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Formulation and Evaluation of Floating Microsphere of Lansoprazole

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ABSTRACT : The objective of the present study was to Prepare the alginate microspheres of Lansoprazole (model drug) using calcium chloride as a crosslinking agent by inotropic gelation method. Microspheres were prepared by using 2%, 2.5% sodium alginate concentrations. Polymers (Eudragit S-100, HPMC K 100 and Chitosan) were used in combination concentration to prepare Microspheres. Microspheres were evaluated for Micromeritic properties like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio and for drug content. The in vitro drug release study was done for microspheres all formulations. The mean particle size, In vitro Buoyancy, Encapsulation efficiency %, Percentage yield (%) were within limits. Among all formulations of floating microspheres F6 was considered as optimised for floating microspheres. From the release kinetics data, it was evident that floating optimised formulation follows Peppas release kinetics.

Keywords: Lansoprazole, GRDDS, Floating Microspheres.

I. INTRODUCTION

To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects[1]. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences.[1]There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. The process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bio erodible polymer, implants, monoclonal antibodies and various particulate. One such approach is using microspheres as carriers for drugs. Microsphere can be used for the controlled release of drugs, vaccines, antibiotics, and hormones[2].

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level[4]. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm)[5]. Recent advances in novel drug delivery system to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for administration. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. There are lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GIT time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability.[6,7]

Floating Microspheres:

Floating microspheres (Hollow Microspheres) are gastroretentive drug delivery system**s** based on non effervescent approach. The word Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid and thus remain buoyant in stomach

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without affecting the gastric emptying rate for a prolonged period of time. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. When a floating capsule is administered to subjects who have consumed a fat and protein meal, it remains buoyant at the surface of the gastric contents in the upper part of the stomach and moves to the lower region progressively as the meal empties from the stomach. The reported gastric retention times range from 4 to 10 h. Pharmacokinetic and bioavailability evaluation studies confirmed the favorable effect of this prolonged gastric residence time.[12]

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells, were prepared by a novel emulsion solvent diffusion method. The ethanol:dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in microspherical particles containing drug.[17]

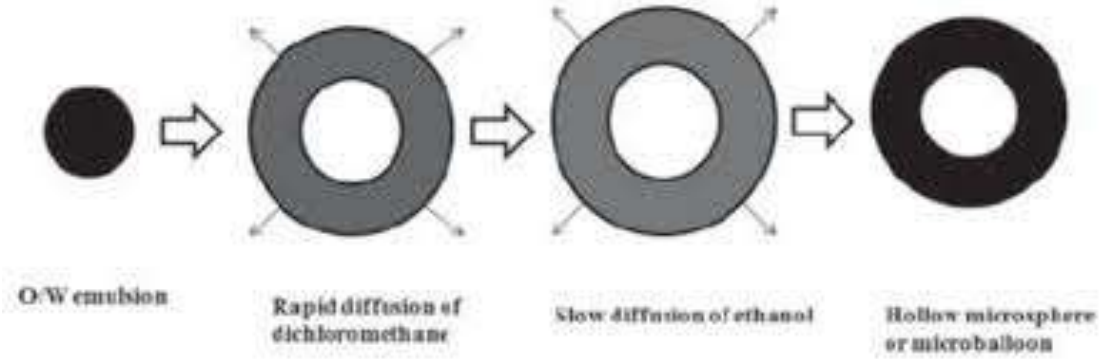

Figure1: Formulation of floating hollow microsphere or microballoon

Advantages of Hollow Microspheres [18-22]

- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
- Improved receptor activation selectivity
- Extended time over critical (effective) concentration
- Less inter- and intra-subject variability.
- Flexibility in dosage form design.
- Improves patient compliance by decreasing dosing frequency.
- Better therapeutic effect of short half-life drugs can be achieved.
- Gastric retention time is increased because of buoyancy.
- Drug releases in controlled manner for prolonged period.
- Enhanced first-pass biotransformation
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT
- Extend patent protection, globalize product, and provide new business opportunities.
- Site-specific drug delivery to stomach can be achieved.
- Enhanced absorption of drugs which solubilize only in stomach.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.

Disadvantages [23-24]

- Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS.eg: NSAIDs, some antibiotics, digoxin,theophylline, corticoster oids, iron (ferrous sulfate), oral contraceptives, and tricyclic
- Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.
- They are not suitable candidates for drugs with stability or solubility problem in stomach.eg.ranolazine.
- Single unit floating capsules or tablets are associated with an “all or none concept,” but this can be overcome by formulating multiple

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unit systems like floating microspheres or microballoons.

- FDDS require sufficiently high level of fluid in stomach so that the system can float and thus sufficient amount of water (200- 250 ml) of water to be taken together with FDDS.antidepressants.

II. MATERIALS AND METHODS:

Lansoprazole as a gift sample from Lee Pharma Limited, Sodium Alginate, HPMC K 100, Chitosan, Eudragit S-100, Sodium bicarbonate, Calcium chloride, Acetic acid and Glutaraldehyde from Research Lab Fine Chem. Industries Mumbai (India) : all other ingredients were used analytical grade from my college's laboratory.

Methods :

Solubility studies:

Take 8.6ml of HCL in a 1000ml volumetric flask and make up the volume with distilled water.

Preparation calibration curve:

100mg of Lansoprazole pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock solution-2 i.e. 100µg/ml). From this take 0.2, 0.4, 0.6, 0.8 and 1.0 ml of solution and make up to 10ml with 0.1N HCL to obtain 2, 4, 6, 8, and 10 µg/ml of Lansoprazole solution. The absorbance of the above dilutions was measured at 235 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The experiment was performed in triplicate and based on average absorbance; the equation for the best line was generated. The results of standard curve preparation are shown in table& figure.

Drug – Excipient compatibility studies by FTIR spectroscopy

Drug Excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies.

