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Formulation and evaluation of glipizide microspheres

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Abstract
The present investigation was aimed to formulate and evaluate the gastro-retentive floating microspheres of glipizide using hydrophilic polymers such as hydroxy propyl methylcellulose (HPMC) and Ethyl cellulose by solvent evaporation technique. The floating microspheres were evaluated for micromeritic properties, scanning electron microscopy, Incorporation efficiency, percentage yield, buoyancy and *in vitro* drug release. From the results of studiesit shows that formulation F9 was found to be satisfactory in terms of excellent micromeritic, Incorporation efficiency 96.38±2.84% percentage yield 93.780±0.55% in-vitro buoyancy 94.95±1.07% and *in vitro* drug release 94.60978±1.00%. The scanning electron microscopy confirmed the hollow nature of microspheres with pores on the surface which imparted floating properties to the prepared floating microspheres. Among all the developed formulations, F9 was found to be the best as it exhibited highest drug release (94.60%) in 12 hr.

Keywords: glipizide, floating, microspheres, gastro retentive and controlled release

Introduction
Floating microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability, target drug to specific sites, decreasing dosing frequency, and to improving patient compliance [1]. Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes. It is used as adjunct to diet and in the management of type II (non-insulin dependent) diabetes mellitus, and in patients whose hyperglycemia cannot be controlled by diet and exercise alone. Glipizide stimulates insulin secretion from the β cells of pancreatic islets tissue, increases the concentration of insulin in the pancreatic vein and may increase the number of insulin receptors [2]. One of the very common and suitable methods to prepare these polymeric microspheres is solvent evaporation method using polymers like hydroxy propyl methyl cellulose, Ethyl cellulose [3]. Various microsphere formulations were prepared using solvent evaporation method as described by Gattani [4]. In the present work Floating microspheres of glipizide were prepared by solvent evaporation method. The drug was encapsulated with Ethyl cellulose and hydroxy methyl cellulose in various combinations of polymers ratios. Which is most simple and of high yield method.

Materials and Methods
Materials
Glipizide was a gift sample from Agrawal Pharmaceuticals, Laxmi Nagar, Delhi, India. Ethyl Cellulose, HPMC K4M, HPMC K15M, HPMC K100M, Ethanol, Dichloromethane, Tween 20 Loba Chemie Pvt. Ltd., Mumbai India. Methanol Nice chemical Ltd, Kerala. All other chemicals and reagents were of analytical grade and were used as they were procured. Distilled water was used in all experiments.

Preparation of Microspheres of Glipizide [5, 6]
In this work, solvent evaporation method has been employed to prepare microspheres of Glipizide with ethyl cellulose, hydroxyl propyl methyl cellulose. The drug and polymer in different proportions are weighed as shown in (Table 1) and the polymer was co-dissolved into previously cooled mixture of ethanol: dichloromethane at room temperature. The mixture was stir vigorously to form uniform drug polymer dispersion. The above organic phase was slowly added to 100 ml distilled water containing 0.01% tween 80 by maintain the temperature at 15 – 20°C and emulsified by stirring at 1200 rpm for 15 min. microspheres formed were filtered, washed with water and sieved between 50 and 30 mesh size, and dried overnight for 40°C.

Table 1: Formulation of floating microspheres of Glipizide

Ingredient (gm)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose	0.500	1.334	2.250	0.500	1.334	2.250	0.500	1.334	2.250
HPMC K4M	0.500	0.666	0.750	-	-	-	-	-	-
HPMC K15 M	-	-	-	0.500	0.666	0.750	-	-	-
HPMCK 100M	-	-	-	-	-	-	0.500	0.666	0.750
Glipizide	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Dichloromethe	30	30	30	30	30	30	30	30	30
Ethanol	30	30	30	30	30	30	30	30	30

Results and Discussion
Pre formulation Studies
Pre formulation studies are necessary to understand the physicochemical properties of the drug and the compatibility of the other excipients used in the formulation. The results of the various pre formulation characterizations such as solubility, melting point, calibration curve, compatibility studied were given below.

