FORMULATION AND EVALUATION OF FLUVASTATIN FLOATING MICROSPHERES

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***Abstract*- The present study is to formulate floating Microspheres of Fluvastatin with a view to control the release of the drug. From the experimental results, it can be concluded that FT-IR study shows no significant shifting of the peaks. Therefore, it confirms the short term stability of the drug in the microspheres. Biocompatible polymers like HPMC K100M, Ethyl cellulose and Eudragit S 100 can be used to formulate floating Microspheres. Good percentage drug entrapment and practical yields were obtained with the polymers. The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules. The floating microspheres of drug with HPMC and Ethyl cellulose were buoyant while those with Eudragit S 100 showed greater buoyancy. Cumulative percentage drug release significantly decreased with increase in polymer concentration. The overall curve fitting into various mathematical models was found to be on average. The formulations F 8 best fitted into zero order and showed Non-Fickian diffusion mechanism. Formulated microspheres were stable and compatible at the room temperature and accelerated temperature and humidity in storage for 90days. From the stability studies it was found that there was no significant change in the drug entrapment, release characteristics of the microspheres.**

***Index Terms*- Biodegradable microspheres, emulsion solvent evaporation, fluvastatin sodium, Eudragit S 100**

I. INTRODUCTION

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products such as starches, *gums*, proteins, fats, and waxes. The natural polymers include albumin and gelatin. The synthetic polymers include poly lactic acid and poly glycolic acid[1,2].

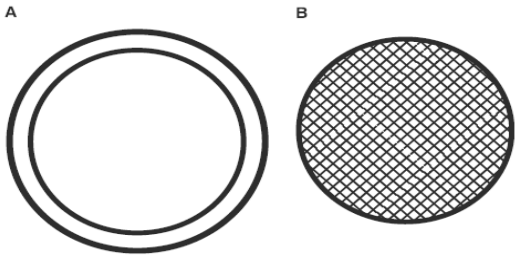


Fig.1: Inter-digestive myoelectric cycle

A) Microcapsule consisting of an encapsulated core particle and
B) Micro-matrix consisting of homogeneous dispersion of active ingredient in particle.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS[3,4]

Gastro-retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro-retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.[5]

Floating systems or hydro-dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[6] Comprehensive knowledge about GI dynamics such as gastric emptying, small intestine transit, colonic transit, etc. is the key for the designing of oral controlled release dosage forms. The rate and extent of drug absorption from different sites of GI tract and factors that govern the absorption further assist the design of dosage form.

Basic Gastrointestinal Tract Physiology

It is well recognized that stomach may be used as "depot" for sustained-release (SR) dosage forms, both in human and veterinary applications.[7] Thestomach is anatomically divided into three parts: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump to accomplish gastric emptying. The process of gastric emptying occurs during fasting as well as fed states; however, the pattern of motility differs markedly in two states. In the fasted states, it is characterized by inter digestive series of electrical events, which cycle both through stomach and intestine every 2 to 3 hrs. This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following four phases:

Phase I (basal phase) lasts from 40 to 60 min with rare contractions. It is characterized by lack of any secretary and electrical activity and contractile motions.

Phase II (pre-burst phase) lasts for 20 to 40 min with intermittent action potential and contractions. Bile enters the duodenum during this phase, while the gastric mucous discharge occurs during the latter part of phase I and throughout the phase III.

Phase III (burst phase) lasts for 10 to 20 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the "housekeeper wave".

Phase IV (transition period) lasts for 0 to 5 min and occurs between phase III and phase I.[8]

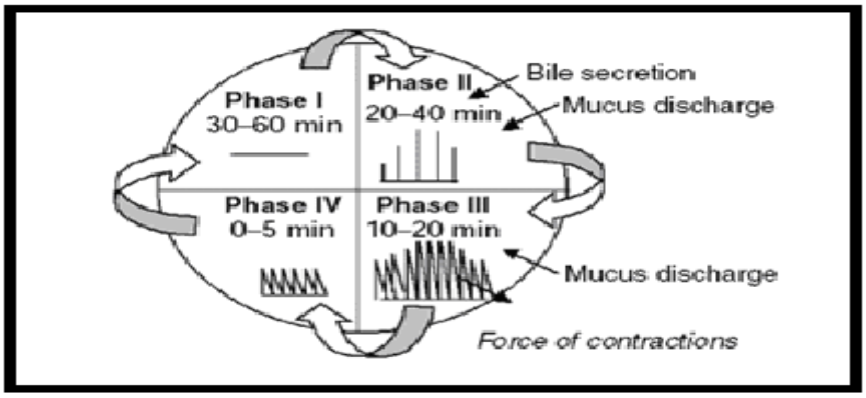


Fig.2: Inter-digestive myoelectric cycle

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[9]

APPROACHES IN GASTRORETENTIVE DRUG DELIVERY SYSTEMS[10]

Various approaches have been worked out to improve the retention of an oral dosage form in the stomach:

1. Floating system.
2. Expanding system.
3. Bio-adhesive system.
4. Modified shape system.
5. High-density system
6. Other delayed gastric-emptying devices.

1. Floating system

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and therefore remain floating

in the stomach without affecting the gastric-emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release; the residual system is expelled from the stomach. This leads to an increase in the GRT and better control over fluctuations in plasma drug concentration.

2. Swelling system

Swelling-type dosage forms are such that after swallowing, these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be referred to as "play-type systems" because they exhibit a tendency to remain blocked at the pyloric sphincter.

3. Bio-adhesive system

Bio-adhesive systems are used to localize a delivery device within the lumen cavity of the body to enhance the drug absorption process in a site-specific manner. In this approach, Bio-adhesive polymers are used that can adhere to the epithelial surface of the gastrointestinal tract. Mechanistically, bio-adhesion involves the formation of hydrogen and electrostatic bonding at the mucus polymer interface.

