

## Development and Evaluation of Sustained Release Microspheres of Glibenclamide by Emulsion Solvent Evaporation Method

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### Abstract

Oral administration of Glibenclamide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas. Gastro intestinal absorption of Glibenclamide in man is uniform, rapid and essentially complete having peak plasma concentration 1-3 hours after single oral dose and half-life of elimination three hours in normal subjects. The objective of the present investigation was to formulate and evaluate microspheres of Glibenclamide by emulsion – solvent evaporation method. Microspheres were prepared using Ethyl Cellulose N100 and characterized for their micromeritic properties, particle size and encapsulation efficiency. The in-vitro release studies were performed using pH 1.2 (0.1N HCL) buffer revealed that the drug release was sustained up to 24 hours. SEM studies showed that the microspheres were spherical and porous in nature. In-vivo studies were performed in healthy rabbits to analyze the floating efficiency of microspheres. Microspheres of glibenclamide were prepared successfully and could help to manage better the complications involved in Type II diabetes.

**Keywords:** Microspheres; Type II Diabetes; *In vitro* release; *In vivo* floating studies

### Introduction

Glibenclamide in oral conventional dosage form has the dosage regime of three times a day due to short elimination half-life of 3 hours [1,2]. The extended release single unit dosage form has the demerits of all and nothing effect, person to person variability and non-uniform drug release [2,3]. These complains certainly can be overcome by the sustained release multiunit dosage form like microspheres. The principal aim of the investigation undertaken was to develop a Multi-Particulate Drug Delivery System for non-insulin dependent diabetes mellitus drug, Glibenclamide. In the present investigation, microspheres were prepared using emulsion-solvent evaporation technique and Ethyl Cellulose N100 was used as a rate retardant polymer. Ethyl Cellulose N100 is a water insoluble polymer which is widely used as a wall material for controlled release microparticles. This is due to its biocompatibility, good stability, easy fabrication and low cost.

### Materials and Method

#### Materials

Glibenclamide was obtained as gift sample from Inga Laboratories, India. Ethyl Cellulose N100 was obtained from Hercules Incorporated, Aqualon division, India. Tween 80 was obtained from Suyojit Chemicals Works Private Limited, India. Other chemicals used were of analytical reagent grade.

#### Preformulation study

The presence of incompatibilities between an active drug substance and different excipients forms an important part of the preformulation. The drug excipient interaction was studied by Differential Scanning Calorimeter (DSC). DSC measures heat flows coupled with transitions in materials as a function of time and temperature in a controlled atmosphere. This provides qualitative and quantitative information about physical and chemical changes that involve endothermic or exothermic reactions.

### Preparation of microspheres

Emulsion Solvent evaporation method was used for the preparation of Glibenclamide microspheres [4-6]. Glibenclamide was dissolved in organic solvent containing polymer by stirring with manual stirring with glass rod till it dissolved completely. This solution was poured slowly into the continuous aqueous phase containing emulsifying agent. This resulted in formation of o/w emulsion. This emulsion was stirred at a constant speed till the organic solvent evaporated which led to the precipitation of polymer, thus encapsulating the drug and hence formation of rigid microspheres. After removal of organic solvent, the microspheres formed were collected by filtration, washed 3-4 times with distilled water. Microspheres were allowed to dry at room temperature for 24 hours. Nine different batches of microspheres were prepared by changing drug to polymer ratio and stirring speed. The composition of formulated batches (Code: EC1-EC9) of Glibenclamide microspheres is shown in Table 1.

### Evaluation of microspheres

The prepared batches of microspheres were characterized for their micromeritic properties (Particle size, angle of repose, bulk density, tapped density and Carrs index) and encapsulation efficiency as per the standard procedures reported in literature [1,3].

The *in vitro* dissolution of batch EC5 was carried out in 900 ml of pH 1.2 Buffer as the dissolution medium using USP Type II apparatus (TDT -08L, Electrolab) apparatus at 75 rpm as per the dissolution

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Batch No.	EC1	EC2	EC3	EC4	EC5	EC6	EC7	EC8	EC9
Drug:Polymer Ratio	1:1	1:1	1:1	1:2	1:2	1:2	1:3	1:3	1:3
Ethanol (ml)	5	5	5	5	5	5	5	5	5
Dichloromethane(ml)	5	5	5	5	5	5	5	5	5
Tween 80(%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Stirring Speed (RPM)	700	800	900	700	800	900	700	800	900
Stirring Time(hours)	4	4	4	4	4	4	4	4	4
Distilled water (ml)	100	100	100	100	100	100	100	100	100

Table 1: Composition of various formulations of Glibenclamide microspheres

conditions recommended by US-FDA OGD. The temperature was maintained at  $37 \pm 0.5^\circ\text{C}$ . The dissolution was carried out for 24 hours. The sampling volume was 5 ml. The time points included were 0.5 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, 9 hr, 10 hr, 11 hr, 12 hr, 22 hr, 23 hr and 24 hrs. The absorbance's of the sample at different time intervals were carried out using UV visible spectrophotometer (UV 1800, Shimadzu) at  $\lambda_{\text{max}}$  of 300 nm. The drug release was calculated using calibration curve subjected to various kinetic models such as zero order, first order, Higuchi model, Hixson crowell model and Korsmeyer Peppas model to study the mechanism of release of drug from microspheres.

