International Journal of Medicine and Pharmaceutical Research

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R E S E A R C H A R T I C L E

Formulation and *In-Vitro* Evaluation of Glibenclamide Floating Microspheres

K Saravanakumar[*1], Pommala Nagaveni[2], Yerikala Ramesh[3]

[1]*Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, A Rangampeta, Tirupati 517102, Chittoor Dist Andhra Pradesh, India.*
[2]*Department of Pharmaceutics, S.V.U. College of Pharmaceutical Sciences, Sri Venkateswara University, Tirupati – 517502, Chittoor Dist Andhra Pradesh, India.*
[3]*Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V), Muthukur (M), SPSR Nellore -524346, Andhra Pradesh, India.*

A B S T R A C T

The aim of present work is prepare floating microspheres of Glibenclamide using Eudragit S 100 and Eudragit L 100 as polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for aprolonged period of time. Glibenclamide is antidiabetic drug with long elimination half life 8-10 hours. The long half life of Glibenclamide and multiple administration doses make Glibenclamide a very good candidate for formulation of floating drug delivery system. Floating microspheres of Glibenclamide were prepared by emulsion solvent diffusion method using Eudragit S 100 and Eudragit L 100 as polymer. The floating microspheres was evaluated such as micromeritic properties, particle size, percentage yield, *In vitro* buoyancy, incorporation efficiency, drug polymer compatibility (IR & DSC study), scanning electron microscopy and drug release of microspheres. The micromeritic properties was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation GFM2 prepared with Eudragit S 100 drug: polymer ratio (1:2) which exhibited excellent micromeritic properties, percentage yield, *In vitro* buoyancy, incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs. Results show that as increase in drug: polymer ratio affects the particle size, percentage yield, *In vitro* buoyancy and drug release of microspheres. The data obtained in this study thus suggest that a floating microspheres of Glibenclamide are promising for sustained drug delivery which can reduce dosing frequency.

Keywords: Glibenclamide, Eudragit S 100, Eudragit L 100, Floating microspheres.

A R T I C L E I N F O

Corresponding Author
K Saravanakumar
Department of Pharmaceutics,
Sree Vidyanikethan College of Pharmacy,
A Rangampeta, Tirupati-517102,
Chittoor, Andhra Pradesh, India.
MS-ID: IJCPS3982

PAPER-QRCODE

A R T I C L E H I S T O R Y: Received 31 August 2018, **Accepted** 18 October 2018, **Available Online**10 December 2018

Citation: *K Saravanakumar, et al.* Formulation and *In-Vitro* Evaluation of Glibenclamide Floating Microspheres. *Int. J. Med. Pharm. Res., 2018, 6(6): 284-289*

C O N T E N T S

1. Introduction

To develop oral drug delivery systems, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drug from the system. Drugs that are easily absorbed from the gastrointestinal tract and have a long half life are eliminated quickly from the blood circulation and require frequent dosing. To avoid these problems, the oral controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract and maintain a constant drug concentration in the serum for a longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time a physiological limitation.

Therefore prolonged gastric retention is important in acheiving control over the GRT because this helps to retain the controlled release system in the stomach for a longer time in a predictable manner. Various attempts have been made to prolong the residence time of the dosage forms within the stomach. The prolongatoion of the GRT of delivery devices could be acheived by adhesion to the mucous membranes, by preventing their passage through the pylorus or by maintaining them in buoyant fashion in gastric juice. Unfortunately floating devices administered in a single unit form (tablet) such as hydrodynamically balanced systems are unreliable in prolonging the GRT owing to their “all or none” emptying process and thus, they may cause high variability in bioavailibility and local irritation due to a large amount of drug delivered at a particular site of GIT[1]. The aim of present study was to develop and evaluate floating microspheres of Glibenclamide using Eudragit S-100 & Eudragit L-100 as polymer and emulsion solvent diffusion as a method of preparation. Glibenclamide whose physicochemical properties and short half life make it suitable candidate for floating drug delivery system[2].