Preparation of microspheres

Floating Microspheres are matrix systems that contains drug throughout their structure and are potential candidates for oral controlled release. Microspheres can be defined as solid spherical particles ranging from 1 to 1000µm in size. The choice of methods for the preparation of microspheres depends on many factors such as the drug solubility, partition co efficient, Polymer composition, molecular weight etc.

The Floating microsphere was prepared by Ionic gelation technique. A solution of sodium alginate is prepared, The gelation medium was prepared by dissolving calcium chloride in 2% glacial acetic acid and was added to solution. In this method cross-linking agent & polymer in combination were dispersed in the purified water to form a homogeneous polymer mixture. Resultant solution was extruded drop wise with the help of syringe and needle into aqueous calcium chloride solution and stirred at 100 rpm. The drug was added to the polymer dispersion and mixed thoroughly on a magnetic stirrer to form a homogeneous dispersion. The homogenous alginate solution was extruded using syringe needle into the gelation medium. Then, microsphere was collected and washed with distilled water twice, dried at room temperature for 24 hr and dried at 60 degrees -2 hours in a hot air oven and stored in desiccator.

Table1 : Composition of Floating Microspheres

INGREDIENTS	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lansoprazole (mg)	15	15	15	15	15	15	15	15	15
Eudragit S-100	20	40	60	-	-	-	-	-	-

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HPMC K 100	-	-	-	30	60	80	-	-	-
Chitosan	-	-	-	-	-	-	50	100	150
Sodium Alginate (%)	2	2	2	2.5	2.5	2.5	3	3	3
Sodium bicarbonate (% w/w	10	10	10	10	10	10	10	10	10
Calcium chloride(% w/v	12	12	12	12	12	12	12	12	12
Acetic acid (%v/v)	2	2	2	2	2	2	2	2	2
Glutaraldehyde %	5	5	5	5	5	5	5	5	5

III. RESULTS AND DISCUSSION:

The present work was designed to developing Floating Microspheres of Lansoprazole using various polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

Analytical Method

Standard graph of Lansoprazole in 0.1N HCL:

The scanning of the 10µg/ml solution of Lansoprazole in the ultraviolet range (200-400 nm) against 0.1 N HCL the maximum peak observed at λ_{max} as 235 nm. The standard concentrations of Lansoprazole(2-10 µg/ml) was prepared in 0.1N HCL showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table2 : Standard curve of Lansoprazole in 0.1N HCL

S.NO	Concentration µg /ml	Absorbance
1	0	0
2	2	0.118
3	4	0.225
4	6	0.341
5	8	0.452
6	10	0.558

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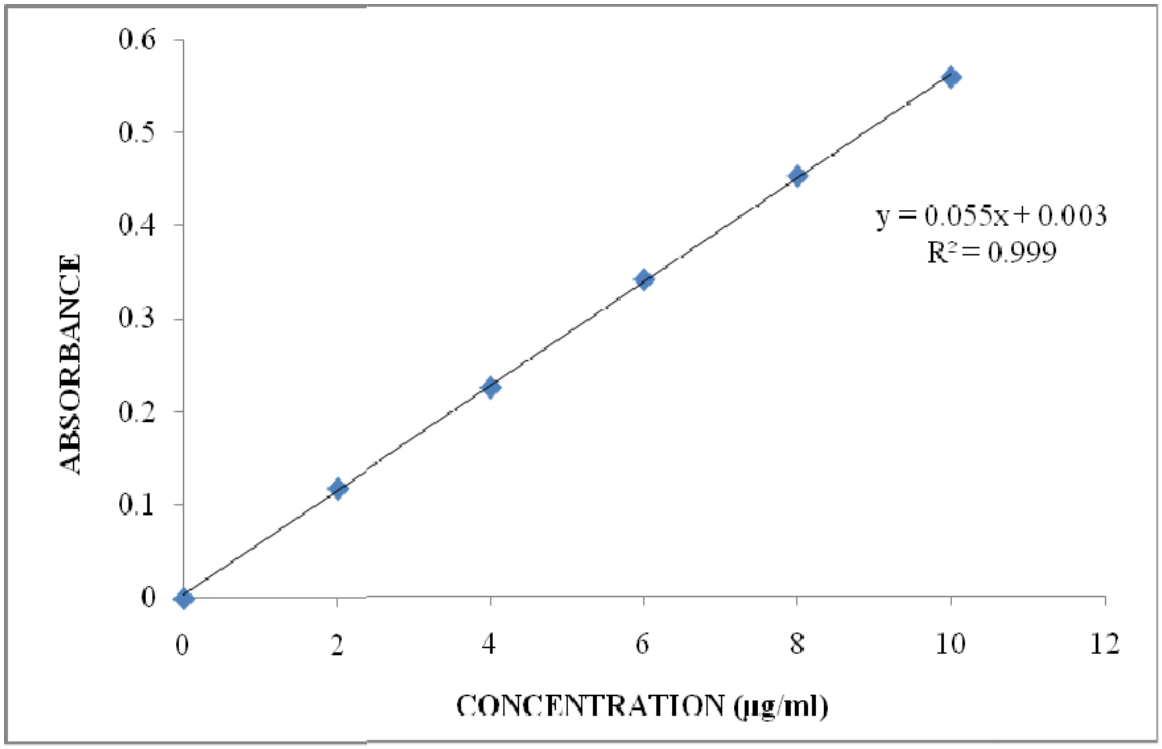

