FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF FLUVASTATIN USING EUDRAGIT RL-100 AND ETHYL CELLULOSE

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Abstract

The emphasis of present work was to modify the drug release characteristics by solvent evaporation method using polymer such as EudragitRL100 and ethyl cellulose. The prepared microsphere was characterized by FTIR, DSC and calculated for size of particle analysis, DEE, and in-vitro delivery. FTIR studies showed no potential chemical interaction between the drug and polymers. Calculated percent yield for all the formulations were found to be in range of 71.01 to 96.00% and the size in range of 28.00 to 51.00µm. Gastrointestinal fluid (SGF) for Half day used to the drug release study and shown extreme amount of drug release in controlled and sustained manner to extended period of time. The in-vitro drug release study was performed using dissolution rate test apparatus in phosphate buffer (pH 7.4). The dissolution profiles of Fluvastatin are given in Tables 6, Tables 7 and Table 8. 74.12, 73.12, 71.76, 68.12, 71.18, 73.01, 74.09, 75.92 and 70.07% drug was released from K1, K2, K3, K4, K5, K6, K7, K8 and K9 formulations respectively. The DSC study indicated that drug uniformly dispersed in amorphous state in molecular level. Non-ficain transport has been followed Drug released mechanism.

Keywords: Fluvastatin, Eudragit RL100, ethyl cellulose, solvent evaporation.

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INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target the introduction of a medication to a specific bodily location has a huge influence on the health- care system. Throughout the course of therapy, the ideal drug delivery system distributes the medication at a pace determined by the body's needs, and it delivers the active component solely to the site of action. As a result, carrier innovation provides an intelligent method to drug delivery by attaching the drug to a carrier particle, such as microspheres, nanoparticles, or liposomes, which modifies the drug's release and absorption properties. Types of drug delivery system are Microsphere, Niosome, Liposome, Nanopartical [1] Microspheres are tiny spherical particles with sizes ranging from one millimeter to one thousand millimeters. They are spherical, free-flowing particles made up of biodegradable proteins or synthetic polymers.

Microcapsules and micrometrics are two different kinds of microspheres, that are referred as Microcapsules are encapsulated substances that are enclosed by a unique capsule wall. Micrometrics, in which the imprisoned material is distributed throughout the framework. Microspheres and micro-particles are two terms used interchangeably to describe microspheres. [2]

MICROSPHERES OFMUCOADHESIVE COMPOUND

Among all drug delivery methods, oral controlled release systems remain the most well-known. It has a few advantages over traditional methods, such as a better plasma level profile, reduced dosage, and toxic city, among others. The incapacity of controlled release dosage forms to build the living arrangement time of the dosage form in the stomach and proximal section of the small digestive system is a common concern. This might be related to the stomach's fast gastrointestinal transit phenomena, Because the majority of drug compounds are absorbed from the upper portion of the digestive system, this may subsequently release the degree of absorption of a variety of drugs. As a result, maintaining release characteristics that persist at the absorption site for a longer length of time is beneficial. The creation of an oral drug delivery mucoadhesive modified release system is one of the techniques that have been explored to extend the stomach residence duration of the dose form at the site of absorption. For some years, microsphere carrier systems built from found naturally biodegradable polymers have piqued interest in the field of prolonged drug administration. Lately, dosage formulations that can accurately regulate release rates have been available.

The ability to target medicines to a specific bodily location has had a huge effect on the design of new therapeutic methods. Microspheres are a key component of these new medication delivery systems. They come in a variety of shapes and sizes and are made from a variety of polymers. However, because to their brief residence duration at the appropriate concentration, the success of these microspheres is restricted As a result, it would be beneficial to have ways of ensuring that the drug delivery system is in close proximity to the absorbent barriers. It can be accomplished by combining cohesion properties with microspheres to create mucoadhesive microspheres.

Due to a high surface-to-volume ratio and a considerably closer interaction with the mucus layer, mucoadhesive microspheres provide features such as efficient absorption and increased medication bioavailability, and specific targeting of drugs to the absorption site mucoadhesive and biodegradable polymers undergo selective uptake by the M cells of payer patches in GI.

Microspheres as a carrier polymer for micros-pheres and polyethylene glycol as a microparticles carrier polymeric, sodium chitosan as a polymeric matrix for sustained release medication delivery owing to its hydrogel forming capabilities. [3]

MATERIAL AND METHODS

Fluvastatin were obtained from Reproduces Pharma, Equipment’s Mumbai, Ethyl cellulose is obtained from HI media lab Pvt Ltd. Mumbai, Eudragit RL100 is received from Lobe chem. Pvt Ltd. Mumbai, Sodium hydroxide (NaOH) pallets and Potassium dihydrogen ortho phosphate (KH2PO4) were received from Central drug house-New Delhi. Dichloromethane (DCM) were received Ozone international Pvt Ltd. Mumbai.

