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Preparation and Characterization of Sustained Release Anti-Diabetic Tablet by Using Natural Polymer

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ABSTRACT

Hyperglycaemia is the result of diabetes mellitus, which is a metabolic condition that is characterized by an inadequate generation of endogenous insulin, with or without resistance to the action of insulin. Type 1 diabetes mellitus is characterized by a failure in insulin production due to the destruction of the β cells of the pancreas. Patients with this condition require insulin treatment. On the other hand, type 2 diabetes can be characterized by defects in both insulin action (also known as insulin resistance) and insulin secretion, and it is associated with elevated basal hepatic glucose production due to the presence of insulin resistance. Gliclazide is a sulfonylurea of the second generation that is commonly recommended to treat type II diabetes. It has the ability to decrease the level of glucose in the blood of humans in an immediate manner by increasing the release of insulin from the pancreas inside the body. Altering the concentration of the guargum/ xanthan gum and carrageenan that was employed as a polymer allowed for the preparation of a variety of different formulations. From the perspective of the release pattern, the promising formulation was evaluated in comparison to the commercially available sample of sustained-release product. It was shown that increasing the concentration of the matrix tablet as well as the viscosity of the polymer resulted in a reduction in the release rate of gliclazide. It is possible that this is the result of greater swelling and a decreased rate of erosion experienced by the matrix tablet.

Keywords: *Gliclazide, Hyperglycaemia, Guargum, Xanthan gum, Carrageenan*

1. INTRODUCTION

In terms of medication administration, the oral route is the one that is used the most often. Although other methods of administration are used for the delivery of medications, the oral route continues to be the most popular form of administration. Patient acceptability, convenience of administration, correct dosage, cost-effective production process, and generally better shelf-life of the product are some of the reasons why the oral route has become so popular. Even when it comes to sustained release systems, the oral route of administration has been the one that has been researched the most. This is due to the fact that the oral route gives considerable flexibility in the design of dosage forms [1]. A steady-state blood level or tissue level that is therapeutically effective and non-toxic for a long length of time is the primary objective of therapy for many medications [2]. This is the aim from the beginning of the treatment process. Controlling the pace at which drugs are delivered, maintaining the length of therapeutic action, and/or directing the distribution of the medication to a specific tissue are the goals of the controlled release drug delivery systems [3]. Because they keep blood levels substantially constant and avoid fluctuations that are associated with conventional immediate-release formulations, such dosage forms not only increase patient compliance by reducing the frequency of dosing, but they also reduce the severity and frequency of side effects. This is because they maintain substantially constant blood levels [4]. Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It has been classified differently according to its drug properties in which based on its chemical structure, gliclazide is considered a first-generation sulfonylurea due to the structural presence of a sulfonamide group able to release a proton and the presence of one aromatic group [5]. On the other hand, based on the pharmacological efficacy, gliclazide is considered a second-generation sulfonylurea which presents a higher potency and a shorter half-life.2,3 Gliclazide belongs to the sulfonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release [6]. Medications in this class differ in their dose, rate of absorption, duration of action, route of elimination and binding site on their target pancreatic β cell receptor. Sulfonylureas also increase peripheral glucose utilization, decrease hepatic gluconeogenesis and may increase the number and sensitivity of insulin receptors. Sulfonylureas are associated with weight gain, though less so than insulin [7]. Due to their mechanism of action, sulfonylureas may cause hypoglycemia and

require consistent food intake to decrease this risk. The risk of hypoglycemia is increased in elderly, debilitated and malnourished individuals. Gliclazide has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control) [8]. The major objective of the present study is to design and evaluate gliclazide sustained release tablets employing synthetic and natural matrix forming polymers. As rate-controlling matrix formers, gliclazide SR tablets were designed using natural gum resins. One further purpose of the research is to evaluate and contrast the effectiveness of these four polymers in terms of their ability to delay the release of gliclazide in a controlled manner.

2. MATERIALS AND METHODS

Formulation of SR tablets:

The tablets prepared by direct compression method. Drug (gliclazide 20mg), guargum, xanthan gum, carragenan, and HPMC, Magnesium stearate and MCC used for formulation. The tablets were prepared by direct compression method. All ingredients sieved through #30 sieves. Magnesium stearate and MCC were sieved through #60 sieves before the use. All the materials were accurately weighed and blended using hand blender and wet granules were dried at 60°C for 2 h. The dried granules were passed through mesh#16 to break the aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh no. 60 onto dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi-station tablet-punching machine using flat-faced, round punches 4 mm in diameter [9].

