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Research Article

Formulation and Evaluation of Floating Microspheres of Glibenclamide Using Muco-Adhesive Polymers by Ion Gelation Method

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Abstract

The aim of the research work was to formulation and evaluation of sustained release microspheres of glibenclamide utilization of various muco-adhesive polymers by ion gelation method. Various polymers like HPMC (GM1), Chitosan (GM2), Methyl-cellulose (GM3), Sodium carboxy methyl-cellulose (GM4), Guar-gum (GM5) and Poly-ethylene glycol (GM6) were used to entrap the drug in proportion of 1:1. Various process variables parameters like rate of stirring, effect of temperature, effect of drug to polymer ratio were analyzed. The in vitro release studies were Sample GM1 and sample GM2, showed better yield and entrapment efficiency while sample GM3 and GM4, showed maximum swelling index and sample GM6 muco-adhesion. Sample GM3 (95.2%) and GM4 (90.9 %) methyl cellulose and sodium CMC respectively as mucoadhesive polymer and they showed maximum release of the drug and sustained the effect from 7 hrs onward release. Such formulations followed zero order kinetic and were stable.

Keywords: *Ion gelation method, Sustained release, Muco-adhesive polymers Glibenclamide.*

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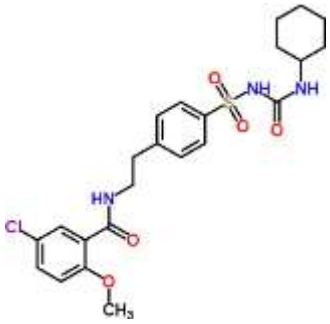
INTRODUCTION

For any drug therapy to be successful, the drug must reach the site of action or systemic circulation in optimum concentration and should be maintained for desired period of time. Therapeutic response of the drug also depends on the pharmacokinetics of the drug in an individual patient and frequency of dosing. Many acute and chronic diseases require frequent medication. Drugs with short half-life also require frequent dosing to maintain their concentration in the systemic circulation. But with frequent dosing, some problems may arise like patient non-compliance to the prescribed drug regimen, particularly in case of chronic treatment or in the treatment of a silent disease such as hypertension. As the drugs are given repeatedly, there may be accumulation which leads to toxicity. In such circumstances, the problem can be solved by developing new drug or dosage form like prolonged release dosage form with similar therapeutic response as that of conventional dosage forms and longer duration of action. [1]

This multiple dosing would give rise to a number of problems, which can be overcome by sustained release drug formulations. Wide ranges of probable methods are available for the development of controlled release dosage form, micro-encapsulation being one of them. The concept of micro-encapsulation has been developed to an unimaginable extent since its introduction for manufacturing carbonless copy paper and later photosensitive paper [2-4]

Floating drug delivery system have a bulk density less than gastric fluids (less than 1.004 g/ml) and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration [5-7]

Glibenclamide (INN), also known as glyburide (USAN), is a second-generation sulfonylurea antidiabetic agent with a potent and prolonged hypoglycemic effect. It is used an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II diabetes) [8].



Glibenclamide is a specific oral hypoglycemic agent. It exhibits its activity through stimulation of β-pancreatic cells which increases the amount of insulin. It is non soluble in water and can be solubilized in acetonitrile by adding co-solvents such as PEG400 or 600. It is well absorbed after oral administration. Its half-life is up to 2 hrs .

In the present investigation, an extended and sustained release microspheres of Glibenclamide prepared by ethyl cellulose was used as the polymer due to its water insolubility, which will help in sustaining the drug release

for a longer time without increasing the polymer concentrationin the formulations. Also, ethyl cellulose has used successfully to produce floating microspheres by various investigators [9,10]. The prepared microspheres were evaluated for size, in vitro drug release, buoyancy, and incorporation efficiency. The effect of various formulation variables on the size and drug release was investigated [11].

MATERIAL AND METHODS

Glibenclamide was obtained as gift from Morepan Lab., Pravanu, Ethyl cellulose was received from Thomas Baker, Mumbai, India.