Estimation of Fluvastatin

The estimation of Fluvastatin is done by measuring absorbance in a UV region at 238nm using pH 7.4 phosphate buffers.

Formulation of standard curve of Fluvastatin in phosphate buffer pH 7.4

In a 100ml VF, 100mg of Fluvastatin was properly balanced and liquified in 40 ml MeOH, and the volume was made to 100ml with phosphate buffer pH7.4. This was the principal stock solution, which had a concentration of

1000ug/ml. 10 ml of the main stock solution was pipette out and transferred to a 100 ml VF, where the volume was made up to 100 ml with phosphate buffer pH 7.4 and the volume was made up to 100 ml. It included a 100g/ml concentration (Second stock solution). Aliquots equating to 10-50g (10, 20, 30, 40, and 50 ml) were pipette out of the second stock solution into a series of 100 ml VFs and volume was brought up to 100 ml with phosphate buffer pH 7.4. The absorbance of these solutions was measured at 238 nm against a phosphate buffer with a pH of 7.4 as a blank. Using a spectrophotometer that can measure UV and visible light Then, using concentration in g/ml on the X-axis and absorbance on the Y-axis, a calibration curve was produced.[4]

Formulation of Fluvastatin microspheres by solvent evaporation method

In a liquid manufacturing vehicle phase, this method is carried out. The microcapsule coating is distributed in a volatile solvent that is incompatible with the liquid production vehicle phase of the process. In the coating polymer solution, a core material to be microencapsulated is digested or distributed. To acquire the required size microcapsule, the core material combination is disseminated in the liquid production vehicle phase by agitation. The combination is then warmed if required to evaporate the solvent, allowing the core material's polymer to distribute in the polymer solution, shrinking the polymer around at the core. Matrix-type microcapsules are produced when the core material is dissolved in the coated polymer solution. Water dissolving or water in soluble materials can be used as the core components. The development of an emulsion between a polymer solution and an insoluble liquid, whether aqueous or non-aqueous, occurs during solvent evaporation [5] (Refer table No.01)

Table 1: Formulation of Microsphere of Fluvastatin

Ingredients	K1	K2	K3	K4	K5	K6	K7	K8	K9
Fluvastatin(mg)	5	5	5	5	5	5	5	5	5
Ethyl cellulose (mg)	800	1	1.2	-	-	-	400	600	800
Eudragit RL 100 (mg)	-	-	-	800	1	1.2	400	600	800
Polyvinyl alcohol (%)	5	5	5	5	5	5	5	5	5
Dichloromethanene and MeOH (1:1) (ml)	20	20	20	20	20	20	20	20	20

The prepared microspheres were evaluated by the following parameters:

Determination of mean particle size

Approximately 100 microspheres were analyzed under optical microscope and their radius and size was calculated by using same microscope with micrometer scale.

Differential scanning calorimetry (DSC)

The pure drug Fluvastatin as well as drug-loaded microspheres was subjected to DSC analysis. The thermal analysis was carried out by recording thermograms for 5-15 mg samples at a heating rate of 10K/60sec throughout a temperature range of 200C to 3000C while using a N2 stream rate of 25ml/min. prior to the test, the trials were closed in metal crucibles with punched lids. As a reference, an empty aluminum crucible was employed.[6]

FTIR analysis

Compatibility is one of the criteria for selecting acceptable excipients or carriers for pharmaceutical formulation. As a result, research was conducted in the current investigation to assess any potential drug-polymer interactions. The pellets were made using KBr at high-level compaction-pressure, with a sample to a KBr ratio of 1:1000. The manufactured pellets were inspected, and data were collected in the 4000-400 cm-1 region.[7]

Drug encapsulation efficiency (DEE)

Prepared by weighing amounts of 50 mg microspheres were utilized for analysis. The amount of medicine enclosed was measured by crushed microspheres and separating with 7.4 pH phosphate buffer and mild warming. The separated product was poured to a 100 mL VF, which had been filled with phosphate buffer at a pH of 7.4. The absorbance was read at 238nm using an acceptable blank following purifying the solution. The DEE in microspheres was determined using the formula below.[8]

$$DEE = \frac{\text{Amount of drug present}}{\text{Load expected of Theoretical drug}} \times 100$$

In-vitro drug release studies

The in-vitro drug release of Fluvastatin microspheres was measured for half-day to use a

dissolving apparatus (Electro lab TDT 08L, India) with 900ml of pH 7.4 phosphate buffer, kept at 370.50C and agitating speed of 100 rpm till the study has been completed (12 hours). Correctly higher revenue of microspheres (50 mg) was utilized in the study. The 5ml samples were removed and replaced with an equivalent amount of fresh pre warmed dissolving media at varied time intervals of 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12hours After appropriate dilution, the contents were analyzed using a Shimadzu-1700 spectroscopic equipment at a maximum wavelength of 238nm. To determine which scientific formula best fits the acquired release profile, the releases fitting the data to several mathematical models as shown below.[9]

- Zero order and first order delivery kinetics.
- Higuchi paradigm.
- Korsmeyer-Peppas paradigm.

