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A RESEARCH ON FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF GLIMEPIRIDE

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ABSTRACT

The Glimepiride is a drug of choice for the physician for Non Insulin Dependent Diabetes (NIDD). The drug in oral conventional dosage form has the dosage regime of three times a day. The repeated administration in a day may cause non compliance by the patients. Thus, it is emphasized to prolong/sustain release delivery of the drug to avoid repeated administration. The study comprises that floating microsphere of Glimepiride, model drug, may increase the gastric residence time. The floating microspheres are prepared by the emulsification solvent diffusion technique using polymers Ethyl cellulose, Eudragit RS100 and Guargum in different ratio 1:1,1:2,1:3,2:2 2:3. The formulated microsphere was evaluated for the percentage yield, percentage encapsulation efficiency, percentage buoyancy and in vitro drug release. Floating microspheres prolong the release of the drug and gastric residence time, release almost 76% drug with in 24hrs.

KEYWORDS: Glimepride, Floating microspheres, Effect of polymers, Solvent Evaporation method.

INTRODUCTION

Oral ingestion has been the most convenient and commonly employed route for drug delivery. The oral route of drug administration has received more attention with respect to the

research on physiological and drug constraint as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than there is for parental route. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration, the drug is well absorbed as the food stuff that are ingested daily.[1]

Floating drug delivery systems (FDDS) or hydro dynamically balanced systems (HBS) are among the several approaches that have been developed to increase the gastric residence time of dosage forms. This Gastro retentive floating drug delivery system (GRFDDS) have a bulk density lower than that of gastric fluids and thus remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system.[2, 3]

The use of oral antidiabetic drugs for the treatment of Type 2 diabetes is increasing rapidly. Glimepiride is an antidiabetic drug belongs to second generation sulphonylurea drug. It lowers the blood glucose level in patients with Type 2 diabetes (non-insulin dependent diabetes mellitus) by stimulating the release of insulin from the pancreatic β-cells. In this way it exerts a long-term effect of reducing the blood glucose levels. In addition, extra pancreatic effects may also play a role in the activity of glimepiride. It has low risk of hypoglycemia because of preservation of physiological suppression of insulin secretion in response to low blood glucose levels1. It is completely (100%) absorbed following oral administration. It has rapid onset of action, 24 hr duration of effect with a half life of 5 hr and once a day dosing.[4, 5]

MATERIALS AND METHOD

Glimepiride was obtained as a gift sample from Ranbaxy Laboratories, Ponta Sahib Eudragit RS100 were obtained from Alembic Pharmaceutical Ltd., Vadodara. and Ethyl cellulose Central Drug House Ltd, New Delhi. All other reagents and solvents used were of analytical grade.

METHOD

Following studies were performed to formulate and evaluate glimepiride microspheres.

Preformulation Studies

Preformulation studies mainly focus on those physiochemical properties of the drug that could affect performance and development of an efficacious dosage form such as determining

the purity of Active Pharmaceutical Ingredient (API) before formulation any dosage form. Preformulation studies are useful in determining the formulation components and physiochemical properties of new drug substance that will affect the final dosage form and its stability.

Description of Drug

The sample of drug was observed for colour, state and odour.

Drug Excipients Compatibility Study

Before formulating a dosage form it is essential to confirm that drug is not interacting with the polymer under certain experimental studies. Interacting among drug and polymer may affect the efficacy of final dosage form.

Fourier transform infra-red spectrum of pure drug, Eudragit RS 100, Ethyl cellulose, Guargum and their Physical mixture were recorded. Drug and different excipients were taken in 1:1 ratio. The samples of pure drug and physical mixture of polymer and drug were taken and subjected to FTIR study.

Standard Calibration Curve

A stock solution of glimepiride (10µg/ml) was prepared by dissolving 10 mg of glimepiride with different buffer solution such as 0.1N HCl and phosphate buffer pH 7.4. Further various dilutions were made with these different pH buffer solutions containing concentration 2, 4, 6 & 8 µg/ml of glimepiride and absorbance was measured against blank at λ_{max} 262 nm and a standard calibration curve between concentration and absorbance was plotted as shown in figure. All spectral absorbance measurements were made on Shimadzu-1700 UV-visible spectrophotometer.[6]

Preparation of Formulations

Formulation of drug-loaded microspheres was carried out by the emulsion solvent diffusion-evaporation method. The polymers ethyl cellulose, Eudragit RS100, Guargum was used in different ratios. Initially a solvent mixture of 10ml of dichloromethane was prepared in the considering their volumes. An accurately weighed quantity of drug and polymer was co-dissolved at room temperature in a solvent mixture. This solution was introduced into 100 ml of 1% PVA aqueous solution at room temperature and dispersed to form emulsion at stirring rates of 800 rpm using a mechanical stirrer equipped with 4-blade propeller. Agitation

provided by stirrer breaks the poured polymer solution to form an oil-in-water (O/W) type emulsion. This emulsion was then stirred for about 45 min at room temperature. After stirring, the solidified microspheres were recovered by filtration and dried.[7]

Table 1: Formulation Batches of Glimepiride Floating Microsphere.

S.NO.	Formulation code	Drug (mg)	Eudragit RS100(mg)	Ethyl cellulose (mg)	Guar gum (mg)	Ratio +Polymer
1	F_1	10	10	10	10	1:1:1:1
2	F_2	10	10	20	10	1:1:2:1
3	F_3	10	10	30	10	1:1:3:1
4	F_4	10	20	10	10	1:2:1:1
5	F_5	10	20	20	10	1:2:2:1
6	F_6	10	20	30	10	1:2:3:1
7	F_7	10	30	10	10	1:3:1:1

Evaluation of the Formulated Microsphere

Percent Yield of Microspheres

Microspheres dried at room temperature were then weighed and the yield of microspheres. preparation was calculated using the following formula.

Mean Particle size = (Mean particle size of the fraction × weight fraction)/ Weight fraction.

Drug Entrapment Efficiency

Encapsulation efficiency of the microspheres was evaluated by deriving percent drug encapsulation. The drug content of drug-loaded microspheres was determined by dispersing 100 mg of microspheres in 50 ml ethanol or the solvent choose according to its solubility followed by agitation with a magnetic stirrer for about 30 min to dissolve the polymer and to extract the drug. After filtration through a 5µm membrane filter, the drug concentration in the ethanol phase was determined by taking the absorbance of this solution spectrophotometrically at 298nm. Eudragit RS100 and ethyl cellulose did not interfere under these conditions. Drug concentration was then calculated. Thus, the total drug encapsulated in total yielded microspheres from the procedure was calculated. It was expressed in percentage called as “Percent drug encapsulation” calculated as.[8]

% Drug Encapsulation = (Actual drug content/Theoretical drug content) × 100

Floating Behavior of Microsphere (Percentage Buoyancy)

The floatation studies were carried out to ascertain the floating behavior of various polymers

Combinations. Beaker method was initially used to have an idea of the floatation behavior of the proposed dosage form .50 mg of floating microsphere 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.[9]

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

Micromeritic Properties

Microspheres were characterized for their micromeritic properties such as bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose.