Figure2 : Calibration curve of Lansoprazole in 0.1 N HCL at 235 nm

EVALUATION PARAMETERS

Table 3: Evaluation of Floating Microspheres

Batch No	Mean Particle size(µm)	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (θ)
F1	356.12	0.538±0.05	0.644±0.05	12.3±0.34	1.12±0.31	34.55'±0.03
F2	366.52	0.423±0.07	0.496±0.04	11.3±.13	1.14±0.23	32.64'±0.03
F3	378.28	0.512±0.05	0.597±0.08	12.1±0.43	1.14±0.13	32.07'±0.02
F4	380.32	0.534±0.03	0.645±0.05	12.2±0.24	1.13±0.23	33.10'±0.02
F5	527.61	0.453±0.04	0.576±0.03	11.2±0.45	1.12±0.564	32.24'±0.02
F6	480.58	0.509±0.05	0.576 ±0.08	13.16±0.76	1.13 ± 0.48	34.55'±0.03

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F7	468.21	0.568±0.05	0.640 ±0.09	11.25±0.72	1.12 ± 0.54	32.64'±0.03
F8	490.89	0.554±0.06	0.625 ±0.07	11.36±0.54	1.12 ± 0.35	32.07'±0.02
F9	389.25	0.592±0.09	0.676 ±0.05	12.4 ± 0.33	1.14 ± 0.87	33.10'±0.02

Table 4: Result of mean Particle Size, In vitro Buoyancy and Encapsulation efficiency%, Percentage yield

Batch No:	In vitro Buoyancy (in sec)	Encapsulation efficiency%	Percentage yield (%)
F1	26	96.28	98.32
F2	59	85.26	89.26
F3	35	98.79	98.12
F4	48	89.35	97.12
F5	29	95.14	95.34
F6	49	98.17	97.59
F7	55	97.38	94.2
F8	36	99.86	99.42
F9	28	98.31	98.89

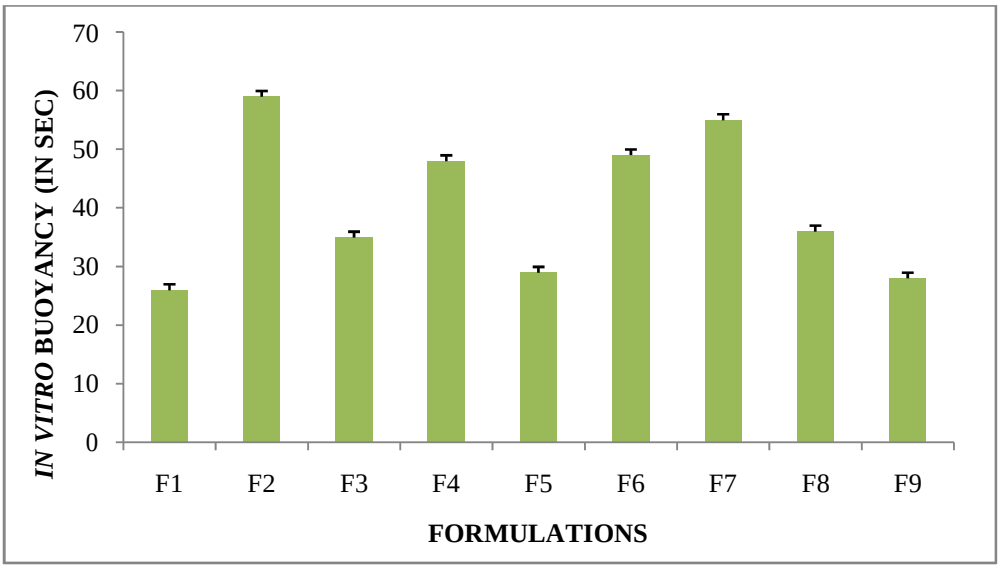

Figure 3: Comparison of In vitro Buoyancy of floating microspheres of Lansoprazole

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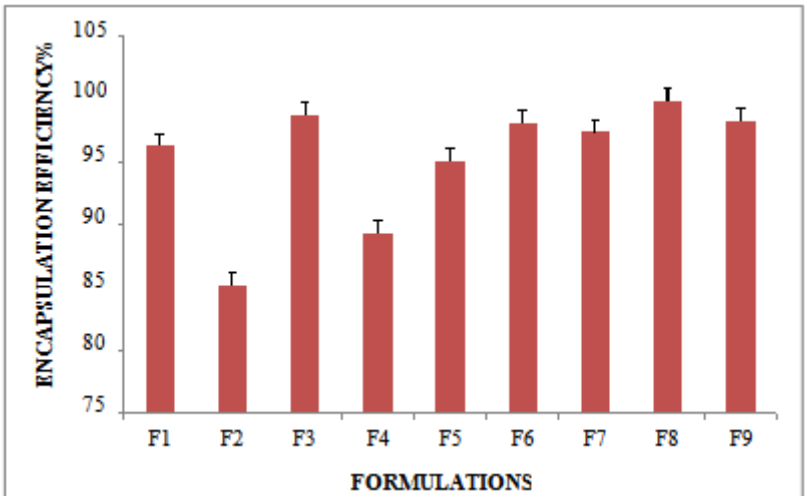

Figure 4: Comparison of Encapsulation efficiency of floating microspheres of Lansoprazole

Drug Entrapment Efficiency (EE), Floating Property and Percentage yield (%)

The floating property of the microspheres was calculated from the fractional amount of drug and polymer density of the microspheres. As shown in above table the Floating efficiency of the microspheres. As the concentration of Chitosan increases in formulation the floating lag time decreases and % drug release is retard as the concentration.

The high levels of sodium alginate lead to increased encapsulation efficiency. The Percentage yield (%) is more for F8, F9 Formulations.

