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RESEARCH ARTICLE

FORMULATION AND *INVITRO* EVALUATION OF BUOYANT DRUG DELIVERY SYSTEM OF GLIPIZIDE USING ACRYLIC POLYMER

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ABSTRACT

Recently, several technical advancements have led to the development of several novel drug delivery systems (NDDS) that could release the active ingredient over an extended period of time and further deliver the drug directly to the site of action, thus minimizing or eliminating side effects. In the present study 8 formulations of Glipizide floating microspheres were prepared using varying concentrations of Eudragit RS100 and HPMC by Emulsification solvent diffusion method. The floating microspheres were evaluated for percentage yield, drug loading, *in-vitro* buoyancy behavior as well as drug polymer compatibility, scanning electron microscopy, and *in-vitro* drug release. The micrometric properties were found to be good and scanning electron microscopy shows that the microspheres were spherical with smooth surface and a hollow cavity inside microspheres. The practical yield was found to be in the range of 69.88-95.98% and with a particle size range of 617.19-882.75 μm . The percent entrapment is about 60.24% to 90.68% and percent drug loading is about 18.21 to 30.85% which decreased with increase in HPMC concentration in the formulations. The microspheres with high concentrations of Eudragit showed higher buoyancy. The *in-vitro* release was slow and extended to more than 12 hours which increased with significant increase in HPMC concentration but decreased in buoyancy character. Release obeys zero order kinetics and the drug release was diffusion controlled. Hence it can be concluded that the floating microsphere of Glipizide may prolong drug release thereby improving bioavailability and enhance opportunity of absorption in stomach.

Keywords: Glipizide, Floating Microspheres, Controlled release**INTRODUCTION**

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), by using gastro retentive dosage forms (GRDFs). GRDF's can remain in the gastric region for several hours and hence prolong the gastric residence time of drug. GRDF's offer several advantages over immediate release dosage form, including the minimization of fluctuations in drug concentration in plasma, and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduce the side effect, reduction of total dose administered, (while providing similar therapeutic effect) and reduction of administration frequency, leading to improved patient compliances. Various approaches have been pursued to increase the retention of an oral dosage form in the stomach among which low density floating drug delivery systems forms major drug delivery devices. These systems maintain a density of less than 1.004 gm/cm^3 which makes them float on the gastric contents. The various types of buoyant preparation include hollow microsphere (micro balloons), granules powder, capsule, tablet (pills) and laminated films.¹⁻³

Hollow microsphere floats immediately upon contact with gastric fluid and gives promising approaches for increasing the bioavailability of drugs with absorption

windows in upper small intestine and stomach. However, immediate floating can only be achieved, when the density of the device is lower than gastric fluid.⁴⁻⁶

Glipizide is a second-generation oral sulfonylurea hypoglycemic agent used in lowering the blood sugar levels in patients with non-insulin dependent diabetes mellitus. Gastrointestinal absorption is uniform, rapid and essentially complete with peak plasma concentration occurring 1 to 3 hrs after a single dose. It is extensively bound to plasma proteins and a half-life of approximately 2 to 4 hrs. In order to maintain therapeutic plasma concentration, the drug must be administered frequently by oral route in divided doses which leads to fluctuations in plasma drug levels.⁷⁻⁹

To overcome inherent drawbacks associated with conventional dosage forms of Glipizide, an attempt is being made to develop an alternative drug delivery system in the form of floating microspheres.

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MATERIALS & METHODS

Preparation of Floating Microspheres of Glipizide:^{10,11}

For present study, acrylic polymer Eudragit combined with Hydroxy Propyl Methyl Cellulose is used with the active ingredient for preparation of floating microspheres (Table 1).

Glipizide floating microspheres were prepared using varying concentrations of Eudragit RS100 and HPMC by Emulsification solvent diffusion method. The drug to

polymer ratio used to prepare the different formulations was 1:7. The drug and polymer mixture is dissolved in a mixture of ethanol (8 ml) and dichloromethane (8 ml) and dropped into 0.75% polyvinyl alcohol solution (200 ml). The solution was stirred with a propeller-type agitator at 40° C temperature for 1 hour at 300 rpm. The formed floating microspheres were passed through sieve no 12 and washed with water and dried at room temperature in a desiccator.