A. **Solubility studies:** Glipizidevery soluble in water, soluble in ethanol, sparingly soluble in methylene chloride.
B. **Determination of Melting Point:** Melting point of glipizide was found to be 182°C.
C. **Determination Of λmax**: Absorption maximum (λ_{max}) was found to be 272 nm.

D. Development of Calibration Curve for Glipizide: The concentration ranges and data are reported in Table 2. Calibration curve of Glipizide was plotted using this data and shown in the Figure 1.

Table 2: Calibration Curve for Glipizide in 0.1 (N) Hcl

Sl. No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	1	0.050± 0.003
3.	2	0.103± 0.011
4.	3	0.156± 0.021
5.	4	0.209± 0.028
6.	5	0.256± 0.040
7.	6	0.312± 0.008
8.	7	0.365± 0.023
9.	8	0.425± 0.026
10.	9	0.485± 0.016
11.	10	0.565± 0.020

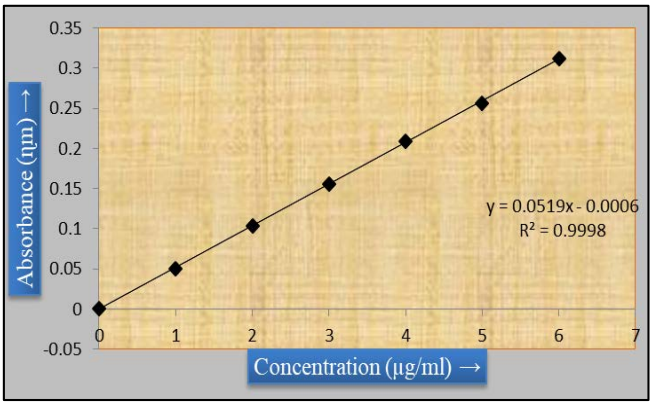

Fig 1: Calibration curve of Glipizide in 0.1 (N) Hcl at 272 nm

E. FT-IR study

FT-IR study was employed to ascertain the compatibility of the drug Glipizide with EC and HPMC. Both the spectra were compared for confirmation of common peaks. Specific peaks functional group of pure drug and formulation showed at 2980.12cm^{-1} (C-H stretching of aromatic), 3367.82cm^{-1} (N-H stretching), 2939.61cm^{-1} (C-H stretching of aliphatic), 1695.49 cm^{-1} (C=O stretching of ester), 1101.39 cm^{-1} (C-O stretching of ester), 1377.22cm^{-1}(C-H bending of aliphatic), 804.34cm^{-1} (C-H bending aromatic). FTIR spectra showed that the characteristics bands of Glipizide were not altered after successful drug loading without any change in their position, indicating no chemical interactions between the drug and used polymers.

Evaluation of Glipizide Microspheres

A. Micromeritic Property of Glipizide Microspheres

Nine batches of Glipizide Microspheres were prepared. The prepared microspheres were evaluated for its micromeritic properties i.e. mean Particle size, Angle Repose, Bulk density, Tapped density, Hauser's ratio, and Carr's index.

Table 3: Micromeritic property of microspheres of Glipizide

Formulation Code	Mean particle size	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hauseners ratio	Carrr's index	Angle of repose
F1	387.32±2.54	0.3572±0.010	0.4019±0.018	0.8902±0.04	11.13±0.11	32.49±1.71
F2	452.9±2.52	0.41240±0.012	0.4647±0.015	0.8840±0.05	12.03±0.64	27.72±1.89
F3	479.52±3.25	0.4308±0.007	0.4955±0.014	0.8681±0.03	13.46±0.24	31.88±2.78
F4	389.5±3.88	0.3575±0.014	0.4026±0.014	0.8879±0.01	11.3±0.33	27.00±1.93
F5	456.84±2.27	0.4150±0.015	0.4678±0.015	0.8871±0.02	11.4±0.26	26.02±1.80
F6	480±2.25	0.4319±0.012	0.4973±0.021	0.8684±0.01	13.2±0.33	26.56±1.43
F7	476.9±2.36	0.3889±0.018	0.4375±0.022	0.8889±0.03	12.7±1.5	26.80±1.68
F8	485.82±2.3	0.4568±0.015	0.5160±0.027	0.8852±0.01	12.4±0.86	27.11±1.59
F9	489.24±3.43	0.5763±0.017	0.6508±0.015	0.8855±0.02	12.8±1.5	26.56±1.68