In vitro drug release:

Table 5: In vitro drug release of containing Lansoprazole F1 to F4 formulations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	15.28	13.90	18.65	14.10	17.89	19.62	10.14	16.41	18.41
1	25.95	18.82	26.85	17.49	26.21	27.11	14.15	26.22	21.22
2	38.45	24.72	37.55	27.86	31.45	36.25	18.84	29.69	28.15
3	44.63	30.86	47.14	32.92	44.94	45.81	22.65	33.95	35.95
4	49.72	38.55	58.48	38.13	47.86	50.49	26.58	42.32	42.32
5	56.85	44.32	69.62	43.54	52.79	58.50	31.87	48.29	48.29
6	60.19	50.12	75.32	50.12	56.26	64.99	38.67	59.64	56.64
7	65.56	58.71	79.21	58.39	62.41	67.78	43.95	61.65	62.65
8	74.49	63.56	81.92	62.82	67.77	75.93	46.87	66.96	67.96
9	77.28	70.21	86.10	68.51	77.31	86.80	57.88	72.58	72.58
10	81.86	76.89	90.26	75.60	82.44	90.39	62.45	76.32	76.32
11	87.74	81.34	94.36	82.32	87.92	95.68	68.22	81.99	88.99
12	92.65	87.41	98.61	90.46	90.58	99.17	79.57	84.15	94.15

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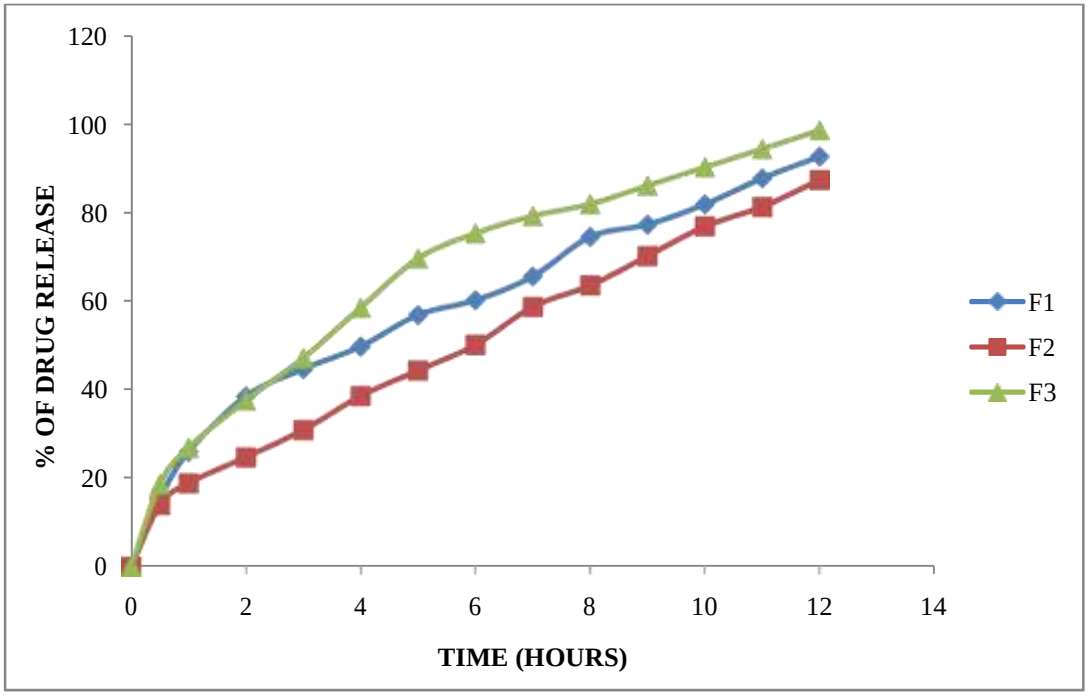

Figure 5: Dissolution study of Lansoprazole Floating Microspheres (F1 to F3)

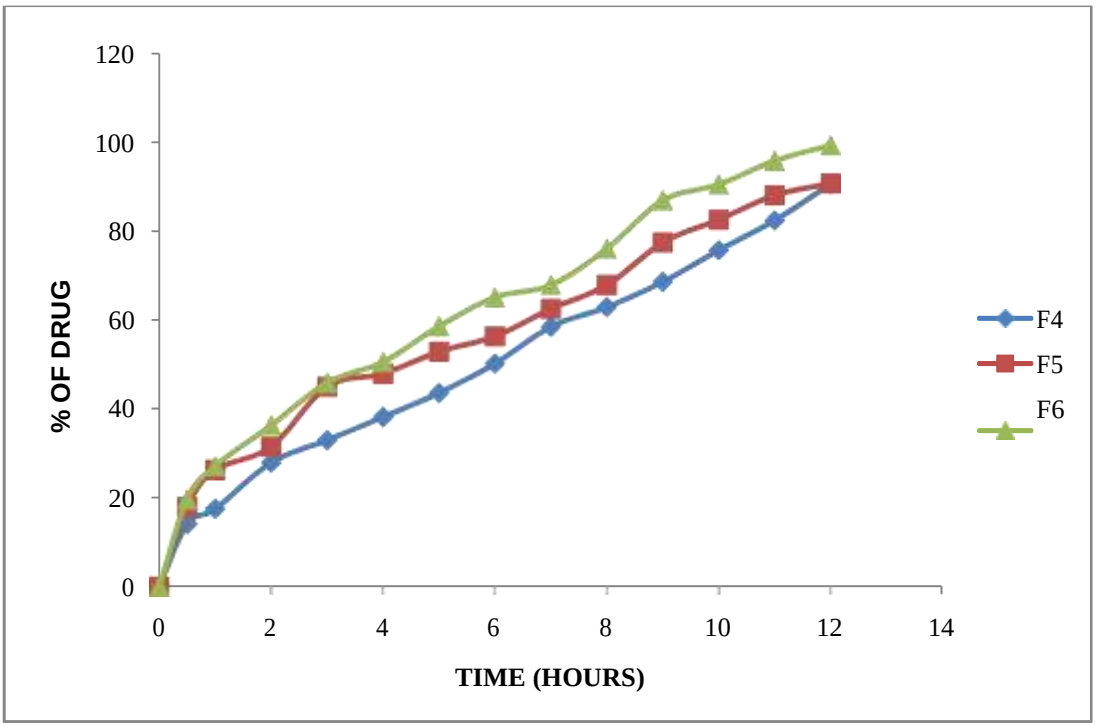

Figure 6: Dissolution study of Floating Microspheres (F4 to F6)

