Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 5, 2014

Original Article

FABRICATION AND EVALUATION OF FLUVASTATIN SODIUM LOADED SUSTAINED RELEASE MICROSPHERES USING POLYMER BLENDS

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Received: 22 Mar 2014 Revised and Accepted: 20 Apr 2014

ABSTRACT

Objective: The emphasis of present work was to modify the drug release characteristics by microencapsulating the Fluvastatin Sodium inside the polymer matrix (Ethyl cellulose and Hydroxyl propyl methyl cellulose K15M polymers blend).

Methods: Fluvastatin Sodium loaded microspheres were formulated by solvent evaporation method and characterized using various methods. Drug Interaction study between drug and excipients was also carried out.

Results: 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 89.16-98.50%. The highest drug content (96.8%) and entrapment efficiency (89.97%) was obtained in FS05 formulation. The particle size analysis data showed that there is increase in mean diameter of particles (72.48 to 129.21μm) with increase in amount of polymer (from 1:1 to 1:7). *In-vitro* drug release studies showed that microspheres releases 98% of drug within 24 hr inferring that all microspheres resulted sustained release effect. Drug release from microspheres followed Higuchi kinetics with non-fickinian diffusion controlled release mechanism. Results of XRD studies revealed that drug was encapsulated inside the polymer matrix. The SEM photographs predicted the spherical shape with smooth topography.

Conclusion: The adopted method is successful in controlling the release of drug from drug loaded microspheres, thus, improving the patient compliance by reduced dosing frequency. FS05 microsphere formulations showed highest drug content and entrapment efficiency with optimum swelling index and percent *In-vitro* drug release.

Keywords: Microspheres, Ethyl cellulose, HPMC K-15M, Non-fickinian diffusion, Higuchi kinetics.

INTRODUCTION

It is well-established that abnormalities in lipoprotein metabolism and high cholesterol levels are associated with an increased risk for stroke, angina, atherosclerosis, circulatory diseases, and ischemic cerebrovascular diseases [1]. In literature many therapeutic strategies has been designed to decrease the augmented levels of circulating lipid which have also been shown to reduce cardiovascular morbidity and mortality [2, 3]. Fluvastatin sodium is widely prescribed an orally active antihyperlipidaemic drug belonging to statin family. It is a selective, potent and competitive inhibitor of enzyme 3-hydroxy-3 methyl glutaryl coenzyme A (HMG-CoA) reductase and controls the synthesis of cholesterol [3]. Although, the drug has contributed to lower serum cholesterol and reduce cardiovascular disease, but it possesses low therapeutic concentration at the target site due to low bioavailability (24%) owing to extensive first pass metabolism, less GI residence time and short elimination half-life (1-3h), and poor aqueous solubility (0.46 mg/l) [4]. The drug requires multiple dosing frequencies (twice a day) to obtain desired therapeutic effect [5]. Many formulations are available in the market to control the blood lipid profile but they require multiple dose administration to obtain an optimum therapeutic concentration at the target which in turn reduces the patient compliance. Moreover, only few formulations with sustained effect are available in the market. An appropriately designed drug microencapsulated in polymer blend for oral administration can be a foot ahead towards controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the drug to a tissue with extended clinical effects and reduced dosing frequency there by overcoming the above mentioned problems.

In literature, many biodegradable and non- biodegradable polymers are used for microspheres fabrication, out of which ethyl cellulose and HPMC K-15M were selected to prepare microspheres due to its dual advantage, it release drug for longer period of time, increasing the bioavailability and increasing the patient compliance with reduced dosing frequency [6].

The objective of the present research was to formulate Fluvastatin sodium loaded sustained release microspheres of ethyl cellulose and HPMC K-15M by solvent evaporation technique using different drug polymer ratios *viz;* 1:1, 1:2, 1:3, 1:4, 1:5, 1:6 and 1:7. The effect of different polymers concentration on *In-vitro* drug release rate, the swelling properties of drug delivery system were investigated along with the determination of drug content, percent yield, entrapment efficiency, particle size distribution and drug-excipient studies.

MATERIALS AND METHODS

Fluvastatin sodium was procured as gift sample from Ranbaxy Laboratories Ltd., Gurgaon and was used without further purification. Ethyl Cellulose and Span 80 was procured from Himedia Laboratories Pvt. Ltd., Mumbai whereas HPMC K-15M from Ranbaxy Laboratories Ltd., Gurgaon. All other solvents and reagents were of analytical grade.

Fluvastatin sodium loaded Ethyl Cellulose/HPMC K-15M microspheres formulations were prepared by solvent evaporation method [7].

Drug-excipeint Compatibility Studies

The successful formulation of a suitable and effective solid dosage form depends upon the careful selection of the excipients. It's necessary to study the compatibility of excipeints with drug. Here IR spectroscopy was used to investigate and predict any physicochemical interaction between the drug and the polymers in a formulation and to the selection of suitable compatible excipient. Infrared (IR) spectroscopy was conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone, polymers alone and mixture of drug and Polymers in potassium bromide (KBr) and compressing into discs by applying a pressure of 7 tons for 5 min in a KBr press. The pellet was placed in the light path and the spectrum was obtained [8].

