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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF GLIPIZIDE HOLLOW MICROBALLOONS FOR FLOATING DRUG DELIVERY

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The present investigation was aimed to formulate and evaluate the gastro-retentive floating microballoons of glipizide using hydrophilic polymers hydroxypropyl methylcellulose (HPMC) and Eudragit RS100 (RS 100) by emulsion solvent evaporation technique. The floating microballoons were evaluated using micromeritic properties, buoyancy, *in vitro* drug release, scanning electron microscopy and stability studies. The densities of floating microspheres (0.475-0.975 g/cm^3) were found to be less than the density of gastric fluid (1.004 g/cm^3), therefore showed an extended floating time of more than 12 h over the gastric fluid. The entrapment efficiency of prepared floating microspheres was satisfactory (41.32-76.19%). The scanning electron microscopy confirmed the hollow nature of microspheres with pores on the surface which imparted floating properties to the prepared floating microballoons. Among all formulations, F4 (Drug:HPMC:RS 100::1:4:3) was found to be the best as it exhibited highest drug release (99.12%) in 12 h followed by diffusion mechanism and was stable for three months at ambient conditions.

Key words: Hollow microballoons, Glipizide, Sustained release, Floating drug delivery.

INTRODUCTION

Floating Drug Delivery Systems (FDDS) are among the several approaches that have been developed in order to increase the gastric residence time of dosage forms. Both single and multiple unit systems have been developed. Drugs that are easily absorbed from the gastrointestinal tract and have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained-controlled release formulations have been developed in an attempt to release the drug slowly into the gastro-intestinal tract and maintain an effective drug concentration in the blood over long period of time. However, such oral drug delivery devices have a physiological limitation of low gastric retention time. Variable and short gastric emptying time can result in incomplete drug release from the drug delivery system in the absorption zone (stomach or upper part of small intestine), leading to diminished efficacy of the administered dose (Shinde and More, 2008; Singh *et al* 2009; Nayak *et al* 2010). To overcome these limitations, approaches being proposed to prolong the gastric residence time, include floating drug delivery systems, swelling or expanding systems, mucoadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices (Ma *et al* 2008).

Floating drug delivery is of particular interest for drugs that (1) act locally in the stomach, (2) are primarily absorbed in the stomach, (3) are poorly soluble at an alkaline pH, (4) have a narrow window of absorption, and (5) are unstable in the intestinal or colonic environment (Jain *et al* 2006). To provide good floating behavior in the stomach, the density of the

device should be less than that of the gastric contents (≈1.004 g/cm^3).

Glipizide is an effective anti-diabetic drug particularly in Type II diabetes (non-insulin dependent diabetes mellitus). It is a second generation sulfonylurea that actually lowers the blood glucose level in human by stimulating the pancreatic cell and thereby releasing the insulin. It has a short biological half-life of 2-5 h, which make it more suitable to be designed as a controlled release formulation. Therefore, present research work was undertaken to develop floating drug delivery system of glipizide for peroral administration using HPMC and Eudragit RS 100 polymers in order to increase its biological half-life and to determine the influence of formulation variables on drug release and other properties.

MATERIALS AND METHODS

Materials

The Eudragit RS 100 (RS 100) and hydroxypropyl methylcellulose (HPMC) were purchased from the Ponmani labs, Coimbatore. Glipizide (GLP) was supplied as a gift sample by Micro labs, Hosur. All other chemicals used were of analytical reagent grade.

Methods

Fourier Transform Infra-red Spectroscopy (FT-IR) analysis

The FT-IR analysis was conducted for the analysis of drug polymer interaction and stability of drug during formulation process (Gupta *et al* 2007). FT-IR spectra of pure GLP, RS 100, HPMC, physical mixture and floating microspheres (formulation) were recorded using Shimadzu 8700 FTIR spectrophotometer.

Preparation of floating microspheres

Floating microballoons containing Glipizide was prepared using emulsion solvent diffusion technique (Sato *et al* 2004). The drug to polymer ratio used to prepare the different formulations was 1:7. The polymer content was a mixture of RS 100 and hydroxypropyl methylcellulose. The drug polymer mixture was dissolved in a mixture (16 ml) of dichloromethane (DCM) and ethanol (1:1). The mixture was dropped in to 0.75% polyvinyl alcohol solution (200 ml) and the resulting solution was stirred with a propeller-type agitator at 300 rpm and 40°C for 1 h. The floating microballoons formed were screened (#12), washed with water and dried at room temperature in a desiccator (**Table 1**).

