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Original research

Development and evaluation of glibenclamide floating tablet with optimum release

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ABSTRACT

Glibenclamide is a poorly soluble drug with narrow absorption window. The strategy of this work was to enhance the dissolution rate of Glibenclamide by solid dispersion (SD) technique with optimum formulation being developed as floating tablets. Binary SDs of drug and poloxamer 407 were prepared at different ratios. Ternary dispersion was prepared by the addition of sodium bicarbonate as third component. For floating tablets, a series of floating formulations was prepared using HPMC k4 (F1), HPMC k15 (F2) and combination of both with Carbopol (F3), using ternary solid dispersion as the drug matrix. Effect of matrix type was studied, F4 and F5 were prepared using the same floating matrix as F3 but drug was either binary poloxamer SD or physically mixed with bicarbonate. Unprocessed drug in floating matrix was used as control. All SDs increased drug dissolution rate, with ternary mixture showing the highest dissolution efficiency reflecting synergism between poloxamer and sodium bicarbonate. Solid state characterization showed evidences of decreased drug crystalline structure. F3 showed the best floating behavior. Considering floating behavior together with the release pattern, F3 was the optimum formulation. Overall, employing drug as ternary SD with optimum dissolution can provide flexibility in developing controlled release floating system.

1. Introduction

Glibenclamide is a potent oral hypoglycemic agent belonging to sulphonyl urea class. It causes hypoglycemia by stimulating insulin release from the beta cells of the pancreas. It may further increase insulin level by reducing hepatic clearance of the hormone [1]. According to biopharmaceutical classification system, glibenclamide belongs to class II (i.e. drugs with low solubility and high permeability) [2]. It is practically insoluble in water and consequently, its dissolution has been considered to be the rate limiting step for absorption. Being weak acid with a pka 5.3, its solubility is pH dependant and its absorption is expected to be better from the upper part of the gastrointestinal tract (GIT) [3]. These specifications resulted in large variation in bioavailability between different commercial brands of glibenclamide with each brand showing inter-subject variability [4,5]. In subjects with normal renal and liver functions, the apparent renal clearance of glibenclamide is in the range of 11.2–230 L/h with an elimination half life being estimated to be 4 h [6]. Being important in the management of chronic disease, patient compliance is an essential part of its therapeutic benefits. This can be achieved by preparing controlled release drug delivery formulation. Many strategies are available for the development of oral controlled release formulations, but selection of the optimum technique should consider the absorption window of the given drug [7]. The acidic nature of the drug and its pka value suggested that the upper part of the GIT as the main site of the absorption. This provides a narrow absorption window which can further explain the variable and low oral bioavailability of the drug after administration of conventional tablets. Accordingly, development of a floating system which ensures continuous release of the drug in the stomach may be useful for controlling the drug release with potential enhancement of the oral bioavailability of the drug. The main difficulty will be the poor solubility of the drug in the acidic environment. Enhancing the solubility of the drug is essential before formulating the floating system.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This system allows slow drug release in the stomach and can be

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considered advantageous for drugs with narrow absorption window like glibenclamide [8]. The controlled release floating system resemble hydrophilic matrices and can be considered as hydrodynamically balanced systems due to their ability to maintain an apparent density, while being hydrated to form a gelled barrier on the surface. Having this structure, the drug is released progressively from the swollen matrix while being buoyant for at least 3 h [9].

The aim of this study was to develop a controlled drug delivery system for glibenclamide that is able to deliver the drug to its target absorption window. This employed the floating technology after optimizing the dissolution rate of the drug in the gastric conditions.

2. Materials and methods

2.1. Materials

Glibenclamide and poloxamer 407 were obtained as a gift sample from sigma for pharmaceutical industries, Egypt. Hydroxypropylmethylcellulose (HPMC) K4M and K15M, Carbopol 934p were purchased from ISO-CHEM, China for fine chemicals. Magnesium stearate, hydrochloric acid, sodium bicarbonate, purified talc and polyvinylpyrolidone K40, microcrystalline cellulose (PH 102), Aerosil also purchased from ISO-CHEM. All other ingredients, reagents and solvents were of analytical grade.

