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Formulation and evaluation of floating microspheres of Glipizide

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ABSTRACT

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half life are eliminated quickly from the blood circulation. To avoid this problem, the oral sustained or controlled release (CR) have been developed as these will release the drug slowly in to the GIT and maintain a constant drug concentration in the serum for a longer period of time. Glipizide is commercially available as conventional tablet form. Single unit dosage form of Glipizide causes gastric irritation. To convert it in to the multiple unit dosage form will release the drug uniformly throughout the stomach which suppresses the irritation. The present study aim towards formulation and evaluation of floating multiparticulate drug delivery system, which can provide control release of the model drug. The work also aims to study various parameters affecting the behavior of floating multiparticulate in oral dosage form.

Keywords: Microencapsulation, GRDF, Glipizide, Floating microspheres.

INTRODUCTION

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at particular frequency. The main function of the stomach is to temporarily store food, start its digestion and to release the resulting chyme slowly through the pylorus in to the duodenum. Because of small surface area of the stomach, absorption in to the systemic circulation is restricted. The jejunum and ileum are the most important site for absorption of nutrient and drugs. The concept of FDDS was

described in the literature as early as 1986, when Davis discovered a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills. The author suggested that difficulty could be overcome by providing pills having a density of less than 1.0 g/ml so that pill will float on water surface [3,4]

EXPERIMENTAL SECTION

Glipizide IP was provided by Aristo Pharmaceutical, Mumbai. Acrycoat S100 USP, Eudragit RS100 were obtained from Corel Pvt. Ltd., Ahemadabad & Degussa India Pvt.Ltd. Mumbai respectively.

Preparation of floating microspheres:

The microspheres were prepared by emulsion solvent diffusion technique (Kawashima Y et al., 1991) or solvent evaporation technique. The polymers and drug were dissolved in a combination of organic solvent (20ml) i.e. Ethanol and Dichloromethane (1:1) at room temperature. The drug solution was poured in to 200 ml of water containing 0.05%, 0.25% and 0.50% polyvinyl alcohol (PVA) for batches using Acrycoat, Eudragit and Ethyl cellulose respectively. Then the solution was stirred at a speed of 300 - 500 rpm with a propeller agitator for 90 minutes at 30 – 40 ^{o}C as control temperature. The finely dispersed droplets were solidified in the aqueous phase via diffusion and evaporation of solvent [6,8]

EVALUATION OF MICROSPHERES:

Micromeritics Studies of Floating Microspheres – [1,2,5,7]

The microspheres are characterized by their micromeritic properties, such as particle size, tapped density, compressibility index, true density, and flow property.

1. **Particle size determination** using an optical microscope under regular polarized light, and the mean particle size was calculated by measuring 100- particles with the help of a calibrated ocular micrometer.

2. Calculate tapped densities and percentage compressibility index using:

i. **Tapped density** = $\frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$

ii. Carr's Compressibility Index:

Method: The bulk density and tapped density was measured and Compressibility index was calculated using the formula,

% Compressibility index $(C.I.) = \{(\rho_t - \rho o) / \rho t\} \times 100$

Where, ρt = tapped density, ρo = bulk density

iii. Hausner ratio:

Method: Tapped density and bulk density were measured and the Hausner ratio was calculated using the formula,

Hausner ratio = $\rho t / \rho o$

Where, ρt = tapped density , ρo = bulk density

3. The Angle of repose (θ) i.e. Flow property of the microspheres, which measures the resistance to particle flow, was calculated as,

$$\tan \theta = 2H / D$$

Where, H is height of the heap, D is diameter of the microspheres heap that is formed after making the microspheres flow from the glass funnel.