Method

The required quantity of sodium alginate was dissolved in 30 ml distilled water and to this mucoadhesive polymer was added. The calculated quantity of the drug was added and homogenized. A 5% w/v solution of Calcium chlorides dehydrate was prepared in distilled water (50 ml) solution. The drug alginate and muco-adhesive polymer mixture were added to the calcium chloride solution drop wise at a constant rate of 30ml/hr with gentle stirring (150 rpm) over thermal controlled magnetic stirrer. Curing was allowed for 5 min and the product formed was filtered, dehydrated with acetone and air dried for 12 hrs followed by drying in oven at 35ºC for 2 hrs. The dried formulations were stored in an amber colored bottle and kept in desiccator until used. (Table 1).

Evaluation

Size analysis and distribution

The mean particle sizes of the microspheres were determined by sieving method. Microspheres were separated into different size fractions by sieving for 103 minutes using mechanical sieve shaker containing standard sieves as per Indian Pharmacopeia specifications. Mean particle size was calculated by using the following formula [12]

$$\text{Mean particle size} = \frac{\Sigma \text{ (Mean particle size of the fraction x weight fraction)}}{\Sigma \text{ (Weight fraction)}}$$

Morphology study of mucoadhesive alginate microspheres

The mean diameter of 50 dried mucoadhesive alginate microspheres and morphological examination were performed using optical microscopy. Glibenclamide–mucoadhesive polymer microspheres were prepared by ion gelation method. Small size and round shaped microspheres were produced. [13] (Table 2).

Swelling Index

Swelling index was determined by measuring the extent of swelling of microspheres in a 7.4 pH phosphate buffer. An accurately weighed amount of microspheres were allowed to swell in the buffer to ensure complete equilibrium. The excess surface adhering liquid drops were removed by blotting paper and the swollen microspheres were weighed using microbalance. The hydrogel microspheres were then dried in an oven at 60º C for 5 hrs until there was no change in the dried mass of the sample. The swelling index of the microspheres was calculated by using the formula [14].

$$\textbf{Mass of swollen microspheres} = \frac{\textbf{Mass of dry microspheres/ x 100}}{\textbf{Mass of dried microspheres}}$$

Mucoadhesive property

Approximately 100 microspheres were taken and spread uniformly over a wet glass slide, which was held to the walls of the beaker with glue. The prepared assembly was then introduced into the USP disintegration apparatus. Number of microspheres still adhering to the glass slide was counted at regular intervals and assessed for the muco-adhesive nature of the microspheres. All the readings were taken in triplicate and results depicted as ± S.D [15]

Percentage yield

The percentage yield of the microspheres was calculated for each batch by dividing the weight of microspheres by the total weight of drug and polymer [16].

Percentage Yield= Practical yield/Theoretical yield x 100

In vitro release

A. Glibenclamide standard plot prepared in Methanol

Glibenclamide (10 mg) was dissolved in 100 ml of methanol. Then suitably diluted for graded solutions in range of 1-35 µg/ml. The absorbance was read using a spectrophotometer at λ max 231 nm. (Table 3, Figure 1)

The spectra of FTIR (Figure 2) show that the sample used was glibenclamide and no interference with drug and excipients.

B. Microspheres i*n vitro* release

In-vitro release studies of the microspheres were carried out in 200 ml of buffer dissolution medium contained in a glass diffusion cell agitated at 100 rpm and temperature maintained at 37 ± 0.5 º C by buffer change method.

The classification is the basis for setting *in vitro* dissolution specifications. The solubility of a drug is determined by dissolving the highest unit dose in 250 ml of buffer adjusted between pH 1.0 to 8.0 At pre-set time intervals; 5 ml of aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. The aliquots were analyzed by UV spectrophotometrically at λ max 231 nm for glibenclamide after proper dilutions (Table 4, Figure 3).

Differential Scanning Calorimetry (DSC) of Glibenclamide formulations

Differential Scanning Calorimetry was carried out to determine the interaction between glibenclamide and polymers. No interactions were observed. Individual peaks of the polymers were present in Differential Scanning Calorimetry thermograms. Extra peaks were of the impurities or solvent residues in the formulations (Figure 4).