In contrast, multiple unit particulate dosage form (e.g. Microspheres) have the advantages that they pass uniformly through the git to avoid the vagaries of gastric emptying and provide an adjustable release, thereby reducing intersubject variability in absorption and risk of local irritation. This drug is used in therapy of Hyperglycemia and its plasma elimination half life is 9-10 hours, and in order to maintain therapeutic plasma level drug must be administered at least thrice a day[3]. On the other hand, eudragit (methacrylate copolymers) have been recently received increased attention for preparing modified dosage forms because of their inertness, solubility, in relatively non toxic solvents of resins with different properties.

2. Materials and Methods

Materials

Glibenclamide was received as gift sample from Lupin Laboratories Ltd., Bangalore, Eudragit S 100 and Eudragit L 100 was received as gift sample from Deggusa india pvt. Ltd., Mumbai. ethanol, methanol, dichloromethane, tween 20 was obtained from SD fine chemicals Ltd., Mumbai (India). All other chemical and reagent used in this study were of analytical grade.

Method of preparation[4]

Floating micropsheres were prepared by emulsion solvent diffusion method. Weighed amount (as shown in Table 1) of Glibenclamide was mixed with Eudragit S 100 and Eudragit L 100 Drug: polymer ratio (1:1, 1:2, 1:3) in a solution of ethanol : dichloromethane (1:1) at room temperature. The resulting drug polymer solution was poured slowly using glass tube into 200 ml of water containing 0.75 % w/v polyvinyl alcohol, maintained at constant temperature of 40 ^{o}C and preparation was kept at High speed homogeniser at 1500 rpm for 1 hr. The finely developed floating microspheres were then filtered, washed with water and seived between 50 and 30 mesh size (as per IP specifications) and dried overnight at 40 ^{o}C.

Evaluation of floating microspheres

Yield of Floating microspheres:

The prepared floating microspheres with a size range of 102 - 192 µm were collected and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microspheres[5].

% yield = (Actual weight of product / Total weight of excipient and drug) x 100

In vitro Buoyancy

Floating microspheres (equivalent to 100 mg) were dispersed in 900ml of 0.1 N hydrochloric acid solution (pH 1.2) containing tween 20 (0.02 W/V%) to simulate gastric fluid at 37°C. The mixture was stirred with a paddle at 100 rpm and after 12 hr, the layer of buoyant microspheres (Wf) was pippetted and separated by filtration simultaneously sinking microspheres (Ws) was also separated[6]. Both microspheres type were dried at 40°C over night. Each weight was measured and buoyancy was determined by the weight ratio of the floating microsphers to the sum of floating microsphers.

Incorporation efficiency

Floating microspheres were dissolved in a minimum amount of methanol and drug was extracted into suitable aqueous media (0.1 N HCl) by evaporating methanol. The solution was filtered through whatman filter paper, diluted suitably and analyzed for drug content spectrophotometrically at 237 nm using 0.1N hydrochloric acid as blank[7].

Micromeritic properties

The floating microspheres were characterized by their micromeritic properties such as particle size, bulk density,tapped density, hausners ratio, carr’s index and angle of repose[8].

Drug release

Drug release from Floating microspheres having a size range between 102 - 192 µm and floating microspheres equivalent to 500 mg of drug was carried out using paddle method at 100 rpm. Each time 5 ml of samples were withdrawn at different time intervals and replaced with fresh phosphate buffer, the amount of drug release was analyzed at 237 nm using shimadzu UV visible spectrophotometer.

IR studies

In the preparation of drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug preformulation studies regarding the drug – polymer interaction are therefore very critical in appropriate polymer[9]. FT – IR Spectroscopy was employed to ascertain the compatibility between Glibenclamide and polymer.

Differential scanning calorimetry

The output of a DSC is a plot of heat flux (rate) versus temperature at a specified temperature rate. DSC provides information about the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and polymers in formulations[10].

