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PREPARATION AND EVALUATION OF GLIPIZIDE MICROSPHERES USING HYDROPHOBIC BIODEGRADABLE POLYMER FOR SUSTAINED DRUG DELIVERY

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ABSTRACT

The objective of the current investigation is to formulate ethylcellulose and eudragit based sustained release microspheres, containing glipizide as a model drug. Glipizide is generally prescribed in type-II anti-diabetic drug and belongs to second-generation sulfonylureas. Due to its short biological half-life, there is an urgent need of such a delivery system which can overcome its multidosing per day through delayed release and extended half-life. Microspheres were prepared by emulsification-solvent evaporation method. Two-Two batches were prepared with different proportions of core to coat meterials (drug: polymer = 0.5:1 and 1:1 w/w). The microspheres were evaluated for various parameters like flow properties, percentage yield, drug content, particle size, surface morphology studies and *in vitro* drug release studies. Ethyl cellulose and Eudragit Microspheres of Glipizide were successfully prepared. Results showed that all the microspheres were found spherical in shape, having smooth surface, high percentage yield and drug content. *In vitro* drug release studies showed effective controlled release of drug from microspheres.

KEYWORDS: Glipizide, emulsification-solvent evaporation method, ethylcellulose, eudragit, etc.

INTRODUCTION

The efficacy of a drug in a specific application requires the maintenance of appropriate drug blood level concentration during a prolonged period of time. However the conventional administration of drugs, gives a poor control of the concentration of these substances in

plasma because of variations in the concentration of the bioactive product, once a specific dose has been administered.[1] The conventional dosage systems can give rise to alternative periods of inefficacy or toxicity. In the recent years, considerable attention has been focused on the development of Novel Drug Delivery Systems (NDDS).[2-3] Number of advances took place in the field of Controlled drug delivery systems in the last few decades. During the preliminary stages of research on controlled drug delivery, major accent was focused on the development of zero-order devices. The primary objective of zero-order release is to up-hold constant drug concentration in blood for a prolonged period of time. Microspheres have played a vital role in the development of controlled/sustained release drug delivery systems.[4, 5] Microspheres have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and controlled drug release. Microsphere carrier systems made from biodegradable polymers have attracted considerable attention for the last several years in controlled/sustained drug delivery.[6-7] In a majority of studies the homo and copolymer have been used for drug delivery application because they can be fabricated into a variety of morphologies, including films, rods, and micro particles by compression molding, solvent casting, solvent evaporation technique and phase separation technique.[8-11] After the employment in the body, biodegradable polymers of natural and synthetic origin like Eudragit (L-100 & S-100) and ethyl cellulose have a unique advantage that after performing their function they degrade into non-toxic monomers.[12]

Wide ranges of microencapsulation techniques have been developed; the selection of the techniques depends on the nature of the polymer, the drug, and the intended use. When preparing controlled release microspheres, the choice of the optimal method has utmost importance for the efficient entrapment of the active substance.[13] Pharmaceutically acceptable techniques using hydrophobic biodegradable polymers as matrix materials include emulsion-solvent evaporation, Phase separation (non solvent and solvent partitioning), Interfacial polymerization and Spray drying.[14]

Glipizide is a second-generation sulfonylurea that lowers the blood glucose level in human by stimulating the release of insulin from the pancreas and typically is prescribed to treat type-II diabetes. Its short biological half-life (3.4 ± 0.7 hrs) necessitates to be administered in two or three doses of 2.5-10 mg per day.[15-18] Owing to its short biological half-life, there is an urgent need of such a delivery system which can overcome its multidosing per day through delayed release and extended half-life. Thus, the development of controlled-release dosage

forms would clearly be advantageous. So an attempt was made in the present investigation to use ethyl cellulose and eudragit as a hydrophobic biodegradable polymer and prepare microspheres of Glipizide using emulsification-solvent evaporation method. The microspheres were evaluated for various parameters like particle size, surface morphology studies, compatibility studies, drug content, percentage yield and *in vitro* drug release studies.