*mean±SD, n=3

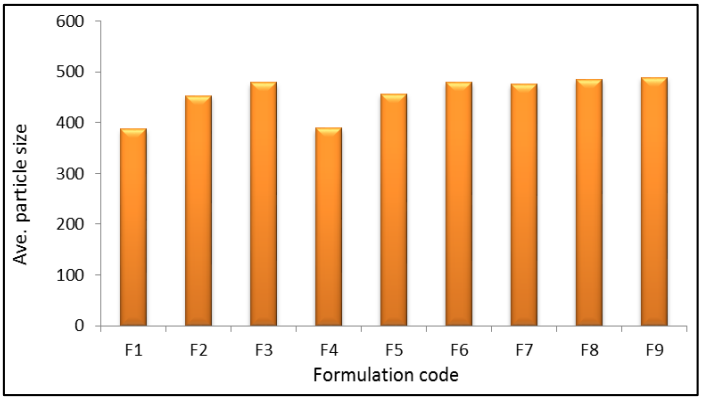

Fig 2: Comparison of average particle size of microspheres of Glipizide

B. Yield of microspheres

The percentage yield of floating microsphere formulation F1 to F9 containing different grades of HPMC & ethyl-cellulose & formulation was in range of 67.84±0.64 to 93.78±0.35. To observe the effect of polymer concentration on the percentage yield of the microspheres, formulations were prepared at varying concentration of polymer. The yield of the microspheres increased with increasing polymer concentration

C. *In-vitro* buoyancy

The purpose of preparing floating microspheres was to extend the gastric residence time of a drug. The buoyancy test was carried out to investigate the flotability of the prepared microspheres. The microspheres were spread over the surface of a simulated gastric fluid and the fraction of microspheres buoyant and settled down as a function of time was quantities. The *In vitro* buoyancy of formulation F1 to F9 containing different grades of HPMC & ethyl-cellulose & formulation was in range from 76.66±2.05 to 94.95± 1.07 respectively (as shown in table). Among all formulation F9 was found to be highest *in-vitro* Buoyancy 94.95±1.07. The results also showed a tendency that the larger the particle size, the longer floating time.

D. Incorporation efficiency

The incorporation efficiency of formulation F1 to F9 containing different grades of HPMC & ethyl-cellulose & formulation was in the range of 77.43±2.72 to 96.38± 2.84 respectively (as shown in table) Among all formulation F9 96.38±2.84 Results demonstrated that increase in concentration of EC increased the entrapment of the drug. The drug entrapment efficiency was found to be good in all the formulation. The results of determination of Percentage yield, *In-vitro* buoyancy, and Incorporation efficiency of the prepared Glipizide microspheres values were shown in Table no 4 and Figure no 2, 3, 4 respectively.

Table 4: Percentage yield, *in-vitro* buoyancy and incorporation efficiency of floating microspheres of Glipizide

Formulation code	Percentage yield Mean±SD*	*In vitro*-buoyancy Mean±SD*	Incorporation efficiency Mean±SD*(%)
F1	67.840.64	76.66±1.52	77.43±2.72
F2	85.59±0.69	82.39±2.07	87.34±2.84
F3	92.5±0.51	89.96±1.04	91.94±2.17
F4	70.67±0.66	75.43±2.02	67.11±3.01
F5	82.26±0.43	83.96±1.07	88.11±2.59
F6	89.84±0.72	90.39±2.00	92.30±2.88
F7	88.63±0.65	79.33±1.32	79.76±1.58
F8	92.29±0.74	87.12±1.00	93.91±2.02
F9	93.780±0.55	94.95±1.43	96.38±2.34