Glibenclamide formulations Stability studies

For countries in Zone III, the stability specifications as per ICH are 30 ± 2ºC and 35 ± 5% RH. The some selected formulations were kept in at room temperature 25 ± 2ºC, freezing between 5 ± 2ºC and an oven at 40 ± 2ºC125. Samples were withdrawn every 15 days and analyzed for total drug content and *in vitro* release characteristics. [17-19]

RESULT AND DISCUSSION

The surface of microspheres showed presence of drug particles when the concentration of the polymers was low, while higher proportions of the polymer resulted in, smother surface of the formulated microspheres.

Microspheres of Glibenclamide, using sodium alginate (primary polymer) and different muco-adhesive polymers (secondary polymer) like- HPMC, chitosan, methyl cellulose, sodium CMC, guar gum and PEG in -1:1, were prepared by

orifice-ionic gelation method. Microsphere with only muco-adhesive polymer could not be prepared because of their hydrophilic nature. The formulated microspheres were spherical, discrete and free flowing in nature. A monolithic matrix nature was observed.

Low coefficient variation of polymers in proportion of 1:1 in percent yield and entrapment indicates the uniformity of drug content in each batch of formulations. The yield was in the range of 77% to 93% and the entrapment was in the range of 70% to 86%. The topographical features of the products depended on the type of polymer used. The polymers selected were water soluble polymer which shows faster hydration and swells in contact with water 20% to 30%. The muco-adhesive property of formulated microspheres was satisfactory 45% to 89%. Swelling index and muco-adhesiveness was different for different polymer. The yield was maximum in case of Chitosan (GM2). (Table 2)

Percent yield (maximum to minimum) Chitosan (GM2)> Hydroxy poly methyl cellulose (GM1) > sodium carboxy methyl cellulose (GM4) > Guar gum (GM5)> Methyl cellulose (GM3)> Poly ethylene glycol (GM6). The size of the microspheres was dependent on the nature of the polymers used.

The release profile of methyl cellulose blended microspheres showed maximum release (GM3 95%) (Table 4 Fig. 3) The faster release of the drug from the formulations is an index of faster penetration of water into the system [20]. Different grades of polymers show different pattern in drug release and absorption [21]. Polymers like HPMC and sodium CMC resulted in thicker gel formation and the release of the drug appears to start from this gel system. Once, the protective gel layer is formed, two different mechanisms play a role: (a) The pseudo gel permits additional water to penetrate into the device, extending the gel layer into the microspheres, and (b) the outer gel layer fully hydrates and gets dissolved by the dissolution fluids [22].

The release was in the order of GM3 (Methyl cellulose)>GMP4 (Sodium carboxy methyl cellulose)>GM1 (HPMC)>GM6 (Polyethylene glycol)>GM2 (Chitosan)>GM5 (Guar gum) (Fig. 3)

Table 1: The formulation prepared by Ionic gelation method for drug glibenclamide

Mucoadhesive alginate microspheres						
Code	**Drug**	**Sodium alginate**	**Mucoadhesive polymers**	**Distilled water**	**CaCl2 (5%)**	**D:P**
GM1	100 mg	+	+	30 ml	100 ml	01:01
GM2	+	+	+	+	+	01:01
GM3	+	+	+	+	+	01:01
GM4	+	+	+	+	+	01:01
GM5	+	+	+	+	+	01:01
GM6	+	+	+	+	+	01:01

Table 2: Physicochemical properties of the glibenclamide mucoadhesive alginate microspheres

Glibenclamide mucoadhesive alginate microspheres						
Code	**Yield (%)**	**Entrapment (%) ± S.D**	**Shape**	**Color**	**Swell. Index (%)**	**Mucoadhesive property (%) ± S.D**
GM1	91.2	86.1±0.10	spherical	White	21.1	45.3±2.2
GM2	92.5	88.2±0.11	spherical	Pale	19.7	61.2±0.9
GM3	83.5	78.2±0.14	spherical	White	36.3	65.1±1.7
GM4	88.2	82.2±0.15	spherical	Buff	30	75.4±1.4
GM5	82.5	83.7±0.10	spherical	Light brown	26.9	77.3±1.3
GM6	77.1	70.4±0.08	spherical	White	28.8	89.1±0.8

Table 3: Standard curve of pure Glibenclamide in methanol.