MATERIALS

Glipizide and Eudragit (S-100 and L-100) were obtained as a gift sample from USV Ltd, Baddi and Evonik Degussa India Private Limited, Mumbai respectively. Ethyl cellulose was procured from HiMedia Laboratories Pvt. Ltd., Mumbai whereas Span-80 and tween-80 were procured from Loba Chemie Pvt. Ltd., Mumbai. Disodium hydrogen phosphate, potassium dihydrogen phosphate, acetone, chloroform, petroleum ether and n-Hexane were purchased from Merck India Pvt. Ltd., Mumbai.

METHODS

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced. Drugs obtained were performed using conventional and reported techniques. The UV-Visible spectrum, solubility, melting point and drug crystallinity were determined.

Spectrum measurement of Glipizide in pH 6.8

The standard stock solution of Glipizide (100 µg/ml) in pH 6.8 buffer was prepared. From this the second stock solution was prepared by diluting 1ml to 10 ml of pH 6.8 buffer (10 µg/ml) and scanned between 200 – 300 nm in Shimadzu UV visible spectrophotometer (Fig. 01). The UV absorption spectrum of Glipizide showed peak at 226 nm. The λ_{max} of 226 nm was selected for the present study.

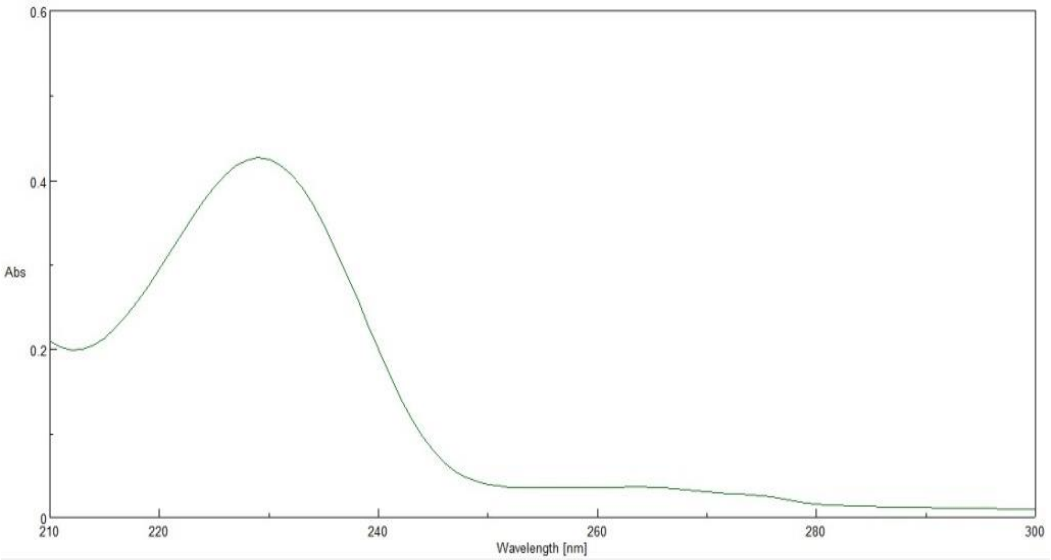

Fig. 01 U.V. Spectrum of Glipizide in pH 6.8 buffer.

Preparation of stock solution for calibration curve of Glipizide in pH 6.8 buffer

The first stock solution was prepared by dissolving 100 mg of Glipizide in 100 ml of pH 6.8 buffer (1 mg/ml). From this the second stock solution was prepared by diluting 10 ml to 100 ml of pH 6.8 buffer (100 µg/ml). Beer – Lambert's law was obeyed in the concentration range of 5 – 25 µg/ml. From the second stock solution 5, 10, 15, 20 and 25 µg/ml dilution were prepared. The absorbance of each sample was measured at 226 nm against blank pH 6.8 buffer. Standard curve of concentration vs. absorbance was plotted in Figure 03.

