TECHNOLOGY DVELOPMENT FOR POLYMER MODIFICATION TO ENHANCE SOLUBILITY OF POORLY SOLUBLE DRUG

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RESEARCH ARTICLE

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ABSTRACT

Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. Solubility of some drugs is very less; these drug molecules are often lipophilic and hence dissolution may be a problem in drug absorption from solid oral dosage forms. The increasing interest of the technology of dosage form with natural biopolymers has become the reason for undertaking present investigation on the possibility of modification of guar gum application in the preparation of an oral solid dosage form of a poorly water soluble drug. Present study examines the effect of modified guar gum on the solubility of a poorly water-soluble Nevirapine. Modified guar gum was prepared using heat treatment (110-120^{o}C for 2 hours) method. It was characterized for viscosity and swelling index etc. The physical and co-grinding mixtures of Nevirapine with modified guar gum were prepared in 1:4 drugs to gum ratio. The physical and co-grinding mixtures were characterized by DSC and FT-IR study. The studies confirmed that there was no interaction between drug and carrier. Prepared mixtures were evaluated for solubility study and *in vitro* dissolution studies. The results of present investigation indicated that modified guar gum can be a used for the development of oral dosage form with increased solubility and hence improved dissolution and oral bioavailability of poorly water soluble drug.

Key words: Solubility, bioavailability, guar gum, Nevirapine.

Introduction:

The usage of natural polymers as drug carriers is on increasing side because of their low cost, biocompatibility and biodegradability. Guar Gum is a natural gum the wider application of Guar gum is due to its unique features such as high swelling and water retention capacity, high viscosity properties and abundant availability. Guar gum is used in solid dosage forms as a binder and disintegrate[1]. Most of the failures in new drug development due to poor biopharmaceutical properties, including water insolubility[2]. The solubility issues complicating the delivery of new drugs. The main possibilities for improving dissolution are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and by optimizing the wetting characteristics of the compound surface[3]. Traditional approaches to drug solubilization include either chemical or mechanical modification of the drug molecule or physically altering the macromolecular characteristics of aggregated drug particles[4].

Nevirapine is a BCS class II compound with poor aqueous solubility[5]. Optimum permeability, poses a challenge in achievement of optimal dissolution kinetics from the dosage form. The pH solubility profile indicated a gradual decline in solubility with an increase in pH from 1.5 to 4 and remained steady at higher pH[6]. Nevirapine is a small, lipophilic molecule that is rapidly absorbed orally, Nevirapine

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particularly at higher doses exhibit characteristics of solubility rate limited absorption with a resultant decrease in bioavailability[7]. Thus present study aimed to improve solubility of Nevirapine by utilizing modification technique of guar gum; since modification of binder and disintegrate was expected to improve solubility of poorly water soluble drug Nevirapine.

Materials and Methods

Materials

Nevirapine was obtained as gift sample from the Emcure pharmaceuticals, Pune, Maharashtra, India. Guar gum was obtained from sigma Aldrich and all other reagents and solvents were of analytical grade.

Methods:

Modification of guar gum:

Modification was done by heating method. 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 guar gum, but viscosity was decreased. In the preparation of modified form of guar gum, no further change in viscosity of guar gum was observed by heating it at 120°C for more than 2 h. Hence, the condition of heating at 120°C for 2 h. was selected to prepare modified form of guar gum. The prepared modified form was finally re-sieved and stored in airtight container [8].

Characterization of modified guar gum:

Swelling and Water Retention Capacity

About 1.0 g of powder was accurately weighed and transferred to a 100 ml stoppered measuring cylinder. The initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100-ml mark with distilled water. The cylinder was stoppered and was shaken gently and set aside for 24 h. The volume occupied by the gum to sediment was noted after 24 h. swelling capacity was expressed in terms of swelling index. The contents from the measuring cylinder from the above test were filtered through a muslin cloth and the water was allowed to drain completely into a dry 100 ml graduated cylinder. The volume of water collected was noted and the difference between the origina1 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.

Viscosity Measurement

The viscosity of 1% (w/v) modified guar gum solution was measured at 37°C using a Brookfield, DV-II Pro Viscometer and Spindle 62.