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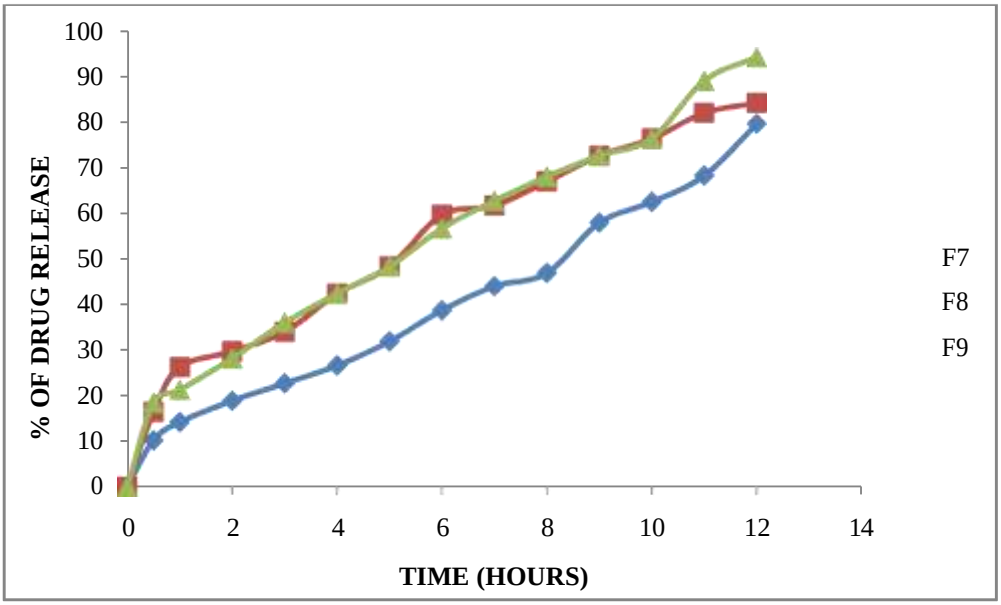

Figure 7: Dissolution study of Floating Microspheres (F7 to F9)

The % drug release of formulations (F1 to F3) containing Eudragit S-100 depends on the concentration of Sodium Alginate (2%). In F3 formulation was maximum drug release was showed at 12 hours.

The % drug release of formulations (F4 to F6) containing HPMC K 100 depends on the concentration of Sodium Alginate (2.5%). In that F6 formulation was maximum drug release (99.17%) was showed at 12 hours.

The % drug release of (F7 to F9) formulations depends on polymer ratio Chitosan. The concentration of Chitosan, Chitosan contain 1:3 ratio showed maximum % drug release i.e. 94.15
% at 12 hours.

Hence based on dissolution data of 9 formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9 formulations showed better release up to 12 hours. Among these formulations F6 formulation showed the drug release (99.17 %) within the specified limits. So F6 formulation is considered as optimised formulation.

Application of release rate kinetics to Dissolution data

Data of in vitro release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Lansoprazole release. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Table 6: Release kinetics data for optimized formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM % RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.62	0.5	0.707	1.293	-0.301	1.905	39.240	0.0510	-0.707	80.38	4.642	4.316	0.326
27.11	1	1.000	1.433	0.000	1.863	27.110	0.0369	-0.567	72.89	4.642	4.177	0.464

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36.25	2	1.414	1.559	0.301	1.804	18.125	0.0276	-0.441	63.75	4.642	3.995	0.647
45.81	3	1.732	1.661	0.477	1.734	15.270	0.0218	-0.339	54.19	4.642	3.784	0.857
50.49	4	2.000	1.703	0.602	1.695	12.623	0.0198	-0.297	49.51	4.642	3.672	0.970
58.5	5	2.236	1.767	0.699	1.618	11.700	0.0171	-0.233	41.5	4.642	3.462	1.179
64.99	6	2.449	1.813	0.778	1.544	10.832	0.0154	-0.187	35.01	4.642	3.271	1.370
67.78	7	2.646	1.831	0.845	1.508	9.683	0.0148	-0.169	32.22	4.642	3.182	1.460
75.93	8	2.828	1.880	0.903	1.381	9.491	0.0132	-0.120	24.07	4.642	2.887	1.754
86.8	9	3.000	1.939	0.954	1.121	9.644	0.0115	-0.061	13.2	4.642	2.363	2.278
90.39	10	3.162	1.956	1.000	0.983	9.039	0.0111	-0.044	9.61	4.642	2.126	2.516
95.68	11	3.317	1.981	1.041	0.635	8.698	0.0105	-0.019	4.32	4.642	1.629	3.013
99.17	12	3.464	1.996	1.079	-0.081	8.264	0.0101	-0.004	0.83	4.642	0.940	3.702