- **Percentage recovery (i.e. Yield) of microsphere formed:**

The prepared microspheres with a size ranging from 75 to 600 μm were collected and weighed. The measured weight of prepared microspheres was divided by the total amount of all drug+ polymer multiplied by hundred used for the preparation of the microspheres, which give the total percentage yield of floating microspheres[9,10]

- **Study of floatation behavior (or buoyancy) of microspheres**:

The floatation studies were carried out to ascertain the floating behavior of various polymer combinations. Beaker method was initially used to have an idea of the floatation behavior of the proposed dosage form .50 mg of floating microparticles were placed in each of four 50 ml beakers containing 20 ml of 0.1N HCl containing 0.02% tween 80. The beakers were shaken in a biological shaker at 37°C ± 0.5°C at 40 r.p.m. Floating microspheres were collected at 4,8 and 12 hrs and dried till constant weight was obtained. The percentage of floating microspheres was calculated by the following equation:[12,13]

$$\textbf{\% Floating microsphere (B \%)} = \frac{\text{Weight of floating microspheres after time t}}{\text{Initial weight of floating microspheres}} \times 100$$

Drug Loading or Incorporation efficiency (Drug Content determination):

Accurately weighted 10mg of floating microspheres. These microspheres were dissolved in 10ml of ethanol and filtered through Whatmann Filter Paper No.42. then 2ml of this solution was diluted to 100ml of 1.2 pH buffer and the absorbance was noted at 276 nm against 1.2 pH buffer with 2% ethanol as a blank. The drug content was calculated from std curve.

Dissolution test (in vitro-drug release) of microsphere*:*

The dissolution medium used was 900ml of 0.1 N HCl (pH 1.2) for Glipizide was filled in a dissolution vessel and the temperature of the medium was set at $37^0 + 0.5^0$ C and rotational speed of paddle was set at 100 rpm. The 5 ml of sample was withdrawn at predetermined time interval

for 12 hours and same volume of fresh medium was replaced. The withdrawn sample was diluted and analyzed by UV-Vis spectrophotometer at the respective λ_{max} values for Glipizide (276 nm). The content of drug was calculated using the equation generated from standard curve.[11,14]

ADVANCE STUDIES OF OPTIMIZED FLOATING MICROSPHERES:

- **Morphological Study using SEM:**

Scanning Electron Microscopy (SEM): The surface topography of the uncoated and coated (optimized) microsphere and cross section of optimized microsphere were examined under a FEI-Philips XL-30 Analytical Electron microscope . The samples were loaded on copper sample holder and sputter coated with carbon followed by Gold.

- **Infrared Spectroscopy Interpretation for interaction between drug and polymer**

Fourier transforms infrared spectroscopy (FTIR) spectra of the pure Glipizide drug and the physical mixture of drug and polymer were produced using by KBr disk method. These mixture were subjected to FTIR with a Nicolet Thermo 200 FTIR. Background spectrum was collected before running each sample. The samples were analyzed between wave-numbers 400and 4000 cm-1.

RESULTS AND DISCUSSION

Micromeritics Studies of Floating Microspheres:

The various batches has the average particle size in the range of 75µm to 600µm. where as Carr's index in between 11-23% and Hausner ratio with in 1.28 and angle of repose was found with in the range of 26^0 to 41^0, which is a appreciable limit for microspheres to show flow property while formulating in the dosage form. As the ratio of the Drug: polymer increased average particle size of the microspheres increased. Particle size of the microspheres using different polymer are in following order: AcrycoatS 100<Eudragit RS 100<Ethyl cellulose.