Table 1: Formulation Design of Glipizide Floating Microspheres

Sl. No	Code	Glipizide (mg)	Eudragit RS100 (mg)	HPMC (mg)
1	F ₁	100	700	0
2	F ₂	100	600	100
3	F ₃	100	500	200
4	F ₄	100	400	300
5	F ₅	100	300	400
6	F ₆	100	200	500
7	F ₇	100	100	600
8	F ₈	100	0	700

Evaluation of Drug Loaded Floating Microspheres:

Percentage Yield:¹²

The prepared microspheres were collected and weighed from different formulations. The measured weight was divided by the total amount of all nonvolatile components which were used for the preparation of the microspheres.

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \times 100$$

Particle size analysis:¹³⁻¹⁵

The sizes of floating microspheres were measured by using an optical microscope, and the mean particle size was calculated by measuring nearly 200 particles with the help of a calculated ocular micrometer.

Buoyancy behavior of Floating microsphere:¹⁶

The floating ability was determined using USP dissolution tester apparatus II (Paddle method). About 100 mg of the floating microsphere were placed in 0.1 N Hcl (300 ml) containing 0.02% of Tween 20. The mixture was stirred with paddle at 100 rpm. The layer of buoyant microspheres was taken out and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in a desiccator over night. The percentage of microspheres was calculated by the following equation:

$$\% \text{ Floating} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of microspheres}} \times 100$$

Encapsulation Efficiency and Drug Loading:^{17,18}

The amount of drug encapsulated in floating microspheres was determined by sonicating known amount of microspheres in ethanol for 15 min and 1 ml of this solution was withdrawn and diluted to 50 ml with

0.1 N Hcl. This solution was assayed for drug content by UV spectrophotometer at 276 nm. Calculating this concentration with the dilution factor we get the percentage drug content.

a. **Encapsulation Efficiency** was calculated as:

$$\text{EE (\%)} = \left[\frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \right] \times 100$$

b. **Drug Loading** was calculated as:

$$\text{DL (\%)} = \left[\frac{\text{Actual Drug Content}}{\text{Weight of Powdered Microspheres}} \right] \times 100$$

Scanning Electron Microscopy:

Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 30KV during scanning. Microphotographs were taken on different magnification and higher magnification (500X) was used for surface morphology.

Drug Polymer Interaction (FT-IR) Analysis:¹⁹

The Fourier transform infra-red analysis was conducted for the analysis of drug polymer interaction and stability of drug during microencapsulation process. Fourier transform infra-red spectrum of pure Glipizide, Eudragit RS 100, HPMC, Physical mixture and floating microspheres (formulation) were recorded.

In-vitro Release Studies:²⁰⁻²³

A weighed amount of floating microspheres equivalent to 100 mg Glipizide were dispersed in 900 ml of 0.1 N Hcl (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. One ml of sample was withdrawn at predetermined intervals and was suitably diluted with 0.1 N Hcl and analyzed spectrophotometrically at 276 nm to determine

the concentration of drug present in the dissolution medium.

RESULTS & DISCUSSION:

In the current research, floating microspheres loaded with Glipizide were developed and evaluated.

IR Studies

The physical mixture showed identical spectrum with respect to the spectrum of the pure Glipizide, indicating there is no chemical interaction between the drug molecule and polymers used. (Fig 1-5)