Bulk Density

An exact quantity 'M' of microsphere was taken and was placed into a measuring cylinder. Volume 'V' occupied by the microspheres was noted without disturbing the cylinder and bulk density was calculated using the following equation;

$$\textbf{Bulk density (Pb) = M/V}$$

Tapped Density

The tapping method was used to determine the tapped density in which the cylinder containing known amount (M) of microspheres was subjected to a fixed number of taps (approximately 100) until the bed of microspheres had reached the minimum. The final volume after tapping 'Vo' was recorded and the tap density was calculated by the following equation.[10]

$$\textbf{Tapped Density } (P_p) = M/V_o$$

Angle of Repose

This property was determined to predict flowability Angle of repose of the microspheres is the maximum angle possible between the surface of the pile of microspheres and the horizontal plane, was obtained by fixed funnel method using the formula

$$\textbf{Angle of repose } (\phi) = \tan\text{-}1[2h/d]$$

Where, h is height and d is the diameter of the microsphere pile that is on a paper after making the microspheres flow from the glass funnel.[11]

Carr's Index or % Compressibility

A high Carr's index is indicative of the tendency to form bridges can be calculated by using following formula:

Carr index or %compressibility Index or C = [1- V0/V] × 100

Hausner Ratio

Hausner's ratio is measures of the propensity of a powder to be compressed and the flow ability of granule. A higher Hausner ratio indicates greater cohesion between particles.[12]

Hausner Ratio = [100/100+C]

Where C is Carr's Index.

In Vitro Drug Release Studies

The drug release rate from microspheres was determined using USP basket-type dissolution apparatus. A weighed amount of microspheres equivalent to 5 mg drug was filled into a capsule (size 0) and placed in the basket. Dissolution medium used was phosphate buffer 7.4 for first hour and maintained at 37 ± 0.5°C at a rotation speed of 100 rpm. Prefect sink conditions prevailed during the drug release studies. 5 ml of sample was withdrawn at each 1 h interval; later this interval was extended to 2 h. Sample was then passed through a 5 µm membrane filter, and analyzed spectrophotometrically at 300 nm to determine the concentration of drug present in the dissolution medium. The initial volume of dissolution medium was maintained by adding 5 ml of fresh dissolution media after each withdrawal. The dissolution study was continued for next 24 h.

Release kinetics

Release kinetic models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter drug release and in vivo performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In this regard, the use of in vitro drug dissolution data to predict in vivo bio-performance can be considered as the rational development of controlled release formulations. Data obtained from the in vitro release studies were fitted to various model dependent kinetic equations such as zero order, first order, Higuchi model and Korsmeyer- Peppas model.

Zero-order model

$Q_t = Q_0 + K_0 t$

First order model

Log C= log C_0- Kt/2.303

Higuchi model

$Q = K_H \times t^{1/2}$

Korsmeyer-Peppas model

$Q/Q_0 = Kt^n$

Where, K_0 to K_H were release rate constants, Q/Q_0 was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism. For Fickian (diffusion controlled), $n \leq 0.5$; for non- Fickian (anomalous) release, 'n' value is in between 0.5 to 1.0; for zero order release, n=1.0; for super case transport II, n > 1.040. Based on the slope and the R^2 values obtained from the above models the mechanism of drug release was determined.[13]

RESULTS AND DISCUSSION

Description of Drug

Various properties of drug related with physical appearance, state, and solubility given in table no.2.

Table 2: Description of Drug.

S. No.	Properties	Inference
1.	Colour	White Coloured
2.	Solubility	Practically insoluble in water, soluble in methanol and acetone.
3.	Odour	Odourless

Drug Identification

The accurately weighed quantity of drug was dissolved in sufficient volume of acetone and scan was obtained on UV-VIS spectrophotometer. The wavelength at which maximum absorbance obtained was considered as maximum wavelength (λ_{max}) i.e. 262 nm for the drug.

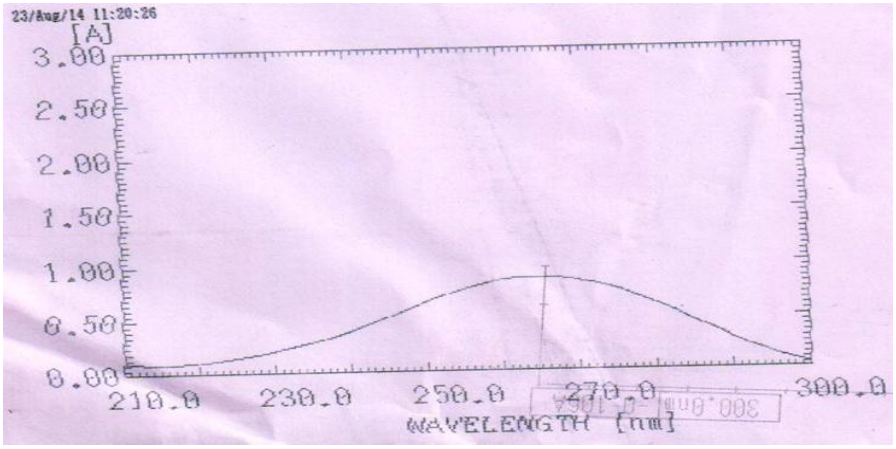


Figure1: Glimepiride standard calibration curve in phosphate buffer 7.4.

Drug- Excipients Compatibility Study

Drug and polymers identified by infra-red spectrum which are compared with its standard IR. The IR spectrum given below shown that the peaks obtained in the test spectrum is similar to that given in standard.