Table 1: Micromeritic studies

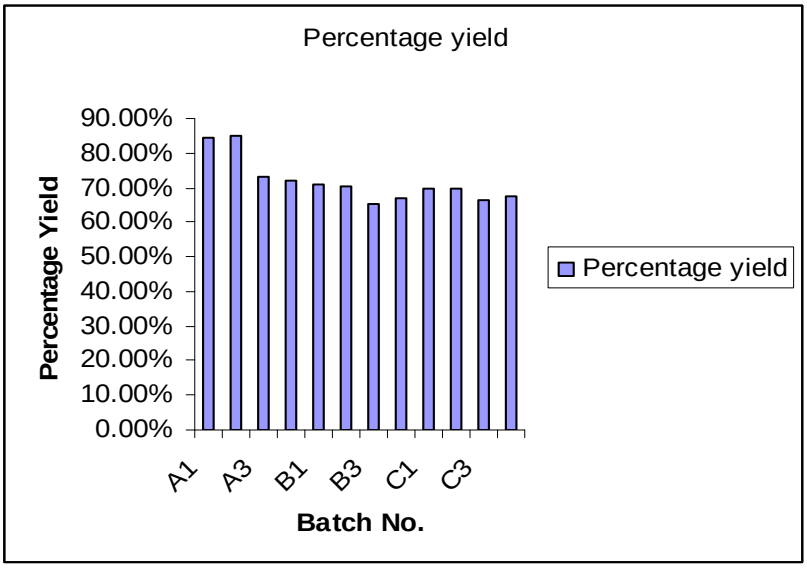
Parametrs / ***Batches***	**Average particle size(µm)**	**Tapped density (g/cm^3)**	**Bulk density (g/cm^3)**	**% *Compressibility***	**Hausner ratio**	**Angle of repose(θ)**
A1	140.0 ± 8.3	0.416	0.357	14.28	1.16	40 ^{o}60'
A2	175.0 ± 13.7	0.454	0.384	15.37	1.18	37 ^{o} 40'
A3	223.8 ± 19.3	0.454	0.384	15.37	1.18	33 ^{o} 69'
A4	233.3 ± 23.3	0.416	0.357	14.28	1.16	34 ^{o} 43'
B1	305.1 ± 8.1	0.333	0.294	11.7	1.13	26 ^{o} 56'
B2	313.6 ± 9.2	0.384	0.312	18.7	1.2	31 ^{o} 32'
B3	334.0 ±18.8	0.357	0.277	22.4	1.28	30 ^{o} 41'
B4	339.7 ±19.9	0.357	0.312	12.60	1.14	30 ^{o} 96'
C1	325.7 ± 15.8	0.416	0.333	19.9	1.124	37 ^{o} 40'
C2	337.0 ± 19.6	0.333	0.294	11.7	1.13	32^o 15'
C3	348.0 ± 23.7	0.357	0.312	12.60	1.14	27 ^{o} 55'
C4	352.0 ±33.6	0.357	0.294	17.64	1.21	31^o 89'

Percentage yield: The maximum percentage yield was found of A2 batch and was noted to be 85.2% among the selected batches A1, A3and C1. It was found that average percentage yield was greater than 60 % for all.

Table 2: Percentage yield

Batch no.	Percentage yield
A1	84.5%
A2	85.2%
A3	73.25%
A4	72%
B1	71%
B2	70.3%
B3	65.5%
B4	66.8%
C1	70%
C2	69.6%
C3	66.25%
C4	67.4%

Fig.1: percentage yield



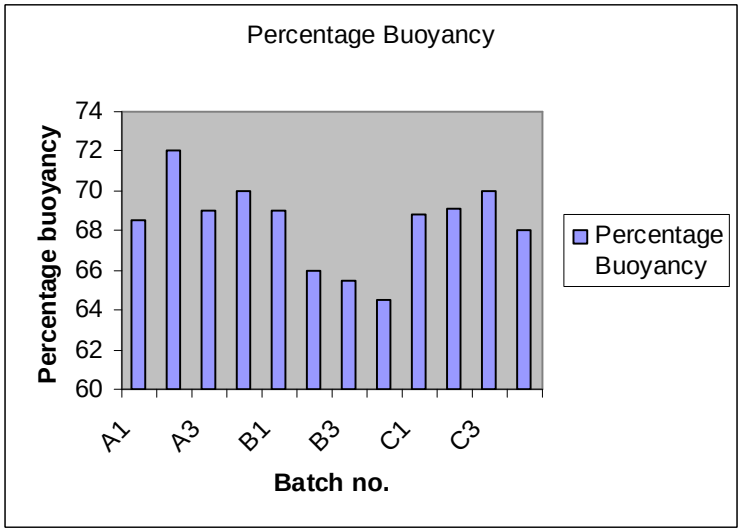
Buoyancy study:

Buoyancy of microspheres was found to be more then 40%,which indicates that most of the microspheres were still floatable after 12 hours because of their low density and internal voids. The microspheres were spread over the surface of a 1.2 pH buffer and the fraction of microspheres settled down as a function of time was quantitated. The fraction of microsphere floating on the medium was almost linearly reduced up to 12 hr, suggesting that the absorption of the drug in vivo can be linear with time for an extended duration, assuming release of a drug is immediate at the intestine.

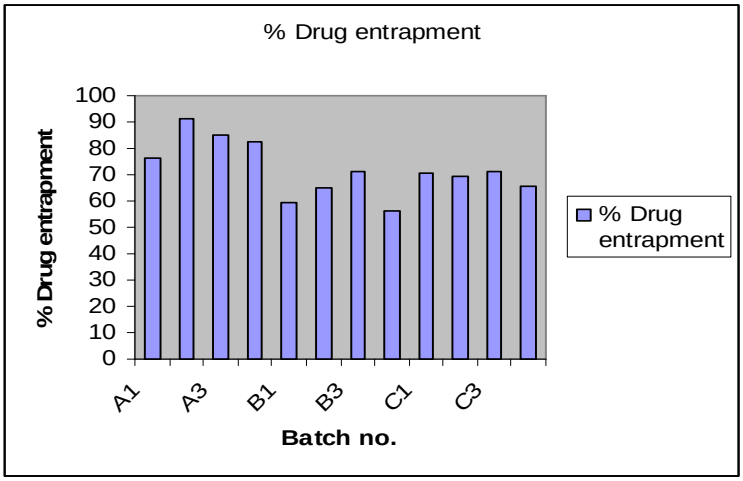
Table 3 : Percentage buoyancy

Batch. No	Percentage Buoyancy
A1	68.5
A2	72
A3	69
A4	70
B1	69
B2	66
B3	65.5
B4	64.5
C1	68.8
C2	69.1
C3	70
C4	68

Fig.2 : Percentage buoyancy



.Fig.3: Percent drug entrapment



Percent drug entrapment: The microspheres of batch A2 formulation showed an entrapment of 91%. While formulation A3, A4 and C2 showed lesser entrapment than the optimized formulation. This can be attributed to the permeation characteristics of each polymer used, that could facilitate the diffusion of a part of entrapped drug to the surrounding medium during preparation of floating microspheres. Percent drug entrapment of Acrycoat was found to be highest

Dissolution (*In-vitro* Drug release) studies:

Release of the drug from floating microspheres was evaluated at pH 1.2 buffer using Glipizide as model drug. The drug release rate of Glipizide was almost linear with time for the first 10 hrs. and gradually decreased with the afterwards. Batch B1,B2,B3,B4,C1,C2,C3,C4, showed Burst release where as Batch A1,A2,A3,A4 did not show this type of release. Drug releasing rate of the polymers are in following order: Acrycoat S100 <Eudragit RS100< EC

In the early incubation stage, the dissolution rates of Glipizide were slightly faster especially during the first hour. This was due to the fast dissolution of the drug present on the surface of the microspheres and the rapid penetration of aqueous solution into the microspheres, which is also called burst effect. EC and Eudragit S100 have shown this type of release.