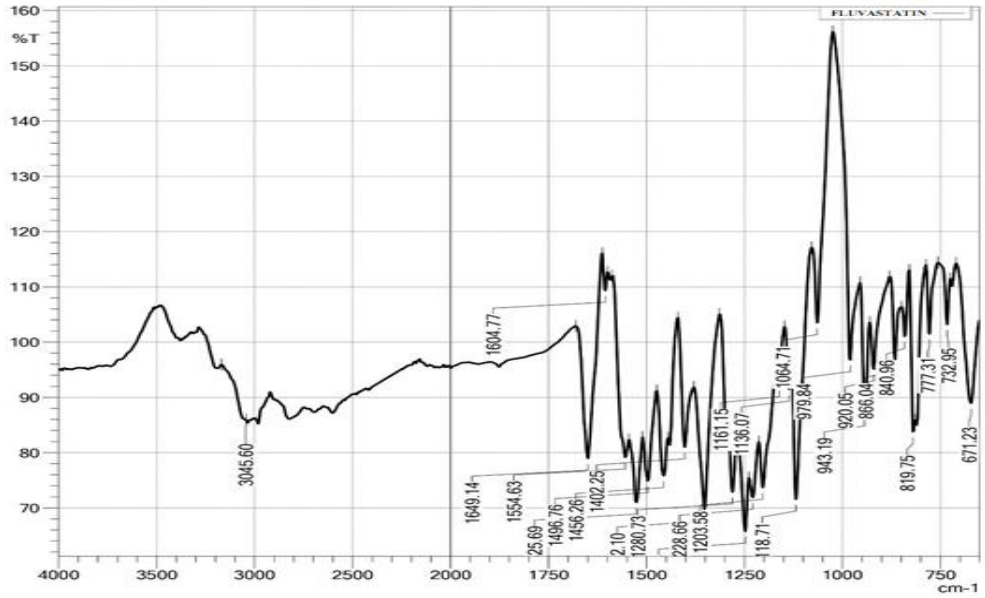
RESULTS AND DISCUSSION

Table 2. Spectrophotometric data for estimation of Fluvastatin in phosphate buffer pH 7.4

Sl. No	Concentration	Absorbance
1.	0mcg/ml	0
2.	1mcg/ml	0.080
3.	2mcg/ml	0.189
4.	3mcg/ml	0.271
5.	4mcg/ml	0.352
6.	5mcg/ml	0.431

Table 3. Typical size and (DEE) Fluvastatin dried micro-spheres

Microspheres	Average size (µm)	DEE (%)
K1	37.5 ± 7.58	94.75%
K2	29.6 ± 6.31	92.6%
K3	24.6 ± 4.14	84.7%
K4	49.4 ± 8.87	78.4%
K5	47.9 ± 6.67	83.10%
K6	49.25 ± 7.62	77.8%
K7	45.2 ± 8.93	69.7%
K8	50.2± 8.3	75.3%
K9	49.4±8.89	71.4%
*The values are average of three determinations. ± indicates SD value		



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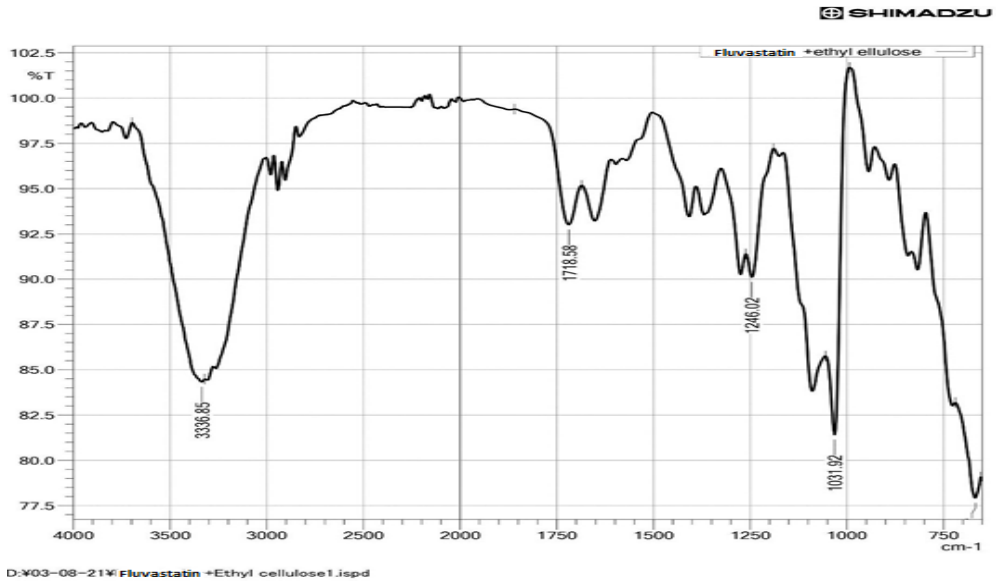