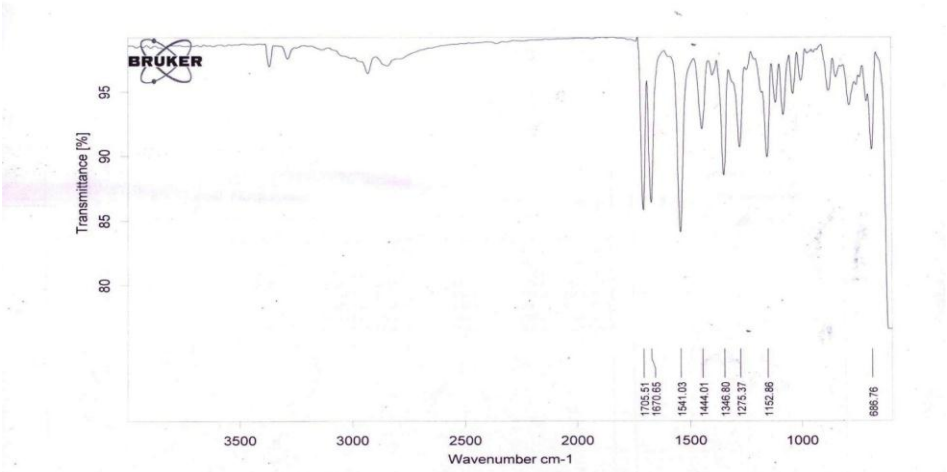


Figure 2: FT IR spectrum of Glimepiride (Fresh sample).

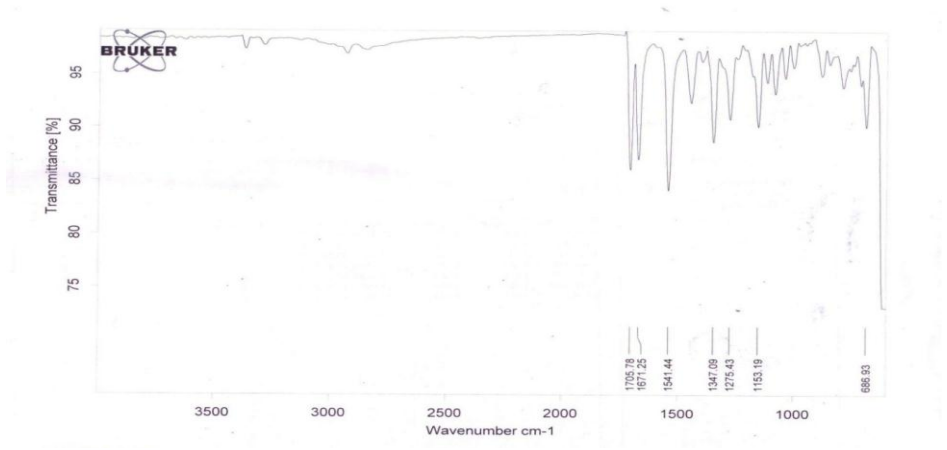


Figure 3: FT IR spectrum of Glimepiride (After 15 days).

The IR spectra indicates characteristic absorption peaks of Glimepiride at 3367 cm-1 (N-H stretch) showing strong absorption peak at 1705 cm^{-1} (C=O) and 1347 cm^{-1} (S=O). Peaks obtained in spectrum of pure drug (immediate & after 15 days) were similar to that given in standard.

Table-3: Quantity used for Drug – Polymer Identification.

S. No.	API and Excipient	Quantity per vial (mg)	No. of Vials	
			Initial	50^0C After 15 Days
1	Glimepiride	10	1	1
2	Eudragit E 100	10	1	1
3	Ethyl cellulose	10	1	1
4	Guargum	10	1	1

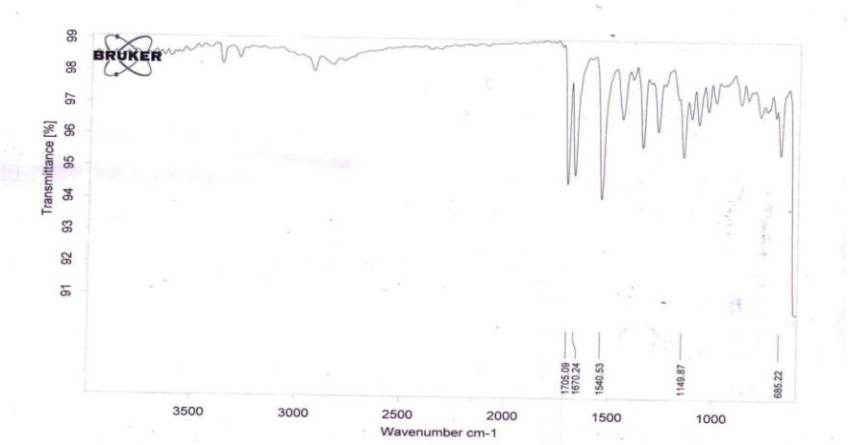


Figure 4: FT IR spectrum of Glimepiride+ Eudragit RS 100 (Fresh sample).

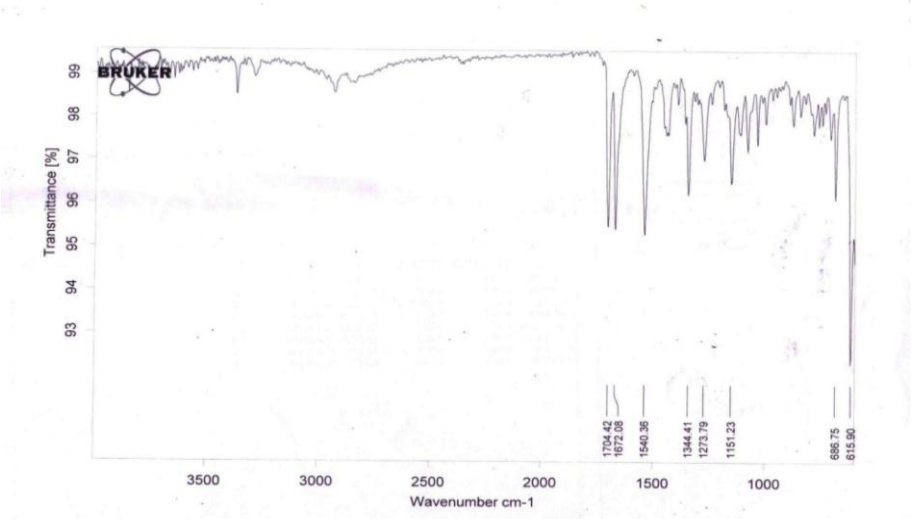


Figure 5: FT IR spectrum of Glimepiride+ Eudragit RS 100(After 15 days).