Preparation of microspheres of Glipizide: Emulsification-solvent evaporation method.

i. Eudragit microcapsules[19]

Accurately weighed Eudragit L-100 and S-100 in 1:2 ratios (0.5 g) were dissolved in 50 ml of acetone to form a homogenous polymer solution. Core material, i.e. Glipizide was added to the polymer solution and mixed thoroughly. This organic phase was slowly poured at 15°C into liquid paraffin (100 ml) containing 1% w/w of Span-80 with stirring at 1000 rpm to form a smooth emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone was evaporated and smooth-walls, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with petroleum ether (40-60 °C), four times and dried at room temperature for 3 hrs. The microspheres were then stored in a desiccator over fused calcium chloride. Two batches were prepared with different proportions of core to coat materials (drug: polymer = 0.5:1 and 1:1 w/w).

ii. Ethylcellulose microspheres[20]

Accurately weighed ethyl cellulose (1 g) was dissolved in 100 mL of chloroform to form a homogeneous polymer solution. Core material, i.e. Glipizide was added to the polymer solution and mixed thoroughly. Sodium Carboxymethylcellulose (0.5% w/v), which acts as an emulsifier and Tween 80 (1% v/v) was dissolved in distilled water (200 ml); to this solution the organic solution was slowly poured with stirring at 1000 rpm to form a smooth emulsion. The stirring was continued until the chloroform was evaporated. The microspheres were collected by decantation and the product was washed with water and dried at room temperature for 3 hrs. The microspheres were then stored in a desiccator over fused calcium chloride. Two batches were prepared with different proportions of core to coat materials (drug: polymer = 0.5:1 and 1:1 w/w).

Table 01: Drug Polymer Ratio for Eudragit and Ethyl cellulose Microspheres of Glipizide.

	Drug Polymer Ratio			
	GL-1	**GL-2**	**GL-3**	**GL-4**
Glipizide	0.5	1	0.5	1
Eudragit	1	1	---	---
Ethyl cellulose	---	---	1	1

Evaluation of Microspheres [19-21]

a) Study of flow properties of microspheres

Flow properties of microspheres were studied by measuring the angle of repose of the formulation by employing fixed funnel method.

Angle of repose $\theta = \tan^{-1}(H/R)$

Where 'H' is the height of the pile and 'R' is the radius of the pile.

b) Percentage Yield

The percent yield of each of the sample was calculated from the expression:

$$\%\text{Yield} = \frac{\text{Wt. of microspheres}}{\text{Total Weight of material used}} \times 100$$

c) Drug content

In a 100 ml volumetric flask, microspheres equivalent to 10 mg of Glipizide were taken and volume was made up to mark with pH 6.8 phosphate buffer. The flask was shaken for 12 hrs using a mechanical shaker. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 226 nm.

d) Particle size

Determination of average particle size of Glipizide microspheres was carried out by optical microscopy in which stage micrometer was employed. A minute quantity of microspheres was spread on a clean glass slide and average size of 100 microspheres was determined in each batch.

e) Surface morphology studies (SEM)

In order to examine the particle surface morphology and shape, Scanning Electron Microscopy (SEM) was used. Microspheres were scanned and examined under Electron Microscope.

f) *In-vitro* dissolution studies

In-vitro dissolution profile of each formulation was determined by employing USP XXIII rotating basket method (900 ml pH 6.8 phosphate buffer, 100 rpm, 37±0.5 °C). Microspheres equivalent to 10 mg Glipizide was loaded into the basket of the dissolution apparatus. 5 ml of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at wavelength 226 nm against pH 6.8 as blank. The amount of drug present in the filtrate was then determined from the calibration curve and cumulative percent of drug release was calculated. Data obtained was also subjected to kinetic treatment to obtain the order of release and release mechanism.

RESULT AND DISCUSSION

Preformulation studies: Glipizide was an off-white crystalline powder. From solubility study it was found out that Glipizide is practically insoluble in water (0.0365 mg/ml), soluble in chloroform (13.8 mg/ml) and slightly soluble in Methanol (1.9 mg/ml) and Acetone (8.9 mg/ml). The melting point of the pure drug Glipizide was found out in the range of 201-203°C, which compiled with the IP standards thus indicating purity of obtained drug sample. FTIR Spectrum obtained with Glipizide is concordant with the standard spectrum given in I.P. Figure 02 shows the IR Spectrum of pure drug glipizide shows characteristic absorption band for its different functional groups and various bonds in the following IR region. The IR spectrum of glipizide shows peaks at 3251 and 3325 cm^{-1} is due to NH Stretching, 3060 cm^{-1} due to aromatic CH stretching, 2854 to 2941 cm^{-1} due to CH stretching of CH3, CH2 groups both symmetric and asymmetric and - 1550, 1525, 1460 cm^{-1} due to C=O Ring Stretching.