Preparation of Microspheres by Solvent Evaporation Method

Drug was accurately weighed and carefully dispersed in polymeric phase of Ethyl Cellulose/ HPMC K-15M in acetone with mechanical stirring. Drug-polymer dispersion was poured slowly into liquid paraffin. The dispersion was stirred continuously at 500 rpm for 3 h to evaporate the solvent. After evaporation of solvent, the formed microspheres were collected and washed thrice with petroleum ether to remove solvents. The collected microspheres are dried at room temperature for 1 h and stored in desiccator over fused calcium chloride till further use [7].

Kinetic Modelling

The *in-vitro* drug release data was fitted into Higuchi equation; $M_t = K\sqrt{t}$ and korsmeyer-peppa's equation; $Mt/M = Ktn$, where K is a constant; n is the release exponent, indicates the drug mechanism and M_t/M_∞ fraction of drug released at time t.

Characterization Of Developed Microspheres

The developed microspheres were characterized by using various parameters like percent yield, particle shape, particles size distribution, drug content, entrapment efficiency and *In-vitro* release study and drug excipeints compatibility studies.

Determination of Percent Yield

The dried microspheres formulations were weighed accurately and percent yield was calculated by using following equation. The theoretical weight of microspheres is the total weight of polymer and the drug used in the formulation [9].

$$\text{Percent yield} = \frac{\text{Actual weight of microspheres}}{\text{Theoretical weight of microspheres}} \times 100$$

(Equation 1)

Determination of Drug Content

Fluvastatin sodium loaded Ethyl Cellulose and HPMC K-15M microspheres were powdered and suspended in Phosphate buffer pH 6.8. The resultant dispersion was kept for 20 min on bath sonicator for uniform mixing and filtered. The filtrate was analyzed using UV spectrophotometer at 304 nm [10].

Determination of Entrapment Efficiency

The drug entrapment efficiency (DEE) was calculated by the equation-

$$\text{DEE} = \frac{\text{Pc}}{\text{Tc}} \text{ X } 100 \text{ (Equation 2)}$$

Where Pc is the Practical content, Tc is the Theoretical content. The practical content was determined through drug content and theoretical content is the total amount of drug incorporated into a formulation [11].

***In-vitro* Drug Release Study**

The dissolution studies were performed using USP II dissolution test apparatus equipped with paddle at 50 rpm in 900 ml pH 6.8 phosphate buffers at 37± 0.5ºC for 24 h. Microspheres equivalent to 40 mg of drug were filled in empty capsule shells and then added to dissolution medium (Phosphate buffer pH 6.8). Dissolution studies were performed in triplicate. Aliquots (10ml) were withdrawn at regular time intervals with replacement of the fresh dissolution media. The samples were filtered through whatmann filter paper into tubes maintained at 37 ± 0.5°C in a water bath. Drug content was analyzed at their respective wavelengths using UV-VIS spectrophotometer at 304 nm [12].

Determination of Particle Shape

The particle shape was determined using Scanning electron microscopy (SEM). Samples of dried optimized formulation were mounted onto the stubs using double-sided adhesive tape and then coated with a thin layer of gold palladium alloy (150–200A°). The scanning electron microscope was operated at an acceleration voltage of 20 KV [13].

Particle Size Distribution

Determination of Particle Size of Ethyl Cellulose and HPMCK15M microspheres

The particle size and size distribution of the prepared microspheres were measured by laser diffraction in a particle size analyzer (Mastersizer, Malvern Instruments, U K). The dried powder samples were suspended in deionised water and sonicated for 1 min with an ultra-sound probe before measurement. The obtained homogeneous suspension was determined for the equivalent volume diameter and triplicate measurements were made for each batch of microspheres. Average particles sizes of all formulations were determined. The measured particles size was adequately represented graphically in the form of distribution curves (non normal frequency distribution, log normal frequency distribution, and cumulative distribution) [14].

The average particle size was determined by using the Edmondson's equation. $D\ \text{mean} = \Sigma nd / \Sigma n$ (Equation 3)

Where n= number of microspheres observed and d= mean size range D_{mean} = mean particle diameter.

Determination of swelling ratio

The swelling ratio of Ethyl cellulose and HPMCK15M was determined by immersing 100mg of microsphere sample in 25ml Phosphate buffer (pH 6.8) at room temperature for 24 h with gentle shaking. At specific time points (1, 2, 3, 4, 6, 8, 10, 12, 22, 24h) samples were removed and the swollen weight of microspheres was measured. The swelling ratio was determined by the following equation:

$$\text{Esw} = \text{Wsw} - \text{Wo} / \text{Wo X } 100 \text{ (Equation 4)}$$

Where, E_{sw} is the Swelling Ratio of the microspheres, W_o is initial dry weight of microspheres and W_{sw} is the weight of the swollen microspheres [15].