Table 1. Composition of microballoons

Formulation Code	Glipizide (g)	RS 100 (g)	HPMC (g)
F1	0.1	0.7	0.0
F2	0.1	0.6	0.1
F3	0.1	0.5	0.2
F4	0.1	0.4	0.3
F5	0.1	0.3	0.4
F6	0.1	0.2	0.5
F7	0.1	0.1	0.6
F8	0.1	0.0	0.7

Evaluation of microballoons

Determination of density and true density

The true density of floating microspheres was determined by liquid displacement method using *n*-hexane as solvent (Lachman *et al* 1976; Manavalen and Ramasamy, 2001). First, weight of pycnometer was noted (a) and then 25 ml of *n*-hexane was added and weight was noted (b). The pycnometer was emptied and weighed amount of floating microspheres was added net weight was noted (c). Now *n*-hexane was added to occupy the void spaces within the floating microspheres until and floating microspheres *n*-hexane together occupied the volume *i.e.* 25 ml. Again weight was noted (d) and then true density was calculated according to following formula:

$$\text{Density of liquid } (\rho) = \frac{b-a}{25}$$

$$\text{True density} = \frac{c-a}{25-\left[\frac{d-c}{\rho}\right]}$$

Percentage yield

The percentage yield of different formulations was determined by weighing the hollow microspheres after drying. The percentage yield was calculated as follows:

$$\% \text{ yield} = \frac{\text{Total weight of hollow microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

Particle size analysis

The particle size analysis of floating microspheres was carried out using an optical microscope, and the mean particle size was calculated by measuring nearly 200 particles with the help of a calibrated ocular and stage micrometer.

Buoyancy study

Microballoons (100 mg) were placed in 0.1 N HCl (300 ml) containing 0.02% Tween 20 and stirred at 100 rpm. The layer of buoyant microballoons was pipetted and separated by filtration at 1, 2, 4 and 6 h. The collected microballoons were dried in a desiccator over night. The percentage of microballoons was calculated by the following equation:

$$\% \text{ yield} = \frac{\text{Weight of hollow microsphere}}{\text{Initial weight of hollow microsphere}} \times 100$$

Drug Entrapment Efficiency

Ten mg of hollow microspheres from all batches were accurately weighed and crushed. The powdered microspheres were dissolved with 10 ml ethanol in 100 ml volumetric flask and volume was made up with 0.1 N HCl. The resulting solution is then filtered (Whatmann filter paper No. 44), suitably diluted and the absorbance was measured at 276 nm against 0.1 N HCl as blank (Sato *et al* 2003). The percentage drug entrapment was calculated as follows:

$$\% \text{ drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Determination of tapped density, compressibility index and angle of repose

Tapped density:

Tapped density of hollow microspheres was determined by the tapping method (Manavalen and Ramasamy, 2001). Accurately weighed quantity of hollow microspheres was transferred in to a 10 ml measuring cylinder. After observing the initial volume of floating microspheres, the tapping was continued on a hard surface until no further change in volume was noted and the tapped density was calculated according to following formula:

$$\text{Tapped density} = \frac{\text{Mass of hollow microspheres}}{\text{Volume of hollow microspheres after tapping}}$$

Compressibility index:

$$\% \text{ Compressibility index} = \left[1 - \frac{V}{V_0}\right] \times 100$$

where V and V_0 are the volumes of the sample after and before the standard tapping respectively. Each determination was made in triplicate.

Angle of repose:

The angle of repose of hollow microspheres was determined by fixed funnel method. The hollow microspheres were allowed to fall freely through a funnel until apex of conical pile just touched the tip of the funnel. The angle of repose ϕ was determined according to the following formula:

$$\phi = \tan^{-1} h/r$$

where, h = height of pile, r = radius of the pile formed by the hollow microspheres.

In vitro release studies

The study of drug release rates from floating microballoons were carried out using USP type II dissolution paddle assembly (Sato *et al* 2004). Floating microballoons equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCl pH 1.2 maintained at 37±0.5°C and stirred at 100 rpm. Five ml sample was withdrawn at predetermined intervals while replacing equal amount of fresh dissolution medium. The samples were filtered, suitably diluted and analyzed spectrophotometrically at 276 nm to determine the concentration of drug present in the dissolution medium.

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The dissolution data of all the formulations was fitted to zero order, Higuchi matrix and Korsemeyer-Peppas to ascertain the kinetic modeling of drug release (Costa and Sausa Lobo, 2001; Kuksal *et al* 2006; Mehrgan and Mortazavi, 2005). The value of 'n' gives an indication of the release mechanism. When n = 1, the release rate is independent of time (typical zero order release / case II transport); n = 0.5 for Fickian release (diffusion/ case I transport); and when $0.5<n<1$, anomalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when $n>1.0$ super case II transport is apparent.