4. Modified system

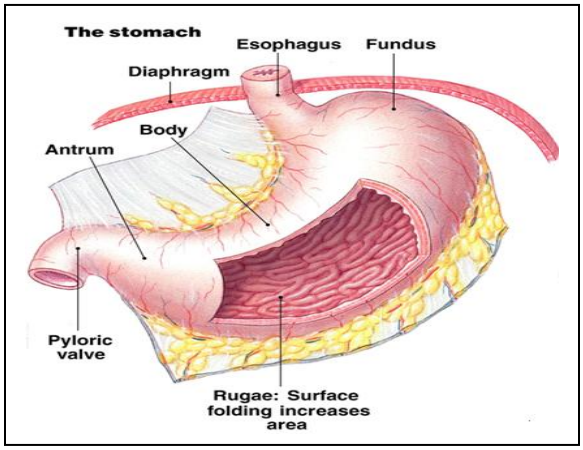
Modified systems are non-disintegrating geometric shapes made up of silastic elastomer or extruded from polyethylene blends, which prolong the GRT, depending on size and shape.

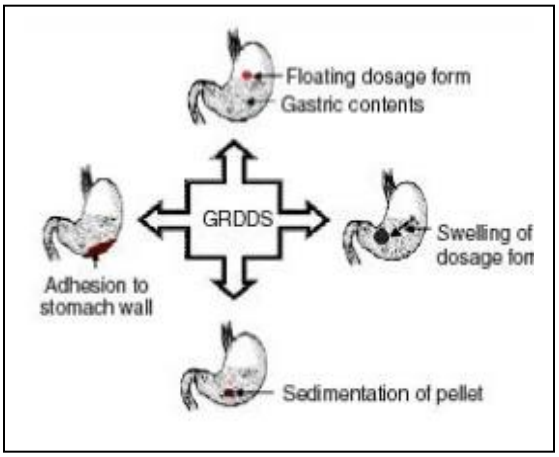
5. High-density system

High-density gastro retentive systems include coated pellets that have a density greater than the stomach contents (~1.004 g/cm^3). This can be achieved by coating the drug with heavy inert material, such as zinc oxide, titanium dioxide, barium sulphate, etc.

6. Other delayed gastric-emptying devices

It includes use of some indigestible polymers or fatty acid salts, which can change the motility of the GI tract leading to an increase in GRT and hence prolonged drug release.[13]





II. METHODOLOGY

ESTIMATION OF FLUVASTATIN

2.1. Standard Graph of Fluvastatin:

Standard Stock solution: 100 mg of Fluvastatin was dissolved in small quantity of Methanol and make up to 100 ml 0.1N HCL to give a concentration of (1000 µg/ml)

Scanning: From the stock solution 100µg/ml was prepared and UV scan was taken between 200 to 400 nm. The absorption maximum was found to be 275 nm and was used for the further analytical studies.

2.2. Calibration curve of Fluvastatinin 0.1 N HCL: The standard solutions were prepared by proper dilutions of the primary stock solution with buffer to obtain working standards in the concentration range of 2-10µg/ml of pure sample of Fluvastatin.The concentration of Fluvastatin present in the microspheres was obtained from the calibrationcurve[11,12].

2.3. Drug-Excipients Compatibility study:

Fluvastatin was mixed with all excipients, used in the formulation in different ratios and subjected to Physical observation/FTIR.

2.4. Drug-Excipient Compatibility study (FTIR):

Prior to the development of the dosage forms the preformulation study was carried out. IR spectral studies lies more in the qualitative identification of substances either in pure form or in combination with polymers and excipients and acts as a tool in establishment of chemical interaction. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. In order to establish this point, comparisons were made between the spectrum of the substances and the pure compound. The above discussions imply that infrared data is helpful to confirm the identity of the drug and to detect the interaction of the drug with the carriers. FTIR spectra were recorded with a Thermo Nicolet. Japan In the range 400–4000 cm−1 using a resolution of 4 cm−1 and 16 scans. Samples were diluted with KBr mixing Powder, and pressed to obtain self-supporting disks. Liquid samples formulations were analyzed to form a thin liquid film between two KBr disks[13].

III. EXPERMENTAL METHODS

3.1 PREPARATION OF FLOATING MICROSPHERES OF FLUVASTATIN

Floating microspheres were prepared by the solvent evaporation method.Various concentration of polymer in suitable solvents were mixed well with the Fluvastatin with different ratios of polymer as shown in Table

Table 1: Formulation of Fluvastatin Floating Microspheres

Ingredients(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Fluvastatin	40	40	40	40	40	40	40	40	40
HPMC	30	40	50	-	-	-	-	-	-
Eudragit S100	-	-	-	30	40	50	-	-	-
Ethyl cellulose	-	-	-	-	-	-	30	40	50
$NaHCO_3$									
Dichloromethane:Ethanol (1:1) (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

q.s – Quantity sufficient

STANDARD CURVE PROCEDURE:

Standard Graph of Fluvastatin(0.1 N HCl):

The standard graph of Fluvastatin has shown good linearity with R^2 values 0.998 in 0.1 N Hcl and which suggests that it obeys the “Beer-Lambert’s law”.