2.2. Determination of glibenclamide by UVvisible spectrophotometeric method

The study employed the previously developed method [10]. Briefly a solution of glibenclamide was prepared by dissolving 10 mg of the drug in 10 ml of acetronitrile to produce a concentration of 1000 μg/ml. This was diluted 1 in 10 using 0.1 N HCl to produce the standard stock solution having the drug at a concentration of 100 μg/ml. This was suitably diluted to prepare serial concentrations in the range of 2–20 μg/ml which was used to construct the calibration curve after measuring the absorbance spectrophotometrically (Thermo, Evo300pc, USA) at 231 nm. The calibration curve was linear in the tested range ($R^2 = 0.989$) with the equation of $Y = 0.061X + 0.0379$.

2.3. Preparation of solid dispersion of glibenclamide

Table 1 presents the composition of the solid dispersion (SD) formulations. The solid dispersions were prepared using the fusion method [11]. The required amount of the polymer was molten at 60–65 °C. The drug and sodium bicarbonate (if present) are then dispersed into the molten polymer with continuous mixing. Mixing was continued away from heat until cooling. The resulting SD formulations were pulverized before passing through a 800 μm sieve.

2.3.1. Preparation of physical mixture

Physical mixture was prepared by geometric dry blending of the drug and sodium bicarbonate (1:2 w/w, respectively) with the aid of a mortar and a pestle. The physical mixture was also passed through a 800 μm sieve before packing in a tightly closed bottle.

2.3.2. Drug content

Samples of SDs and physical mixture (equivalent to 10 mg of the drug) were dissolved in Acetonitrile (10 ml). The solution was suitably diluted with the same solvent and spectrophotometrically assayed at 231 nm.

2.4. Physical characterization of solid dispersions

2.4.1. Differential scanning calorimetry

Thermograms of the samples (Glibenclamide, polymer, binary physical mixture and SDs) were recorded using differential scanning calorimetry (DSC) (DSC-60, Shimadzu, Kyoto, Japan). Samples equivalent to 2.4 mg of the drug were loaded into aluminum pans and the lids were crimped using a Shimadzu crimper. The thermal behavior of each sample was investigated under nitrogen at a heating rate of 10 °C/min, covering temperature ranges of 25–300 °C. The instrument was calibrated with an indium standard. Data analysis was conducted using TA-60WS thermal analysis software.

2.4.2. Fourier-Transform infrared spectroscopy

FTIR spectra of Glibenclamide, poloxamr 407, sodium bicarbonate and their ternary SDs were recorded using FTIR spectrophotometer, Jasco, Japan. Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000 to 400 cm^{-1}.

2.5. Preparation of floating tablets of glibenclamide

A series of floating formulations was selected according to the previously published data after the necessary modification [12]. The drug was included in the form of solid dispersion, physical mixture with sodium bicarbonate or as pure non-processed form (Table 2).

The tablets were prepared by the wet granulation technique. The components of each formula, excluding the binder and the lubricant system, were geometrically mixed. This mixture was transferred into a wet mass with the aid of ethanolic solution of PVP K40. This was granulated by passing through 1.25 mm sieve. The granules were dried in conventional hot air oven adjusted to 45 °C. The dry granules were sized through the same sieve, lubricated with magnesium stearate, purified talc and Aerosil. The prepared mixture was evaluated for the flow properties by determining the angle of repose [13], before compression on a single punch tablet machine (ROYAL ARTIST, 7, Kapadia industrial Estate, Bldg. No1. India).

2.6. Evaluation of glibenclamide floating tablets

The USP weight variation test was conducted by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The allowed

Table 1
Solid dispersion used in formulating glibenclamide floating tablets % w/w.

ph mix/SD	Glibeclamide	Poloxamer 407	Na bicarbonate	Dissolution efficiency (%)
A	1	1	–	27.93 (±1.17)
B	1	2	–	33.07 (±0.29)
C	1	4	–	47.13 (±0.97)
D	1	1	2	65.52 (±0.17)
Ph mix	1	–	2	19.63 (±0.78)

Ph. Mix is physical mixture. Values between brackets are SD, n = 3.