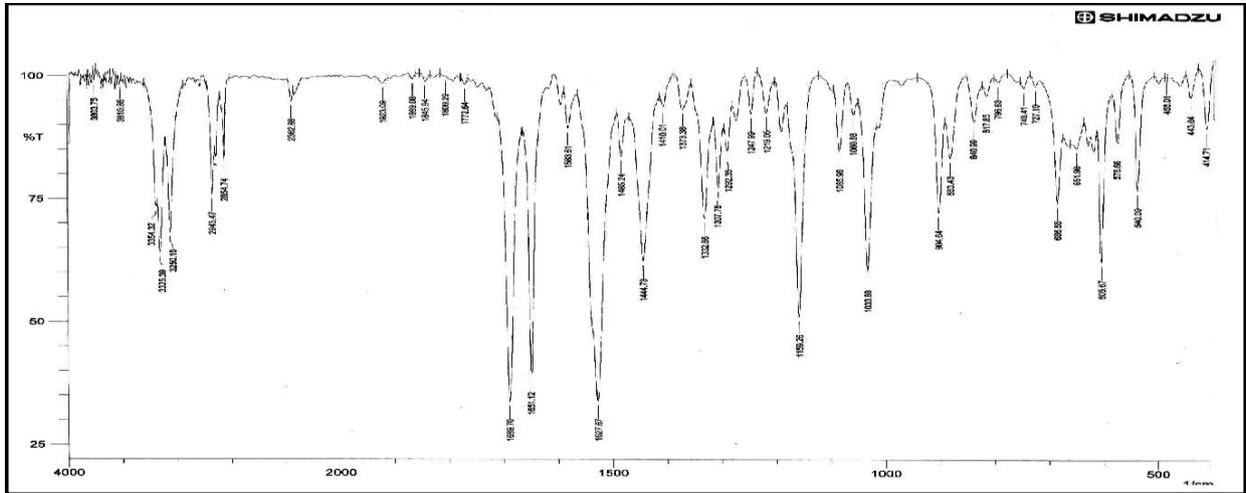


Fig 1: FTIR spectrum of pure Glipizide

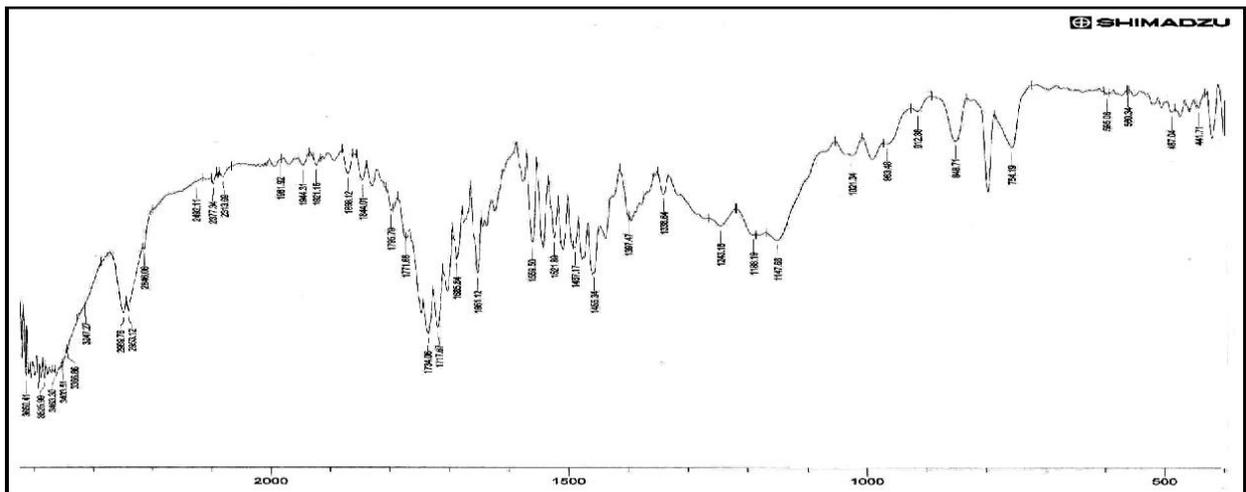


Fig 2: FTIR spectrum of Eudragit

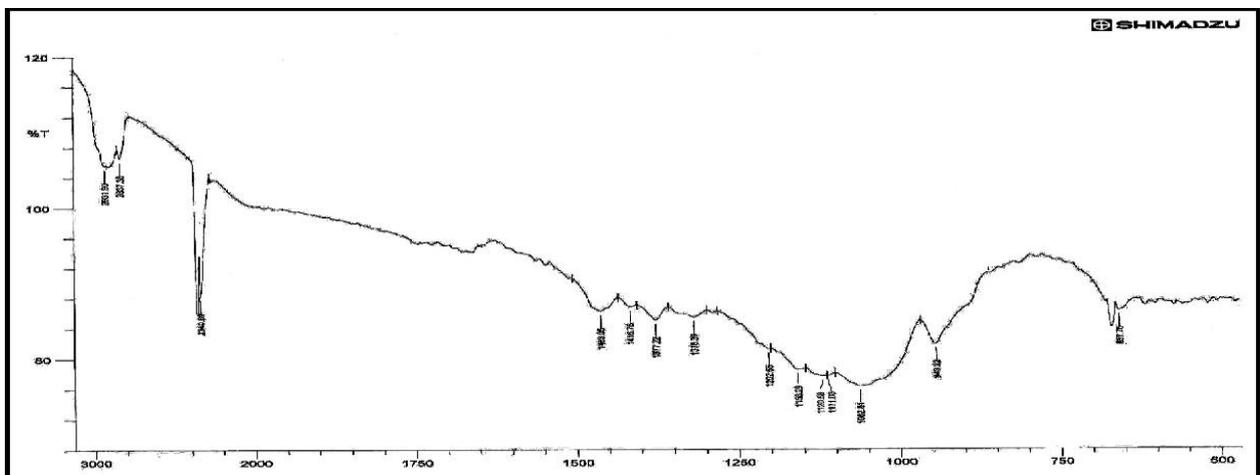


Fig 3: FTIR spectrum of HPMC

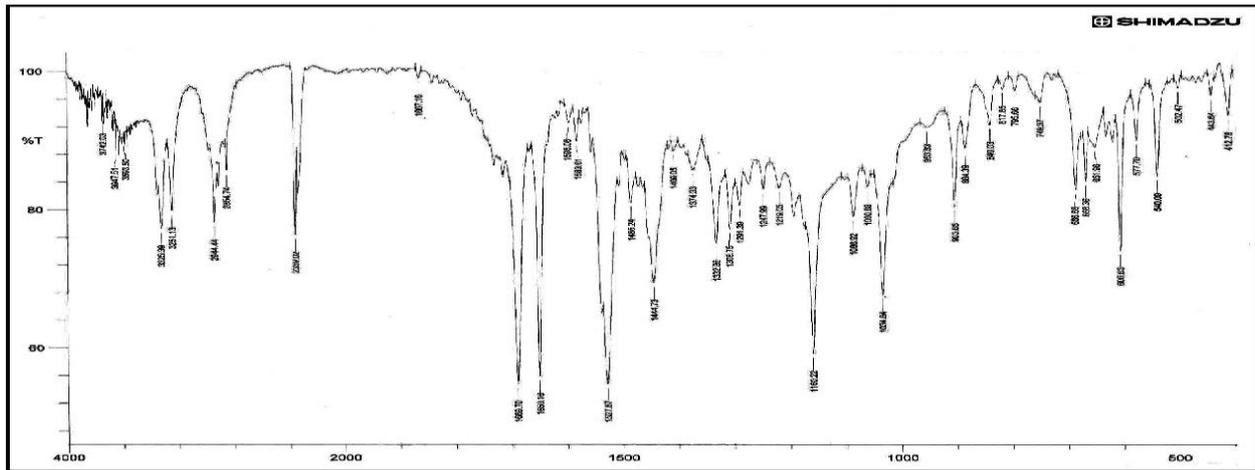


Fig 4: FTIR spectrum of physical mixture of Drug + Eudragit + HPMC

