International Journal of Biological Macromolecules 66 (2014) 15–25

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac

Gastrointestinal transition and anti-diabetic effect of Isabgol husk microparticles containing gliclazide

Vipin Kumar Sharma [a,*], Bhaskar Mazumder [b]

[a] Department of Pharmaceutical Sciences, Faculty of Ayurved and Medical Sciences, Gurukul Kangri University, Haridwar 249404, Uttarakhand, India
[b] Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh 786004, Assam, India

ARTICLE INFO

Article history:
Received 3 December 2013
Received in revised form 28 January 2014
Accepted 7 February 2014
Available online 14 February 2014

Keywords:
Isabgol husk
Cross-linking
In vitro release
X-ray imaging

ABSTRACT

Isabgol husk with sodium alginate was formulated into gliclazide loaded microparticles which were characterized for particle size, swelling index, entrapment efficiency, *in vitro* release, release kinetics, stability, hypoglycemic effect, surface morphology, and gastrointestinal transition. The particle size in different formulations varied from 752.83 ± 0.630 to 872.03 ± 0.293 μm. It was analyzed by dissolution study that up to 98% of loaded gliclazide was released in simulated intestinal fluid (SIF, pH 7.4) within 8 h. The formulations containing sodium alginate and Isabgol husk–sodium alginate showed bioequivalency with marketed sustained release tablets (Glizid MR 60®) in terms of release pattern. The drug maintained its integrity in terms of functional groups after fabrication in formulations as observed by FTIR analysis. The hypoglycemic effect of gliclazide loaded Isabgol husk–sodium alginate microparticles was found to be 37 ± 6.356% in terms of changes of blood glucose level from base glucose level (100%) in diabetic condition after 24 h of oral administration and it was more than marketed conventional tablets (95.5 ± 3.286%). The retention of microparticles was observed in small intestine up to 10 h during whole body X-ray imaging. The study revealed that microparticles composing of Isabgol husk may have the potential for regulating blood glucose level in diabetic animals with controlled release of gliclazide.

1. Introduction

The goal of conventional and controlled release formulations can be achieved by making the availability of incorporated drug(s) at desired site of action in required quantity(s). The modified release drug delivery devices have more advantages than conventional dosage forms as the fluctuations of drug concentration in blood occurring after conventional formulations administration create the available dose level of drug below and upper to the therapeutic window. The solid formulations administered through oral route are generally considered more convenient than other categories of drug delivery devices, *e.g.* more patients' compliance and a certain rate for the achievement of therapeutic drug concentration. In sustained release dosage forms, the minimal loss of drug is observed in gastrointestinal track (GIT) by presystemic metabolism as the rate of drug release is slow and compatible to the rate of drug absorption [1]. Numbers of sustained release formulations of different drugs are available in market but a special attention is given to microparticulate drug delivery devices due to their efficient volume to surface area ratio, small spherical size and retention to desired sites in body [2].

The performance of the formulation to achieve the desired goal of therapeutics is also governed by polymeric network. The polymeric carrier of natural origin such as gums, mucilage, resins, and latex have been extensively applied in development of conventional and modified drug delivery devices and draw a remarkable consideration due to their eco-friendly nature, low cost, safety, biocompatibility, and availability [3]. Isabgol husk, obtained from epidermal and collapsed adjacent layers removed from the seeds of *Plantago sps.* is well known for its enormous water holding capacity. It is widely used as herbal remedy in different diseases, *e.g.* ulcerative colitis, hemorrhoids, constipation, hypercholesterolemia, diabetes mellitus, colorectal cancer, *etc.* [4]. Besides these, the husk has also been used for the development of hydrophilic matrix and microparticulate system for different drugs [5]. Grafted Isabgol structure with polyacrylamide and polyacrylonitrile has also been reported for the use in flocculation study [6]. Alginates are naturally occurring polysaccharides obtained from marine brown-algae consisting of two monomeric units; β-D-mannuronic acid (M) and α-L-guluronic acid (G). These residues are arranged in homopolymeric blocks (GG, MM) and in heteropolymeric blocks

* Corresponding author. Tel.: +91 01334212144.
E-mail addresses: vipin@gkv.ac.in, sharmadibru@gmail.com, v_k05s@rediffmail.com (V.K. Sharma).

http://dx.doi.org/10.1016/j.ijbiomac.2014.02.014
0141-8130/

(MG). Sodium alginate exhibits gelling properties due to crosslinking of branched chain structure containing acidic contents with multivalent cations such as Ca^{++}, Ba^{++}, and Al^{+++}. The egg-box like junctions box formed after crosslinking are responsible for water retention capacity of sodium alginate hydrogel.

Gliclazide, an oral hypoglycemic drug of second generation sulfonyl urea is used for long term treatment of non-insulin dependent diabetes mellitus (NIDDM) [7]. It possesses good general tolerability, low incidence of hypoglycemia, and low rate of secondary failure [7]. However, the absorption rate of gliclazide from gastrointestinal tract is slow and varied amongst subjects. The time to reach plasma concentration (t_{max}) ranged from 2 to 8 h following a single oral administration of conventional tablet containing 80 mg of gliclazide [7]. The slow absorption is considered due to either hydrophobic nature or poor permeability of gliclazide across the gastrointestinal membrane [8]. Due to this, controlled release formulations of gliclazide are available in market. Hence, the present study was undertaken to assess the participation of Isabgol husk with sodium alginate in sustained release microparticles development for gliclazide. The impact of process variables was also studied on entrapment efficiency, *in vitro* release and other formulation related factors. Due to insoluble nature of gliclazide in water, aqueous ionic gelation-crosslinking technique was applied as an appropriate method for formulations development.

