pm 1.04$ |
| Loose Bulk Density | $0.477 \pm 0.023$ | $0.536 \pm 0.022$ |
| Tapped Bulk Density | $0.646 \pm 0.021$ | $0.733 \pm 0.041$ |
| Carr’s Index (%) | $31.08 \pm 0.83$ | $30.36 \pm 0.53$ |

$n=3$

| Table 3. Evaluation Parameters for the different formulations |
|--------------------------|----------------|-------------------|
| **Formulation Code** | **Percentage Yield (%)** | **Drug Content (%)** |
| PM$_1$ | $93.01 \pm 0.90$ | $96.54 \pm 0.71$ |
| PM$_2$ | $91.24 \pm 0.67$ | $94.13 \pm 0.53$ |
| PM$_3$ | $91.73 \pm 0.23$ | $94.57 \pm 0.48$ |
Table 4. DE values of PHC, Physical Mixtures, Ground mixtures and Solid Dispersions

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Fig. 1. DSC thermograms of pure PHC (A), Physical Mixture (B), Ground Mixture (C) and Solid Dispersion (D).

Fig. 2. FTIR spectra of Modified Guar Gum, Propafenone Hydrochloride, Physical Mixture, Ground Mixture and Solid Dispersion

Fig. 3. X-ray diffraction pattern of Modified Guar Gum (MGG), Propafenone Hydrochloride (PHC), Physical Mixture (PM), Ground Mixture (GM) and Solid Dispersion (SD)

Fig. 4. Cumulative % release of Propafenone Hydrochloride pure drug and physical mixture, ground mixture & solid dispersion formulations.
CONCLUSION

The Physical Mixture, ground mixture and solid dispersion of propafenone hydrochloride with modified guar gum as carrier were prepared and evaluated. The study shows that the dissolution rate of propafenone hydrochloride can be enhanced to a great extent by solid dispersion technique. A maximum increase in dissolution rate was obtained with PHC: MGG solid dispersion with a weight ratio of 1:3 prepared by solvent evaporation method.

REFERENCES