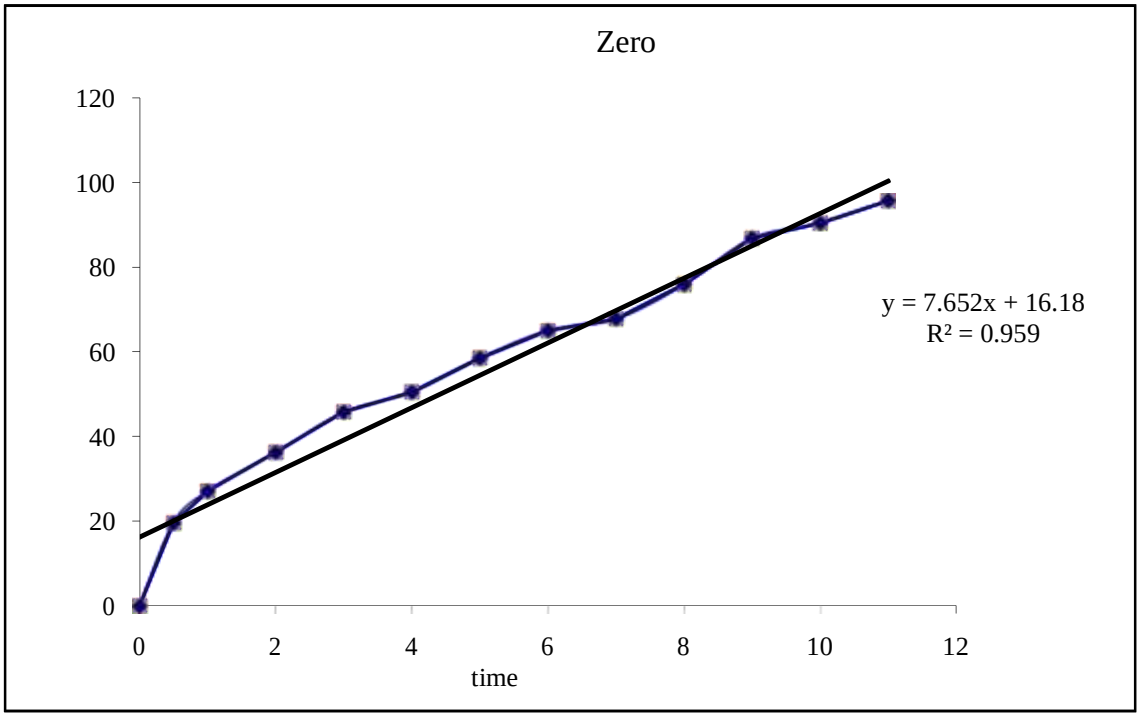

Figure 8 : Graph of Zero Order kinetics

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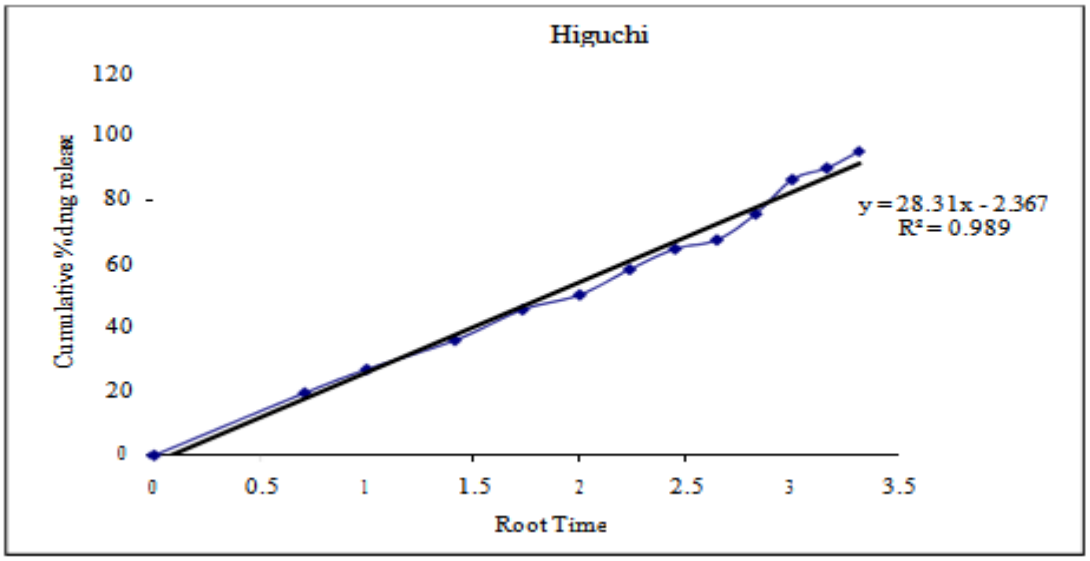