*Standard deviation (SD), n=3

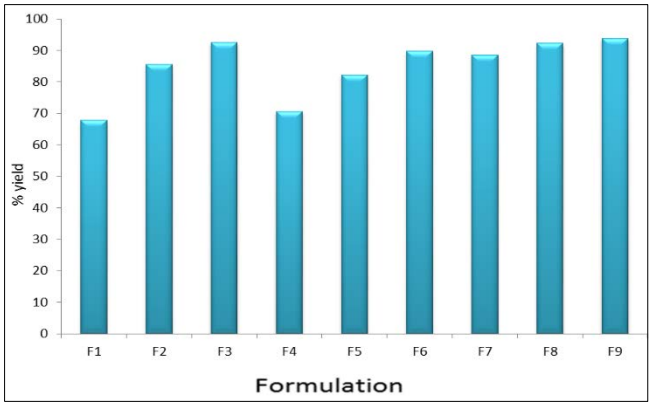

Fig 3: comparison of yield of microspheres of Glipizide

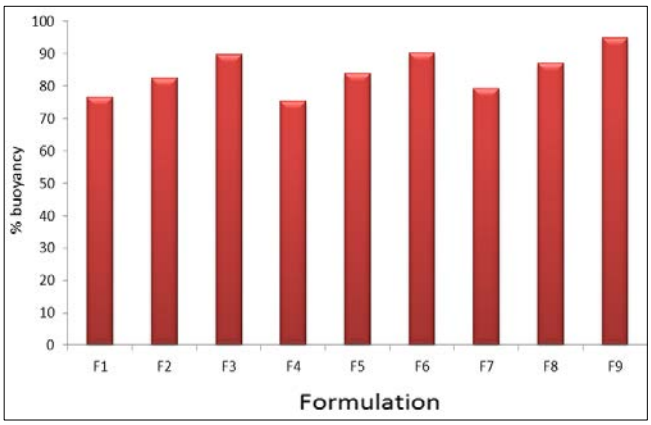

Fig 4: comparison of percent *in-vitro* buoyancy of microspheres of Glipizide

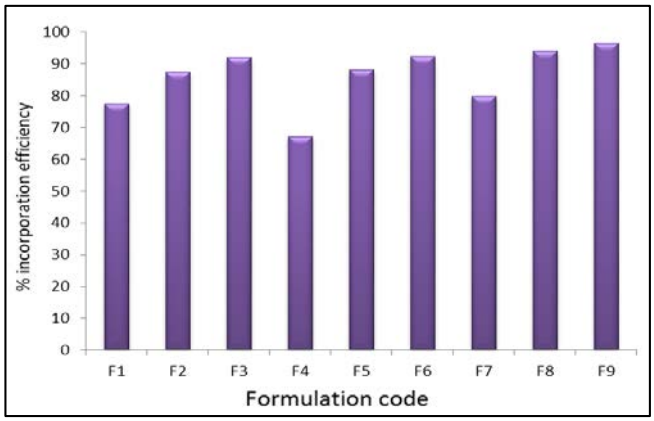

Fig 5: Comparison of drug incorporation efficiency microspheres of Glipizide.

E. *In-Vitro* Release Study of Glipizide Microspheres

In-vitro drug release studies of Glipizide from floating microspheres were performed in pH 1.2 for 12 hrs. by using dissolution test apparatus. It was found that *in vitro* drug release of formulation F1 to F9 containing ethyl-cellulose and various grades of HPMC. F1, F2, F3, F4, F5, F6, F7, F8 show percentage drug release 84.91±0.95 to93.31±2.11 at end of 12 hour. Amongst the formulation F9 was found to be the best formulation as it release Glipizide 94.06% in a sustained manner with constant fashion over extended period of time (after 12 hr). After performing the *In-vitro* Drug release of the prepared Metoclopramide microspheres, the result which was found is given below.

