

FORMULATION AND *IN-VITRO* EVALUATION OF HOLLOW MICROSPHERES OF GLIPIZIDE

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RESEARCH ARTICLE

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ABSTRACT

Present work involves attempts to improve floating time of glipizide by formulation of hollow microspheres incorporating Glyceryl Monostearate and acryflow. The floating microspheres were evaluated for percentage yield, drug loading, In-vitro buoyancy behavior as well as 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 83.88-90.98% and with a particle size range of 320-480 μm . The percent entrapment is about 76 % to 91 % which decreased with increase in HPMC concentration in the formulations. The microspheres with high concentrations of Acrycoat S100 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: Hollow microspheres, floating time, glipizide, HPMC.

INTRODUCTION

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.(1-3) 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

Glyceryl Monostearate has been used in preparation of hollow microspheres by

emulsification solvent diffusion technique. It works as wall membrane reinforcing agent.

Acryflow is hydrogenated castor oil which has been used in the novel pharmaceutical composition containing an active ingredient which is retained in the stomach or upper part of gastrointestinal tract for controlled delivery of medicament. It has been shown that the nature of the drug formulation can influence the dissolution process. Solubility of glipizide increases by addition of HPMC which act as release modifying ingredient of the formulation. Present work involves attempts to improve floating time of glipizide by formulation of hollow microspheres incorporating Glyceryl Monostearate and acryflow. Further studies were done for the improvement of dissolution of the Glipizide by addition of HPMC polymers.

EXPERIMENTAL

Material and Methods

Preparation and Optimization of Acrycoat S100 microspheres of Glipizide (4, 5)

Glipizide, Acrycoat S100, Acrycoat L100, Hydroxy propyl methyl cellulose, Glyceryl Monostearate and acryflow in quantities shown in Table 1 and 2 were dissolved in a mixture of Ethanol, IPA and Dichloromethane (4:6:5). This mixture was poured in a 500 ml water containing 1% PVA maintained at a temperature of 30⁰ C with stirring at 250 rpm. Stirring was continued for 1 hr. to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with D.M.water and dried overnight at 40⁰ C in oven.

Table 1: Composition of microspheres of Batch 1 to B3

Ingredients	B1	B2	B3
Glipizide	500 mg	500 mg	500 mg
Acrycoat S100	1000 mg	1000 mg	1000 mg
Acryflow	-	500 mg	-
GMS	-	-	200 mg

Table 2: Composition of microspheres of Batch B4 to B7

Ingredients	B4	B5	B6	B7
Glipizide	500 mg	500 mg	500 mg	500 mg
Acrycoat S100	800 mg	800 mg	800 mg	800 mg
Acrycoat L100	150 mg	250 mg	-	-
GMS	-	-	300 mg	-
HPMC	-	-	100 mg	100 mg
Acryflow	300 mg	300 mg	-	350 mg

Percentage Yield (6, 7):

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: (8)

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 (9):

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: (10, 11)

Drug Loading was calculated as:

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

In vitro drug release study (5)

Drug release study from the hollow microspheres is complicated because the hollow microspheres float and hence adhere to the inside surfaces of the dissolution basket while the dissolution experiments are in progress, which leads to the nonparticipation of the hollow microspheres or their surface in the release study. Hollow microspheres have the propensity to exhibit a buoyancy effect in vivo, but the development of a dissolution method as a quality control tool with the simulated buoyant condition is difficult.

The drug release rate from floating microspheres was determined using USP XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 10 mg glipizide was taken for dissolution study. The microspheres were placed in a non-reacting mesh nylon bolting cloth that had a smaller mesh size (200 #) than the microspheres. The mesh was tied with a nylon thread to avoid the escape of any microspheres, and glass marble

was used in the mesh to help induce any possible sinking of the microspheres in the dissolution medium. Simulated gastric fluid (SGF, pH 2.0) (500 ml) containing Tween 20 (0.02 w/v %) was used as the dissolution medium and maintained at 37°C at a rotation speed of 100 rpm. 10 ml sample was withdrawn at 1 hr interval and analyzed spectrophotometrically at 276 nm to determine the concentration of drug present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 10

ml of fresh dissolution fluid after each withdrawal. The dissolution studies were repeated using pH 6.8 All experiments were conducted in triplicate. Results of Drug release study are shown in figure 5 and 6.

RESULTS AND DISCUSSION

Preparation and optimization of Acrycoat S100 microspheres of Glipizide

Formulation B1 was found good with Morphology, Yield and Drug Entrapment.