Figure 9: Graph of Higuchi Release kinetics

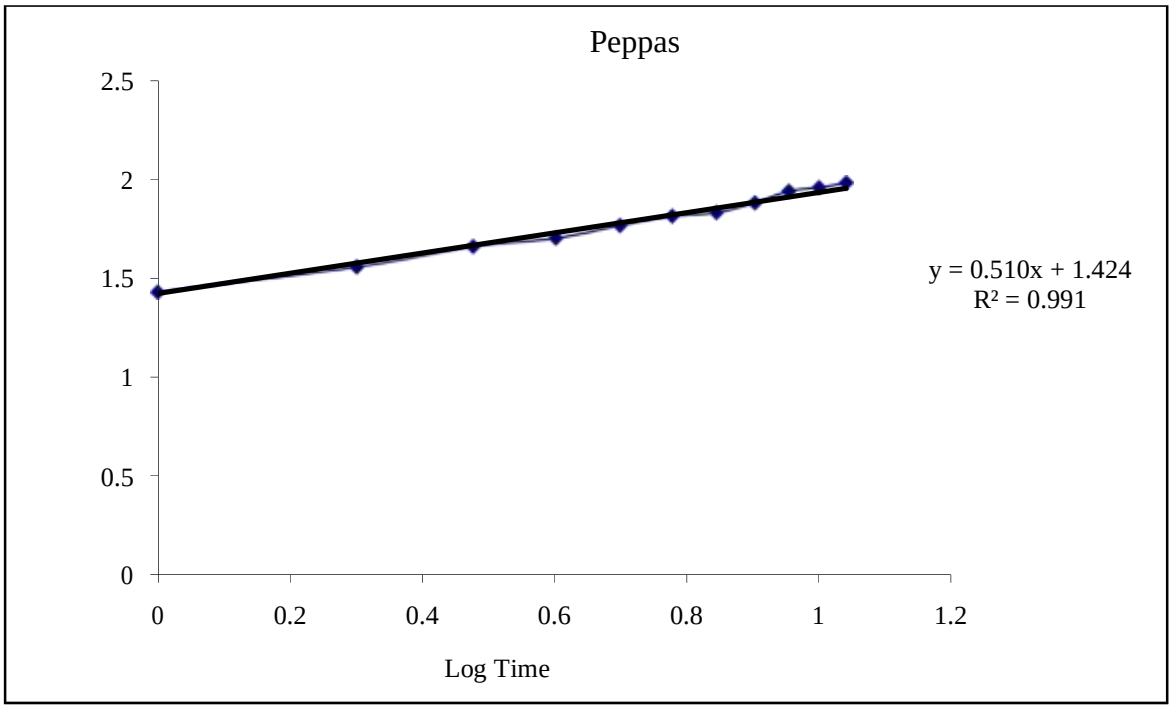

Figure 10: Graph of Peppas Release kinetics

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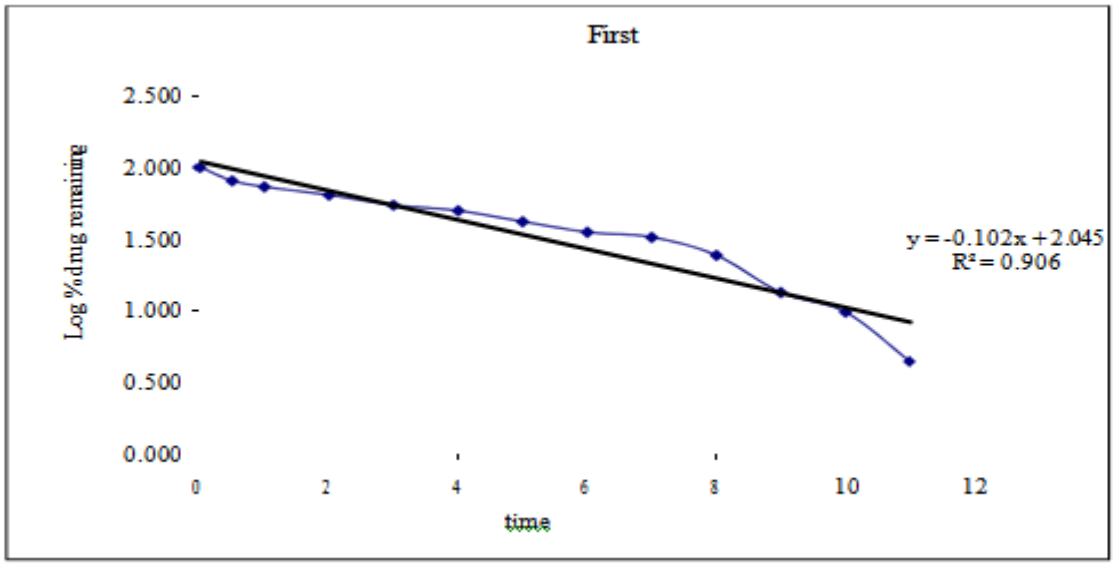

Figure 11: graph of First Order release kinetics

Based on the data above results the optimized formulation followed Peppas release kinetics.

FTIR:

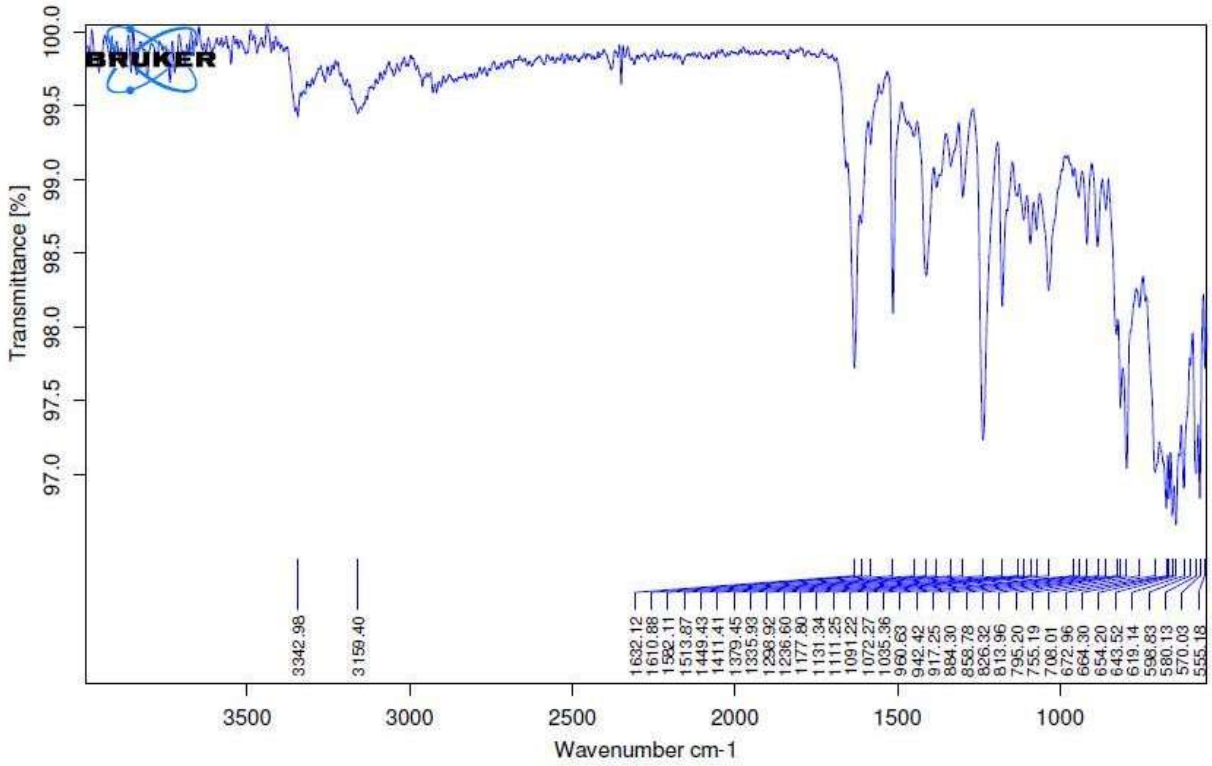

Figure 12: FTIR of Lansoprazole pure drug

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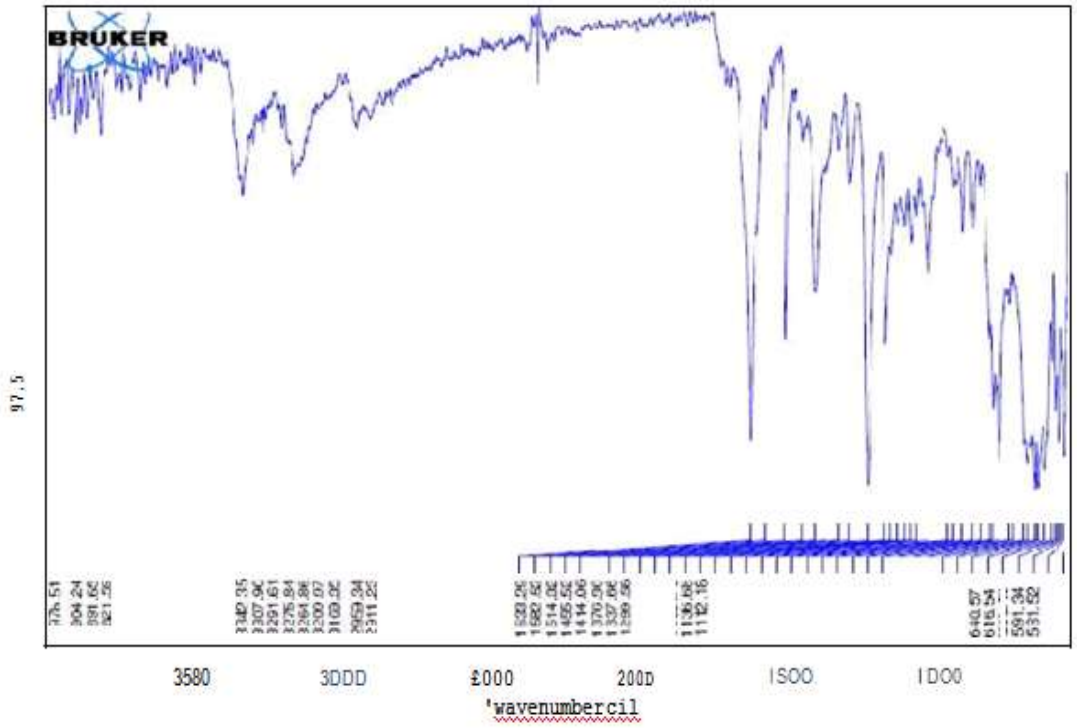

Figure 13: FTIR of Lansoprazole Optimised formulation

From the FTIR studies, those studies were revealed that good compatibility between drug and excipients.

SEM:

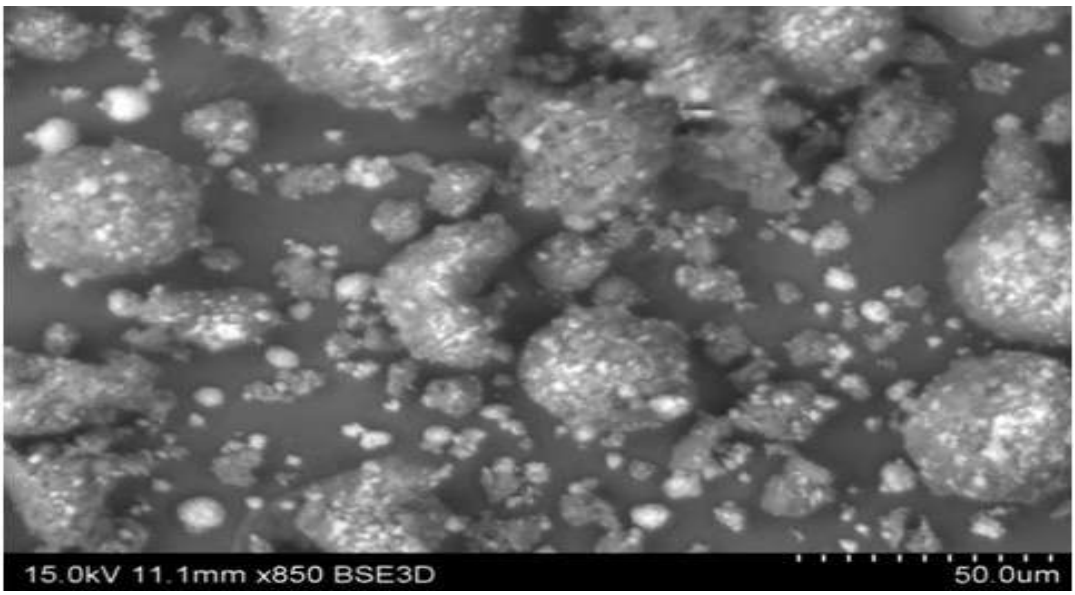

Figure 14: SEM of Lansoprazole Floating Microspheres optimised formulation

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IV. CONCLUSION

Microspheres are one of the microparticulate systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance.

The purpose of present work was to develop floating microspheres of Lansoprazole for sustained drug delivery. From the results it seem that formulation F6 was found to be satisfactory in terms of excellent micromeritic properties, yield of microsphere, Encapsulation efficiency, In vitro Buoyancy and highest in vitro drug release of 480.58 %, 98.17%, 49 sec and 99.17% in a sustained manner with constant fashion over extended period of time for 12 hrs. Hence the prepared floating microspheres of Lansoprazole may prove to be potential candidate for safe and effective sustained drug delivery. Among these formulations F6 formulation showed the drug release (99.17%) within the specified limits

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