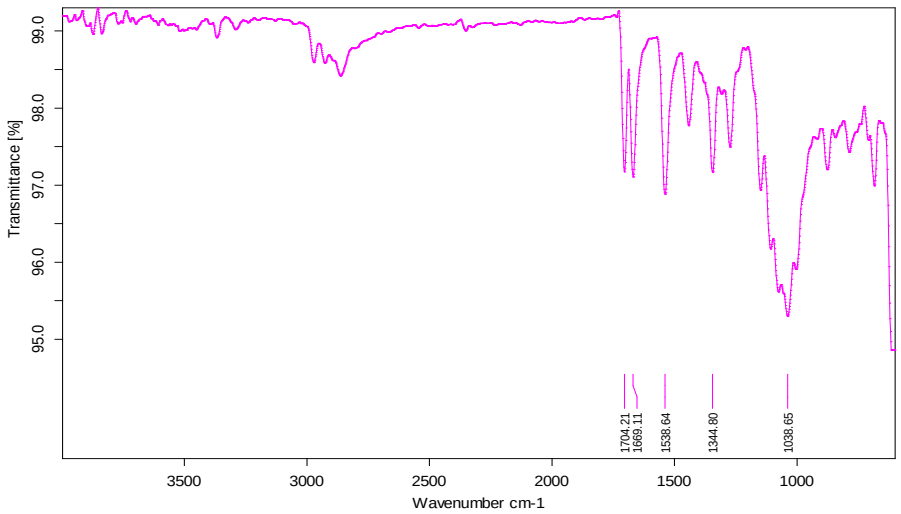


Figure 6: FT IR spectrum of Glimepiride+ Ethyl cellulose (Fresh sample).

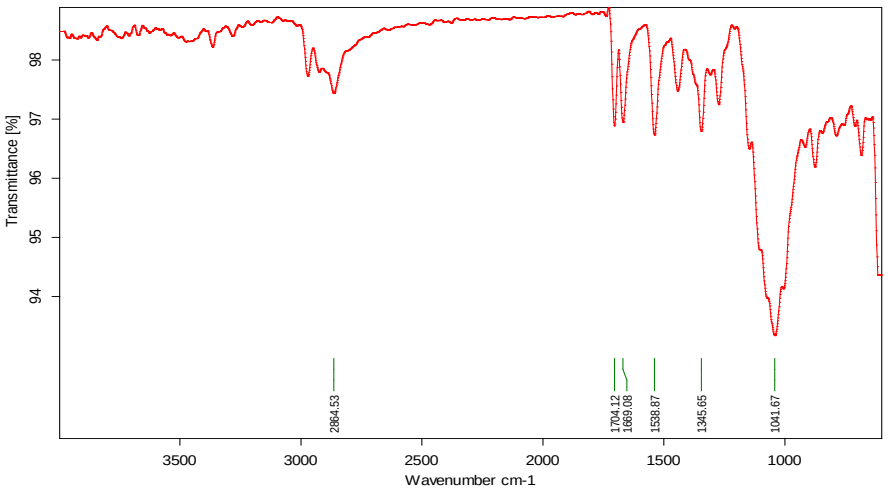


Figure 7: FT IR spectrum of Glimepiride+ Ethyl cellulose (After 15 days).

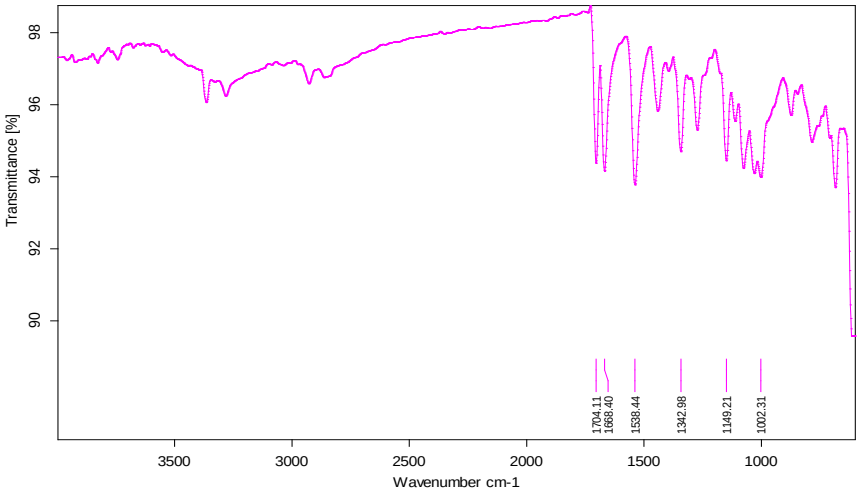


Figure 8: FT IR spectrum of Glimepiride+ Guar gum (Fresh sample).

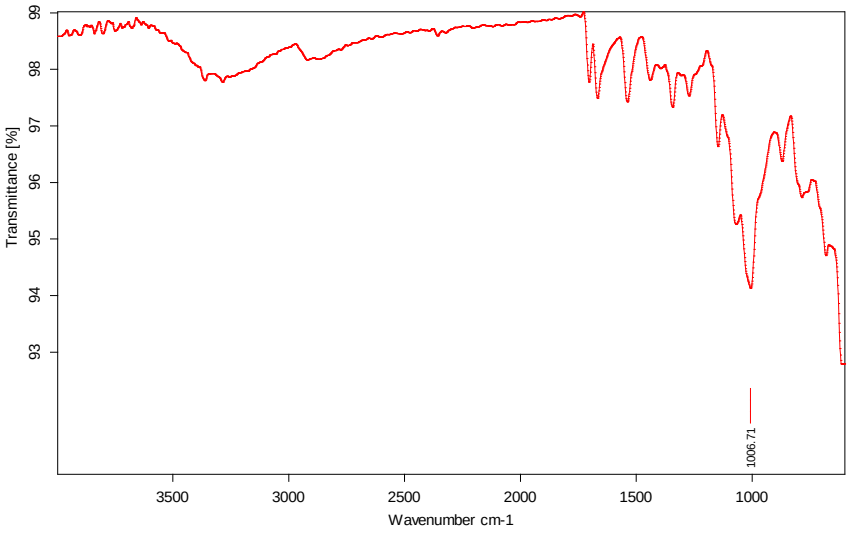


Figure 9: FT IR spectrum of Glimepiride+ Guar gum (After 15 days).

Preparation of standard calibration curve: Obtained absorbances are shown in the tables 4 and standard calibration curves of glimepiride in different solvents of varying pH are shown in figures.[10]

Table-4: Standard calibration curve in Phosphate buffer 7.4 at λ_{max} 262 nm.