Table 3: Evaluation parameters of microspheres of Glipizide batches B1 to B3

Batches	Mean particle size (µm)	% Yield	% Floating	Incorporation Efficiency
B1	330±35	89%	48%	76%
B2	420±45	87%	87%	94%
B3	370±45	84%	56%	89%

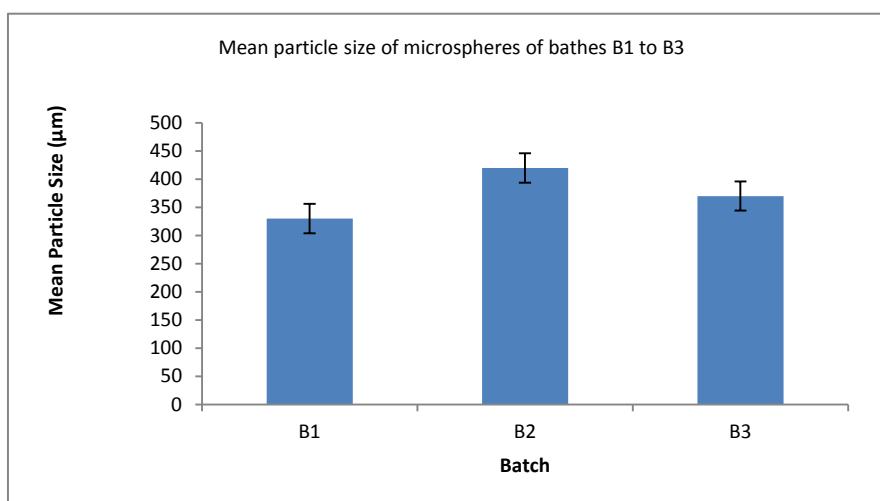


Figure 1: Mean particle size of microspheres of batches B1 to B3

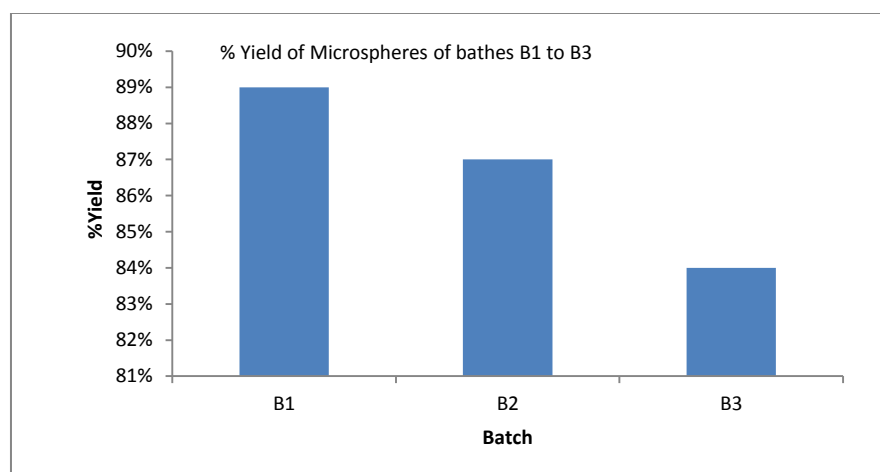


Figure 2: % Yield of Microspheres of batches B1 to B3

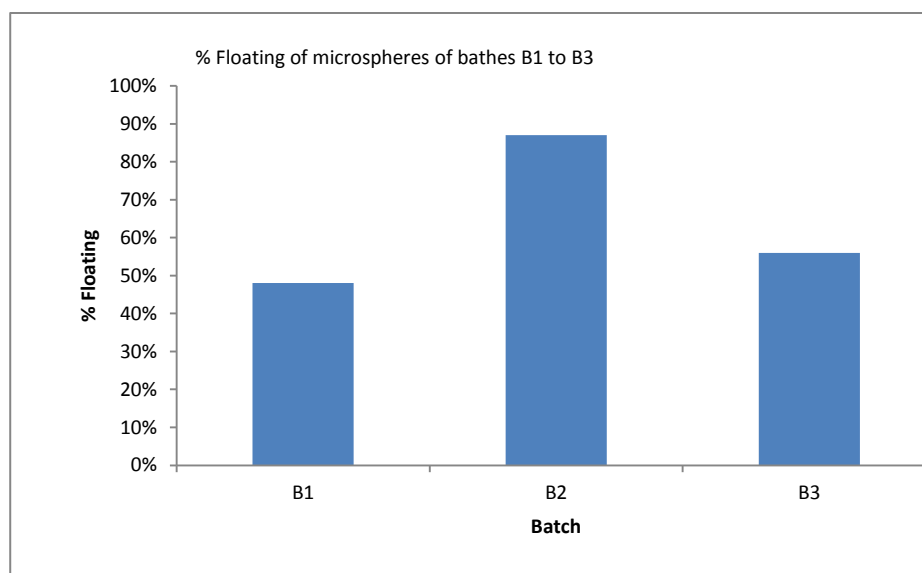


Figure 3: % Floating of microspheres of bathes B1 to B3

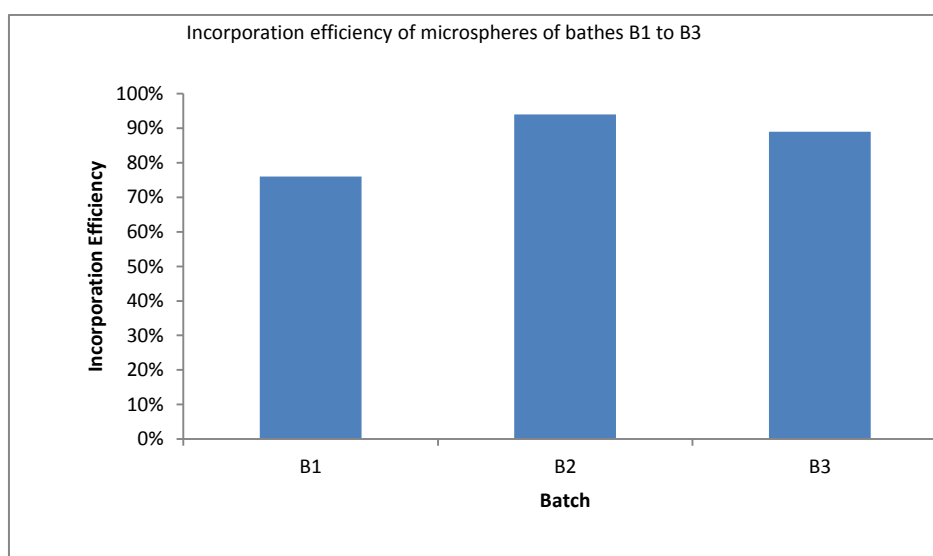


Figure 4: Incorporation efficiency of microspheres of bathes B1 to B3

In Formulation B2, Glyceryl Monostearate was replaced with Acryflow. Acryflow is Hydrogenated Castor Oil, which is having low density and it helps the microspheres to float. Formulation B3 was evaluated for Mean particle size (μm), %Yield%, Floating and Incorporation Efficiency as shown in Table 3. It is comparable to Formulation B1 with respect to all parameters except % floating. Floating is reasonably good in Formulation B2 as compared to Formulation B1.

In dissolution study, due to their floating nature, the microspheres were forcibly immersed into the dissolution media to avoid adherence to the surface of the dissolution jar, thus leading to nonparticipation in the dissolution process. The drug release was extended to more than 12 hr.

From Table 4 it can be seen that drug release rate of the formulation B2 is much less as compared to formulation B1. . As a result there is some improvement in drug release and floating was also satisfactory. So we further decreased the amount of Glyceryl Monostearate and acryflow in formulation B3 but there is no significant increase in dissolution profile while % floating was decreased. So in further experiment, we have to use at least 0.25 mg of Glyceryl Monostearate or acryflow.

Thus, in order to enhance the drug release rate from the microspheres, they were prepared by mixing hydrophilic or hydrophobic polymer in Acrycoat S100. (Batches B4 to B7)

The microspheres prepared upon mixing Acrycoat L100 in Acrycoat S100 (batches B4) was having rough surface. The amount of Glipizide released from microspheres prepared by mixing Acrycoat L100 was high, probably due to facilitated penetration of dissolution

media in the microspheres. Increased amount of Acrycoat L100 (0.2 gm) was used in formulation B5 for further improvement of dissolution rate but it didn't improve dissolution rate significantly.