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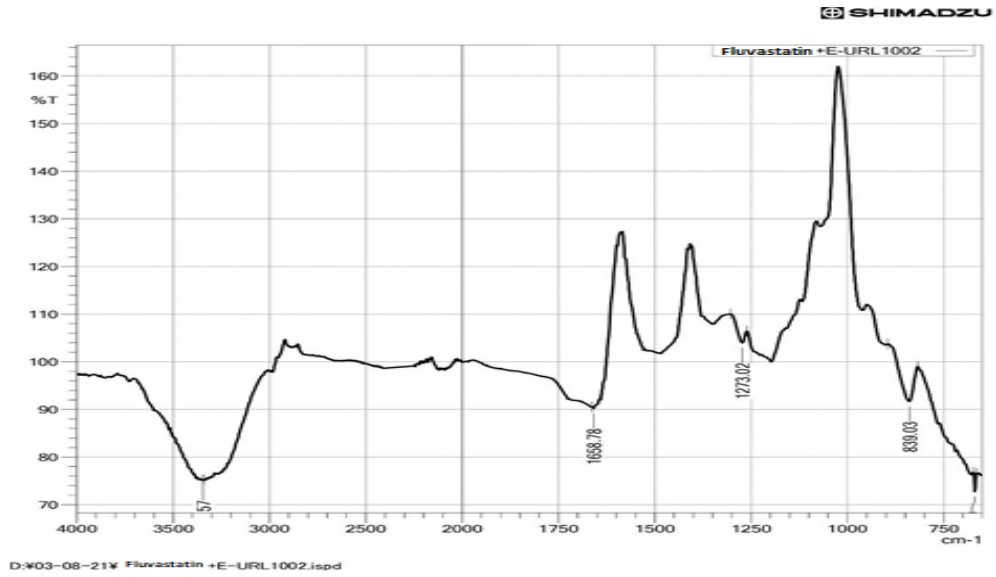

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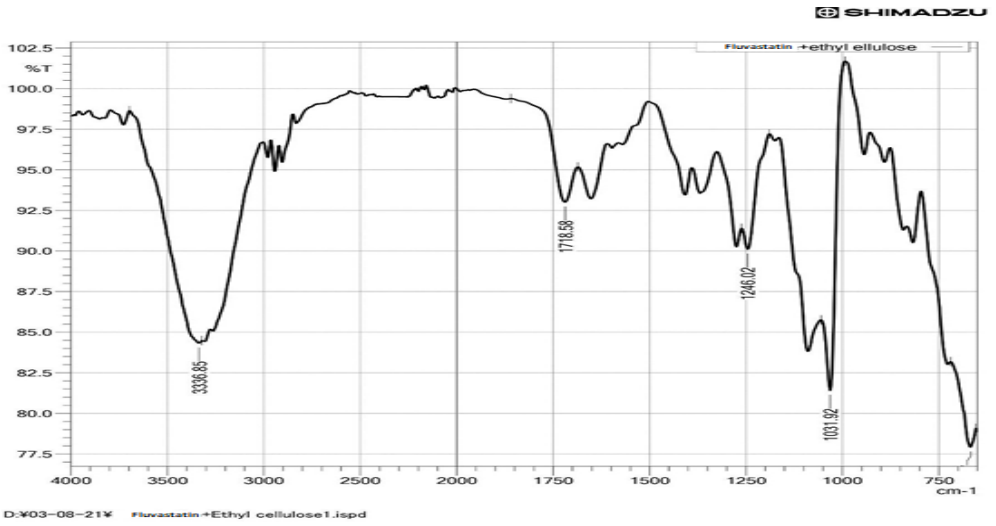
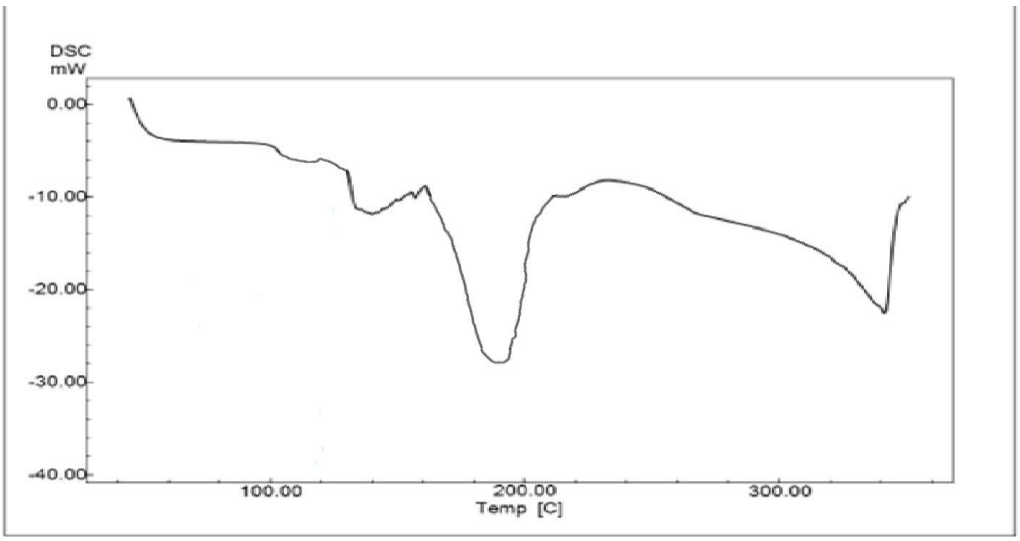