Concentration	Absorbance
2	0.149
4	0.364
6	0.565
8	0.803
10	1.044
12	1.162

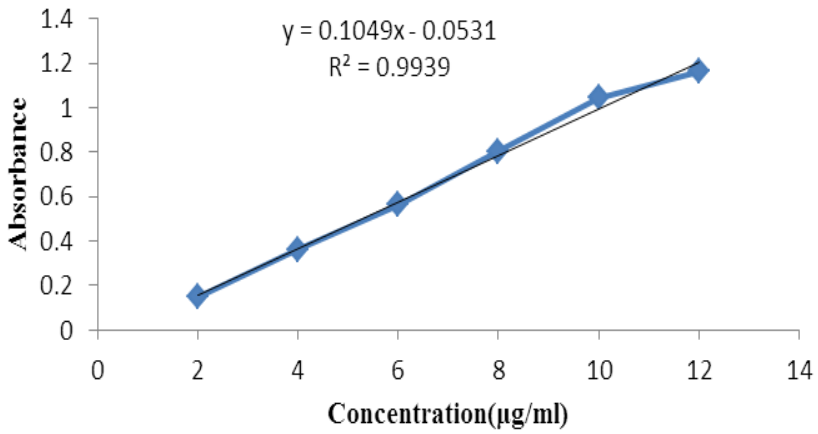


Figure 10: Standard calibration curve in Phosphate buffer 7.4 at λ_{max} 262 nm.

Evaluation Test

Percentage Yield

Percentage yield of different formulation was determined by weighing the granules after drying. The percentage practical yield of different formulation was in range of 54- 65% as shown in Table 5. The maximum percentage practical yield was found in F_5 to shown to figures.[11]

Table 5: Percentage yield of the formulated floating microsphere.

S. No.	Formulation no.	% yield
1.	F_1	55
2.	F_2	56
3.	F_3	58.6
4.	F_4	54
5.	F_5	65
6.	F_6	60
7.	F_7	58

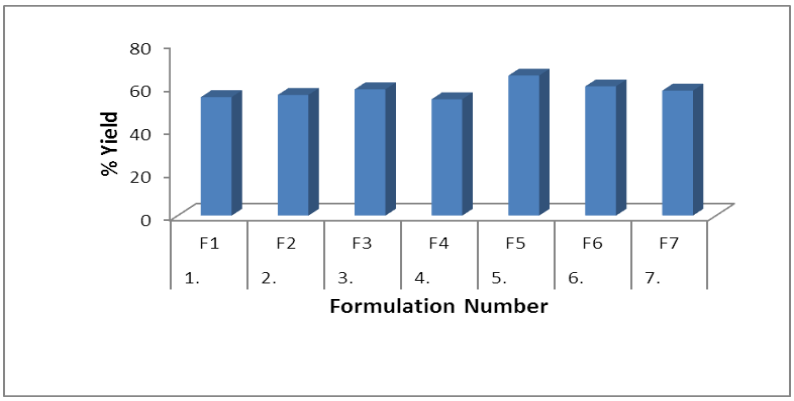


Figure11: Percentage yield of floating microsphere.

Encapsulation Efficiency of Microsphere

The encapsulation efficiency was found to be abruptly increasing when both polymers were used together. Encapsulation efficiencies of batches F1-F7ranged from 35.24% to 87.78%. Maximum encapsulation efficiency was observed of the batch F5, where ratio of 2:2:1 of the ethyl cellulose and Eudragit RS100 and Guargum was used. Table no.6 and Fig. 12 represent the encapsulation efficiency.

Table 6: Encapsulation Efficiency of the formulated floating microsphere

S. No.	Formulation no.	% Encapsulation efficiency
1.	F_1	35.24
2.	F_2	62.17

3.	F_3	42.94
4.	F_4	60.25
5.	F_5	87.78
6.	F_6	68.96
7.	F_7	75.26

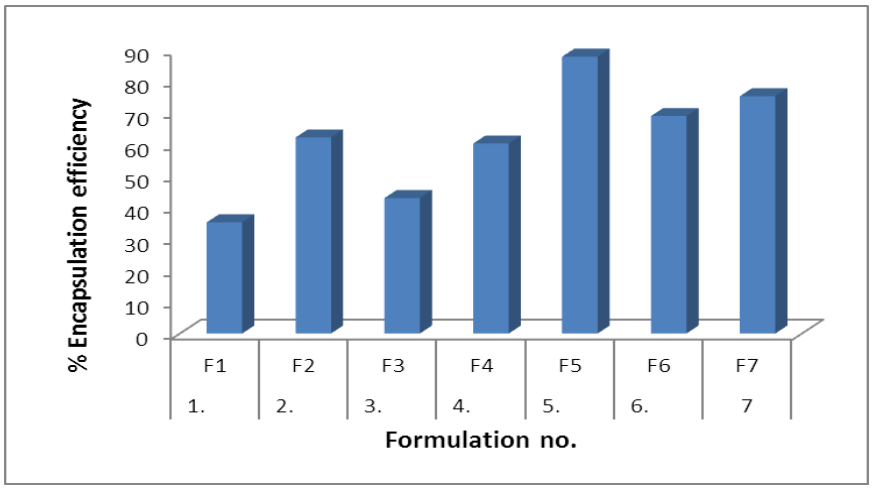


Figure 12: Encapsulation efficiency.

Floating Behaviour of Microsphere (Percentage Buoyancy

The percentage Buoyancy was found to be abruptly increasing when both polymers were used together. Percentage Buoyancy of batches F1-F7 ranged from 67.32% to 80%. Maximum percentage Buoyancy was observed of the batch F5, where ratio of 2:2:1 of the ethyl cellulose and Eudragit RS100 and Guargum was used. Table no.7 and Fig. 13 represent the floating behaviour.

Table7: Percentage Buoyancy of the floating microsphere.

S. No.	Formulation no.	% Buoyancy
1.	F_1	67.32
2.	F_2	72
3.	F_3	69.04
4.	F_4	75.56
5.	F_5	80
6.	F_6	70
7.	F_7	69.1

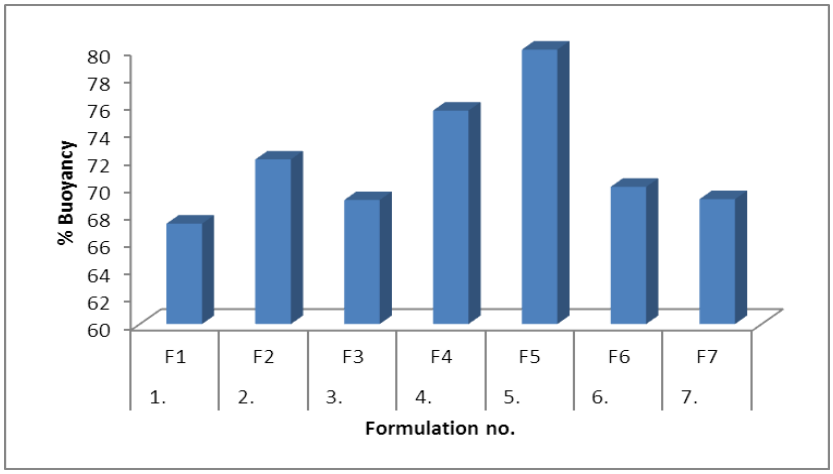


Figure 13: Percentage Buoyancy Of The Floating Microsphere.