*In-vivo* floating efficiency of microspheres was studied in healthy rabbits [7]. Scanning electron microscopy (SEM) was performed on optimized batch of microspheres to study the surface morphology of microspheres.

## Results and Discussion

The thermograph of DSC of glibenclamide pure drug (Figure 1) showed a sharp endothermic peak around  $175^\circ\text{C}$  whereas no such peaks were observed in the thermograph of the formulation (Figure 2) indicating the drug has been dispersed thoroughly at molecular level in the formulation. Therefore, it may be concluded that the drug is in intact form within the formulated microspheres.

Thermal behavior of glibenclamide microspheres with Ethyl cellulose N100 by DSC shows no peak indicating no drug polymer interaction. But its mixture with Ethyl cellulose N100 reduce the number of peaks and peak heights which suggest that the crystalline form got converted to amorphous form and it is in good agreement with enhanced solubility. Scanning electron microscopy images demonstrated spherical shaped microspheres.

The prepared glibenclamide microspheres by solvent evaporation technique were discrete, spherical and free flowing having good drug entrapment. The results of micromeritic properties of microspheres and percentage drug entrapment (Entrapment efficiency) of various batches of microsphere are summarized in Table 2. The results indicated that all the prepared microspheres possess good flow property with particle size ranging from  $111.13 \mu\text{m}$  to  $140.12 \mu\text{m}$ . The batch EC5 showed highest drug entrapment of about 82.33%.

The *in vitro* release data indicated that batch no. EC5 shows satisfactory sustained release through microspheres for 24 hrs and hence was considered as optimized batch. The *in-vitro* drug release data of optimized batch is represented in Table 3.

The *in vivo* floating behavior of ethyl cellulose microspheres loaded with barium sulphate was investigated by radiographic images (X-ray photographs) of rabbit's stomach at specific periods. The amount of X-ray opaque material in these hollow was sufficient to ensure visibility by X-ray but at same time the amount of barium sulphate (15 mg) was low enough to enable the hollow microspheres to float. The

hollow microspheres did not adhere to the gastric mucous and floating on the gastric fluid for more the 12 h. This was evident by the X-ray photographs taken at 12 h & 24 h (Figure 3) [8,9].

The *in-vivo* study carried out in rabbits confirmed that the microspheres remained in the floating state till 24 hours.

In order to assess the kinetic release of the formulation, it was subjected to various kinetic release models as summarized in Table 4.

It could be seen that the formulation followed Korsmeyer-Peppas model with highest regression coefficient value of 0.991.

Korsmeyer and Peppas (1983) equation i.e  $Q_t / Q_\infty = K_k t^n$ , where  $Q_t / Q_\infty$  is the fraction released by the drug at time  $t$ ,  $K_k$  is a constant incorporating structural and geometric characteristic and  $n$  is the release exponent characteristic for the drug transport mechanism. Table 5 summarizes the release exponent 'n' value for different release kinetics reported in literature [10].

The value of  $n$  as estimated by linear regression of  $\log Q_t / Q_\infty$  vis  $\log t$  of formulation EC5 was 0.964 indicated that drug release from microspheres followed Anomalous (non-fickian) Diffusion.

The SEM photomicrographs of optimized batch no. EC5 depicted in Figure 4. Photomicrographs show that the microspheres are white, spherical with smooth surface.