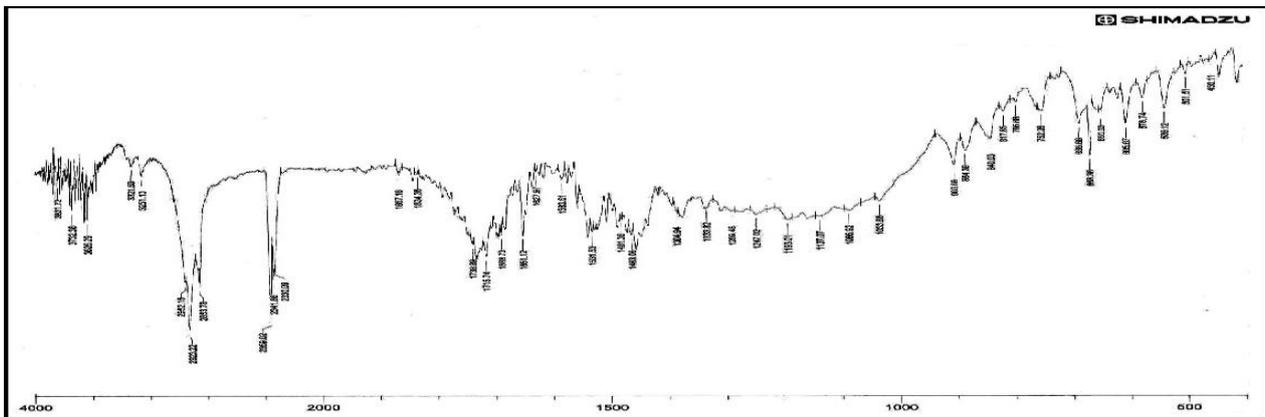


Fig 5: FTIR spectrum of Formulation F₄

Percentage Yield:

For different formulations percentage yield was calculated by weighing the microspheres after drying. The percentage yield of floating microspheres was in range of 54.35 - 82.87% (Table 2 & Fig 6).