Powder X-Ray Diffraction (PXRD) Studies

The X-ray diffraction study was carried out to characterize the physical form of Fluvastatin sodium. The powder diffraction patterns were recorded on an X-ray diffractometer (XPERT-PRO, Analytical, Netherlands) with Copper as tube anode. The diffractograms were recorded under following conditions: voltage 35 kV, 20 mA, angular range 2Θ range of 2–40° with scan step size of 0.020° (2Θ) and fixed divergence slit. Care was taken to avoid crystal changes during sample preparation. Approximately 200 mg of samples were loaded into the sample holder, taking care not to introduce preferred orientation of the crystals [16].

RESULTS AND DISCUSSION

Percent Yield

Percent yield was calculated for all the drug loaded microspheres and the result of percent yield is given in Table 1. From all Formulations, FS05 have shown the highest percent yield whereas FS01 has resulted lowest percent yield. The low % yield in all the formulations may be due to sticking of sample or polymer with vessels or stirrer used during evaporation or may lost while washing and recovering process.

Table 1: Evaluation of Fluvastatin Sodium loaded Microspheres

Parameters	FS01	FS02	FS03	FS04	FS05	FS06	FS07
Percent yield (%)	89.16	91.25	98.80	97.33	98.50	96.75	95.91
Particle Shape	Spherical	Spherical	Spherical	Spherical	Spherical	Spherical	Spherical
Particle size (µm)	72.48	78.62	89.39	98.38	104.16	116.18	129.21
Drug content (%)	86.1	88.3	89.6	92.5	96.8	94.9	93.8
Entrapment Efficiency (%)	77.70	78.95	79.12	88.85	89.97	86.80	85.21

Drug Content

A successful microsphere formulation may be the one, which has a high drug loading capacity with reduced quantity of the carrier. Drug content of all the microspheres was found to be in range of 86.1 to 96.8 %. FS05 showed highest drug content whereas FS01 have lowest drug content as shown in Table 1.

Entrapment Efficiency

Drug entrapment is the amount of drug entrapped inside the polymer matrix which is freely available for diffusion when comes in contact with buffer. Entrapment efficiency lies in the range of 77.70% to 89.97%. It is clear from table 1 that the drug entrapment efficiency increases as the concentration of polymer increases (FS01-FS05) and then followed by decrease in entrapment efficiency with further increased polymer concentration in formulations (FS06-FS07). Increase in entrapment efficiency is due to increased drug: polymer ratio as observed in formulations FS01-FS05. The percentage drug entrapment decreases (FS06-FS07) as total polymer quantity increases relative to drug leading to increased bulkiness while drug quantity remains constant. Thus high amount of the polymers resulted in formation of microspheres with decreased overall percentage entrapment. Out of all the formulations encapsulation efficiency was found to be maximum for formulation FS05 (89.97%).

FTIR Studies

Fluvastatin sodium showed peaks at 3390cm^{-1}, 1779cm^{-1}, 1646cm^{-1}, 1215cm^{-1}, 1158cm^{-1} due to O-H stretch, ester stretch (C=O), carboxyl stretch (C=O), amine (C-N), ether stretch (C-O) respectively. In physical mixture and formulation, ester stretch (C=O) of Fluvastatin sodium is shifted from 1779cm^{-1} to 1772cm^{-1}. Whereas amine (C-N), ether stretch (C-O) of complex shifted from 1215 cm^{-1} to 1218 cm^{-1} and 1158cm^{-1} to 1162 cm^{-1} confirm the presence of drug in all the complexes. FTIR spectra of the physical mixture and formulation are quite similar to the corresponding Fluvastatin sodium because of concurrent absorption of both the Drug and polymer molecules in same region of the spectra. The FTIR spectra of physical mixtures depicted that there was no significant change in the peaks of spectra of Fluvastatin sodium, as incorporation/ in comparison to individual components as shown in Figure 1. Hence, there is no potential incompatibility between the drug/polymers and therefore selected to formulate microspheres.

***In -Vitro* Release Studies**

The Percent release data of drug loaded EC/HPMC K-15M microsphere formulations showed initial burst release for an hour followed by slow continuous release of drug for 24hr in phosphate buffer (pH 6.8) (Figure 2). The initial burst release could be attributed to the presence of free (unentrapped) drug on the surface of microsphere. The release pattern followed buffer infiltration into the dry matrix, hydration of the system, gel formation of the polymer material, dissolution of the drug substance and eventually the diffusion of the dissolved drug via the resultant gel membrane. This suggests that there is homogeneous entrapment of the drug in the polymer matrix system. It was concluded that with increase in polymer concentration the mean % drug release increases (FS01-FS05). As the drug is more solubilized in the presence of EC/HPMC K-15M, it improves the release of drug from the microparticles. Literature shows that the polymer enhances the release of hydrophobic drugs from the microparticles. With further increase in polymer concentration (FS06-FS07) results in increased viscosity of polymeric gel which could be responsible in the valuable diffusion coefficient of drug and ultimately for a reduction in the drug release.

