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Design of modified xanthan mini-matrices for monitoring oral discharge of highly soluble Soluplus®–glibenclamide dispersion

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ABSTRACT

In this work, Soluplus® was used as a hydrophilic carrier for the preparation of solid dispersion (SD) of a model BCS class II drug, glibenclamide by applying hot melting process and microwave irradiation in combination. Increasing the concentration of carrier relative to drug significantly increased the drug solubility, which corresponded to a maximum 75 fold increase at a drug:carrier ratio of 1:7. Scanning electron microscopy, differential scanning calorimetry, and x-ray diffraction analyses confirmed complete amorphization of the drug in SD. In animal study, about two fold reductions in hyperglycemic level were achieved by SD compared to pure drug. SD-loaded *O*-carboxymethyl xanthan mini-matrices controlled the release of drug into gastro-luminal fluid over longer duration. The drug release corroborated with pH-dependent swelling behavior of the matrices and approximated anomalous diffusion mechanism. This study proved the potential of Soluplus®-based dispersion in improving the clinical performance of the drug, especially when embedded in modified xanthan mini-matrices.

1. Introduction

The major limitation associated with the therapeutic use of poorly water soluble drugs is their dissolution rate-limited absorption, which usually results in poor bioavailability after oral administration [1]. Unfortunately, many potential molecules are rejected in early stages of drug development due to low water solubility [2]. It therefore requires methods for overcoming the problems of solubility so that their therapeutic benefits can be substantiated.

Solid dispersion (SD) technology has been proven itself successful in improving dissolution rate and bioavailability of poorly soluble drugs [3]. The term solid dispersion is mostly linked to glass solutions of poorly soluble compounds using at least one inert hydrophilic carrier or matrix [4]. In conventional hot melt SD samples, the uniform mixing of drug and carrier in their molten sate is questionable [5]. Further, the conventional heating of drug with carrier involves the transfer of energy by common diffusion mechanisms, which often lead to non-uniform distribution of heat throughout the materials. On contrary, microwave (MW) irradiation can penetrate any substance and cause uniform heating of materials at the same time. However, it must be recalled that the efficient heating of materials by microwaves depends on the capacity of a specific material to absorb microwave energy. In addition, MW-assisted melting process does not necessitate organic solvents for making SD, thus barring the risk of potential health hazards, originating from residual organic solvents [6].

Some of the published literatures have demonstrated the use of MW-irradiated SD technology in solving solubility-related issues for various kinds of drugs. In most of the reports, a solid drug–carrier mixture is exposed directly to MW heating with multiples of heating/cooling cycles to ensure complete melting/mixing of the drug with carrier. The hydrophilic polymers like Poloxamer 188 [7], poly(ethylene glycol) [8] and hydroxypropyl-β-cyclodextrin [9] have been tested as carriers for preparing MW-assisted SD. Different combinations of polymers or polymers with surfactants have also been proposed as a means of obtaining new carrier systems. Due to hygroscopic nature of many carriers in SD and limited improvement in water solubility, a continuous search for the new carriers and new techniques is still under progress to overcome the problems.

Soluplus® is a polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer, which shows excellent solubilizing power for BCS class II drugs [10]. Recently, solvent evaporation, spray-drying, extrusion and freeze-drying techniques have been employed for preparing SD using Soluplus® as hydrophilic carrier [11–18].

To the best of our knowledge, literature lacks data on Soluplus®-based SD that uses a combination of conventional and MW heating. Glibenclamide, a BCS class II anti-diabetic has been selected as a model drug for this investigation. Thus, the primary objective of this study was to improve water solubility of glibenclamide by preparing SD with Soluplus®.

Xanthan gum (XG) is a polysaccharide consisting of repeated pentasaccharide units formed by two glucose and mannose units and one glucuronic acid unit [19]. XG has been approved by US FDA for use as food additive. Herein, XG material was tailored to its carboxymethyl

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derivative and mini-matrices of either xanthan gum (XG) or modified xanthan gum (MXG) were prepared in order to dictate the amount of drug release in gastro-luminal fluids.

2. Materials and methods

2.1. Materials

Glibenclamide and Soluplus® were a gift from Mylan Laboratories Ltd., Hyderabad, India. Xanthan gum, monochloroacetic acid, and alloxan (Loba Chemie), sodium hydride (Spectrochem), microcrystalline cellulose (Merck Specialities), and magnesium stearate (Otto Chemie) were purchased from Mumbai, India. All other materials were used as received.

2.2. Preparation of physical mixtures and solid dispersions

Glibenclamide and Soluplus® were mixed in various weight ratios (1:1, 1:3, 1:5, 1:7 and 1:9) in glass mortar with a stainless steel spatula. The physical mixtures (PMs) were passed through 85 mesh sieve and kept for future studies.

SDs of glibenclamide and Soluplus® were prepared by the conventional hot melt process, described below. The drug and carrier were used in different weight ratios (1:1, 1:3, 1:5, 1:7 and 1:9). Known amount of Soluplus® was melted at 80 °C and the drug was added to the molten carrier. The drug and carrier were thoroughly mixed and the temperature of liquid paraffin bath was raised to 174 °C to effect complete melting of the drug. The molten mass was cooled to room temperature, solidified, pulverized and passed through 85 mesh sieve for uniform particle size distribution. Hot melt solid dispersions (HMSDs) were preserved in desiccators.