'n' is the slope value of log M_t/M_∞ versus log time curve.

Scanning electron microscopy

The surface morphology of microballoons was examined using scanning electron microscope (JEOL, JSM-670F Japan). Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 3.0 KV during scanning. Microphotographs were taken on different magnification and higher magnification (500X) was used for surface morphology.

In vivo anti-diabetic study

In vivo evaluation of glipizide floating microballoons were performed on best selected formulation using normal healthy Wistar rats weighing 250-300 g each (Patel *et al* 2005). The approval of the Institutional Animal Ethics Committee was obtained before starting the study (NCP/IAEC/PG/08/2008-2009) and the study was conducted in accordance with standard institutional guidelines. Two groups of Wistar rats (5 in each group) that were fasted with free access to water for at least 12 h before the experiments. Before drug administration, a blood sample as a control was taken from each rat from behind the eyeball through the angle of ocular cavity using small capillary tubes. The blood glucose level for the control and test samples was determined using glucometer (Abbott Laboratories, Bedford, MA). The instrument was self-calibrated, and the samples were allowed to dry before the results were read to avoid contamination of the lens. Pure glipizide and floating microballoons of glipizide were administered orally to each group using stomach intubations. A dose of 800 mg/kg of glipizide was administrated in a suspension form (freshly prepared) for each rat. Blood samples were collected at predetermined time at 1 h intervals up to 24 h, and the blood glucose level was performed as described above. The percentage reduction in blood glucose level was measured and recorded.

Stability study

From the prepared floating microballoons, best formulation was selected on basis of buoyancy and the percentage drug released (Prakash *et al* 2007). The selected formulation was placed in borosilicate screw capped glass containers and stored at different temperatures (27±2°C), oven temperature (40±2°C) and in the refrigerator (5-8°C) for a period of 90 days. The samples were assayed for drug content at regular intervals.

RESULTS AND DISCUSSION

FT-IR spectra of Glipizide, Eudragit RS 100, HPMC, physical mixture of drug and polymers were recorded. The Glipizide present in the formulation F4 was confirmed by FT-IR spectra. The characteristic peaks due to pure Glipizide at 3250.16, 2943.47, 1689.70, 1651.12, 1373.36, 1159.26, 686.68 for N-H stretching, C-H stretching, C=O stretching, -CONH- stretching, C-H bending, S=O stretching, C-H bending respectively. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Glipizide and polymer. The study suggested that glipizide can be used with RS100 and HPMC.

The hollow microspheres of glipizide were successfully prepared using RS100 and HPMC as a polymer by emulsion–solvent diffusion method. Mean particle size range was varied from 609 to 874 μm and was found to be affected by change in drug and polymer ratio. If sizes of microballoons are less than 500 μm, release rate of drug will be high and floating ability will reduce, while microbaloons ranging between 500μm-1000μm, the floating ability will be more and release rate will be in sustained manner. All the formulations showed satisfactory entrapment efficiency ranging in 41.32 to 76.19% (**Table 2**) and its efficiency slightly decreased with increasing the HPMC content. When the distribution coefficient was high efficiency of drug entrapment into microballoons was elevated. This phenomenon was due to the lack of retention of drugs with low distribution coefficient in the emulsion droplet aqueous solution during the process, which led to reduced entrapment of drug into microballoons.

Table 2. Drug entrapment efficiency of prepared formulations

Formulation	% Drug entrapment
F1	76.19
F2	70.59
F3	66.23
F4	64.76
F5	61.01
F6	57.38
F7	48.47
F8	41.14

Density values for all formulations were less than that of gastric fluid (1.004 g/cm^3), suggesting that they exhibit good buoyancy. Buoyancy of the microballoons decreased with increasing drug release. The floating ability pattern differed according to the formulation tested and medium used. F4 showed the best floating ability in 0.1 N HCl, as evidenced by the percentage of particles floated at different time intervals. This can be mainly due to its low bulk density value obtained before and after tapping respectively. All formulations showed excellent flowability as represented in the terms of angle of repose (<40°) and compressibility index (<1.2). SEM study suggested that hollow microballoons were found to be spherical in shape with smooth surface texture. The photomicrograph also indicated presence of small cavity in microballoons which may be due to solvent evaporation during drying process. The microballoons remained buoyant for prolonged time over the surface of the dissolution medium without any apparent gelation, which might be responsible for good floating property. SEM surface morphology of formulation F4 exhibited smooth surface of floating microballoons (**Figure 1**).