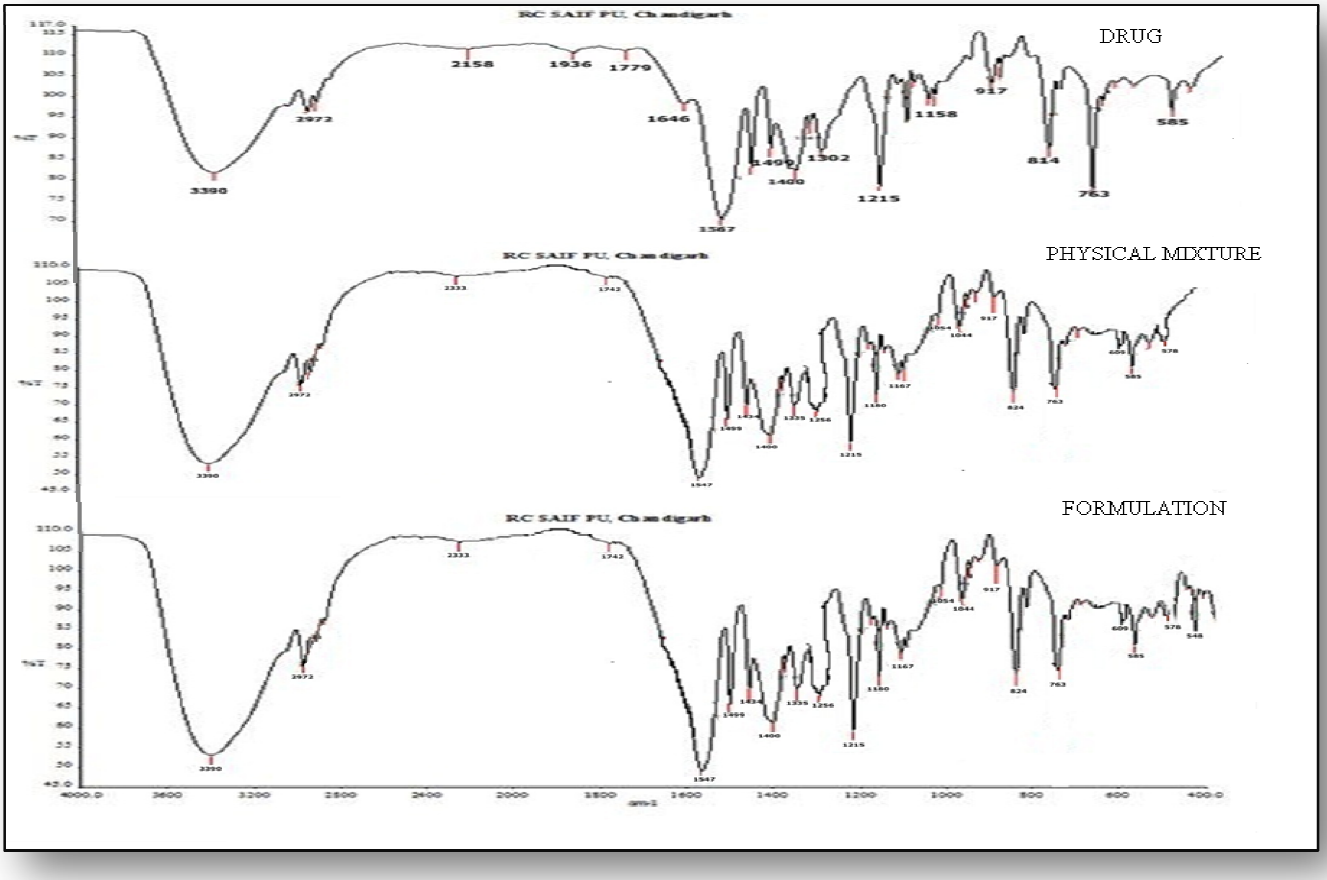


Fig. 1: FTIR Graph of (a) drug (b) physical mixture (c) formulation (FS05).