(D)

Figure 1.FTIR spectra of pure drug (A) Fluvastatin and (B) Fluvastatin, ethylcellulose (C) Fluvastatin Eudragit RL100 (D) Fluvastatin, ethyl cellulose and Eudragit RL100



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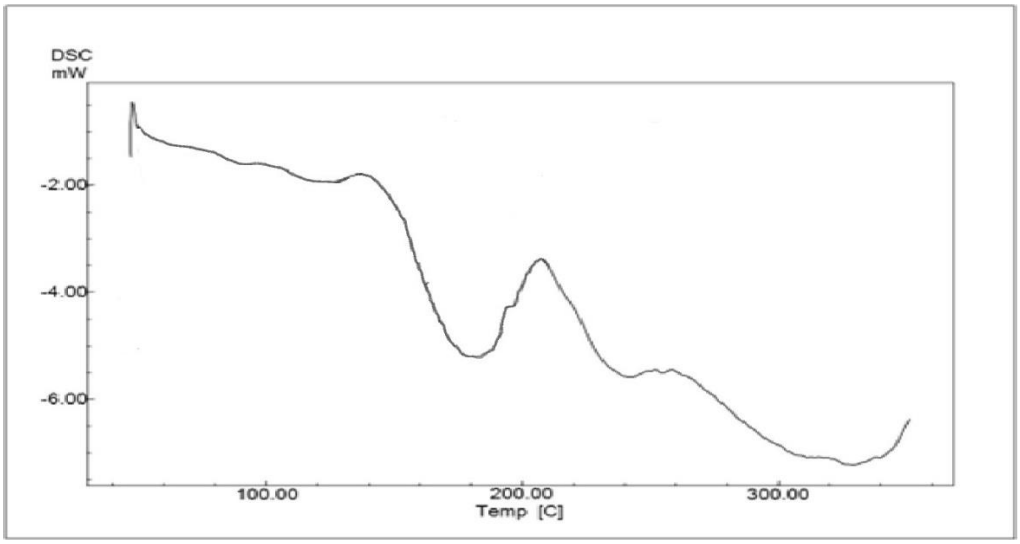

(B)

Figure 2. DSC Thermograms of Fluvastatin and (B) Fluvastatin, ethyl cellulose

Table 4. In-vitro release of Fluvastatin from K1, K2 and K3 microspheres in intestine fluids