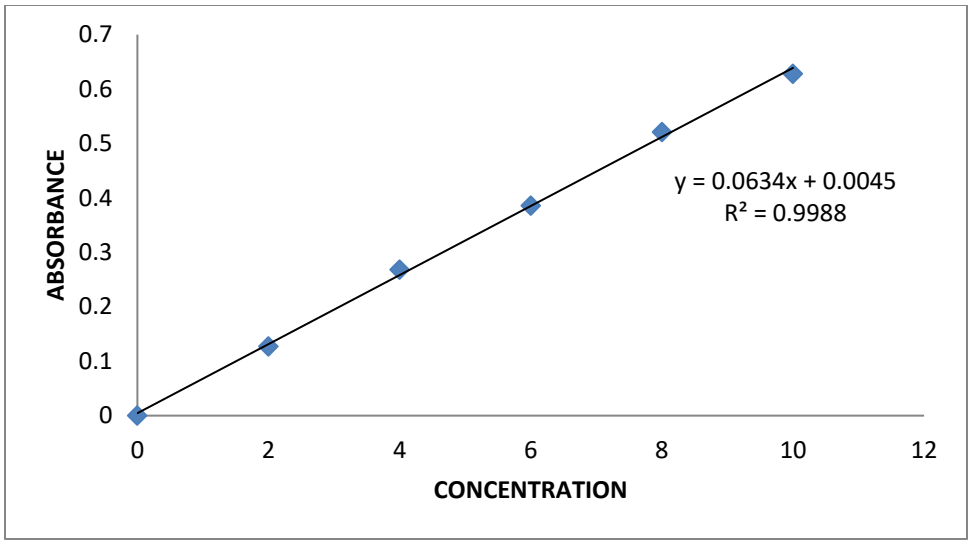


Fig. 5: Calibration curve for Fluvastatin in 0.1N HCl at 280nm

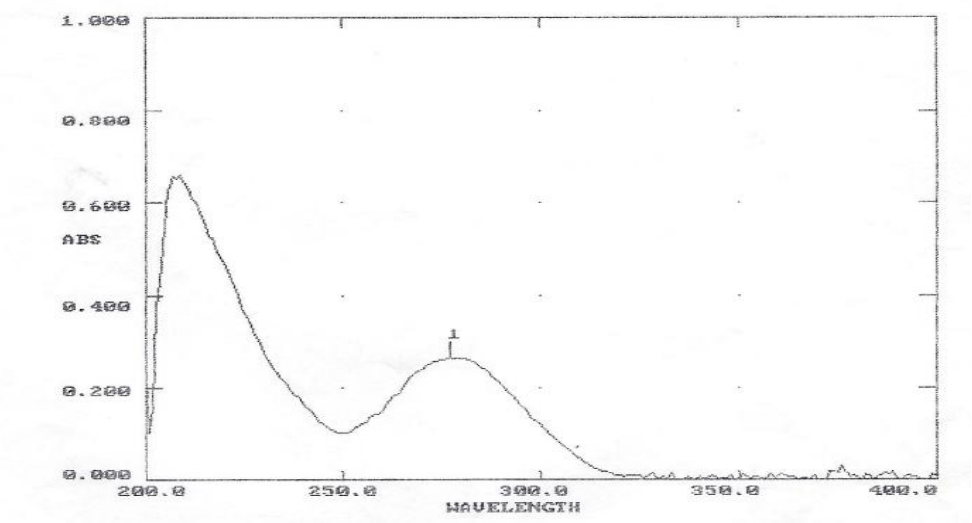


Fig.6: UV Spectrum for Fluvastatin at 280nm

Compatibility studies:

FT-IR spectroscopy was employed to ascertain the compatibility of drugs with polymers. The individual drug and drug with polymers were separately scanned. Both the spectra were compared for confirmation of common peaks. Fluvastatin with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and excipients were compatible. There is no interaction between drug and polymer. Hence, it can be concluded that the drug is in free state and can release easily from the formulation the spectra are reported in the below table and figure.