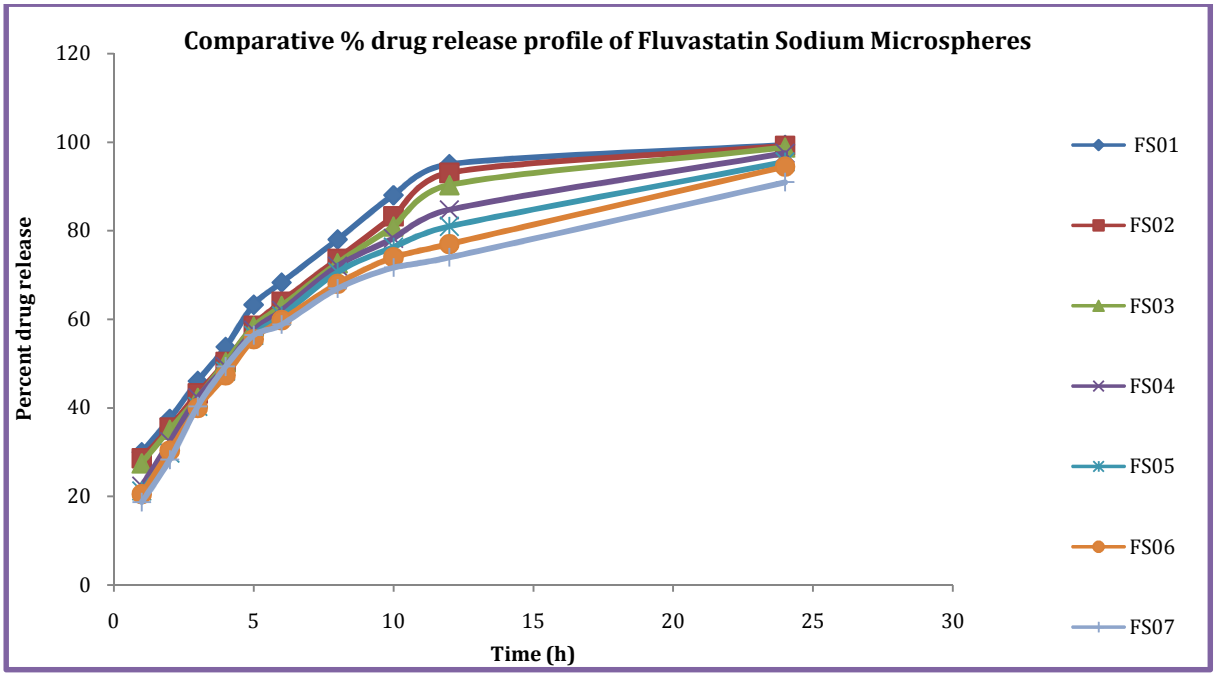


Fig. 2: Dissolution Profile of Comparative *In-vitro* drug release of Fluvastatin Sodium loaded EC/HPMC Microspheres.

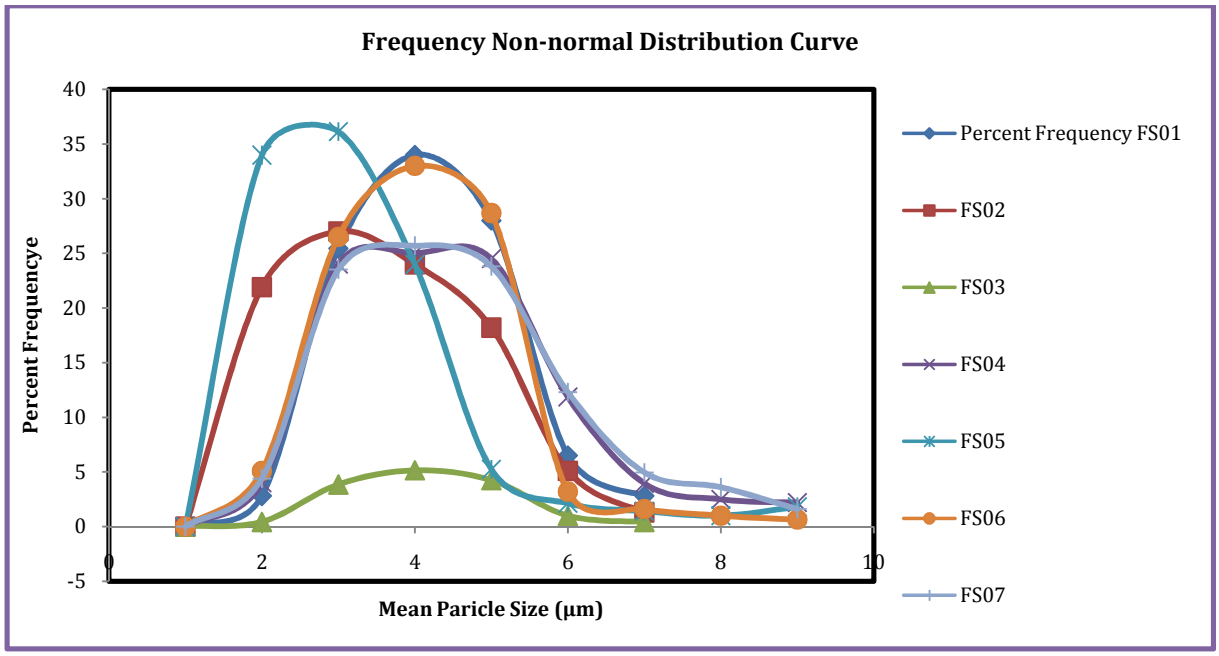


Fig. 3: Graphic representation of frequency non-normal distribution curve of formulations FS01-FS07