Microwave-assisted solid dispersions (MWSDs) were prepared by a little modification of the conventional melting process. Herein, the drug:Soluplus® binary mixture was melted completely in paraffin bath. The molten mass was exposed to MW-irradiation (Cata 2R, Catalyst Systems, Pune, India) for 10 min at a power of 560 W. The solid dispersion was cooled to room temperature, powdered, passed through 85 mesh sieve and kept in desiccators.

2.3. Determination of saturation solubility

The saturation solubility of PM, HMSD and MWSD in water; and that of MWSD samples in different media (HCl solution, pH 1.2 and phosphate buffer, pH 6.8) was determined by the shake-flask method at 25 °C.

2.4. Gibb's free energy calculation

Gibb's free energy (ΔG^0) associated with the solubility of drug in the presence of Soluplus® was calculated by the following equation

$$\Delta G^0 = -2.303\ \mathrm{RT} \log \frac{S_s}{S_0}.$$

S_s/S_0 was the ratio of the molar solubility of drug before and after treatment at 25 °C. The value of gas constant (R) was 8.314 J/K/mol and T was temperature in Kelvin (K).

2.5. Scanning electron microscopy

The morphology of pure drug, PM (1:7) and MWSD (1:7) was examined under scanning electron microscope (JEOL-JSM-6360, JEOL Datum Ltd, Tokyo, Japan). The photographs of gold-coated samples were captured at an acceleration voltage of 17 kV and chamber pressure of 0.6 mm Hg.

2.6. Drug content of SD

Ten milligrams of SD sample was dispersed into 25 ml of methanol. The volumetric flask was placed on mechanical shaker under continuous agitation at 140 rpm for 24 h. The liquid was then filtered through Whatman filter paper (No. 1). One milliliter of the filtrate was pipette out, suitably diluted and spectrophotometrically analyzed at 228 nm. The drug content for each sample was estimated in triplicate.

2.7. Elucidation of physical state of drug

Thermal and x-ray scanning of pure drug, PM (1:7) and MWSD (1:7) were done in a PerkinElmer calorimeter (Pyris Diamond TG/DTA, Singapore) and in x-ray diffractometer (Ultima III, D/Max 2200, Rigaku Corporation, Japan), respectively. The thermograms were traced at 12 °C/min in N_2 atmospheres (150 ml/min) up to 250 °C. Indium was used as a reference for calibration of heat flow. Cu-Kα radiation was used as a source of x-ray and the crystallograms were recorded at a speed of 5° per min.

2.8. In vivo anti-diabetic study

The approval of Institutional Animal Ethics Committee (955/RO/a/2006/CPCSEA) was obtained for the experiment on normal healthy rabbits (1.2–1.6 kg). The animals were exposed to 12 h light/dark cycle (23 ± 2 °C and 40–60% RH). Initially, normal blood glucose levels of the fasted animals were measured. Hyperglycemia was produced by single IV injection of alloxan (80 mg/kg BW) dissolved in water for injection. Rabbits were fed 5% glucose solution to avoid hypoglycemic shock for 72 h and their glucose level was monitored for 7 days until stabilized. The hyperglycemic rabbits were divided into three groups containing 5 in each group. Group I served as control. Group II (2.5 mg/kg BW) received pure drug dispersion and Group III received solid dispersion (equivalent to 2.5 mg drug/kg BW) per oral. Blood samples were collected from the marginal ear vein. The blood samples were analyzed by Accu-Check Glucometer Sensor comfort (Roche Diagnostics, Germany) test strips.

2.9. Derivatization of XG

XG (5 g) was dispersed in 25 ml of DMF and heated on a water bath (ITC-901M, Integrated Electrolife System, Kolkata, India) at 50 °C and then cooled (10 °C). To this dispersion, 7.5 g of sodium hydride was added and stirred for 30 min. Then, 3.75 g of monochloroacetic acid in 10 ml of DMF was added drop wise and mixed for 1 h. The resulting mixture was heated to 65 °C in water bath and mixed well for another hour. The product was washed with 80% methanol (3 × 50 ml) and the pH was adjusted to 7.0 with 0.1 N glacial acetic acid. The carboxymethyl XG (MXG) was then filtered off, washed with methanol, and air-dried.

2.10. Characterization of MXG

The modified gum was characterized by measuring degree of *O*-carboxymethyl substitution and infrared spectroscopy.

Sodium form of carboxymethyl xanthan gum was converted into its protonated form by treating its methanolic dispersion with excess concentrated hydrochloric acid. Accurately weighed, 200 mg of dried protonated sample was dispersed into 20 ml of water and 5 ml of 0.5 N NaOH was added to this. The sample was magnetically stirred for 4 h until it dissolved completely. The solution was then back titrated with 0.4 N HCl to phenolphthalein end point. The degree of substitution (DS) of carboxymethyl ($-CH_2COO^-$) group was calculated from the equation: DS = 0.162A / (1–0.058A), where A was milliequivalents of NaOH required per gram of sample [20].