Sloe	Time (hrs.)	Squareroot oftime (hrs.)	Log Time (hrs.)	K1		K2		K3	
				% Drug released	Log % drug released	% Drug released	Log % drug released	% Drug released	Log % drug released
1	0	0	0	0	0	0	0	0	0
2	0.5	0.707	0.801	7.47	0.87	8.11	0.909	8.06	0.906
3	1	1	0.081	15.58	1.19	14.32	1.156	14.05	1.148
4	1.5	1.225	0.176	23.57	1.37	22.45	1.351	22.92	1.360
5	2	1.414	0.301	31.28	1.50	30.54	1.485	29.56	1.471
6	3	1.732	0.477	39.25	1.59	37.31	1.572	36.72	1.565
7	4	2	0.602	44.13	1.64	43.01	1.634	42.33	1.627
8	5	2.236	0.698	52.23	1.72	50.23	1.701	49.44	1.694
9	6	2.449	0.778	60.45	1.78	58.65	1.768	53.78	1.731
10	7	2.646	0.845	62.31	1.79	62.58	1.796	57.23	1.758
11	8	2.828	0.903	67.43	1.83	67.56	1.830	61.59	1.790
12	10	3.102	1.000	70.36	1.85	69.43	1.842	65.78	1.818
13	12	3.464	1.079	74.12	1.87	73.12	1.864	71.76	1.856

Table 5. *In-vitro* release of Fluvastatin from K4, K5 and K6 microspheres in intestine fluids

Sloe	Time (hrs.)	Square root of time (hrs.)	Log Time (hrs.)	K4		K5		K6	
				% Drug released	Log % drug released	% Drug released	Log % drug released	% Drug released	Log % drug released
1	0	0	0	0	0	0	0	0	0
2	0.5	0.707	0.801	13.22	1.121	13.99	1.146	14.24	1.154
3	1	1	0.081	17.66	1.247	18.99	1.279	19.11	1.281
4	1.5	1.225	0.176	22.23	1.347	23.45	1.370	24.44	1.388
5	2	1.414	0.301	27.54	1.440	26.54	1.424	29.89	1.476
6	3	1.732	0.477	31.98	1.505	31.44	1.497	32.21	1.508
7	4	2	0.602	36.43	1.561	32.04	1.506	35.26	1.547
8	5	2.236	0.698	43.22	1.636	43.45	1.638	39.49	1.596
9	6	2.449	0.778	48.11	1.682	50.06	1.699	45.43	1.657
10	7	2.646	0.845	52.33	1.719	54.34	1.735	52.87	1.723
11	8	2.828	0.903	60.24	1.780	61.21	1.787	59.69	1.776
12	10	3.102	1.000	64.69	1.811	66.31	1.822	68.09	1.833
13	12	3.464	1.079	68.12	1.833	71.18	1.852	73.01	1.863

Table 6. In-vitro release of Fluvastatin from K7.K8. K9 microspheres in intestine fluids

Sloe	Time (hrs.)	Square root of time (hrs.)	Log Time (hrs.)	K7		K8		K9	
				% Drug released	Log % drug released	% Drug released	Log % drug released	% Drug released	Log % drug released
1	0	0	0	0	0	0	0	0	0
2	0.5	0.707	0.801	15.68	1.195	16.01	1.204	15.17	1.181
3	1	1	0.081	19.56	1.291	21.07	1.324	19.19	1.283
4	1.5	1.225	0.176	24.77	1.394	27.58	1.441	23.76	1.376
5	2	1.414	0.301	27.89	1.445	34.39	1.536	27.02	1.432
6	3	1.732	0.477	32.43	1.511	41.76	1.621	33.01	1.519
7	4	2	0.602	37.79	1.577	49.28	1.693	37.38	1.573
8	5	2.236	0.698	42.03	1.624	53.45	1.728	42.79	1.631
9	6	2.449	0.778	47.23	1.674	57.58	1.760	46.27	1.665
10	7	2.646	0.845	54.59	1.737	62.80	1.798	53.76	1.730
11	8	2.828	0.903	59.12	1.772	67.01	1.826	57.89	1.763
12	10	3.102	1.000	67.86	1.832	71.27	1.853	63.86	1.805
13	12	3.464	1.079	74.09	1.870	75.92	1.880	70.07	1.846

Table 7. Kinetic values of Fluvastatin release

Microsphere Eres	Zero order Equation		FIRST ORDER Equation		Higuchi Equation		Kielmeyer's Equation	
	N	R	N	R	N	R	N	R
K1	15.13	0.875	68.76	0.296	2.363	0.982	1.015	0.581
K2	14.26	0.831	67.50	0.233	1.776	0.985	1.112	0.593
K3	14.36	0.942	67.65	0.205	3.657	0.987	1.101	0.571
K4	14.13	0.928	63.61	0.181	1.987	0.999	1.003	0.541
K5	15.03	0.911	65.33	0.266	0.989	0.989	1.002	0.501
K6	14.33	0.811	64.83	0.245	1.776	0.987	1.119	0.493
K7	14.53	0.871	67.36	0.224	0.876	0.985	1.008	0.492
K8	17.29	0.829	68.88	0.952	1.707	0.971	1.121	0.481
K9	16.13	0.929	66.2	0.244	0.434	0.983	1.123	0.479