3. Results and Discussion

Method of introducing polymer solution

The high surface tension of water caused the solidification and aggregation of Eudragit S100 and Eudragit L 100 on the surface of aqueous phase. To minimize the contact of polymer solution with the air - water interface and to develop a continuous process for preparing microspheres, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the introduction of the polymer solution through the glass tube without contacting the surface of water. This method improved the yield of microspheres and reduced the extent of aggregate formation and made it possible to make microspheres continuously. As the polymer solution is continuously introduced into the main vessel, it will overflow from the top of the vessel together with the prepared microspheres, since most of the formed microspheres will float on the top of the aqueous phase.

Yield of microspheres

The percentage yield of microspheres was in range of 62.14± 0.13 to 89.19 ± 1.59 (as shown in Table 2). To observe the effect of polymer concentration on the percentage yield of the resulting microspheres formulation were prepared using varying drug: polymer ratios with tween 20 (0.02 W/V%) to simulate gastric fluid. The percentage yield of the microspheres was found to be increased with increasing Eudragit S100 and Eudragit L 100 concentrations.

Micromeritic properties

The mean particle size of floating microspheres formulation GFM 1 to GFM 6 was found to be 0.658 ± 0.03 to 182.33 ± 26.50 (as shown in table 3). The effect of polymer concentration on the particle size of floating microspheres was determined. The mean particle size of the icrospheres was found to be increase with increasing Eudragit concentration (as shown in table 4). The viscosity of medium increases at a higher Eudragit concentration resulting in enhanced interfacial tension. Shearing effieincy is also diminished at higher viscosities. This results in the formation of larger particles. The bulk density, tapped density, hausners ratio of formulation GFM 1 to GFM 6 ranges from 0.591 ± 0.05 to 0.722 ± 0.01gm/cm³, 0.652 ± 0.05 to 0.773 ± 0.001gm/cm³, 1.04 ± 0.02 to 1.75 ±0.01 respectively. The carr's index ranges between 1.09 ± 1.61 to 10.01± 1.05 %. The angle of repose of microspheres ranges from 14.0 ± 2.15 to 19.11 ± 2.42 (as shown in table 3). The values of carr's index and angle of repose indicate excellent flow properties.

***In vitro* buoyancy**

The *In vitro* buoyancy test was carried out to investigate buoyancy of prepared microspheres. The microspheres formulations GFM 1to GFM 6 showed good floating ability range from 80.66 ± 1.08 to 90.33 ± 1.52.(as shown in Table 2). The results also showed a tendency that, larger the particle size longer the floating time.

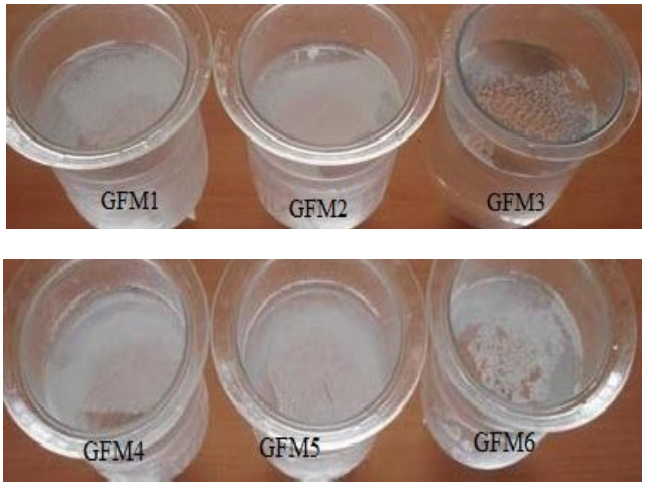

Fig No. 1. *In vitro* buoyancy of floating microspheres of Glibenclamide formulation

Incorporation efficiency

The incorporation efficiency of formulation GFM 1 to GFM 6 was carried out and found to be in a range 61.59 ± 1.57 to 81.70 ± 2.02 (as shown in table 2.)