Particle Size and its Distribution

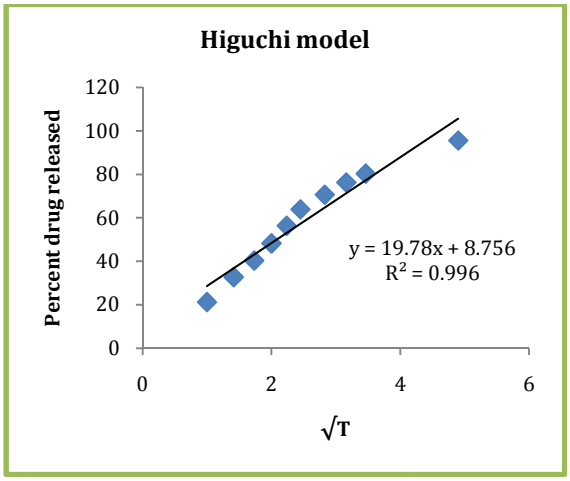
The microsphere offers higher absorption of drug in GI tract due to the large surface area to volume ratio of the particles. The particle size of microspheres determines the biopharmaceutical properties and targeting ability of these delivering systems. In a study, smaller sized microspheres were able to penetrate throughout the sub-mucosal layers of the intestinal loop while the large sized micro particles were predominantly accumulated in the epithelial lining which demonstrated the improved permeability of micro sized particles.

All the prepared microspheres lies in micro range (72.48 - 129.21 µm). The average particle size of all formulations FS01, FS02, FS03, FS04, FS05, FS06, and FS07 was found to be 72.48, 78.62, 89.39, 98.38, 104.16, 116.18, and 129.21µm. It is observed from the pattern of particle size distribution (Figure 3) that as the concentration of polymer increases in the particles, size of drug loaded microspheres also increases in the formulations (FS01-FS07).

Kinetic Modeling

The cumulative drug release obtained for microsphere formulations prepared by solvent evaporation method was fitted to various kinetic models (Figure 4) (zero order model, first order model, Korsemeyer Peppas model, Higuchi model and Hixson Crowell model) [17]. The *In-vitro* drug release of optimized batch of fluvastatin sodium loaded microspheres (FS05) was best fitted in

Higuchi model. The value of n obtained (0.607) was greater than 0.455 indicates non-fickian diffusion as possible mechanism of drug release. Table 2 enlist the regression parameters obtained after fitting various release kinetic models to the *In-vitro* drug release data of FS05.



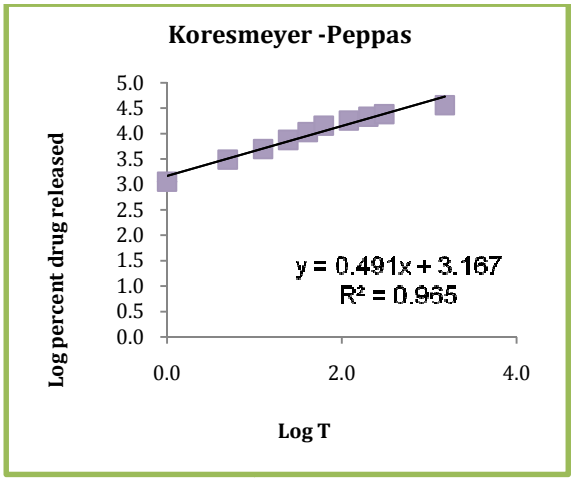


Fig. 4: Kinetic modeling as applied to Formulation FS05

Determination of Swelling Index

Measurement of swelling index of all the Fluvastatin Sodium loaded microspheres formulations using polymer blends of Ethyl cellulose and HPMC K-15M were carried out.

Table 2: Kinetic modeling parameters for microsphere formulations (FS05)

Regression parameters	Zero order	First order	Korsemeyer Peppas model	Higuchi model	Hixson Crowell model
Slope	3.051	-0.123	0.491	19.38	-0.246
R^2	0.904	0.937	0.965	0.996	0.912