S.NO.	Concentration (µg/ml)	Absorbance at 231 nm
1	0	0
2	5	0.117
3	10	0.275
4	15	0.423
5	20	0.612
6	25	0.714
7	30	0.844
8	35	0.994

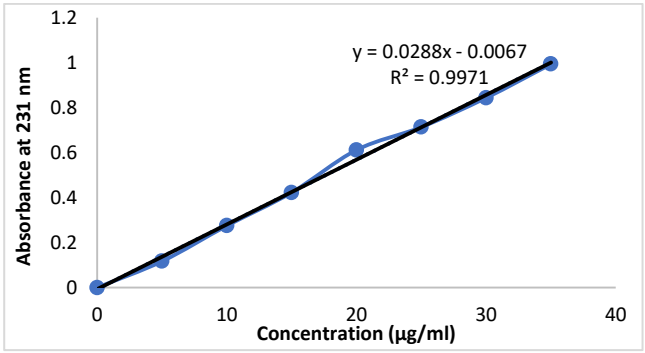


Figure 1: Glibenclamide Standard curve in methanol

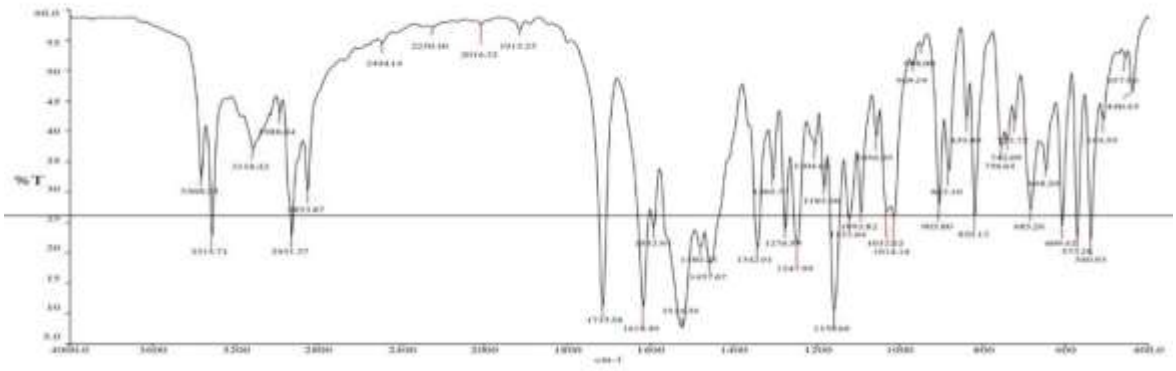


Figure 2: FTIR Spectra of Glibenclamide

Table 4: *In-vitro* release kinetic equation data of glibenclamide mucoadhesive alginate microspheres

Code	Zero order	First order	Higuchi	Korsmeyer Peppas
	R_0	R_1	R_H	R_K
GM1	0.998	0.987	0.986	0.995
GM2	0.977	0.972	0.978	0.992
GM3	0.974	0.952	0.983	0.991
GM4	0.985	0.954	0.967	0.983
GM5	0.98	0.988	0.982	0.989
GM6	0.989	0.969	0.979	0.99