Infrared spectroscopy

This was compared with standard functional group frequencies of Glibenclamide as shown in Table 4. From FTIR study, the characteristic peaks of drug such as of NH Stretching (Aromatic) (3000 cm^{-1}), OH Bending (Aliphatic) (2250 cm^{-1}), CH -Bend (1250 cm^{-1}), Di amido group (1750 cm^{-1}), Dimethyl group (1500 cm^{-1}). The Eudragit S 100 the peak contain NH Stretching (Aromatic) (3010 cm^{-1}), OH Bending (Aliphatic) (2750 cm^{-1}), CH -Bend (1250 cm^{-1}), Di amido group (1754 cm^{-1}), Dimethyl group (1509 cm^{-1}). The Eudragit L 100 NH Stretching (Aromatic) (3500 cm^{-1}), OH Bending (Aliphatic) (2200 cm^{-1}), CH -Bend (1253 cm^{-1}), Di amido group (1768 cm^{-1}), Dimethyl group (1512 cm^{-1}). remaining peaks also either shifted or replaced in the IR spectrum of formulation shown in Fig. 2, 3 & 4.

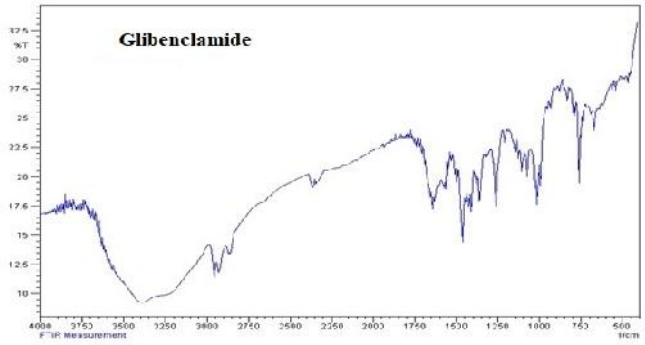

Fig No. 2. FT – IR of Glibenclamide

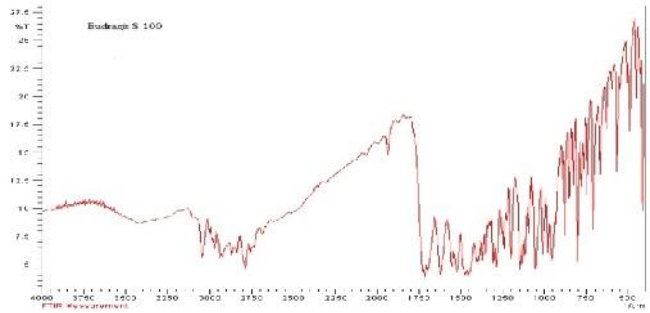

Fig No. 3. FT – IR of Eudragit S 100

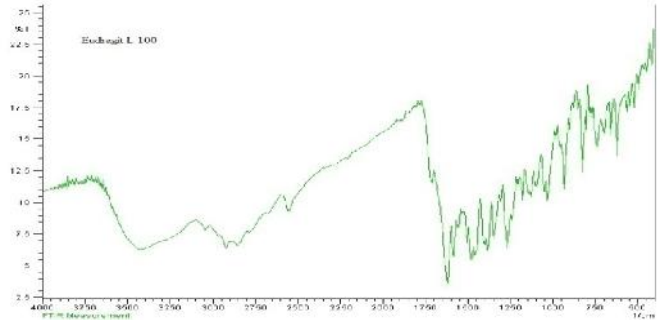

Fig No. 4. FT – IR of Eudragit L 100

DSC studies

The pure drug Glibenclamide shown as an endothermic peak at 191.28^{o}C. The peak neither is nor shifted in the case of DSC of the Glibenclamide microspheres formulation. The DSC of physical mixture of the Eudragit S 100 as showed an endothermic peak at 131.83 ^{o}C and as compared to Eudragit L 100 contain 120.09 to 150.6^{o}C. The DSC spectra as shown in fig.5, 6 & 7**.**