Particle Size Analysis:

The mean particle size of floating microspheres was in range of 617.42-882.75 μm (Table 2). As the particle size increased the rate of release decreased showing good controlled release nature along with optimum buoyancy character.

Percent Encapsulation Efficiency and Percent Drug loading:

The drug entrapment efficacies and percent drug loading of the prepared microspheres were in the range of 60.24

to 90.68% w/w and 18.21 to 30.85% (Table 2 & Fig 6). Drug entrapment efficacy and drug loading slightly decreased with increased HPMC content and decreased Eudragit ratio in microspheres. This can be attributed to permeation nature of HPMC that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of hollow microspheres.

Buoyancy Character of Microspheres:

Floating ability was found to be altered according to Eudragit and HPMC ratio. F₁-F₄ formulations showed best floating ability with 80.64 to 93.74% and formulations F₅-F₈ showed less floating ability of 58.39 to 71.82% in 6 hours (Table 2). The floating ability of microspheres is decreased by increasing the HPMC ratio in the formulations.

Table 2: Particle Size, Percentage Yield, % Encapsulation, % Drug Loading

Code	% Yield	Particle Size (μm)	%Encapsulation	% Drug Loading	% Buoyancy
F ₁	95.98	882.75	90.68	30.85	93.74
F ₂	90.68	841.19	89.13	28.69	91.32
F ₃	85.36	799.84	86.64	27.46	88.19
F ₄	81.92	768.28	81.39	25.13	80.64
F ₅	76.38	747.31	70.56	20.89	71.82
F ₆	74.13	740.12	68.16	19.22	69.95
F ₇	71.65	681.86	65.81	19.01	62.17
F ₈	69.88	617.19	60.24	18.21	58.39

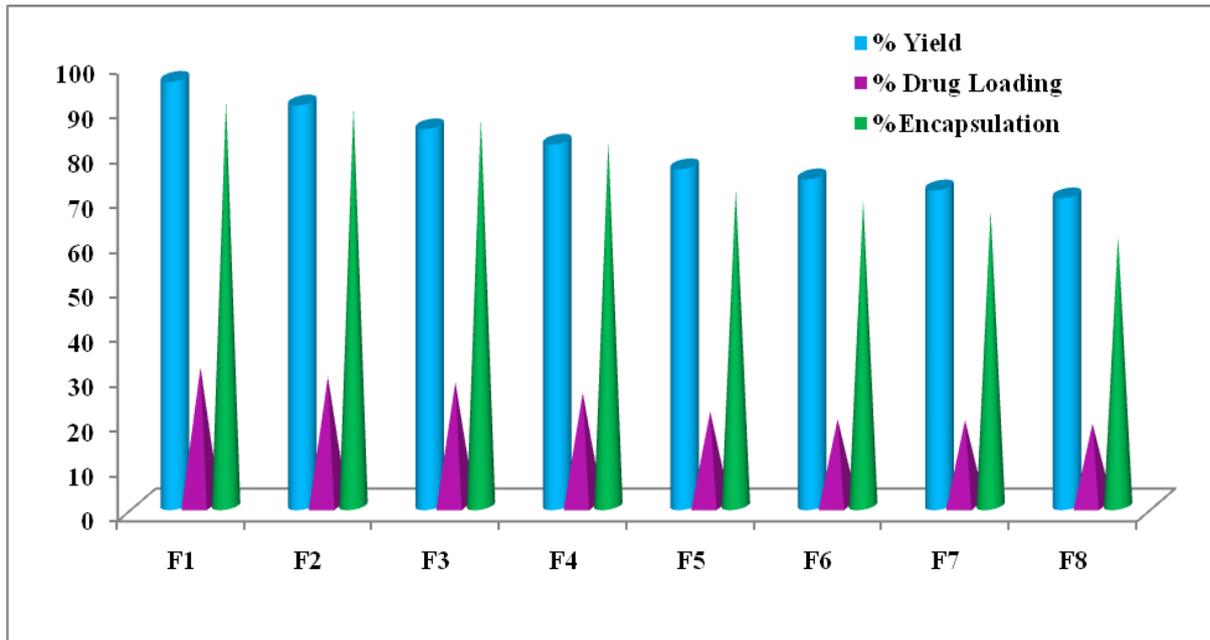


Fig 6: % Yield, % Encapsulation Efficiency & % Drug Loading

Scanning Electron Microscopy:

Surface morphology of the optimized formulation showed a smooth surface and small hollow cavity present inside the microspheres which is responsible for their floating behavior (Fig 7).