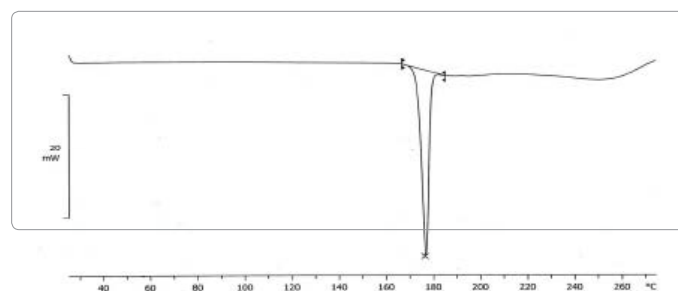


Figure 1: DSC of pure Glibenclamide

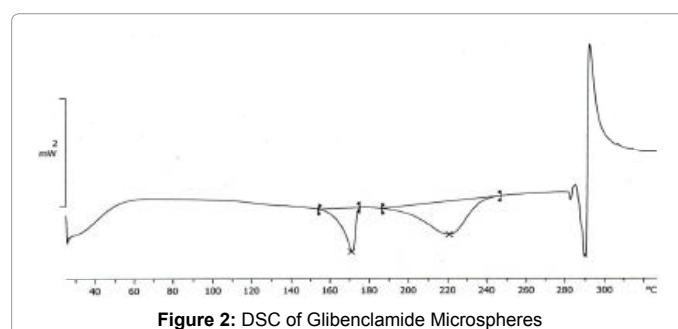


Figure 2: DSC of Glibenclamide Microspheres

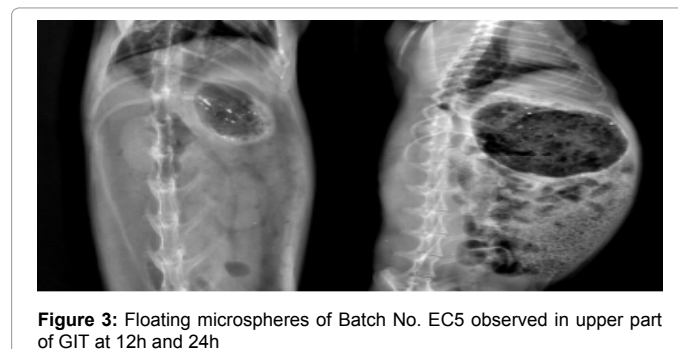


Figure 3: Floating microspheres of Batch No. EC5 observed in upper part of GIT at 12h and 24h

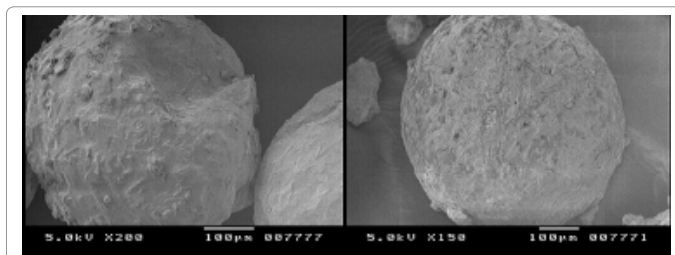


Figure 4: SEM images of glibenclamide loaded microspheres of Batch No. EC5

Batch No.	Angle of Repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index	Average Particle Size (µm)	Drug entrapment (%)
EC1	25.16	0.767	0.898	14.58	126.52	59.59
EC2	23.87	0.523	0.604	13.41	129.56	74.12
EC3	30.43	1.32	1.53	13.72	125.42	61.39
EC4	28.26	1.11	1.25	11.2	111.13	64.8
EC5	29.42	1.16	1.60	12.29	131.21	82.33
EC6	25.21	0.519	0.606	13.64	136.91	78.5
EC7	23.31	0.781	0.903	13.49	134.51	72.59
EC8	27.53	0.749	0.884	15.28	134.49	76.03
EC9	27.14	0.508	0.591	13.98	140.12	78.3

Table 2: Evaluation of Glibenclamide microspheres

Time (Hours)	% CR (pH 1.2)	Time (Hours)	% CR (pH 1.2)
0.5	4.1222	8	62.3749
1	9.1764	9	67.3850
2	20.4807	10	71.6949
3	24.0329	11	78.1270
4	31.1184	12	81.0368
5	41.0352	22	96.6556
6	50.2572	23	100.2917
7	55.96	24	101.8141

% CR: Percentage cumulative drug release

Table 3: *In vitro* dissolution study of Batch No. EC5

Model	Regression Coefficient (R <sup>2</sup> )
Zero Order	0.870
First Order	0.949
Korsmeyer Peppas	0.991
Higuchi	0.969
Hickson Crowell	0.975

Table 4: Regression analysis of different models for Batch No. EC5

'n' values	Mechanism of Release
n < 0.5	Quasi-Fickian Diffusion
0.5	Fickian Diffusion
0.5 < n < 1.0	Anomalous (non-fickian) Diffusion
1	Non-Fickian Case II Zero Order
n > 1.0	Non-Fickian Super case II

Table 5: 'n' value for different release kinetics

## Conclusion

Based on the results obtained for *in-vitro* drug release, it was concluded that microspheres formulated with glibenclamide to ethyl cellulose ratio 1:2 and keeping as stirring speed 800 RPM shows satisfactory drug release up to 24 hrs. These microspheres were also evaluated for *in-vivo* floating ability in the upper part of the GIT (gastric fluid), so that it would be retained in the upper part of GIT and subsequently sustain the release of drug for a period of as long as 24 h. The *in-vivo* floating ability of microspheres was captured at different

time intervals with the help of X-Ray machine and it was concluded that the microspheres withstood the motility of the stomach and were successfully retained in the GIT. Microspheres of glibenclamide were prepared successfully and could help to manage better the complications involved in Type II diabetes.

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