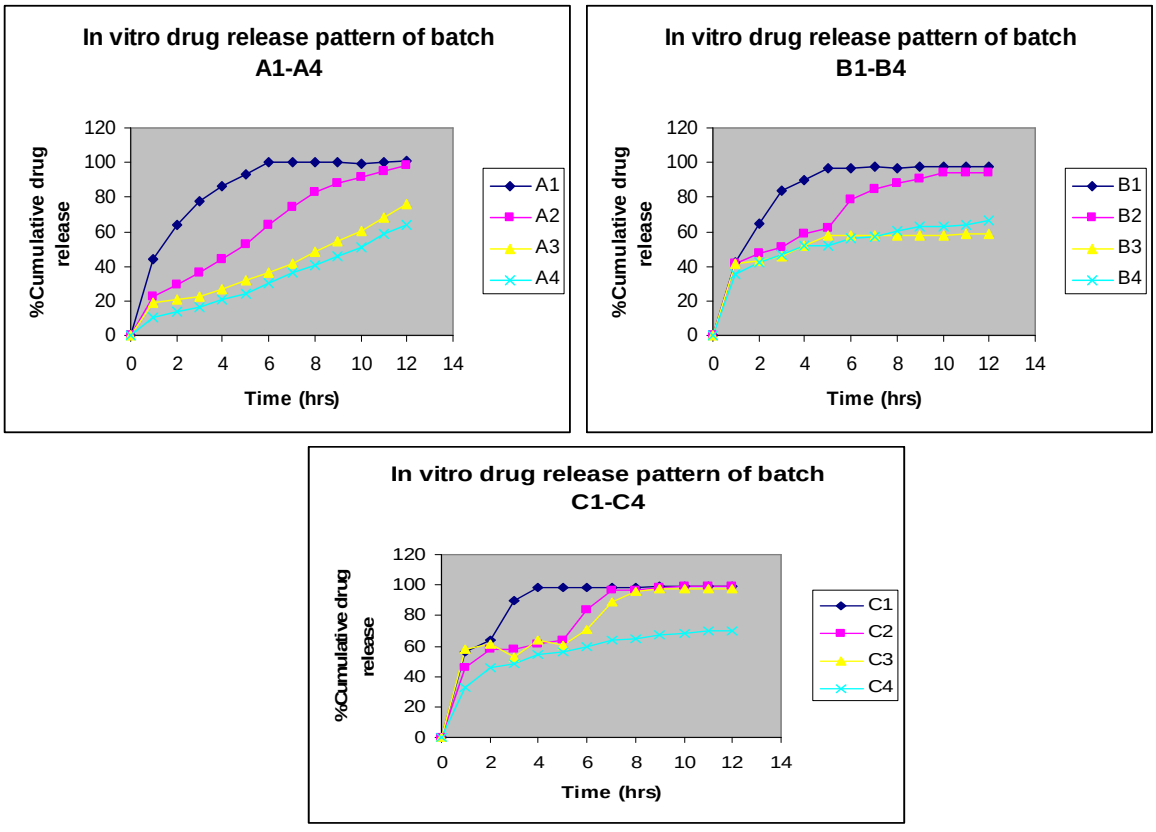


Fig.4: Drug release pattern of microspheres

SEM Study:

Morphology of microspheres was examined by scanning electron microscopy. The smooth surface of such microspheres as seen by SEM might be due to this complete homogeneity of

drug and polymers. The outer surface or the microsphere was smooth and dense, while the internal surface was porous. Some of the microspheres showed a dented surface structure, but they did not fail to float on the surface of the medium, indicating they are not open to the outside.