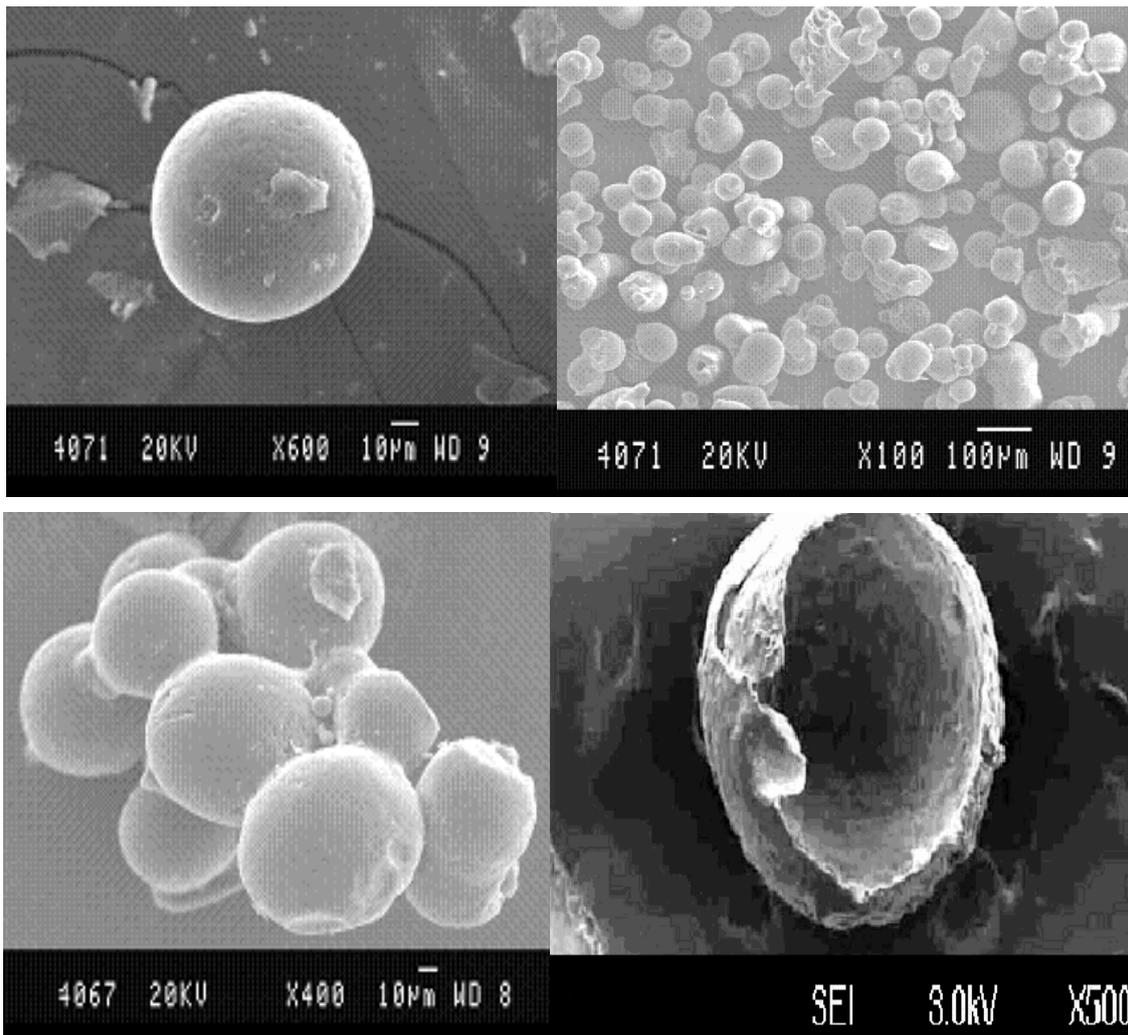


Fig 7: SEM Photograph of Mucoadhesive Microspheres (F4)