In Vitro Drug Release

In vitro dissolution studies of all the formulations of floating microspheres Phosphate buffer 7.4 were carried out in solution. It was observed that the type of polymer influences the drug release pattern. These polymers showed sustained release and gastric retention of drug. Table 8 shows the cumulative % release.

Table 8: Percentage drug release.

Cumulative % Release at Different Time Intervals							
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
0 min	0	0	0	0	0	0	0
15 min.	17.74	19.73	21.98	19.817	16.70	24.05	17.13
30 min.	20.08	23.30	24.87	20.619	20.94	32.58	19.73
45 min.	22.96	25.94	29.68	23.243	25.13	32.16	23.39
60 min.	25.69	28.41	32.00	25.275	29.16	29.30	25.34
90 min.	25.65	31.17	30.80	26.798	33.65	33.26	30.06
120 min.	27.70	34.71	34.24	22.617	36.86	34.84	33.43
3hrs.	30.19	37.93	35.30	26.114	39.31	37.19	38.03
4hrs.	32.69	41.68s	38.44	30.149	43.85	39.64	42.04
5hrs.	36.15	45.89	43.58	32.821	47.03	43.23	44.95
6 hrs.	37.04	49.17	42.08	34.382	49.02	46.06	48.83
7hrs.	39.40	50.64	46.37	36.643	53.52	47.52	52.21
8 hrs.	40.65	52.99	49.48	38.916	57.70	52.96	55.34
10 hrs.	42.08	57.95	52.68	41.806	61.47	54.02	58.06
12 hrs.	44.81	61.37	55.56	44.018	66.21	55.78	62.18
14 hrs.	46.34	64.29	56.11	47.453	72.10	57.20	62.94
24 hrs.	49.96	67.66	58.48	50.041	76.47	61.57	65.94

Formulations with F_5 showed (Table) the high release of drug when compared to other formulations with combination of drug. The plot of cumulative percentage drug release V/s time (hr.) for all formulations was plotted and depicted in Figure 14 respectively.

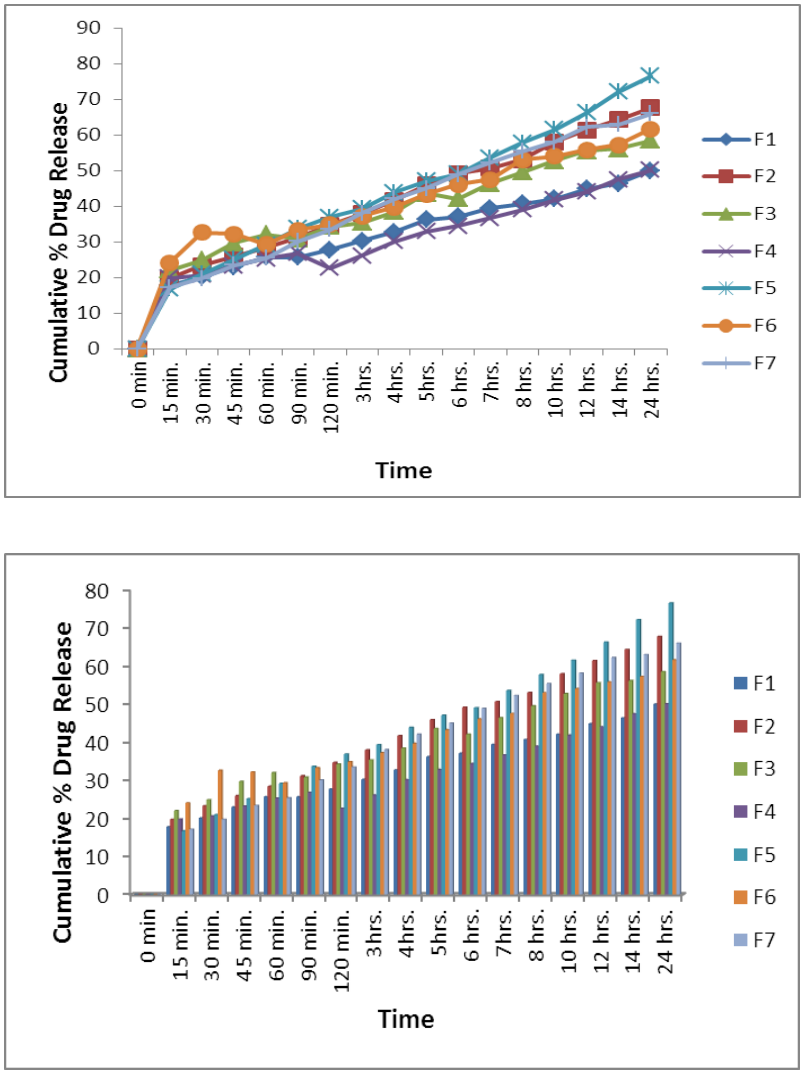


Figure 14: Comparison of drug release of different batches.

Micromeretic Properties

Microspheres were found to be spherical and discrete. But the particle size of microspheres varied in range. The particle size increased with increase in ethyl cellulose concentration.

Table 9: Micromeretic properties.