R=Regression coefficient

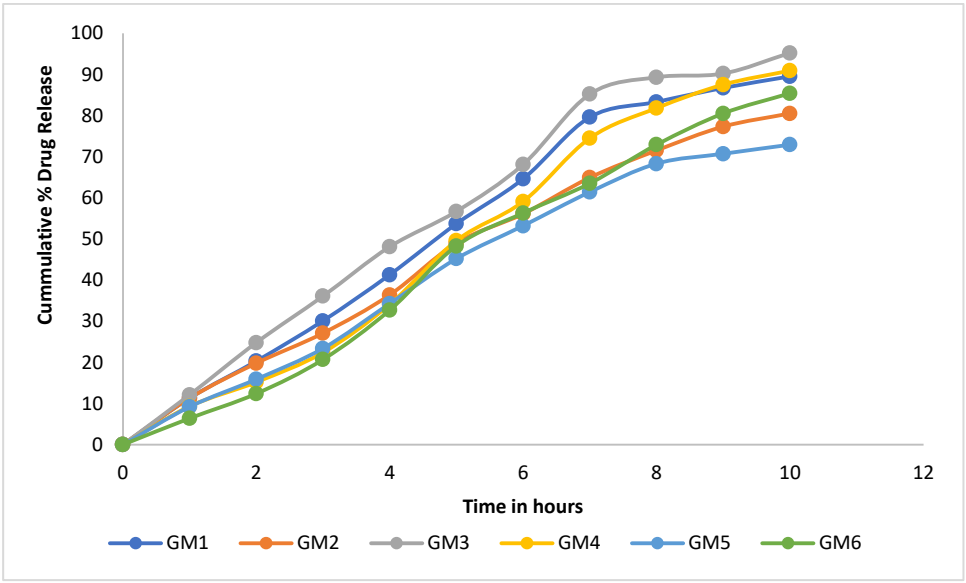


Figure 3: *In-vitro* release profile for formulation *GM1-GM6*

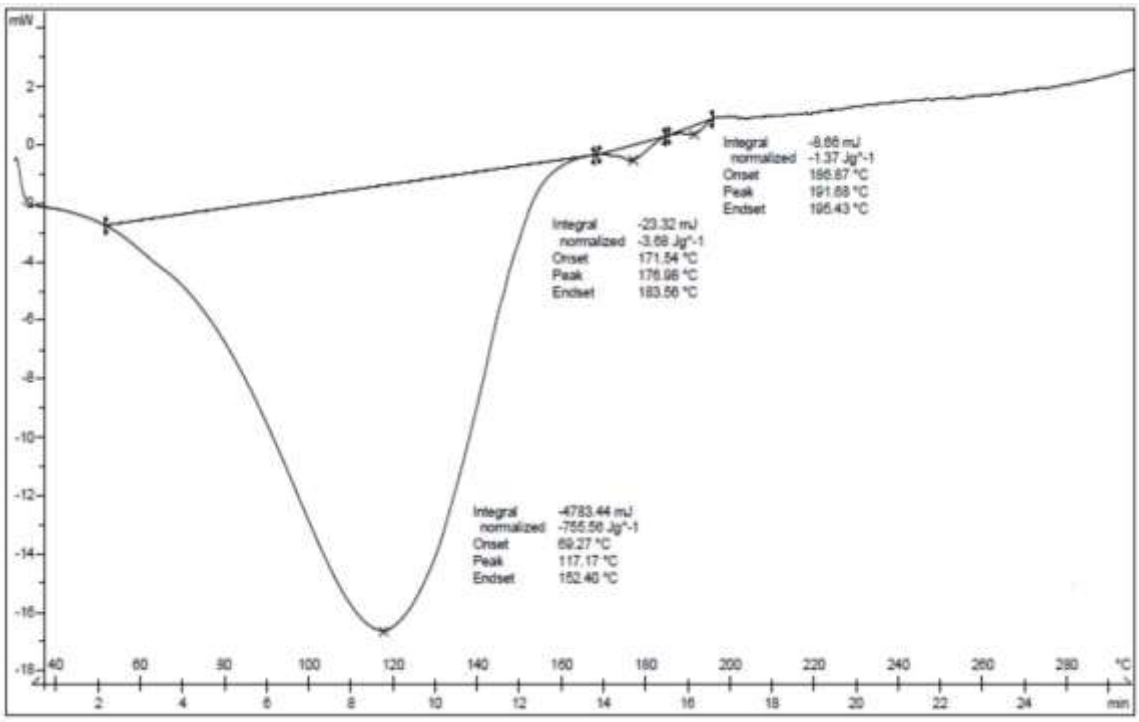


Figure 4: Differential Scanning Calorimetry thermogram of Glibenclamide + Mucoadhesive polymer.

CONCLUSION

In these formulated muco-adhesive microspheres, the adhesiveness was less in the intestinal pH as compared to gastric acidic pH. Recent advances in polymer sciences and drug carrier technologies have promulgated the development of novel drug carriers such as bio-adhesive microspheres that have boosted the use of bio-adhesion in drug delivery

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