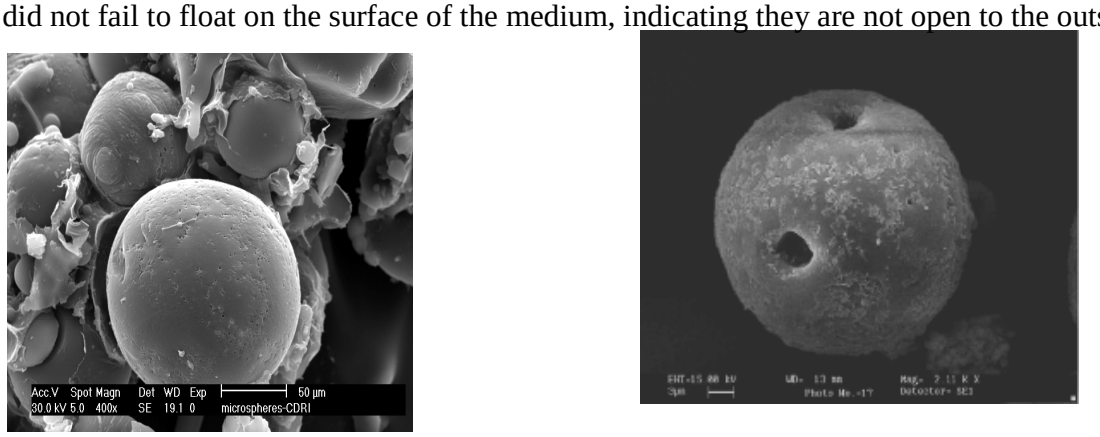


Fig.5: Morphological results with Scanning Electron Microscopy (SEM)

IR INTERPRETATION FOR DRUG AND POLYMER:

Interpretation: Major IR peaks shown of Glipizide are 606, 686, 1160,1332,1528,1688 cm-1(KBr disk).So there is no interaction between drug and polymer.

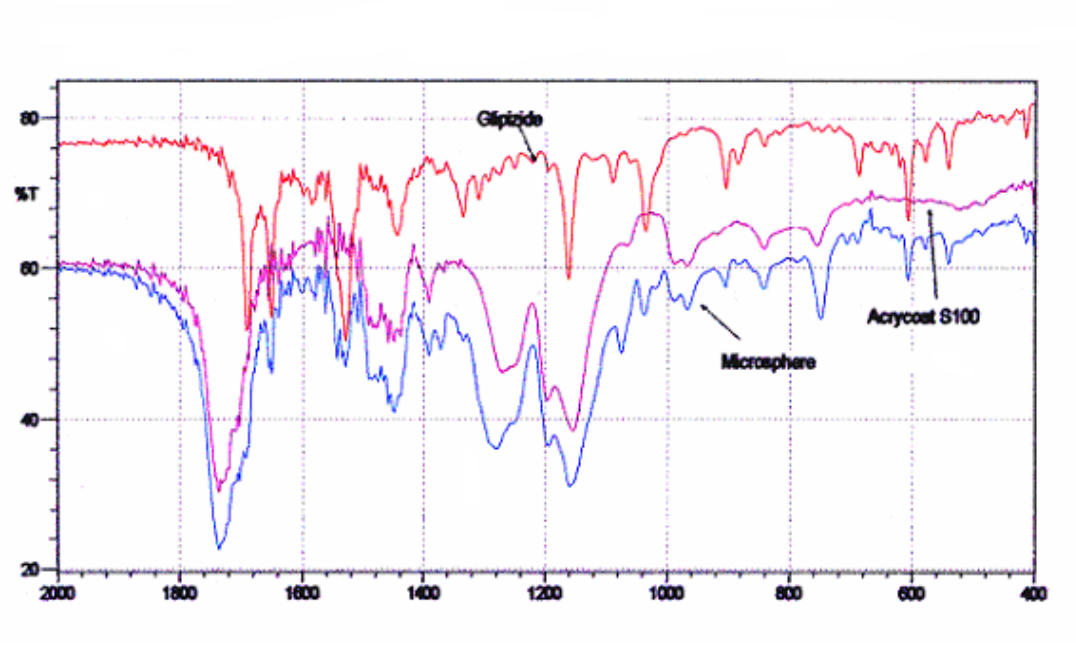


Fig.6 : IR for physical mixture of drug and polymer

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