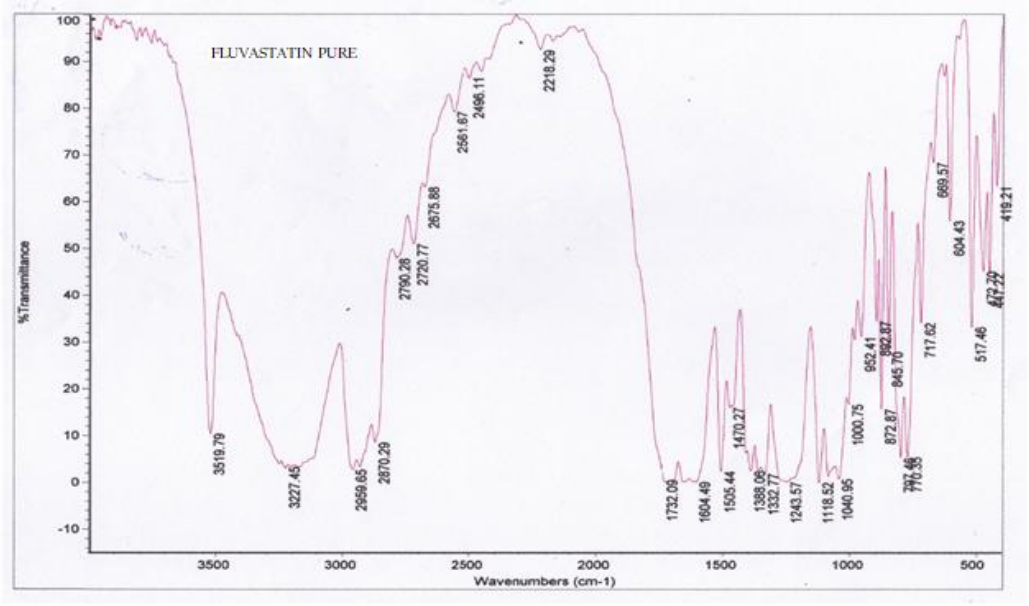


Fig.7: FTIR spectra of Fluvastatin pure drug

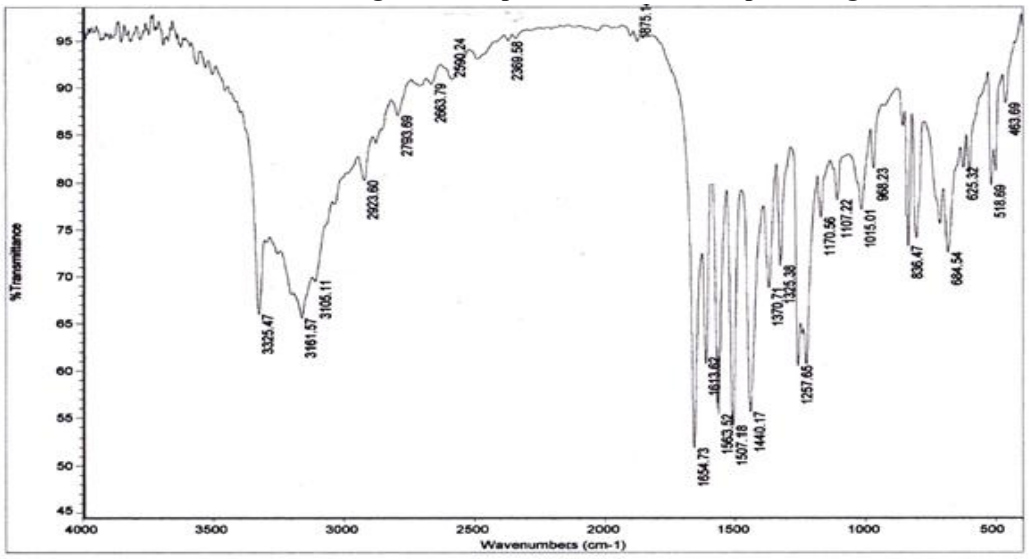


Fig.8: FTIR Spectra of optimized formulation

FTIR studies were performed to understand the compatibilities between the drugs with different excipients. The figures above illustrate that the functional groups like C=O stretch with the observation range of 1740-1650 has peaks at 1732.09 in pure drug and 1654.73 in optimized formulation. Similarly the functional group O-H has a peak range of 3550-3200 has peaks at 3519.79 in pure drug and 3325.47 in optimized formulation. The functional groups in both the pure drug and optimized formulation are found. Hence it can be concluded that the pure drug is compatible with the excipients used in the study.

Table 2: Preformulation Parameters of Fluvastatin Microspheres

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner Ratio	Angle of repose(θ)
F1	0.44±0.045	0.51 ± 0.09	13.72±0.2	1.15±0.02	26.06± 0.31
F2	0.45±0.045	0.50 ± 0.07	12.01±0.6	1.11±0.04	27.18± 0.15
F3	0.44±0.044	0.52 ± 0.09	15.38±0.8	1.18±0.08	28.14± 0.11
F4	0.45±0.045	0.52 ± 0.04	13.46±0.1	1.15±0.06	27.38± 0.13
F5	0.44±0.044	0.51± 0.01	13.72±0.6	1.15±0.08	27.30± 0.19
F6	0.45±0.045	0.52 ± 0.04	13.46±0.8	1.13±0.09	28.32± 0.19
F7	0.51±0.045	0.58 ± 0.04	12.06±0.8	1.13±0.09	27s.19± 0.19
F8	0.46±0.041	0.52 ± 0.10	11.53±0.21	1.15±0.04	27.06± 0.41
F9	0.44±0.041	0.52± 0.11	15.38±0.54	1.18±0.12	27.52± 0.15

All the formulations were evaluated for bulk density, tapped density, % compressibility, Hausner's ratio and angle of repose. The results of % compressibility, Hausner's ratio and angle of repose were found to be <16, <1.25 and <30 respectively. These results show that the formulations have very good flow properties.

EVALUATION AND CHARACTERISATION OF MICROSPHERES

PERCENTAGE YIELD

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution tothe magnetic bead and microspheres lost during the washing process. The percentage yield of the prepared microspheres is recorded in Table below and displayed in the figure.

DRUG ENTRAPMENT EFFICIENCY

Percentage Drug entrapment efficiency of Fluvastatin arranged from 56 to 92% for microspheres. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in the table below and displayed in the figure.

Table 3: Percent yield and percent drug entrapment efficiency of the prepared microspheres

S. No.	Formulation code	% Yield	% Buoyancy	% Drug entrapment efficiency	%Swelling Index
1	**F1**	78	62	72	52.14
2	**F2**	81	66	84	54.26
3	**F3**	84	70	86	53.48
4	**F4**	82	72	84	52.37
5	**F5**	84	74	82	55.11
6	**F6**	85	79	86	54.18
7	**F7**	84	81	87	54.78
8	**F8**	88	89	94	56.32
9	**F9**	85	85	86	55.66