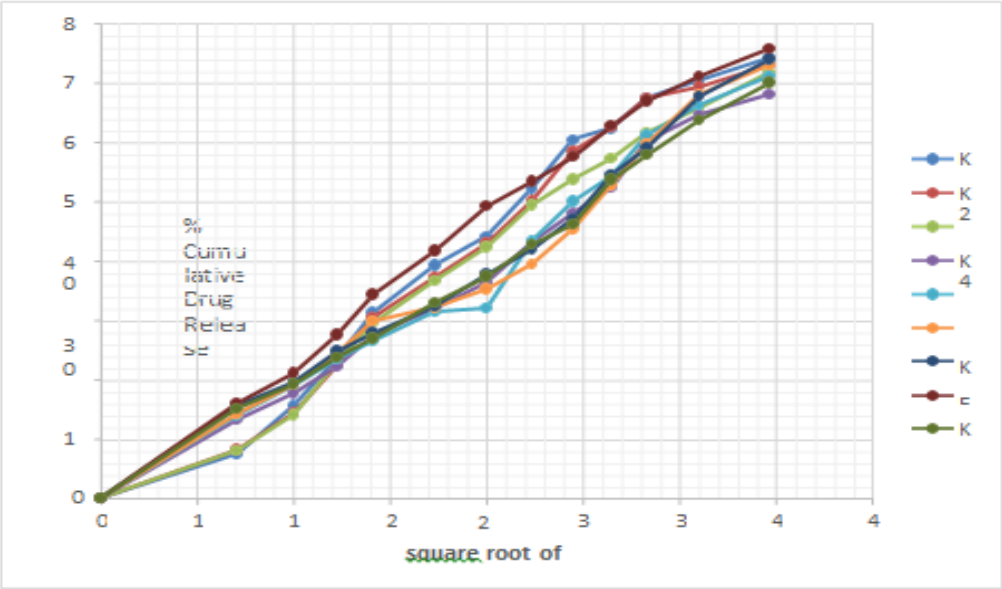

Figure 2.CUMULATIVE % DRUG RELEASED Vs TIME PLOTS (ZERO ORDER) OF FORMULATIONS F1 TO F9

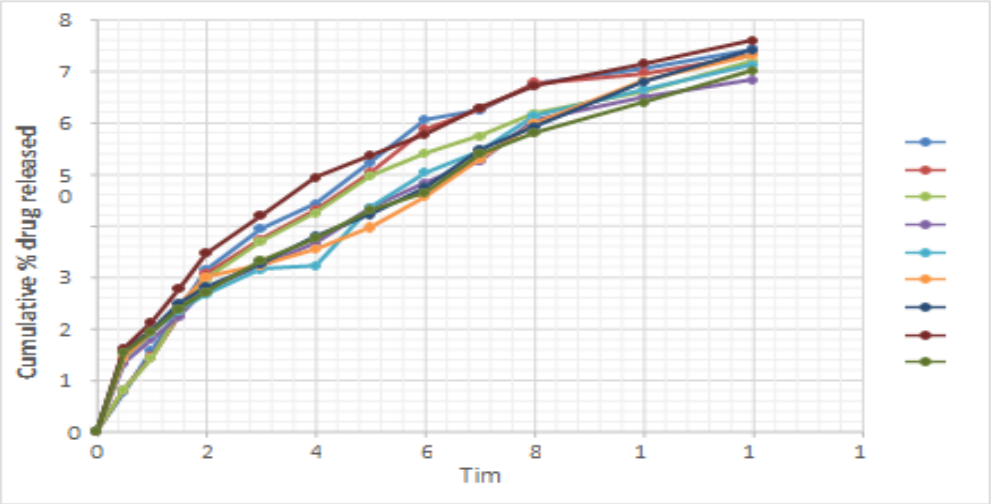

Figure 3. Cumulative % drug released Vs square root of time (Higuchi plots) of formulations K1 to K9