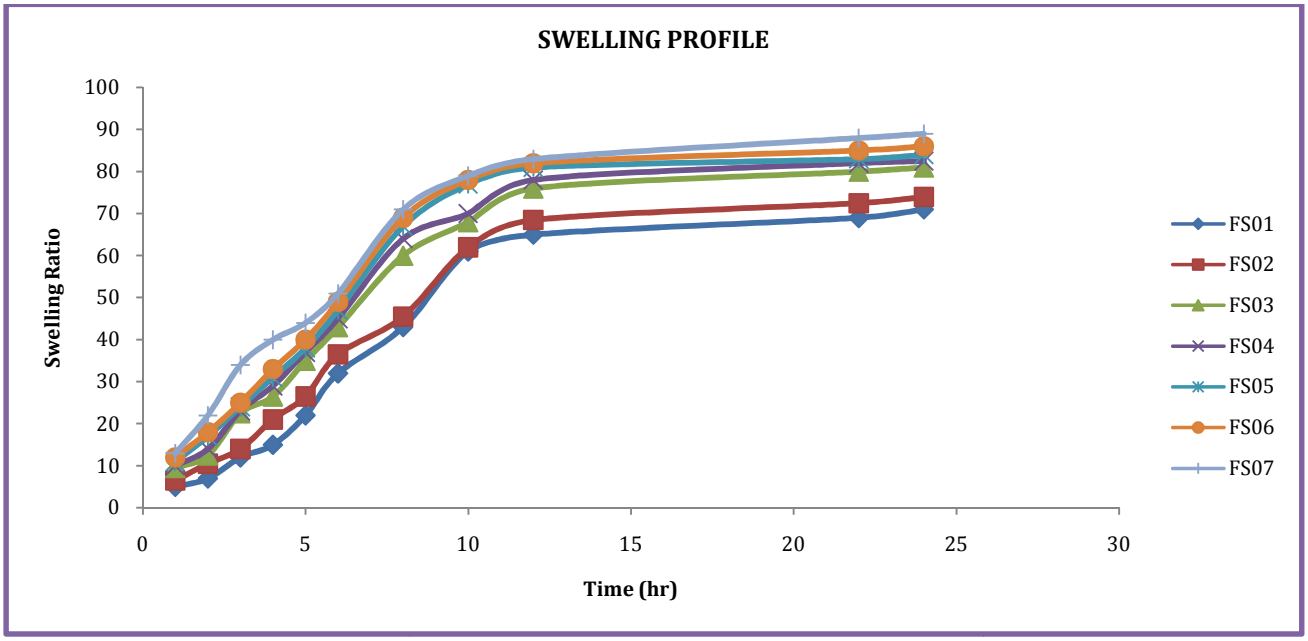


Fig. 5: Comparison of swelling ratio of all formulations in Phosphate buffer pH 6.8

Visual and tactile observations of the all the microspheres formulations confirmed that swelling was dominant in these formulations due to the presence of HPMC, a hydrophilic polymer as it undergoes swelling in presence of liquid solvent forms a polymeric chains. Microspheres from formulations (FS07) comprising higher concentrations of polymer blend showed the maximum increase in rate of swelling (89%) whereas minimum swelling was reported in formulation (FS01) containing lowest polymer blend concentration (70.5%). This was conceptualized, that enhanced amount of polymer absorbs large quantity of solvent from the system and forms a jelly-like network around the system with the passage of time. This mechanical feature of surface hydrated polymer forms a viscous barricade that plays a crucial role in the whole drug release rate. Swelling profiles for microspheres formulations (FS01-FS07) are shown in Figure 5.

X-ray Powder Diffraction Studies

X-ray powder diffraction has been identified as a powerful technique for the identification of crystalline and non-crystalline phase. The characteristics diffraction peaks of Fluvastatin sodium are at (2θ) 9.23°, 11.54°, 12.90°, 13.89°, 14.56°, 15.78°, 18.24°, 19.74°, 20.90°, 22.84°, 26.58°, 27.47°, 32.51°, 35.17° and 38.23° indicate the crystalline nature of the drug. Comparison of X-ray diffraction pattern of the pure individual drug with the drug entrapped in microsphere showed slight change in positions of the peaks. Moreover, characteristic peaks of individual drug were still detectable in their respective formulation with much reduction in intensity depending upon the amount of individual drug present in the formulation and the much diffused pattern observed in FS05 may be due to the amorphous nature of polymers. Thus, no sign of interaction were detected in formulation under the ambient conditions. The X-ray powder diffraction studies of Fluvastatin sodium and formulation is shown in Figure 6.

SEM of Fluvastatin Sodium Microspheres

The SEM photograph of Fluvastatin sodium showed that microspheres were spherical in shape and also posses smooth surface indicating uniform dispersion of the drug in the polymeric matrix of the polymer. The SEM analysis also revealed that the prepared microspheres were found to devoid of aggregation particles and poses negligible surface charges indicating physical stability of formulation. Insignificant effect was observed in shape of microspheres on increasing the concentration of polymer. The SEM of optimized microsphere formulation of Fluvastatin sodium FS05 is shown in Figure 7.