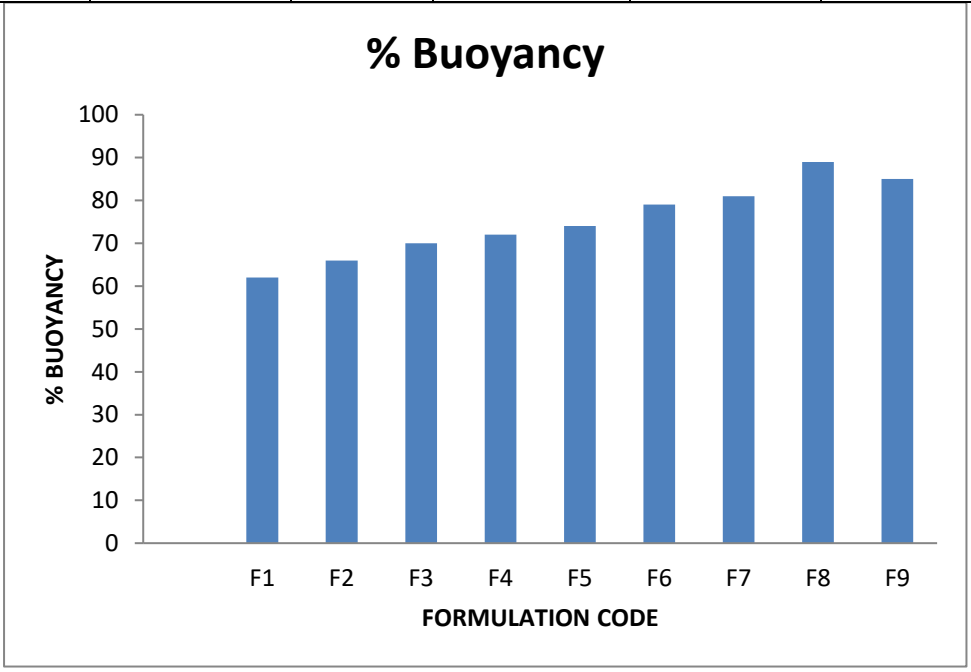


Fig.9: Evaluation of Percent Buoyancy for F1 -F9 Fluvastatin formulations

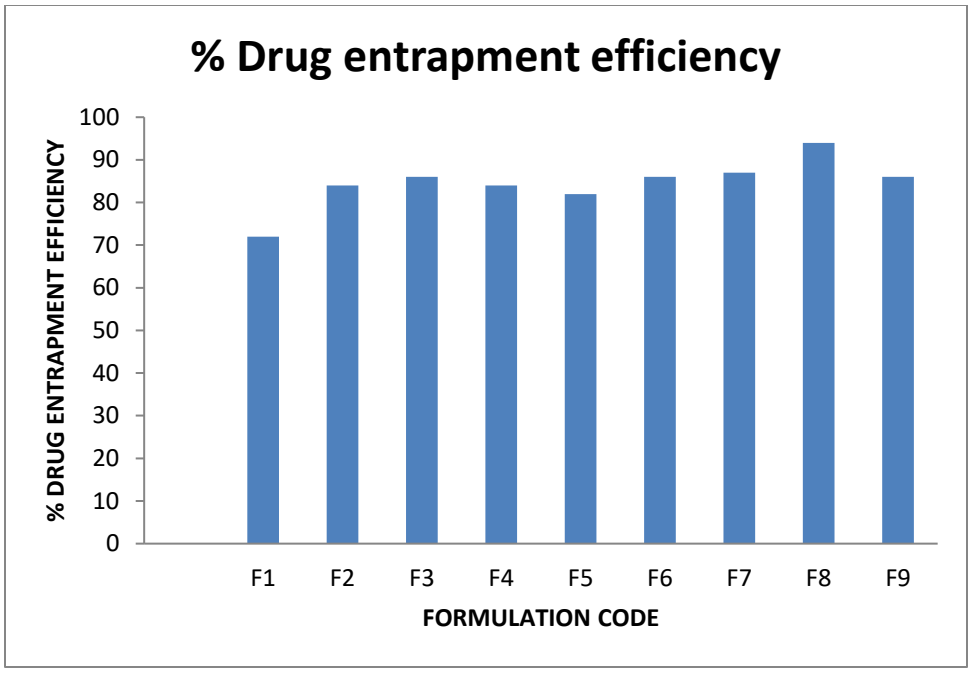


Fig.10: evaluation of % Drug entrapment efficiency for F1 -F9 formulations

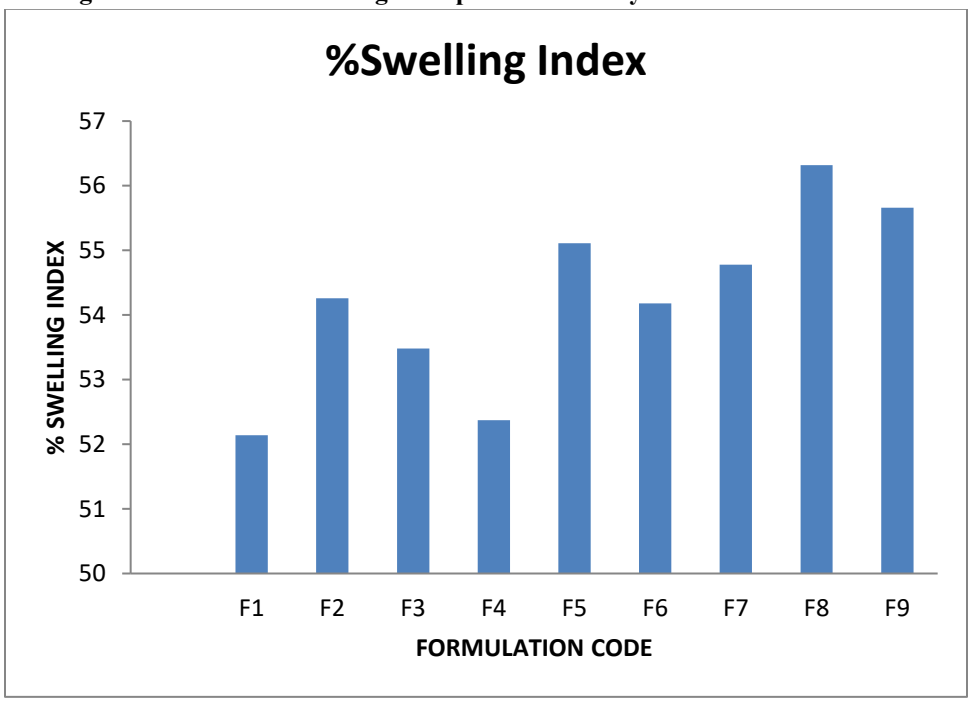


Fig.11: Graph for evaluation of % Swelling Index for F1 -F9 formulations

Mean Particle Size

Mean particle size was determined by optical microscopy and the average particle size was calculated. The results were shown in table below

Table 4: Average particle sizes of Fluvastatin microspheres

S.No	Batches	Mean Particle Size(µm)
1	F_1	585 µm
2	F_2	594 µm
3	F_3	586 µm
4	F4	584 µm
5	F5	574 µm
6	F6	592 µm
7	F7	585 µm
8	F8	567 µm
9	F9	590 µm

***IN-VITRO* DRUG RELEASE STUDIES:**

Dissolution studies of all the formulations were carriedout using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2. The results of the in-vitro dissolution studiesof formulations F_1 to $F_9$are shown inthe table below. The plots of Cumulative percentage drug release Vs time figure shows the comparison of %CDR for formulations F1 to F9.