Table 5: *In-vitro* Drug release from formulation F7 to F9

Sl.No.	Time (hrs.)	Cumulative % Drug release (CPR) Mean ± SD		
		F7	F8	F9
1	1	1.158301±0.67	1.853282±030	5.328185±0.36
2	2	8.108108±0.29	17.60618±0.29	13.89961±0.19
3	3	22.47233±0.98	31.97117±0.21	31.28005±0.19
4	4	33.37066±3.45	40.33256±1.61	41.03115±2.10
5	5	41.7444±1.67	58.45714±1.48	51.96937±2.10
6	6	51.99949±1.02	62.939±1.74	59.23115±1.10
7	7	58.80103±1.82	67.45019±2.37	66.28417±1.25
8	8	64.69653±1.29	75.2296±1.67	70.57735±1.55
9	9	69.68417±1.72	82.55547±0.91	78.82445±2.15
10	10	76.539±2.32	86.65148±1.20	83.84067±1.10
11	11	85.95393±1.01	89.374±1.35	89.56551±1.05
12	12	90.2852±1.65	93.96216±3.30	94.60978±1.00

*Standard deviation (SD), n=3

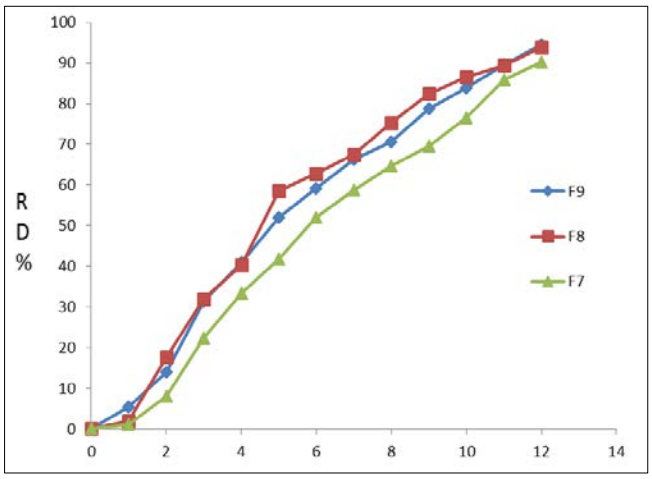

Fig 6: CPR of Glipizide from formulation F7 to F9

F. Release kinetics profile

The results suggest that, the drug was released by mixed order kinetics. To ascertain, the drug release mechanism the in-vitro release data were also subjected to Higuchi's diffusion equation (Q=k.t1/2) the r-values of all the formulations of Higuchi's equations were 0.9800 and above (as shown in table). It suggests that the Higuchi diffusion plots of all the formulations were fairly linear and we can conclude that the drug released by Higuchi's diffusion mechanism. The formulations are also treated to Peppa;s plots by taking log percent versus log time. The plots are found to be fairly linear and the regression values (n value) of all formulations ranges from lowest 0.5004 to highest 0.6572 (as shown in table) which in the range of $0.45 < n < 0.89$. This suggests that the drug was released by non-Fickian control (Anomalous diffusion) with swelling.

Table 7: Kinetics data obtained from *In-Vitro* drug release profile for microspheres of Glipizide

Formulation Code	Zero order (r^2 Value)	First order (r^2 Value)	Higuchi Matrix (r^2 Value)	korsmeyer – Peppas	
				r^2 Value	'n' Value
F1	0.9767	0.9707	0.9927	0.8967	0.3349
F2	0.9360	0.9625	0.9811	0.7731	0.5642
F3	0.9816	0.9436	0.9965	0.8915	0.4540
F4	0.9850	0.9471	0.9944	0.8977	0.3542
F5	0.9760	0.9585	0.9929	0.9362	0.5244
F6	0.99804	0.9369	0.9954	0.9135	0.5728
F7	0.9860	0.9487	0.9942	0.9173	0.3849
F8	0.9547	0.9768	0.9887	0.9551	0.8553
F9	0.9738	0.9449	0.9956	0.8687	0.6580

Conclusion

The purpose of present work was to develop floating microspheres of Glipizide for controlled drug delivery. From the results it seem that formulation F9 was found to be satisfactory in terms of excellent micrometrics properties, yield of microsphere (93.78%), incorporation efficiency (96.38%), buoyancy (94.95%) and highest *in-vitro* drug release of (94.60%) in a controlled manner with constant fashion over extended period of time for 12 hrs. It was observed that concentration of ethyl cellulose affected all the evaluation parameter significantly. Hence, finally it was concluded that the prepared floating microspheres of Glipizide may prove to be potential candidate for safe and effective controlled drug delivery over an extended period of time which can reduce dosing frequency.

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