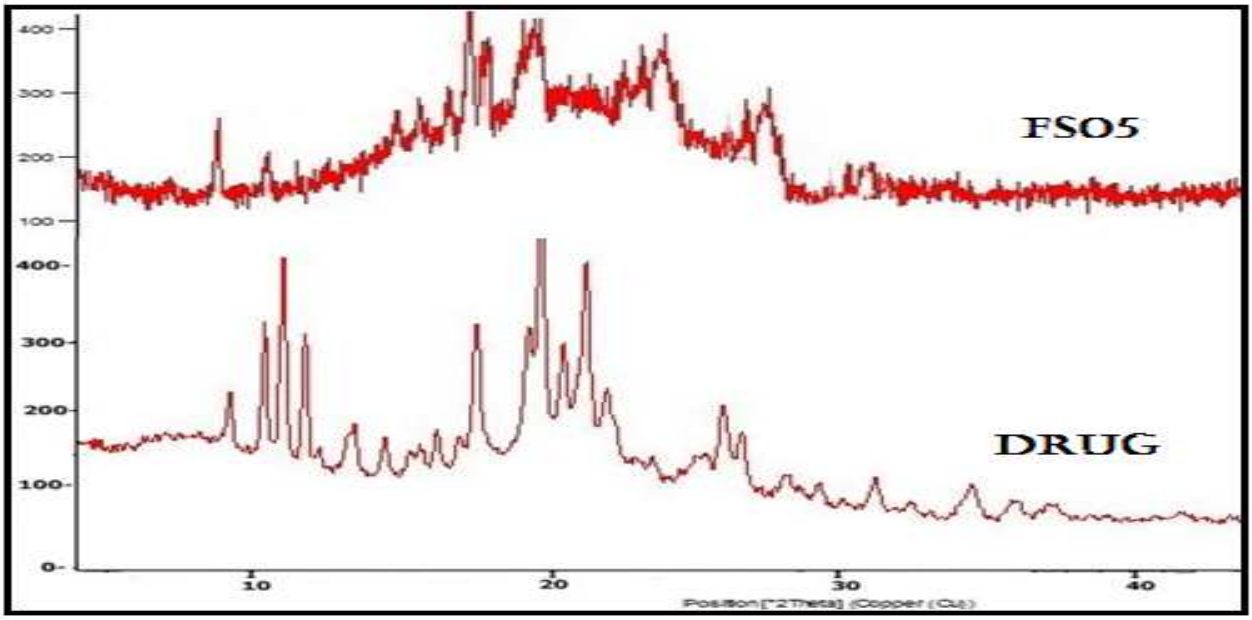


Fig. 6: X-ray diffraction of (a) Fluvastatin Sodium loaded microspheres (b) Pure drug (Fluvastatin Sodium)

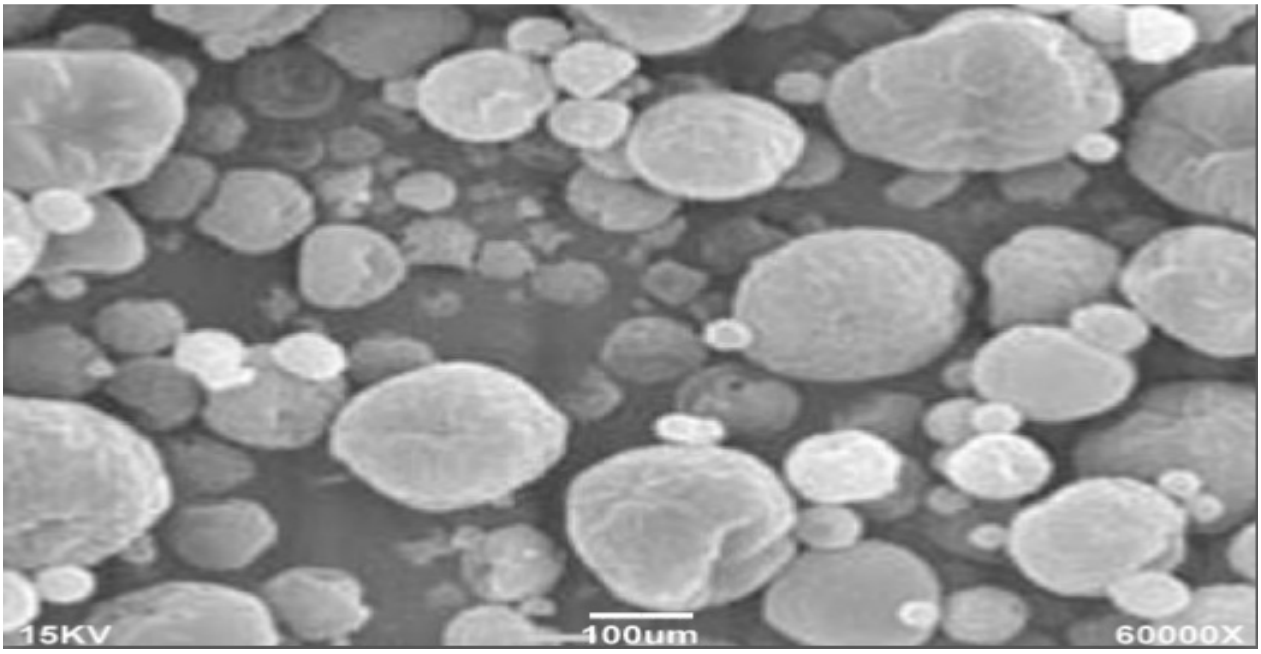


Fig. 7: SEM of optimized Fluvastatin sodium loaded Microsphere formulation (FS05)

CONCLUSION

Fluvastatin sodium microspheres were successfully prepared using polymers blend with sustained release effect. FTIR studies showed that drug and polymers are compatible with each other. Particle size of all the seven prepared microsphere formulations of Fluvastatin sodium were in micromeretic range. Microsphere formulation FS05 have shown the best result out of seven formulations due to optimum percent drug release, swelling index and highest drug content, entrapment efficiency. Results of XRD studies revealed that drug was encapsulated inside the polymer matrix. Thus, polymeric microspheres have shown great promise for the delivery of therapeutic agents due to their biocompatibility, ease of administration and capability for long-term sustained release.

ACKNOWLEDGEMENT

This research was performed with support from Swami Vivekanand College of Engg. and Technology

CONFLICT OF INTERESTS

The authors show no conflict of interest.

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