Formulation No.	Bulk density(g/ml)	Tapped density(g/ml)	Angle of repose	% compressibility	Hausner's Ratio
F1	0.349	0.397	28.10	13.09	1.13
F_2	0.352	0.405	21.12	13.08	1.15
F3	0.625	0.714	26.70	12.46	1.14
F4	0.624	0.716	28.20	12.84	1.14
F_5	0.341	0.397	21.60	14.10	1.16
F6	0.622	0.713	29.66	12.76	1.14
F_7	0.240	0.282	21.04	14.28	1.14

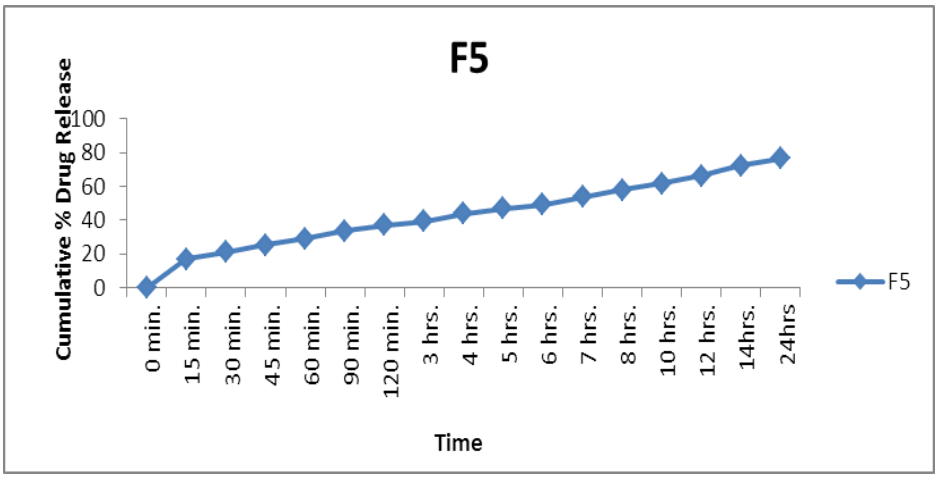
Angle of repose (excellent) and compressibility index were indicated good flowability of microspheres, showing no need for addition of glidants to enhance flowability. The better flow property of microspheres indicates that the microspheres produced were non-aggregated.

Dissolution of final formulation

Formulation F5 reveals the highest % encapsulation efficiency and cumulative % drug release formulated by the 2:2:1 ratio of ethyl cellulose and eudragit RS100 and Guargum. F5 batch yields the highest recovery and fine particle size and shape due the suitable combination of polymer. Table 10 and fig.15 shows the in vitro drug release of final formulation.

Table 10: Cumulative % drug release.

Time	F_5
0 min.	0
15 min.	16.70
30 min.	20.94
45 min.	25.13
60 min.	29.16
90 min.	33.65
120 min.	36.86
3 hrs.	39.31
4 hrs.	43.85
5 hrs.	47.03
6 hrs.	49.02
7 hrs.	53.52
8 hrs.	57.70
10 hrs.	61.47
12 hrs.	66.21
14hrs.	72.10
24hrs	76.47



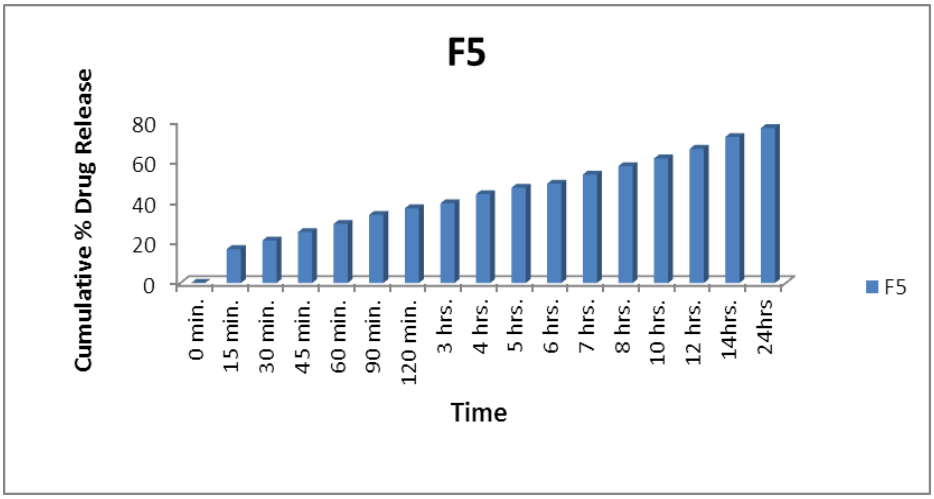


Figure 15: Drug release of final formulation.

Release kinetics

The in vitro release data obtained from Formulation F_5 was fitted to kinetic models shown in Table. In case of zero order $(Q_t = Q_0 + K_0 t)$the graph was plotted in cumulative percent of drug released versus time and in first order release kinetics (Log C= log C_0- Kt/2.303) the graph was plotted in log cumulative percent of drug remaining versus time. For Higuchi model kinetics ($Q= K_H \times t^{1/2}$) the graph was plotted in cumulative percent of drug released versus square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = Kt^n$) the graph was plotted in log cumulative percent of drug released versus log time. The release of glimepiride from the floating microsphere was Korsmeyer-Peppas model diffusion controlled as indicated by highest R^2values in zero order. The n values obtained from the Korsmeyer-Peppas model showed that the release mechanism was non Fickian. Table 11 and fig.16-19 shows the in release kinetics of F_5 formulation.

Table 11: Release kinetics of glimepiride from formulation F_5.

Time	Square root of time	log time	%CDR	log % CDR	log % CDR remaining
0 min.	0	0	0	0	0
15 min.	0.5	-0.602	16.70	1.22271647	1.92064500
30 min.	0.707	-0.301	20.94	1.32097667	1.8979568
45 min.	0.866	-0.1249	25.13	1.40019248	1.87430783
60 min.	1	0	29.16	1.46478752	1.85027855
90 min.	1.2247	0.17609	33.65	1.52698506	1.82184092
120 min	1.414	0.301	36.86	1.56655533	1.80030457
3 hr.	1.732	0.4771	39.31	1.59450304	1.78311713
4 hr.	2	0.602	43.85	1.64196959	1.74934976
5 hr.	2.236	0.6989	47.03	1.67237497	1.72402997
6 hr.	2.449	0.7781	49.02	1.69037330	1.70739983

7 hr.	2.645	0.845	53.52	1.72851610	1.66726611
8 hr.	2.828	0.903	57.70	1.76117581	1.62634036
10 hr.	3.162	1	61.47	1.78866321	1.58579900
12 hr.	3.464	1.0791	66.21	1.82092358	1.52878819
14 hr.	3.741	1.1461	72.10	1.85793526	1.44560420
24 hr.	4.898	1.3802	76.47	1.88349109	1.37162192