Peak at 1649 cm^{-1}, 1610 cm^{-1}, 1442 cm^{-1} and 687 cm^{-1} are due to N-H bending , C=N bending, CH bending of CH3 and CH2 and C=O of CONH respectively.

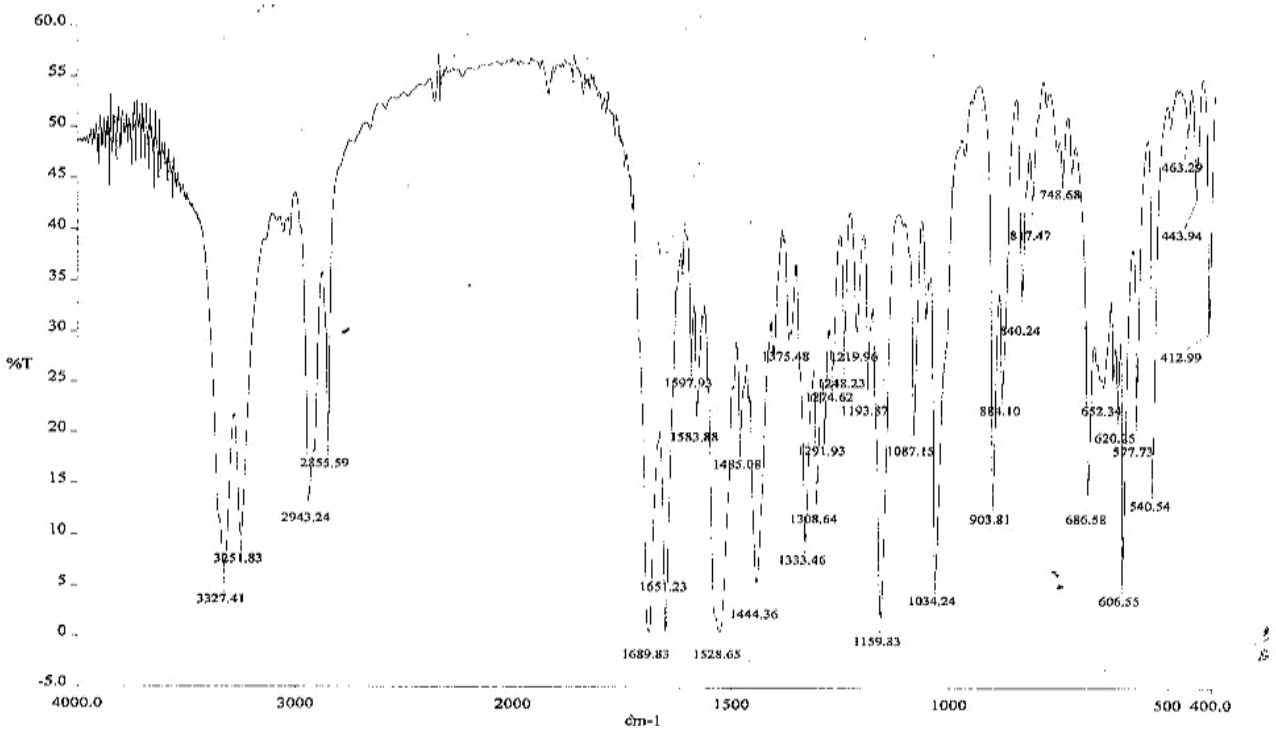

Fig. 02 FTIR spectra of Glipizide

Calibration curve of Glipizide in pH 6.8 buffer

The UV absorbance of Glipizide in the range of 0-25µg/ml of the drug in pH 6.8 (PBS) buffer showed linearity at λ_{max} of 226nm. Linearity was observed by linear regression equation method for Glipizide in different concentration range in pH 6.8 buffer. The Correlation coefficient of these drugs was found to be close to 1.00, indicating good linearity.