Table 5: Percentage cumulative drug release for formulations F1 to F9

TIME IN HRS	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	20.12	18.02	14.02	29.18	23.02	14.01	25.15	16.27	11.31
2	38.26	26.23	20.02	45.34	36.04	24.02	37.41	24.32	17.62
3	51.57	37.04	28.03	52.75	44.05	28.03	46.26	31.63	24.43
4	64.68	48.05	37.04	59.36	50.05	32.03	54.27	38.43	27.23
5	75.27	56.05	44.05	66.46	55.05	39.04	60.48	46.24	34.34
6	86.78	71.07	62.06	74.37	64.06	44.04	65.74	51.34	40.44
7	95.27	84.07	85.78	81.98	71.07	52.05	72.35	58.65	46.85
8	--	96.1	98.5	89.28	79.08	59.05	79.29	68.26	53.36
10	--	--	--	96.26	94.1	72.06	95.57	82.38	62.46
12	--	--	--	--	--	84.08	--	98.3	75.28

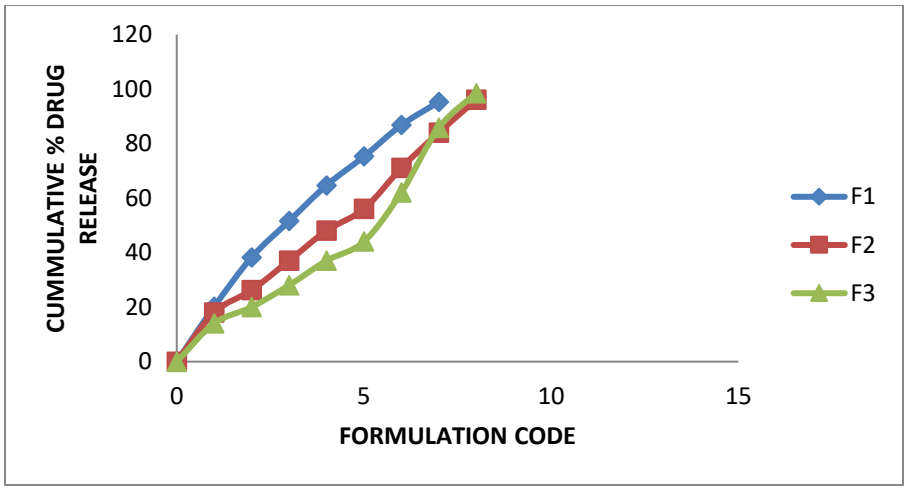


Fig.12: Comparative *IN-VITRO* drug release for formulations F1-F3

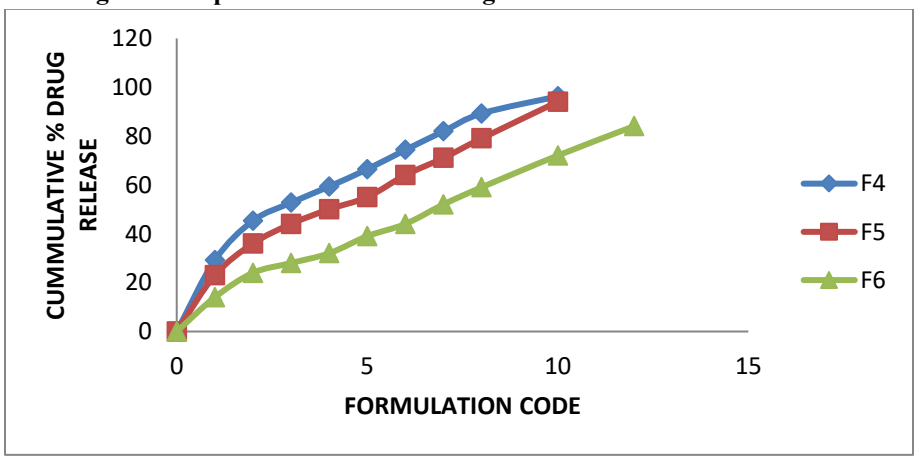


Fig.13: Comparative *IN-VITRO* drug release for formulations F4-F6

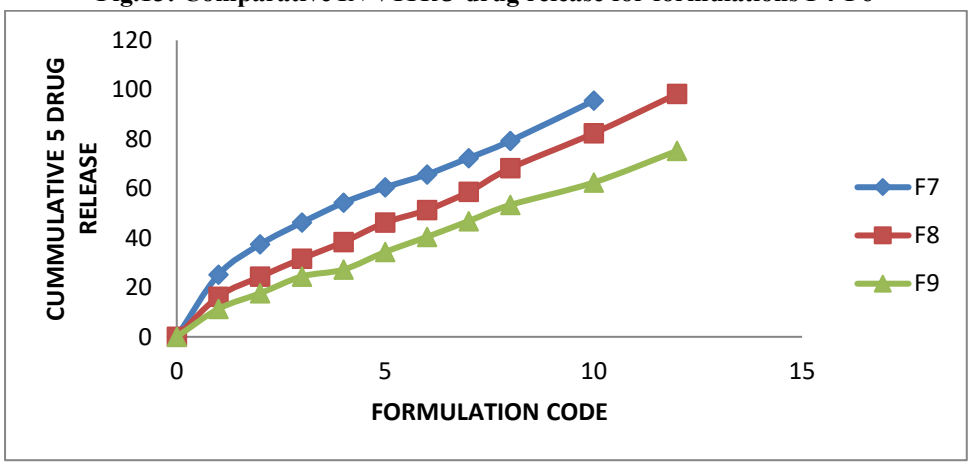


Fig.14: Comparative *IN-VITRO* drug release for formulations F7-F9

IN-VITRO DRUG RELEASE KINETICS

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the *in-vitro* drug dissolution data obtained was fitted to various mathematical models such as zero order, first order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in the tables below. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the

formulations reached higher coefficient of determination with the zero order (R^2 = 0.992). From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