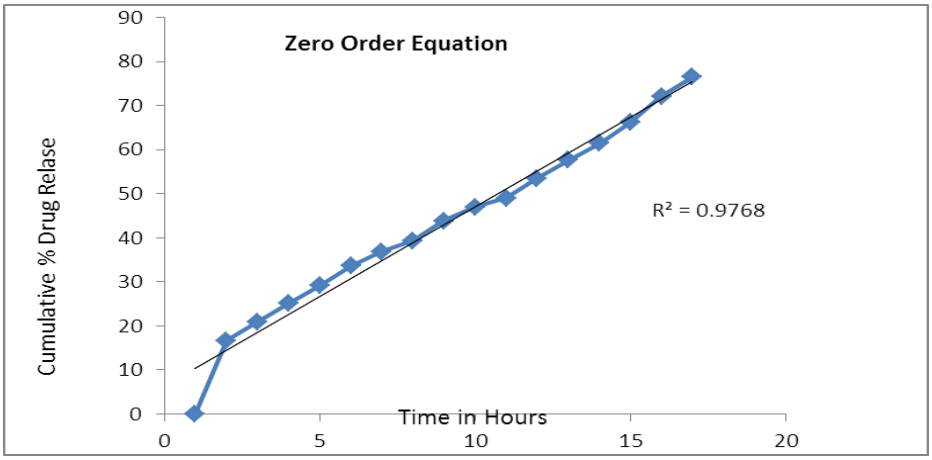


Figure 16: Zero order release kinetics of Formulation F_5.

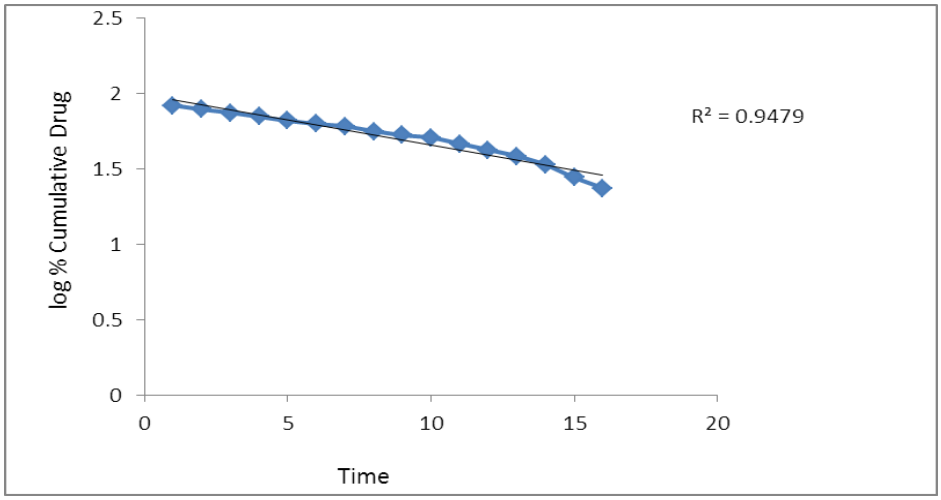


Figure 17: First order release kinetics of Formulation F_5.

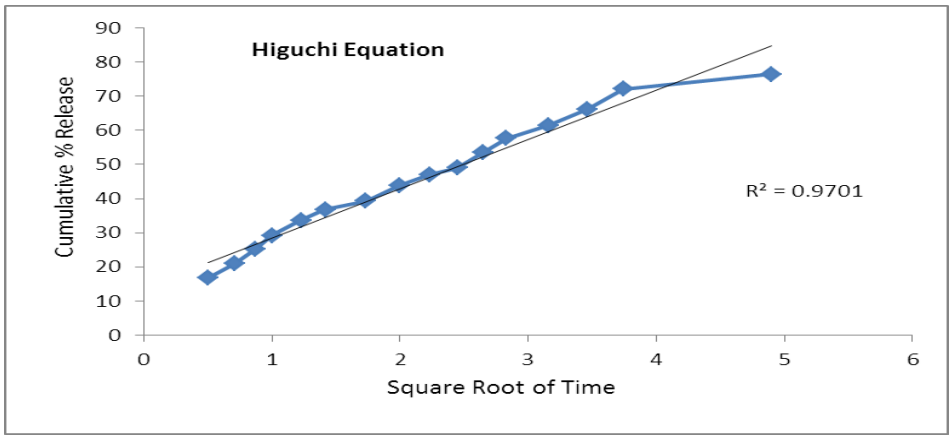


Figure 18: Higuchi model release kinetics of Formulation F_5.

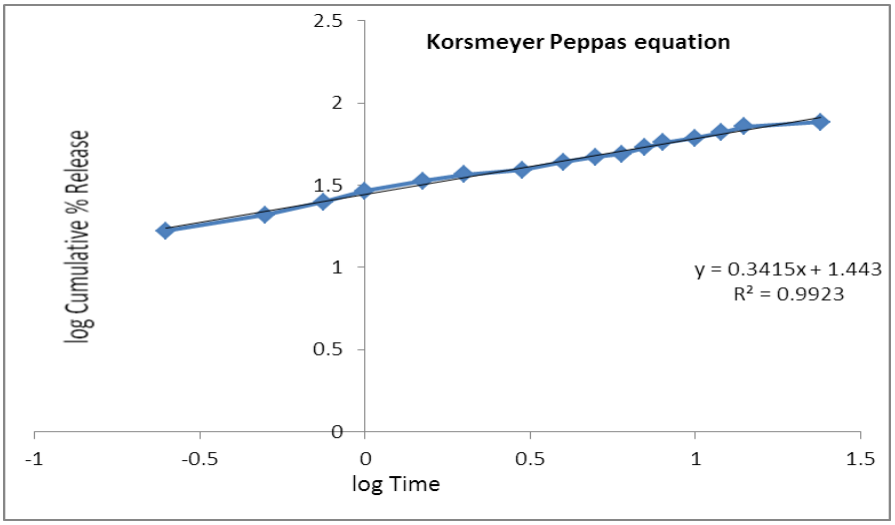


Figure 19: Korsmeyer peppas model release kinetics of Formulation F_5.

CONCLUSION

After the formulation of the microsphere and evaluating these spheres it may be concluded that this sustained release formulation would be a promising drug delivery system to sustain the drug release for about 24 h enhancing the patient compliance. In the formulation, the combination of cost-effective and biocompatible polymers Eudragit RS100, Ethyl cellulose and Guargum had been successfully used and there is scope of scale up of the batches to the commercial level. The best formulation from the 7 batches, found to be efficient with good recovery yield, percent drug entrapment and drug release was F5, prepared using 2:2:1 ratio of polymer. The surface structure, particle size, and flow analysis revealed that the microspheres showed good flow and packability, indicating that it can be successfully handled and filled into a capsule dosage form.

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