In-vitro release studies:

The *In vitro* release studies of mucoadhesive microspheres were carried out in 0.1 N Hcl as a dissolution medium. Eudragit RS100 is less soluble in acidic pH, therefore release of drug in 0.1 N Hcl was generally low. The release rates of formulations F₁-F₈ after 12 hours were found to be 39.78%, 50.14%, 63.67%, 74.96%, 93.81%, 94.29%, 95.65% and 96.82% respectively. The release was slow and incomplete for the first four formulations (F₁-F₄) containing more amount of Eudragit than HPMC. But they showed good buoyancy character. Formulations F₅-F₈ containing more amount of HPMC than Eudragit showed complete drug release with less buoyancy character. Finally formulation F₄ is considered as the best formulation with an

appropriate balance between buoyancy and drug release rate. (Table 3 & Fig 8)

Table 3: In vitro release of floating microspheres in 1.2 pH buffer

Formulation	% Drug release at 12 th hour in 0.1 N Hcl
F ₁	39.78
F ₂	50.14
F ₃	63.67
F ₄	74.96
F ₅	93.81
F ₆	94.29
F ₇	95.65
F ₈	96.82

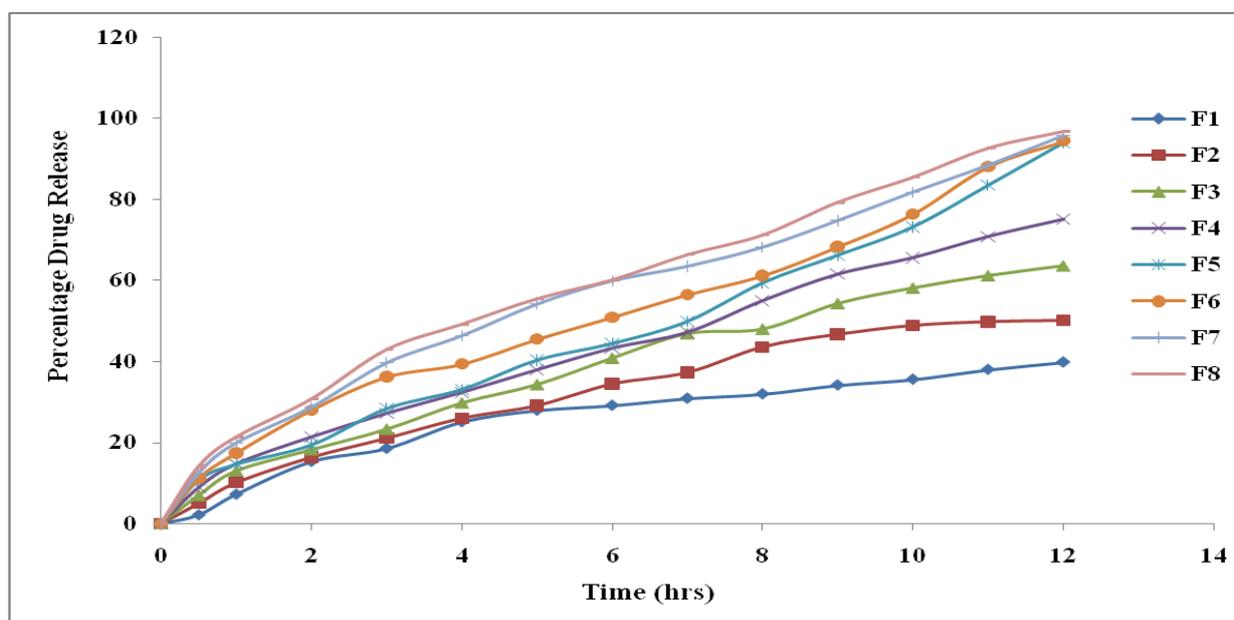


Fig 8: In-vitro dissolution profile of floating microspheres of Glipizide in pH 1.2 buffer

CONCLUSION:

By studying all the experimental results floating microspheres encapsulated with Glipizide can be successfully formulated by emulsification solvent diffusion method. By incorporating hydrophilic polymer such as HPMC in the shell of microspheres, the rate of

drug release can be enhanced. Characteristic property of floating microsphere includes high buoyancy and sufficient release of drug in gastric contents. Formulation F₄ showed best appropriate balance between buoyancy and drug release rate, which can be considered as a best fit for floating microspheres.

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