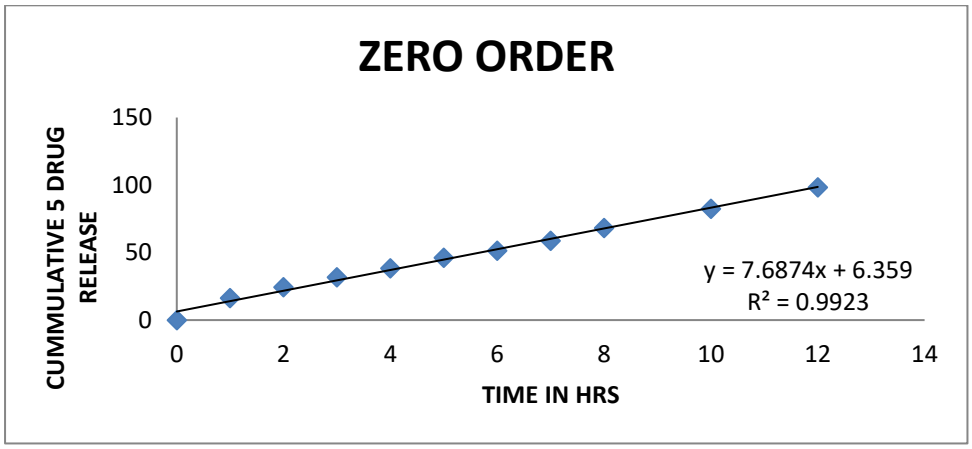


Fig.15: Zero order kinetic graph for F8 batch

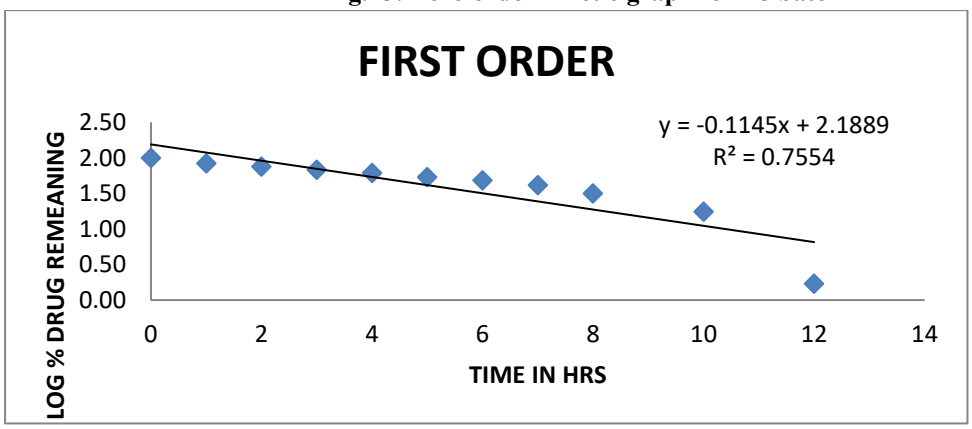


Fig.16: First order kinetic graph for F8 batch

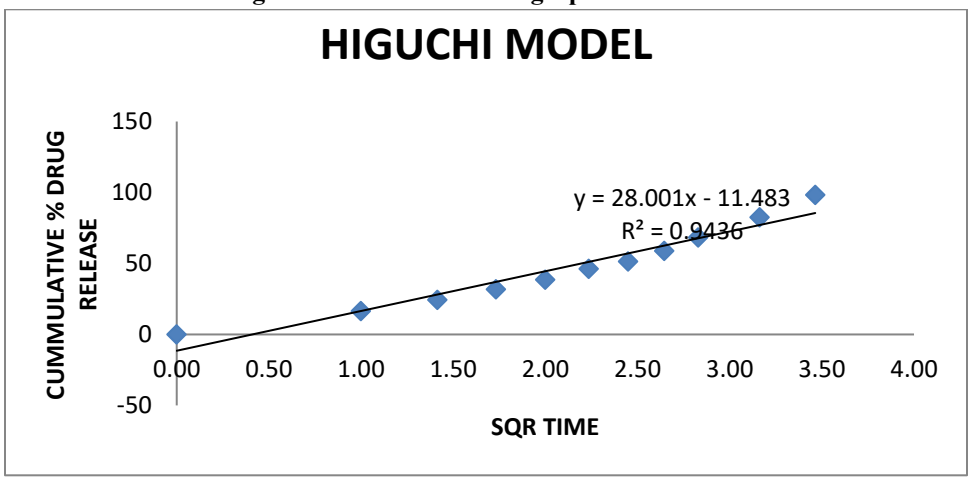


Fig.17: Higuchis model kinetic graph for F8 batch

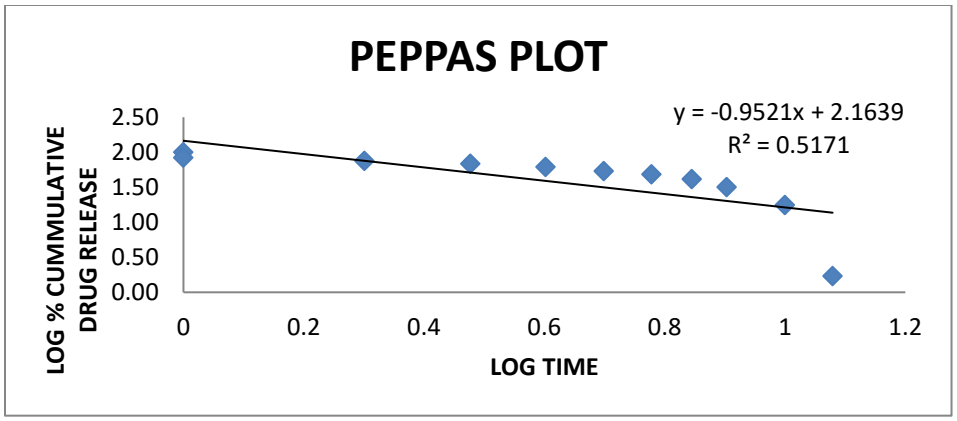


Fig.18: Peppas model kinetic graph for F8 batch

Table 6: R² values for release kinetics

RELEASE KINEITCS				
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**
	Q Vs T	**Q Vs √T**	**Log C Vs Log T**	**Log % Remain Vs T**
Slope	**7.687**	**28.00**	**-0.952**	**-0.114**
Intercept	**6.359**	**-11.48**	**2.163**	**2.188**
Correlation R 2	**0.992**	**0.943**	**0.517**	**0.755**