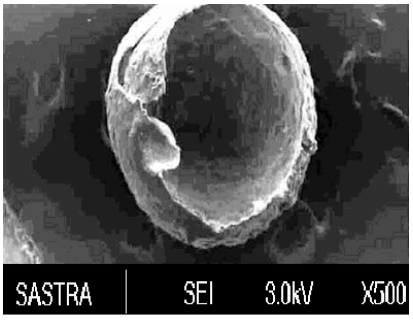

Fig. 1. SEM photomicrograph of F4

Ideal property of hollow microspheres includes high buoyancy and sufficient release of drug in pH 1.2. Percent drug release rate of F1, F2, F3 formulations (43.791%, 56.311%, 78.809% respectively) in 12 h, which is slow and incomplete. In order to increases the percent drug release rate, the ratio of RS100 and HPMC is decreased and increased respectively. F5, F6 formulations showed high release rate (94.681%, 97.348%) in 10 h and F7, F8 formulations showed high release rate (96.295%, 95.329%) in 12 h, with less buoyancy. F4 formulation showed appropriate balance between buoyancy and drug release rate of 99.12% in 12 h, which is considered as a best formulation (**Table 3**).

Table 3. Summary of buoyancy study of formulations

Formulation	1 h	2 h	4 h	6 h
F1	98.41	97.08	93.23	91.47
F2	98.11	95.58	92.17	87.34
F3	98.54	95.64	85.34	78.45
F4	99.54	92.49	80.57	72.97
F5	98.72	91.95	73.49	66.12
F6	98.45	86.62	65.14	57.76
F7	88.34	75.41	56.04	45.09
F8	81.51	67.23	52.20	36.18

Percentage drug release for the formulations F1, F2, F3 (43.791%, 56.311%, 78.809%) in 12 h, is slow and incomplete drug release. In order to increases the percentage drug release, the ratio of RS100 and HPMC is decreased and increased respectively. F5, F6 formulations showed high release rate (94.681%, 97.348%) in 10 h and F7, F8 formulations showed high release rate (96.295%, 95.329%) in 9 h, with less buoyancy. F4 formulation showed appropriate balance between buoyancy and drug release rate of 94.68% in 12 h, which is considered as a best formulation.

Drug release pattern was evaluated in 0.1 N HCl and phosphate buffer pH 1.2. Release rate of F1, F2, F3 formulations were found to be slow and incomplete in both dissolution medium. It was found that drug release rate increased by decreasing and increasing the ratio of RS100 and the HPMC respectively (**Figure 2**).

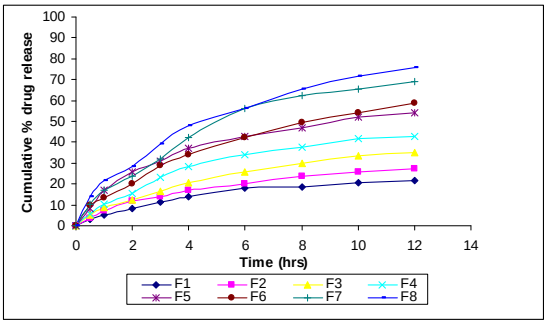

Fig. 2. Comparative drug release profiles of formulations zero order kinetics.

Kinetics and mechanism of drug release from all formulation was evaluated on the basis of zero order, Higuchi equation and Peppas model. Correlation coefficient (r^2) and slope value for each equation in the range of (r^2=0.752-0.937 and n=0.568-0.785 for Peppas model. Zero order plots for all formulations were found to be linear in acidic and buffer solution of pH 1.2 which indicates that it may follow zero order kinetics.
Higuchi plot was found to be linear, which indicates diffusion may be the mechanism of drug release for each formulation. Peppas plot was found with good linearity, its n>0.5 for all formulations, indicating that drug release may follow anomalous diffusion (range=0.993-0.998).

Zero order plots for F4 formulation was found to be linear in both dissolution medium, and is considered as a best fit for drug release. That indicates it may follow zero order mechanism. The *in vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism. The *in vitro* release data was applied to various kinetic models to predict drug release kinetic mechanism. The zero order plots for all formulation were found linear in acidic and buffer medium pH 6.8. Result shows that, drug release rate may follow zero order mechanism. Higuchi and Peppas plot was found good linear, which indicates diffusion may be mechanism of drug release and n>0.5 indicated drug release may follow anomalous diffusion (**Table 4**).