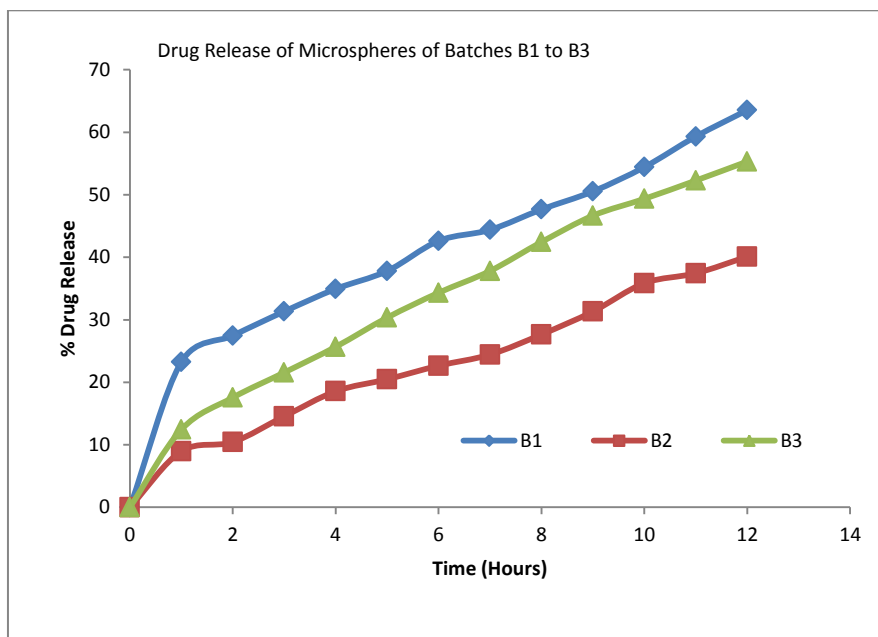


Figure 5: % Drug Release of Microspheres of Batches B1 to B3

Table 4: Evaluation of microspheres of batches B4 to B7

Batches	% Yield	Incorporation Efficiency	% Floating	Mean particle size (μm)
B4	89%	92%	71%	390 \pm 54
B5	87%	78%	80%	480 \pm 32
B6	92%	91%	77%	310 \pm 20
B7	90%	84%	73%	325 \pm 30

In the case of hydroxypropyl methyl cellulose (HPMC) batches B6, buoyancy was high. HPMC was considerably soluble and gelled in dissolution media. Additionally, microspheres are having smooth surfaces. Thus, buoyancy appeared to be high due to the difficulty in penetration of dissolution media through the rigid smooth surfaces.

It has been shown that presence of HPMC improves the solubility of Glipizide in the formulation. This was based on the assumption that polymer dissolution during the time course of study changes the surface tension of the medium and increases drug solubility. This can be attributed to the surface activity of the

polymer. The surface tension of water (at 20°C) is ~72 mN/m and that of HPMC polymer at the same temperature ranges from 42 to 64 mN/m. This reduction in surface tension can increase the wetting of the drug particles and as a result, increase the solubility³.

It was found that the drug release rate and buoyancy of microspheres prepared by co formulating HPMC was relatively improved due to gelation in dissolution media. Therefore, the effect of HPMC mixing ratio on physicochemical properties and drug releasing behaviors of the microspheres were investigated as shown in Table 4. Although the recovery of microspheres appeared unchanged by HPMC

ratio, the buoyancy decreased with increasing HPMC ratio. These results were attributable to the conversion of spherical microspheres to needle-like particles possessing no hollow structure. In addition, the dissolution media can readily penetrate into microspheres the increased dissolution of HPMC in the solution. The amount of Glipizide released from microspheres in 0.1N HCl containing 0.02% Tween 20 (pH 1.2) increased with increasing HPMC ratio. This behavior was explained by the increased contact area of particles with the medium due to the poor buoyancy associated with increased HPMC ratio. The amount of Glipizide released from microspheres in dissolution media significantly increased in association with increased HPMC ratio. In conclusion, a recommendable preparation formulation of microspheres to increase the bioavailability of Glipizide is formulation B6 due to their desired drug release and floatable properties. Formulation B7 containing 0.25 gm acryflow still need improvement in drug release. So quantity of HPMC was increased to 0.2 gm. Similarity values between drug release profile of formulation B6 to that of theoretical profile IS 86.509.

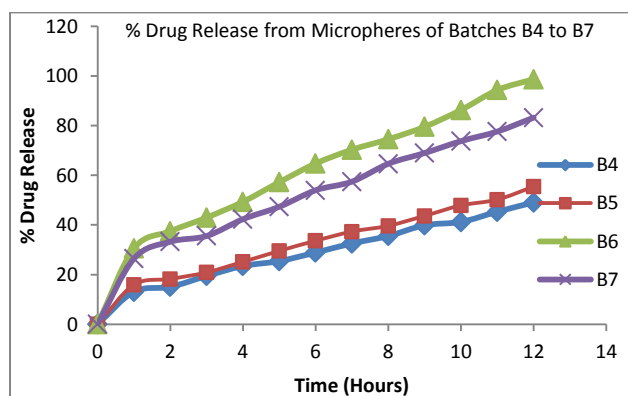


Figure 6: % Drug Release from Microspheres of Batches B4 to B7

CONCLUSION

Present work involves attempts to improve floating time of glipizide by formulation of hollow microspheres incorporating Glyceryl Monostearate and acry flow. The floating microspheres were evaluated for percentage yield, drug loading, in-vitro buoyancy behavior as well as in-vitro drug release. The micrometric properties were found to be good and scanning electron microscopy shows that the

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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