Preparation of Physical Mixtures

The physical mixtures of drug and modified guar gum was obtained by blending the drug and modified guar gum in a 1:4 w/w ratio (drug: polymer) in double cone blender.

Preparation of Co-Grinding Mixtures

Co-grinding mixtures of drug and modified guar gum was obtained by grinding physical mixture of drug with modified guar gum in a 1:4 weight ratio for 15 minutes in a ceramic mortar and then sieved through 100 meshes and stored in a desiccator at room temperature.

Characterization of Co-Grinding and Physical Mixtures:

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) curves were obtained by a differential scanning calorimeter (DSC 60, TA-60WS, Shimadzu, Japan) at a heating rate of 10°C/min from 30 to 300°C in an air atmosphere.

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Infrared Spectroscopic Studies

Fourier–transformed infrared (FT–IR) spectra were obtained on a Shimadzu, FT-IR 8400 spectrophotometer. The scanning range was 450 to 4000 cm^{-1}.

Solubility Studies

The apparent solubility of drug, co-grinding mixture and physical mixture was determined in water at 37°C. For each preparation, an equivalent of 50 mg of drug was added to 50 ml of water in a conical flask with Teflon-lined screw caps. The conical flasks were kept on a shaker incubator maintained at 37 ± 0.5°C for 24 hours. After shaking, the flasks were kept equilibrated in an incubator at 37 ± 0.5°C for 12 hours. Then solution was filtered through a 0.45-µm Millipore filter and the filtrate was assayed spectrophotometrically at 277 nm[9].

In vitro Dissolution Studies

Dissolution rates from different solid mixtures were determined in 900 ml of Phosphate buffer solution (pH 7.2) at 37°C with a stirrer rotation speed of 100 RPM using the USP XXIII dissolution rate test apparatus employing a paddle stirrer (Method II). A 5-ml aliquot of dissolution medium was withdrawn at 5, 10, 15, 20, 30, 40, 50, 60, and 90 min with a pipette. The samples were suitably diluted and assayed spectrophotometrically at 277 nm.

Statistical Analysis

All the data of solubility studies and *in vitro* dissolution rate studies were analyzed statistically by ANOVA (analysis of variance) test.

Results & Discussion

Characterization of modified guar gum:

Swelling index, water retention capacity and viscosity:

The results of the characterization of the modified guar gum shown in **Table 1**. The results indicated that the viscosity of modified guar gum was markedly lower. The swelling and water retention capacity also was not reduced significantly. Due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution, and the dissolution rate of deposited drug expected to increase further in dissolution study.

Differential Scanning Calorimetry (DSC)

The DSC thermo grams of drug and modified guar gum are compared with co-grinding mixture and physical mixtures. The DSC thermo grams of physical mixtures as well as co-grinding mixtures showed peak corresponding to the melting point of pure drug; indicating the absence of chemical interaction between drug and modified guar gum.

Infrared Spectroscopic Studies

The FT-IR spectra of Nevirapine, physical mixtures and co-grinding mixtures are shown in **Figure 1**. Physical mixtures and co-grinding mixtures of Nevirapine with modified guar gum was also found to be identical. The principal IR absorption peaks of drug were also observed in the spectra of drug and solid mixtures with modified guar gum. This spectral observation also thus indicated no interaction between the drug and modified guar gum.

Solubility Studies

The solubility of drug from co-grinding mixtures increased significantly, the solubility of Nevirapine from the physical mixtures not increased significantly. ANOVA performed on the solubility parameter demonstrated that there was a statistically significant difference between the solubility of drug from co-grinding mixtures with that of plane drug.

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In vitro Dissolution Studies

In vitro dissolution profiles of the physical mixtures and the co-grinding mixtures in comparison with pure drug are shown in **Figure 2**. The physical mixture had slightly improved dissolution patterns compared with the drug. The increase in dissolution rate of drug from co-grinding mixture with modified guar gum was found to be greater. ANOVA ($P < 0.005$) demonstrated that the differences were statistically significant. Due to the hydrophilic nature of the carrier hydrodynamic microenvironment around the particles was changed. 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. The viscosity of modified guar gum was found to be low. Hence, the dissolution rate of drug is higher from physical and co-grinding mixture containing modified guar gum. 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. It was observed that drug particles with modified guar gum dispersed rapidly. This factor is also play major role to the significant difference between the dissolution rates of plane drug and drug formulations with modified guar gum.