Table 4. Summary of model fitting data of formulations

Formulation	Zero Order		Higuchi Equation		Peppas Equation	
	r^2	K_0	r^2	K_H	r^2	n
F1	0.950	1.81	0.989	6.946	0.937	0.756
F2	0.954	2.08	0.998	8.141	0.817	0.785
F3	0.963	2.86	0.994	11.04	0.872	0.769
F4	0.948	3.49	0.996	13.66	0.835	0.634
F5	0.930	4.03	0.993	16.09	0.752	0.664
F6	0.964	4.68	0.996	18.08	0.822	0.612
F7	0.956	5.80	0.998	22.42	0.833	0.581
F8	0.954	5.85	0.997	22.86	0.759	0.568

In stability study, there was no remarkable change in content of F4 formulation during 90 days in which it was stored at various temperatures. Stability study was carried out for the F4 formulation by exposing it to 5-8°C, 27°C and 40°C for 3 months. The sample was analyzed for drug content at regular intervals. There was no remarkable change in content of F4 formulation during 90 days in which it was stored at various temperatures (**Table 5**).

Table 5. Summary of stability study data

S. No.	Days	% Entrapment efficiency (5-8°C)	% Entrapment efficiency (27±2°C)	% Entrapment efficiency (42±2°C)
1.	0	100 ± 00	100 ± 00	100 ± 00
2.	30	99.6 ± 0.015	99.9 ± 0.003	99.4 ± 0.041
3.	45	99.5 ± 0.013	99.8 ± 0.027	99.2 ± 0.036
4.	90	99.4 ± 0.15	99.6 ± 0.012	99.1 ± 0.02

In vivo efficiency was performed for the optimized formulation and it signifies that the hypoglycemic activity of the optimized formulation is decreased when compared to pure drug. Significant hypoglycemic effect (25%) was maintained only from 0.5-5 h after oral administration of glipizide, whereas in the case of glipizide floating microspheres, significant hypoglycemic effect (25%) was maintained for a period of 2-12 h. *In vivo* efficiency of the optimized batch F4 was performed in healthy normal Wistar rats by measuring the hypoglycemic effect produced after oral administration. The drug was administered at a dose equivalent to 800 mg/kg pure glipizide, and glipizide floating microspheres were used for the study. Pure glipizide drug was administered in a suspension form at the same dose. When pure glipizide suspension was administered, a rapid reduction in blood glucose levels was observed and maximum reduction of 42.83% was observed

within 2 h after oral administration. Blood glucose levels were recovered rapidly to the normal level within 8 h. In the case of glipizide floating microspheres, the reduction in blood glucose levels was slow and reached maximum reduction of 41.16 within 4 h after oral administration. This reduction in blood glucose levels was sustained over longer periods of time (12 h). Kahn and Shechter have suggested that a 25% reduction in blood glucose levels is considered a significant hypoglycemic effect. Significant hypoglycemic effect (25%) was maintained only from 0.5 to 5 hours after oral administration of glipizide, whereas in the case of glipizide floating microspheres, significant hypoglycemic effect (25%) was maintained for a period of 2-12 h.

The hypoglycemic effect observed over a longer period of time in the case of floating microspheres is due to the slow release and absorption of glipizide over longer periods of time. Glipizide formulation is significantly more effective than the immediate release formulation of glipizide in reducing fasting plasma glucose levels and side effects. So the F4 formulation signifies that the hypoglycemic activity of the optimized formulation is decreased when compared to pure drug. Significant hypoglycemic effect (25%) was maintained only from 0.5-5 h after the oral administration of glipizide, whereas in the case of glipizide floating microspheres, significant hypoglycemic effect (25%) was maintained for a period of 2-12 h (**Table 6**).

Table 6. Comparative percent blood glucose reduction data of pure drug and F4

Time (h)	Pure Glipizide	F4
0	0	0
2	42.83	31.16
4	28.33	41.16
6	31.5	39.33
8	12.16	36.16
10	6.33	22.16
12	2.16	19
14	-	14.83
16	-	10.83
18	-	8.83
20	-	6.16
22	-	3
24	-	1.16

CONCLUSION

Floating hollow microspheres are prepared with enteric coated polymer (RS 100) successfully by the solvent evaporation technique. Upon incorporation of the hydrophilic polymer such as HPMC in the shell of microballoons, the amount of drug released from microspheres could be enhanced. *In vitro* data obtained from floating microspheres of Glipizide showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion (Anomalous transport diffusion) was found to be the main release mechanism. Thus the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intra gastric condition.

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