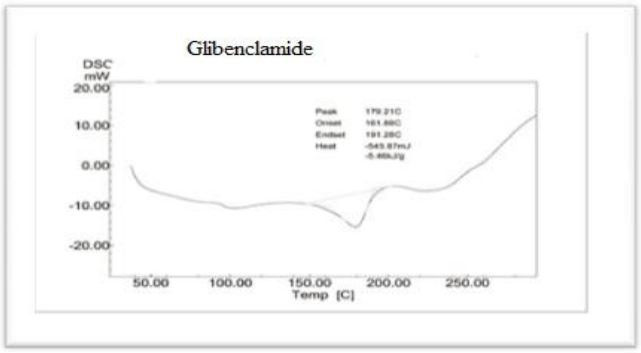

Fig No. 5. DSC of Glibenclamide

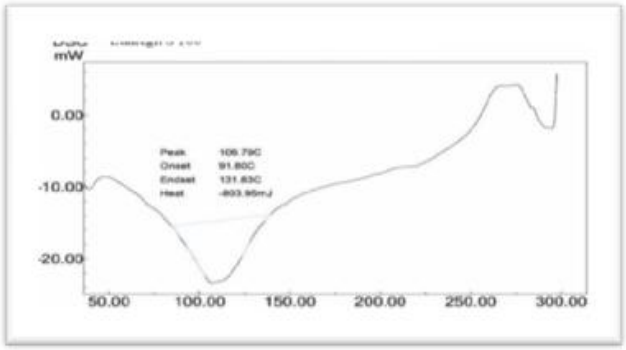

Fig No. 6. DSC of Eudragit S 100

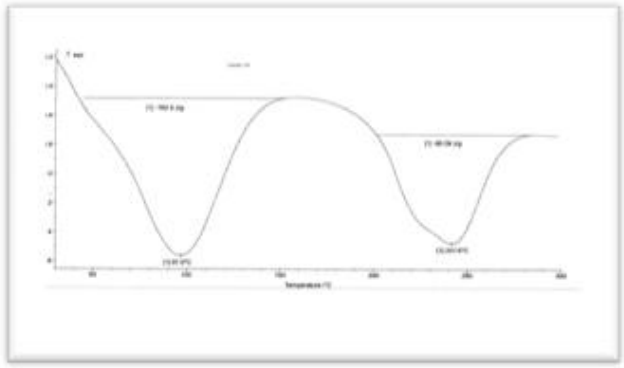

Fig No. 7. DSC of Eudragit L 100

Scanning electron microscopy (SEM)

Morphology of floating microspheres was examined by scanning electron microscopy. The outer surface of microspheres was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer observed in fig No.8.

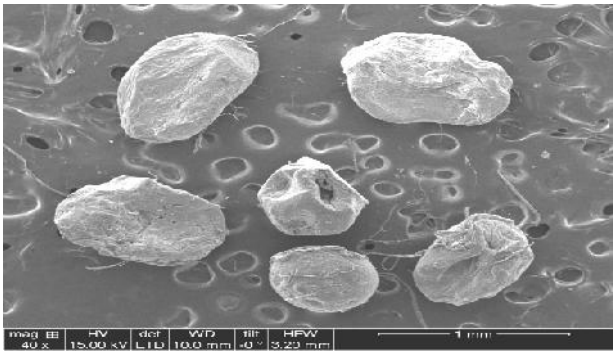

Fig No. 8. SEM of floating microspheres of Glibenclamide.

Drug release

The drug release from formulation GFM 1 to GFM 6 showed percentage drug release 80.12 ± 0.17 to 92.26 ± 1.81 at end of 12 hour and formulation. Among all formulation GFM 2 was found to be the best formulation as it drug release 92.26% Glibenclamide in a sustained manner with constant fashion over extended period of time

(after 12 hr). It was observed as the concentration of Eudragit S 100 and Eudragit L 100 was increased percent release of Glibenclamide decreases. The increase in Eudragit S 100 and Eudragit L 100 concentration leads to the increased density of polymer matrix into the microspheres which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix. Furthermore smaller microspheres are formed at lower polymer concentration and have larger surface area exposed to dissolution medium.