Table 1: Various composition of sustained release tablets of gliclazide

F. Code	Drug (mg)	Guar gum (mg)	Xanthan gum (mg)	Carrageenan (mg)	HPMC (mg)	Magnesium stearate (mg)	Microcrystalline cellulose (mg)
GDT1	20	35	20	10	5	5	5
GDT2	20	30	25	10	5	5	5
GDT3	20	20	35	10	5	5	5
GDT4	20	35	20	7.5	7.5	5	5
GDT5	20	30	25	7.5	7.5	5	5
GDT6	20	20	35	7.5	7.5	5	5
GDT7	20	35	20	5	10	5	5
GDT8	20	30	25	5	10	5	5
GDT9	20	20	35	5	10	5	5

Pre-compression characterization: Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated for powder blend.

Flow properties: Flow properties depend on particle size, shape, porosity and density of the bulk powder. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Angle of repose: A weighed quantity of microspheres was passed through a funnel fixed on a stand at a specific height upon a graph paper. A static heap of powder with only gravity acting upon it was tending to form a conical mound. The height of the heap (h) and radius (r) of lower part of cone were measured and calculated.

$\theta = \tan\text{-}1h/r$

where θ = angle of repose, h = height of cone and r = radius of cone base

Carr's index: The Carr's index was evaluated for the flow ability of the powder by comparing the pour density and tapped density of microspheres and was calculated using:

Carr's index = $\{(\rho t\text{-}\rho b) \times 100\}/\rho t$

where ρb is bulk density and ρt is tapped density which was measured in a 10ml graduated cylinder and the number of tapings was 100 as it was sufficient to bring about a plateau condition. Carr's index less than 15 % gives good flow characteristics and above 25 % indicates poor flow characteristics

Hausner's ratio: Hausner's ratio (H), another index of flow ability, was calculated using:

$H = \rho t/\rho b$

A value < 1.2 is preferred for free flow; however, a value close to 1 indicates good flow properties [10].

Post Compression Evaluation

Weight variation: The average weight by more than the percent shown below and none deviates by more than twice that percent.

Hardness: Hardness of tablet is defined as the force required to break a tablet a in a diametric direction. A tablet was placed between two anvils. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing.

Friability: Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches and allowed to rotate for 100 revolutions. The difference in the weigh is calculated and the weight loss should not be more than 1%.

Thickness: The thickness of tablets was performed on 20 tablets from each formulation by using Vernier caliper.

Swelling index (%): Swelling ratio was determined using following equation:

Swelling Ratio (%) = $(A_t - A_0) / A_{tablet}*100$

A_t, weight of the tablet and basket at time t (g);

A_0, weight of the tablet and basket at the beginning (g);

A_{tablet}, weight of the dry tablet (g).

The prepared tablets were placed in the wire basket of six basket dissolution apparatus. The basket was immersed in a beaker containing 0.1 N HCl (900 ml) for 2 h and allowed to swell at 37 ºC. The tablets were removed and changes in weight were measured before and after swelling.

Percent Drug content estimation: Crushed 10 tablets from all batches in pestle-mortar and weighed equivalent 20 mg as drug dose using for single tablet was taken in volumetric flask (100ml) and dissolved in 0.1 N HCL (pH 1.2 phosphate buffer) and filtered. This solution was analyzed in UV spectrophotometer at λmax 225 nm [11].

in-vitro ex-vivo mucoadhesive strength: The mucoadhesive strength of the prepared tablet was determined by modified physical balance. The assembly consist of a modified double beam physical balance in which left sided pan is removed and attached with glass slide with an additional weight is added with slide to balance the weight of both the pan. Fresh intestine mucosa of goat was used as membrane obtained from local slaughter house and kept in kerb solution during transportation and 0.1 N HCl (pH 1.2 phosphate buffer) was use for moistening the mucosa. The underlying mucous membrane was separated by the help of surgical blade and tied with the glass slide with the help of thread. Now the tablet was made to stick with the wooden block and made contact with the mucous membrane and the tablet. The additional weight was increased on the right pan until the tablet detaches from the membrane and the weight used was noted as mucoadhesive strength in grams and force of adhesion was calculated.

in-vitro Dissolution study: In vitro dissolution study was carried out using USP type II (basket type) apparatus with 0.1N HCl (pH 1.2 phosphate buffer) as a dissolution medium. The temperature was maintained at 37 ± 0.5^0C with 50 rotations per minute. 1ml of aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were analysed for drug content at λ max 225 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported [12].