Table 1. Characterization of Guar Gum and Modified Guar Gum

Formulation	Viscosity (cps)	Swelling Index (%)	Water retention capacity (ml)
Guar gum	4132 ± 11	28.22 ± 31	25.67 ± 2.82
Modified guar gum	2542 ± 23	26.77 ± 45	18.31 ± 2.26

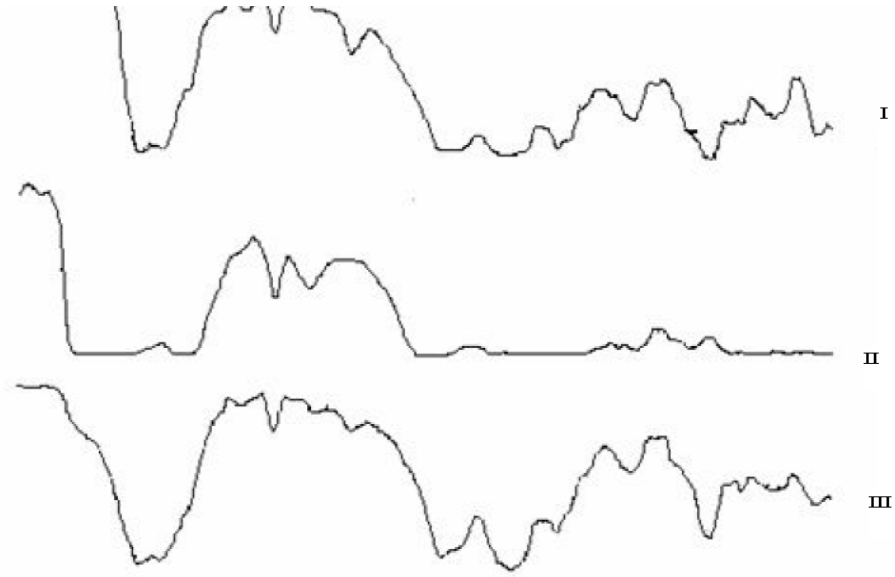

Figure 1. FTIR Spectrum of plane drug (I), physical mixtures (II) and co-grinding mixtures(III) of Nevirapine.

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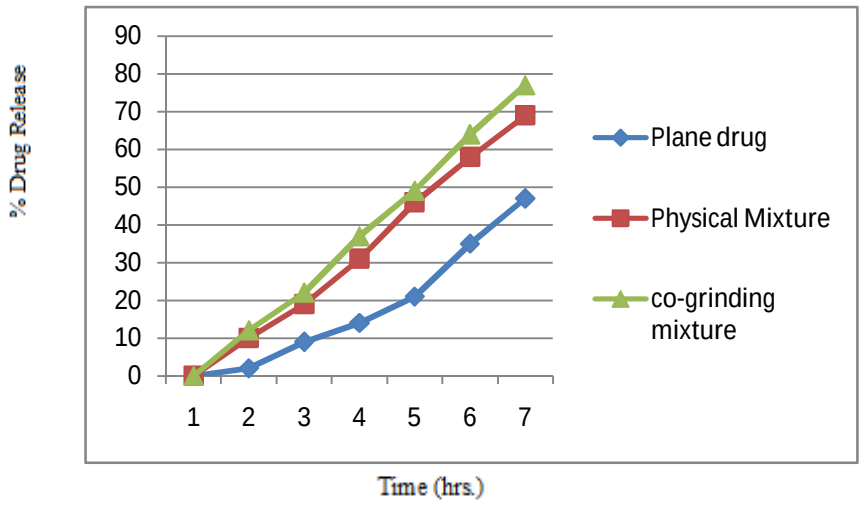

Figure 2. Dissolution profile of plane drug, physical mixtures and co-grinding mixtures of Nevirapine.

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