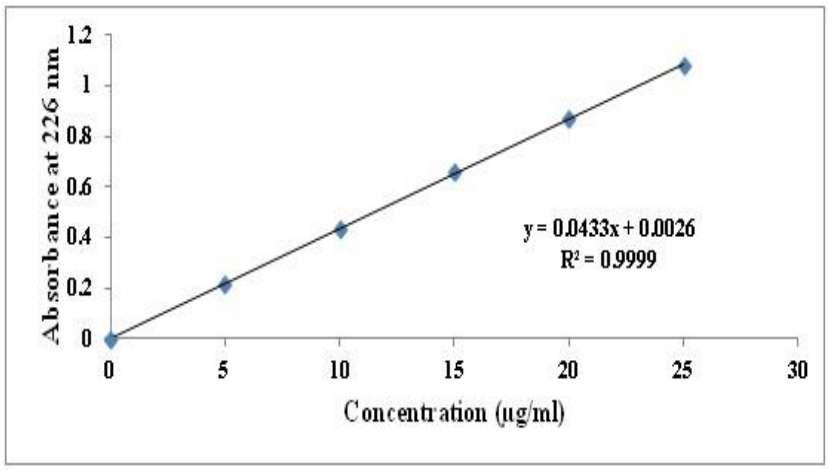

Fig. 03 Calibration curve of Glipizide in pH 6.8 buffer at 226 nm.

Preparation of microspheres

Ethyl cellulose and Eudragit microspheres were successfully prepared using emulsion – solvent evaporation method. The microspheres were then stored in a desiccators over fused calcium chloride till further evaluations.

Evaluation of Microspheres

a) Study of flow properties of microspheres

Flow properties were characterized by measuring the angle of repose (Table 02). All the formulations showed good flow properties. The value of θ between 21-28°θ indicates that the flow of the particles was reasonable and the microspheres were found to be fit in respect to flowability and were thus suitable for further processing in filling of the capsules.

b) Percentage Yield

The percentage yield of all the formulations is given in the Table 02. The mean percentage practical yield for all the formulations was more than 91%. A positive correlation between the solid content and percentage yield was observed. This may be explained by the fact that, though a constant material is always lost in processing, this loss is proportionately less significant when the solid content is more.

c) Drug content

The percentage drug content of all the formulations are given in the Table 02. The drug content was found to be very high in all the cases. All the formulations showed % drug content in range of 96-98%.

Table 02 Flow property, Percentage yields and drug content of Glipizide.

Formulation	Angle of Repose*	% Drug content*	% Yield*
GL-1	28.75 ± 0.5932	98.43 ± 0.7392	93.27 ± 0.5934
GL-2	23.38 ± 0.6118	97.58 ± 0.5639	91.70 ± 0.8188
GL-3	25.92 ± 0.4382	96.88 ± 0.4991	94.33 ± 1.0532
GL-4	21.49 ± 0.4967	96.54 ± 0.6137	92.67 ± 0.3855

**Each value is the mean ± SD; n=3*

d) Particle size

The mean particle size of the Eudragit microspheres was ranged between 30-55 µm. While the Ethylcellulose microspheres ranged between 38-61 µm.

e) Surface morphology studies (SEM)

It was observed that the prepared microspheres were spherical with smooth surface; might be due to complete homogeneity of drug and polymers. Although distinct pores were evident on the surface of microspheres, which may be subsequently responsible for drug release [Fig. 04].