Table 1: Effect of *EJ+CZ* on Oral Glucose Tolerance Test (OGTT)

Table: 1. Formulation table of floating microspheres of Glibenclamide

S.No	Ingredients	Formulation code					
		GFM1	GFM 2	GFM3	GFM 4	GFM 5	GFM 6
1	Glibenclamide (mg)	500	500	500	500	500	500
2	Edragit S 100 (gms)	-	-	-	1.5	0.5	1
3	Edragit L 100	1.5	1	1.5	-	-	-
4	Ethanol	8	8	8	8	8	8
5	Dichloromethane	8	8	8	8	8	8

Table: 2. Percentages Yield, *in vitro* buoyancy and incorporation efficiency of floating microspheres of Glibenclamide

Formulation code	Percentage Yield	*In vitro* buoyancy	Incorporation efficiency
GFM 1	81.08±1.91	87.00±1.00	61.59±1.59
GFM 2	77.73±1.51	83.00±1.02	81.70±2.01
GFM 3	62.14±0.13	80.66±1.08	61.59±1.57
GFM 4	85.89±2.13	90.33±1.52	79.03±2.00
GFM 5	89.19±1.59	71.66±4.04	81.72±2.02
GFM 6	86.13±2.00	87.00±4.04	81.70±2.02

Table: 3. Micrometric properties of floating microspheres of Glibenclamide

SI.No	Formulation code	Mean Particle size	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausners ratio	Carr's Index	Angle of repose
1	GFM 1	125.33±15.27	0.622±0.03	0.173±0.01	1.75±0.01	1.09±1.61	16.01±2.81
2	GFM 2	182.33±26.30	0.674±0.03	0.692±0.07	1.06±0.02	10.1±1.05	17.07±1.61
3	GFM 3	0.722±0.001	0.591±0.05	0.652±0.05	1.16±0.03	5.00±2.34	14.01±2.15
4	GFM 4	0.658±0.003	0.655±0.03	0.707±0.02	1.04±0.02	9.16±0.81	15.27±1.52
5	GFM 5	102.22±2.750	0.722±0.01	0.773±0.01	1.10±0.01	4.73±2.73	16.77±1.42
6	GFM 6	161.33±11.01	0.632±0.02	0.684±0.03	1.07±0.03	7.63±2.66	19.11±2.42

Table: 4. IR Interpretations for Pure drug and Polymer

Functional groups	Glibenclamide	Eudragit S 100	Eudragit L 100
NH Stretching (Aromatic)	3000 cm^{-1}	3010 cm^{-1}	3500 cm^{-1}
OH Bending (Aliphatic)	2250 cm^{-1}	2750 cm^{-1}	2500 cm^{-1}
CH-bend	1250 cm^{-1}	1250 cm^{-1}	1253 cm^{-1}
Di amido group	1750 cm^{-1}	1754 cm^{-1}	1768 cm^{-1}
Dimethyl group	1500 cm^{-1}	1509 cm^{-1}	1512 cm^{-1}

4. Conclusion

Floating microspheres of Glibenclamide with enteric acrylic polymers such as Eudragit S 100 and Eudragit L 100 were successfully prepared by the emulsion solvent diffusion method. The formulation GFM2 with drug:polymer ratio (1:2) was found to be satisfactory in terms of excellent micromeritic properties, yield of microspheres (89.19 %), incorporation efficiency (81.72 %), *In vitro* buoyancy (90.33 %) and highest *In vitro* drug release of 92.26 % in sustained manner with constant fashion over extended period of time for 12 hrs. From the results it was observed that Drug: Polymer ratio influences the particle size, *in vitro* buoyancy, as well as drug release pattern of floating microspheres.

5. Acknowledgements

Glibenclamide was received as gift sample from Lupin Laboratories Ltd. Bangalore, India, We also thank our beloved Chairman and Principal, Sree Vidyanikethan College of Pharmacy, A Rangampeta, Tirupati 517102, Chittoor Dist Andhra Pradesh, India for providing infrastructure facilities for the work.

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