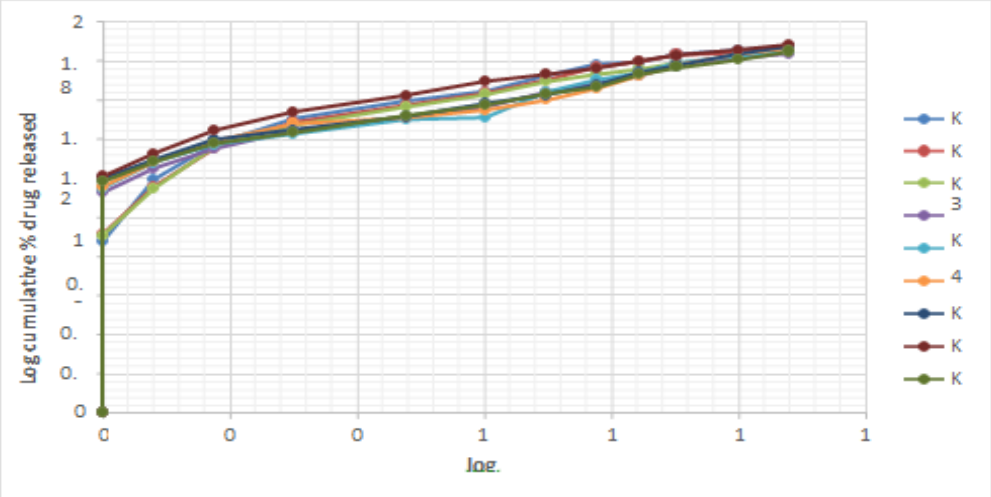

Figure 4. Log cumulative % drug released Vs log time (papas plots) of formulations K1 to K9

DISCUSSION

The Fluvastatin microspheres were made using a solvent evaporation process with Eudragit RL100 and ethyl cellulose, with the drug loading, Eudragit RL100/ethyl cellulose ratio, varied. Different physicochemical tests were performed on the produced microspheres, including particle-size, DEE, and in-vitro drug delivery behavior. Preliminary experiment conducted on formulation of the microsphere showed that Eudragit RL100/ethyl cellulose of greater than 1:1, stirring rate 500-1000 rpm should be used in order to obtain microsphere of adequate characteristic. The size of the microsphere was measured with an optical microscope and a standard micrometer, and the results were noted in table 2. The microspheres ranged in size from 29.6 ± 6.31 to 51.00±8.89 micrometers in diameter. The size of the microsphere increased as the polymer's strength of cross-linking increased, while the size of the microsphere dropped as the stirring rate increased. Table 2 summarizes the drug entrapment efficiency (DEE) of produced microspheres. The drug entrapment efficiency was found to be in the range of 94.75 percent to 71.4 percent, with the DEE decreasing as the crosslinking concentration in the microsphere rose. For a chosen combination of medication with various excipients, the drug-polymer interaction was investigated using FTIR spectroscopy. Figure 1 shows the FTIR spectra that were obtained. Fluvastatin has a wide peak at 3045 cm-1 corresponds to -OH, C=O at 1456 cm-1 and sharp peak at 1203 cm-1 corresponds to C-O-C. The –C=O groups related to ketone have strong absorption peaks at 1720 cm-1 and 1651 cm-1. When Fluvastatin was combined with ethyl cellulose and Eudragit RL100, the same peaks linked to Fluvastatin were seen with minor variations, indicating that there was no drug-polymer interaction.

Plain Fluvastatin, microspheres, and drug-loaded microspheres all had an endothermic peak at 180°C, but drug-loaded microspheres had endothermic peaks at 170 and 185°C, according to DSC analyses. Due to melting, the pure drug Fluvastatin showed an endothermic peak between 187°C and 174°C, but was evenly disseminated in an amorphous condition in the microspheres. The in-vitro drug release study was performed using dissolution rate test apparatus in phosphate buffer (pH 7.4). The dissolution profiles of Fluvastatin are given in Figure 2, 3 and 4. Data are presented in Tables 4, Tables 5 and Table 6. 74.12, 73.12, 71.76, 68.12, 71.18, 73.01, 74.09, 75.92 and 70.07% drug was released from K1, K2, K3, K4, K5, K6, K7, K8 and K9 formulations respectively. The results showed that the concentration of ethyl cellulose is directly proportional to drug delivery, at the same time the Eudragit RL100 inversely proportional to the drug release, as primary formulate charging into dissolution apparatus, the release as started. I observed that RPM of dissolution also effected on the drug release i.e., while the RPM rate was enhanced from 500 to 800rpm, the drug released was increased, vice versa. The release data were fitted according to zero order. Release, Higuchi's equation and Kielmeyer's equation and the mechanism of Drug release was calculated according to pep as equation. The values have been shows in Table 7

CONCLUSION

From the results it can be concluded that biocompatible polymer like Eudragit RL100 and Ethical can be used to prepare an effective Fluvastatin microsphere with a good percentage impingement effectiveness and practical yield. The particle size analysis indicated that particle was in the size range 25.7 to 51.2µm, shows good flow properties. In-vitro release shows that release from the microsphere gets successfully retarded for over 12hr and Studies have shown promising result, further, there exists a scope for pharmacokinetic evaluation in experimental animals.

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