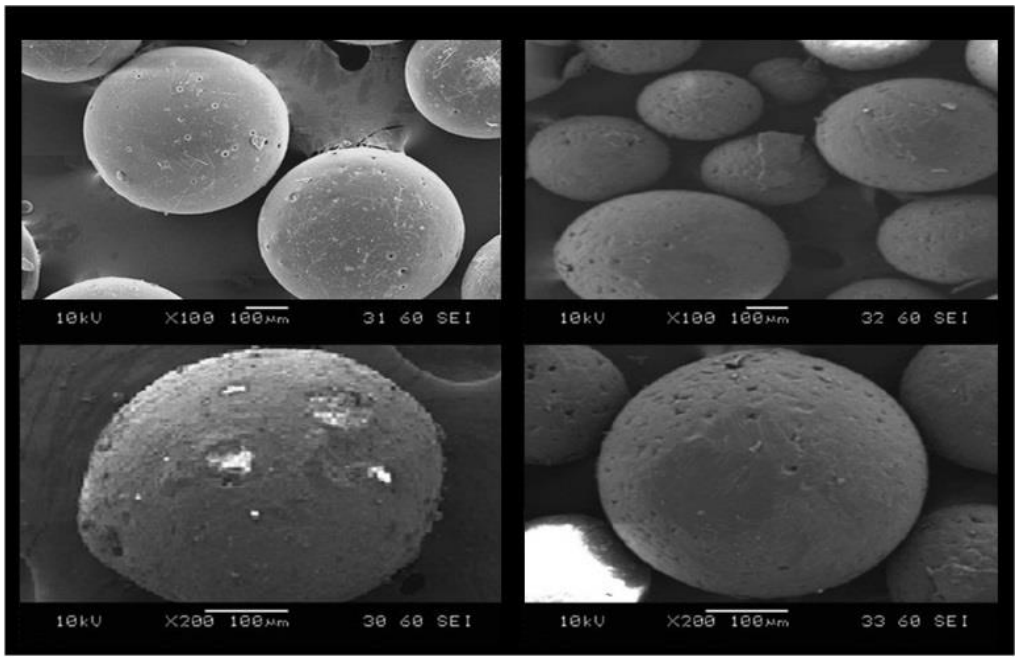

Fig. 04 Scanning Electron Micrographs of Glipizide microspheres.

a) GL-1, b) GL-2, c) GL-3 and d) GL-4

f) *In-vitro* release studies for microspheres

In vitro release studies were carried out using USP-XXIII dissolution assembly. *In vitro* drug release data of Glipizide microspheres is shown in Table 03 and *in vitro* drug release profile is shown in Figure 05. In Glipizide microsphere formulations, the cumulative percentage drug release after 11 hrs for the formulations GL-1, GL-2, GL-3 and GL-4 was found to be 79.27%, 92.16%, 86.98% and 98.18% respectively. Among all the formulations, microspheres prepared using Eudragit (0.5:1) showed slow release as compared to others. From *in vitro* drug release data it was found out that Ethylcellulose microsphere was less retarding as compared to eudragit microspheres. The order of drug release from formulations were as follow GL-4 > GL-2 > GL-3 > GL-1.

Kinetic analysis of *in vitro* release data

In order to determine the release mechanism that provides the best description to the pattern of drug release, the *in vitro* release data were fitted to zero order, first-order, and Higuchi matrix. Based on the *in vitro* drug release data, considering the highest regression values the

best fit model for Glipizide Microspheres was Higuchi-Matrix diffusion model except formulation GL-1 where Korsmeyer-Peppas was the best fitting model. This can be illustrated in Table 04.

Table 03 % Cumulative Drug Release data of Glipizide for microspheres.

Time (Hr)	% Cumulative Drug Release*			
	GL-1	GL-2	GL-3	GL-4
0	0.00 ± 0.0000	0.00 ± 0.0000	0.00 ± 0.0000	0.00 ± 0.0000
0.5	9.64 ± 0.2193	14.99 ± 0.1145	12.08 ± 0.3176	19.69 ± 0.1854
1.0	17.88 ± 0.0275	25.81 ± 0.0198	22.26 ± 0.1116	29.18 ± 0.2132
1.5	25.44 ± 0.2294	32.68 ± 0.0432	29.01 ± 0.0958	36.70 ± 0.1182
2.0	29.80 ± 0.2009	37.06 ± 0.0532	33.33 ± 0.0632	41.58 ± 0.1034
2.5	32.91 ± 0.1893	41.68 ± 0.0683	37.48 ± 0.0638	46.22 ± 0.1321
3.0	36.81 ± 0.1219	45.00 ± 0.1245	40.93 ± 0.0885	49.92 ± 0.1096
3.5	39.17 ± 0.1109	48.46 ± 0.2143	44.08 ± 0.0453	52.99 ± 0.2174
4.0	42.24 ± 0.1054	51.35 ± 0.1198	47.45 ± 0.0217	56.96 ± 0.2296
4.5	44.83 ± 0.2165	54.22 ± 0.1436	50.00 ± 0.0663	60.27 ± 0.2146
5.0	47.87 ± 0.2067	57.79 ± 0.1842	53.47 ± 0.1240	63.40 ± 0.0423
5.5	50.55 ± 0.2173	60.67 ± 0.1469	56.20 ± 0.1970	67.41 ± 0.0735
6.0	53.23 ± 0.2254	63.76 ± 0.1475	59.20 ± 0.2145	70.84 ± 0.0437
6.5	55.66 ± 0.1984	67.02 ± 0.2476	61.91 ± 0.2091	74.08 ± 0.0119
7.0	58.67 ± 0.1092	70.09 ± 0.0389	65.15 ± 0.0921	76.88 ± 0.0953
7.5	61.68 ± 0.3006	73.32 ± 0.5145	68.02 ± 0.0672	80.50 ± 0.0924
8.0	64.80 ± 0.1332	76.66 ± 0.3424	70.93 ± 0.1175	83.83 ± 0.0764
8.5	67.61 ± 0.1564	79.61 ± 0.4214	73.79 ± 0.2178	86.82 ± 0.1024
9.0	69.74 ± 0.1217	82.57 ± 0.1257	76.57 ± 0.1631	89.78 ± 0.1743
9.5	72.47 ± 0.1316	85.51 ± 0.2574	79.54 ± 0.1286	91.83 ± 0.2009
10.0	75.20 ± 0.1336	87.75 ± 0.3628	81.98 ± 0.1076	93.77 ± 0.1209
10.5	77.14 ± 0.1893	90.09 ± 0.2894	84.62 ± 0.2157	96.49 ± 0.0689
11.0	79.27 ± 0.1673	92.16 ± 0.2167	86.98 ± 0.1095	98.18 ± 0.2121