2. Materials and methods

2.1. Materials

Isabgol husk, as readymade herbal remedy was procured from local market (Sidhpur, Gujarat, India). Gliclazide was procured as gift sample from Comed Pharmaceuticals Ltd., Baroda. HPLC grade solvents such as methanol, water and acetonitrile were procured from Rankem, New Delhi. All other regents and chemicals were of analytical grade and applied as such without further purification and modification.

2.2. Methods

2.2.1. Development of gliclazide loaded microparticles containing Isabgol husk and Isabgol husk–sodium alginate by aqueous ionic gelation cross-linking technique [9]

The formulations of gliclazide were prepared by using Isabgol husk and sodium alginate in aqueous solution of various concentrations of calcium chloride as crosslinking agent. Gliclazide was added in polymeric dispersion of sodium alginate and Isabgol husk–sodium alginate and homogenized at 500 rpm at room temperature. The drug containing polymeric dispersion was added *via* 23-gauge needle-syringe into a gently agitated calcium chloride solution. The droplets instantaneously gelled into discrete, free flowing, brown colored spherical forms which were left for 30 min in cross-linker solution for curing and hardening. After curing, calcium chloride solution was decanted and each batch was washed three times successively with 500 mL distilled water for removing unreacted calcium chloride from the surfaces of spherical bodies and then, these were dried at 60 °C in hot air oven for 10 h. The effects of variables such as calcium chloride concentration and ratio of Isabgol husk to sodium alginate were studied on particle size, swelling behavior, drug entrapment efficiency, *in vitro* release, and release kinetics. In all formulations, 1:5 ratio of drug to polymer was maintained.

2.2.2. Determination of particle size

The particle size of formulations was measured microscopically by observing about 250–300 microparticles on a glass slide at 5×. The optical micrometer was calibrated previously by stage micrometer. The particle size distribution was also determined.

2.2.3. Determination of swelling capacity

The swelling behavior of formulations was assessed gravimetrically by taking initial dried weight and weight after swelling for 48 h in distilled water at room temperature on single pan electronic balance (least count of 0.1 mg). The swelling index of microparticles was calculated by following expression:

$$\text{Swelling index}\,(\%) = \frac{\text{Weight after sewelling} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (1)$$

2.2.4. Drug loading efficiency

In this study, a 50 mg of formulation was contained in 50 mL soaking media composing of 30 mL of phosphate buffer (pH 7.4) and 20 mL methanol taken in 50 mL volumetric flask for 48 h with occasionally shaking. After it, the microparticles were disintegrated in media for 30 min by ultrasonicator, crushed by pestle-mortar and then filtered through Whatman filter paper. After suitable dilution of filtrate, gliclazide content in diluted samples was analyzed at 227 nm. The quantification of gliclazide was performed by reverse phase high performance liquid chromatography (RP-HPLC) method (CE 4200, CECIL, UK) with UV detector. The mobile phase consisted of phosphate buffer (pH 3.4):acetonitrile (20:80, v/v) and the flow rate was set at 1 mL/min. The mobile phase was filtered through 0.45 μm membrane filter under vacuum and ultrasonicated before pumping into HPLC system. The drug entrapment efficiency was determined by following relation [9]:

$$\text{Drug entrapment efficiency}\,(\%) = \frac{\text{Practical drug content}}{\text{Theoritical drug content}} \times 100 \quad (2)$$

2.2.5. Surface morphological study

The surface morphology of the preparations was studied by scanning electron microscopy (ZIESS EVO 40EP, Carl Zeiss, Cambridge, UK). The surface structure of microparticles remained after dissolution was also observed to assess the impact of dissolution process on superficial texture of formulations.

2.2.6. Study of gliclazide release from microparticles

It was performed in basket type dissolution test apparatus (DR-08, Campbell Electronics, Mumbai) in triplicates for each formulation at 50 rpm. In this study, the applied dissolution media were distilled water, simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.4) maintained at 37.5 ± 0.5 °C. The sampling during dissolution was performed by withdrawing 5 mL at preset time interval, *e.g.* 0, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 300 and 480 min respectively, and the medium in dissolution vessel was replenished by pre-warmed medium to maintain the constant volume of it throughout the study. Gliclazide content was analyzed in samples after suitable dilution by determining absorbance at 227 nm by RP-HPLC method. The respective concentration of gliclazide was calculated from calibration curve obtained from pure sample of gliclazide. The dilution factor was used as a correction factor for determining the exact concentration of gliclazide in diluted samples.

2.2.7. Gliclazide release kinetics

The release mechanism of gliclazide from formulations in dissolution media was analyzed by zero order, first order, Korsmeyer–Peppas, Higuchi model, and Hixon–Crowell model and the following expressions were applied for determination of respective constants [10]:

$$\text{Zero order}: M_t = K_o t \quad (3)$$

$$\text{First order}: \log M_t = \log M_0 - \frac{K_1 t}{2.303} \quad (4)$$