STABILITY STUDIES OF FLUVASTATIN OPTIMIZED FORMULATION:

The optimized formulation of Fluvastatin (F8) were subjected to short-term stability testing by storing the microspheres at room temperature 25°C/60%RH.

Table 7:Stability studies of optimized formulation at room temperature

Time	**Colour**	**Drug entrapment efficiency ± S.D. at Room Temperature**	**Cumulative % drug release ± S.D.**
First day	White	94.00± 0.52	98.30±0.51
30days	White	93.42 ± 0.21	98.01±0.68
60 days	White	92.06 ± 0.47	97.47±0.61
90 days	White	92. 45 ± 0.11	97.20±0.54

Results from stability studies indicate that the formulated microspheres are stable for a period of 3 months under room temperature i.e., 30˚C temp and 65±5% RH. There were no remarkable changes were observed during the period of storage.

The optimized formulation of Fluvastatin (F8) were subjected to accelerated stability testing by storing the microspheres at accelerated temperature 40°C/70% RH.

Table 8: Stability studies of optimized formulation at Accelerated temperature

Time	**Colour**	**Drug entrapment efficiency ± Std. at accelerated Temperature**	**Cumulative % drug release ± St. D.**
First day	White	94.12± 0.91	96.20±0.55
30days	White	94.62 ± 0.21	95.71±0.10
60 days	White	93.12 ± 0.90	95.12±0.88
90 days	White	93. 06 ± 0.01	95.00±0.12

Results from stability studies indicate that the formulated microspheres are stable for a period of 3 months under accelerated temperature i.e., 40˚C temp and 70% RH. There were no remarkable changes observed during the period of storage.

IV. SUMMARY OF FINDINGS

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of the drug for a particular period of time. However, incomplete release of the drug, shorter residence times of dosage forms in the upper GIT leads to lower oral bioavailability. Such limitations of the conventional dosage forms have paved way to an era of controlled and novel drug delivery systems.

Therefore, in the present study an attempt has been made to formulate Fluvastatin floating microspheres which can be expected to prolong the gastric residence time of active compounds and reduce the variability of transit. They are capable of increasing the bioavailability of drugs that are mainly absorbed in the upper gastrointestinal tract. For that purpose, drug release has to be controlled. It would be faster and more economical to alter beneficially the properties of the existing drugs than developing new drug entities.

For the formulation, three biocompatible polymers HPMC, Ethyl cellulose and Eudragit were chosen in varying proportions with the drug. Solvent evaporation method was used to prepare microspheres employing different solvent to dissolve the drug and the polymer.

The prepared formulations were characterized for their percentage yield, micro-meritic properties, morphology, buoyancy studies, drug entrapment, and drug release studies. Percentage Drug entrapment efficiency of F1 to F3 ranges from 72 to 86% for microspheres containing HPMC as polymer, formulations F4 to F6 ranges from 82 to 86% for microspheres containing Eudragit S 100 as polymer and formulations F7 to F9 ranges from 86 to 94% for microspheres containing Ethyl cellulose as polymer.Almost all the formulations showed fairly acceptable values for all the parameters evaluated.

The average particle size of floating microspheres was in the range of 567µm- 594µm and improved drug entrapment efficiency could be depending upon the type and ratio of polymer used. The particle size increased significantly as the amount of polymer increased. The formulations showed good flow properties, suggesting that, in future they could be easily and successfully packed and developed into a capsule dosage form.

Among all formulations F8 formulation with drug: polymer (1:2) was found to be satisfactory in terms of excellent micro-meritic properties, percent yield(88%), drug entrapment efficiency (94%), percentbuoyancy (89%), and highest *invitro* drug release of 98.3% in sustained manner over an extended period of time for 12 hrs.

Thus the prepared microspheres proved to be a potential candidate as a microparticulate controlled release drug delivery device in this era of patenting novel and controlled release formulations.

V. CONCLUSION

The present study has been a satisfactory attempt to formulate a floating Microspheres of Fluvastatin with a view to control the release of the drug. From the experimental results it can be concluded that,

•FT-IR study shows no significant shifting of the peaks therefore it confirms the short term stability of the drug in the microspheres.

•Biocompatible polymers like can be HPMC, Ethyl cellulose and Eudragit S 100 used to formulate a floating Microspheres.

•Good percentage drug entrapment and practical yields were obtained with the polymers.

•The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules.

•The floating microspheres of drug with HPMC and Ethyl cellulose were buoyant while those with Eudragit S 100 showed greater buoyancy.

•Cumulative percentage drug release significantly decreased with increase in polymer concentration.

•The overall curve fitting into various mathematical models was found to be on average. The formulations F 8 best fitted into zero order and show non-fickian diffusion mechanism.

•Formulated microspheres were stable and compatible at the room and accelerated temperature and humidity in storage for 90days.

• From the stability studies it was found that there was no significant change in the drug entrapment, release characteristics of the microspheres.

Thus, the formulated floating microspheres seem to be a potential candidate as an oral gastro retentive controlled drug delivery system in prolonging the drug retention stomach and increasing the bioavailability of drug.

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