3. RESULTS AND DISCUSSION

Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated for powder blend. Sustained release tablets were prepared by the direct compression method, using HPMC, Guargum, Xanthan gum and carragennan as natural polymers. The effect of the nature of polymers was studied by preparing various formulations of swelling of adhesive tablets. In all these formulations, a constant amount of drug (20 mg) was maintained, and the prepared granules was initially characterized for flow properties and all other parameters. The different characterization as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio includes angle of repose (26.02), bulk density (0.174 g/cm^3), tapped density (0.173 g/cm^3), Carr's index (23.31 %) and Hausners ratio was found to be (1.18). The oral sustained release dosage form with prolonged residence time in the stomach helps in absorption of the drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper gastrointestinal tract. In the present study an attempt was made to develop a sustained release action properties tablet of gliclazide with variation of natural polysaccharide polymeric combination with adhesion properties at gastric mucosa. Such type of proposed formulations increases the gastric residence time, thus increase the bioavailability.

The other characterization includes thickness, hardness, friability, weight variation, drug content and in-vitro drug release. The thickness of all the tablets was in the range of 4.01 to 4.09 mm. The average weights of the entire prepared tablet were 240.17 mg to 240.71 mg which was within the specified limit. The hardness of all the formulated tablets was found to be in the range of 5.04 to 5.36 kg/cm^2. Friability was found to be 0.31 to 0.38 %. The preliminary and screening studies were performed using different polymers and the polymers guargum, xanthan gu, carragennan, promised excellent properties for controlled release and muco-adhesion. Using selected polymers, the final batches were prepared by direct compression method. The formulation GDT4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. The regression coefficient (r^2) value of various models was found to be non-fickinon drug release diffusion mechanism and followed supercase II transport mechanism respectively.

Table 2: Evaluation of sustained release tablets of gliclazide

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Swelling Index (%)	Percent Drug content (%)
GDT1	91.21±.49	4.09±.01	5.51±.11	0.36±.13	150.23±0.17	99.52±0.26
GDT2	89.17±.01	4.01±.02	5.54±.12	0.31±.16	159.55±0.28	99.08±0.18
GDT3	91.12±.02	4.06±.01	5.31±.13	0.38±.11	156.17±0.21	99.29±0.98
GDT4	90.19±.04	4.04±.01	5.04±.18	0.32±19	158.18±0.22	99.15±0.15
GDT5	91.21±.01	4.03±.03	5.14±.11	0.34±.17	157.62±0.03	98.65±0.14
GDT6	90.15±.05	4.01±.02	5.36±.10	0.38±.16	156.71±0.31	99.91±0.32
GDT7	91.11±.01	4.06±.03	5.25±.44	0.35±.17	157.58±0.11	99.16±0.44
GDT8	91.73±.03	4.09±.03	5.11±.27	0.32±.13	156.59±0.25	99.14±0.08
GDT9	90.21±.06	4.06±.02	5.10±.21	0.34±.13	156.25±0.19	101.32±0.16

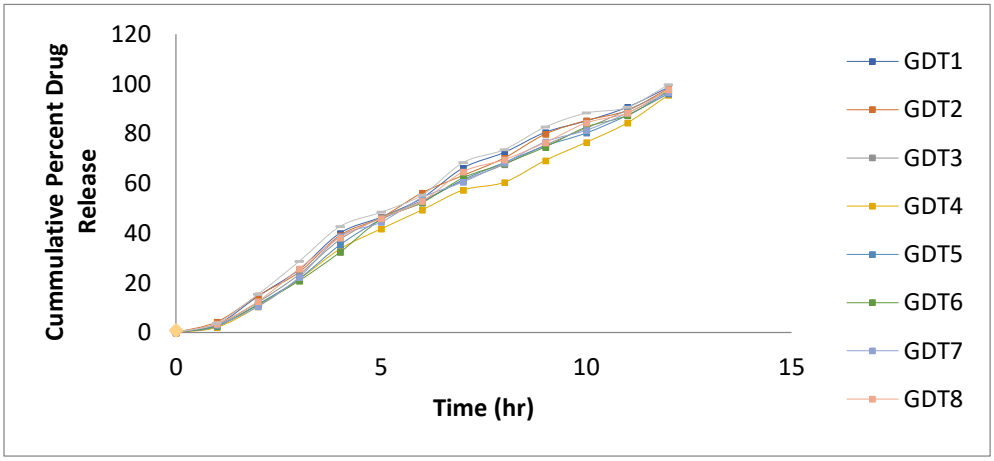

Figure 1: Zero-order kinetic plot of the prepared sustained release tablets of gliclazide (GDT1 - GDT9)

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