**Average of 3 determination*

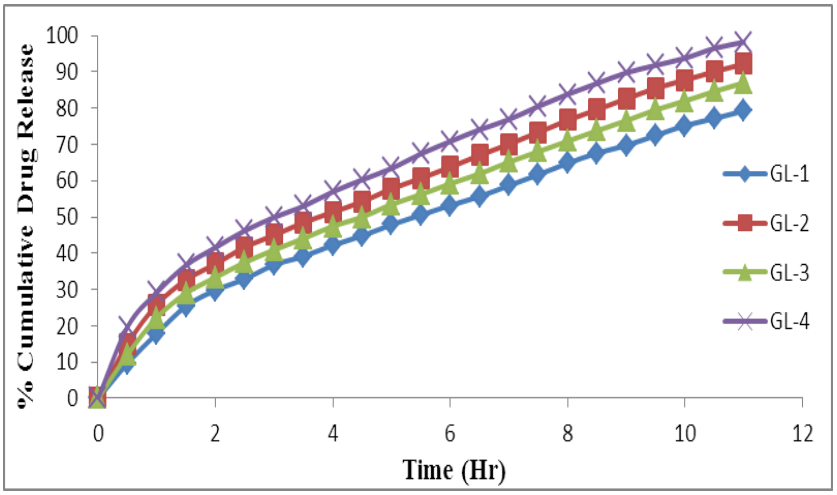

Fig. 05 Comparative % Cumulative drug release of Glipizide from Eudragit and Ethylcellulose microspheres.

Table 04 Kinetic analysis of *in vitro* drug release data of Glipizide microsphere.

Release models		Glipizide microspheres			
		GL-1	GL-2	GL-3	GL-4
Zero order	R^2	0.9664	0.9557	0.9613	0.9465
	k	0.0107	0.0120	0.0115	0.0126
First order	R^2	0.9886	0.7396	0.9759	0.8996
	k	-0.0010	-0.0018	-0.0012	0.0021
Higuchi matrix	R^2	0.9916	0.9956	0.9991	0.9982
	k	3.2145	3.6425	3.4655	3.8555
Peppas	R^2	0.996	0.9855	0.9922	0.9754
	k	0.6657	0.6653	0.6669	0.6645
Best fitting model		Peppas	Higuchi	Higuchi	Higuchi

**Average of 3 determination*

CONCLUSION

The research was carried out with the aim to formulate and evaluate the sustained release microspheres of glipizide using hydrophobic polymers by using emulsion-solvent method. Ethyl cellulose and Eudragit Microspheres of Glipizide were successfully prepared. Results showed that all the microspheres were spherical in shape, had smooth surface, high percentage yield and drug content. *In vitro* drug release studies showed effective controlled release of drug from microspheres. Ethyl cellulose microspheres were found less retarding than Eudragit microspheres. From the results, it was concluded that the formulation of sustained release microspheres of glipizide containing eudragit in ratio of 0.5:1 as ideal or optimized formulation for 16 hour release.

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