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Formulation and evaluation of efavirenz microspheres

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ABSTRACT

The present research work is aimed to design sustained release microspheres of Efavirenz a anti retroviral drug which is used in the treatment of HIV and these are designed in such a way that release of the drug is for 10 to 12 hours. The Microspheres were prepared by the Solvent Evaporation method using varying concentrations of sustained release polymers Eudragit RS PO and Ethyl cellulose100cpc, Ethyl cellulose N22. The compatibility of the polymers was ruled out by FT-IR studies and found to be compatible. Total 15 formulations were prepared. The Efavirenz microspheres were evaluated for their physical properties like angle of repose, bulk density and swelling index and found to have good flow property. The prepared microspheres were evaluated for in process and finished product quality control tests including appearance, Bulk density, Entrapment efficiency and in- vitro drug release. The dissolution medium used was pH 7.0 phosphate buffer. All formulations showed acceptable pharmaco-technical properties and complied with in-house specifications for tested parameters. The results of dissolution studies indicated all formulations released up to 12hours and formulation containing Eudragit RS PO i.e. F_{14} was the most successful formulation with 96.82% drug release at the end of 12 hours.

Keywords: Antiretroviral; Efavirenz; Eudragit RS PO; Krosmeyer- peppas kinetics, Highuchi model; microsheres formulation.

INTRODUCTION

"Microspheres can be defined as solid, approximately spherical particles with a diameter ranging from 1 to 1000µm, containing dispersed drug in either solution (or) microcrystalline form". The terms microcapsules and microspheres are often used synonymously. The micro-particulate drug delivery systems are considered and accepted as reliable means to deliver the drug to the target with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.[1]

Efavirenz is a Non nucleotide reverse transcriptase inhibitor of HIV-1. Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase. It is a BCS class –II drug ie., it has low solubility and high permeability. As the solubility of drug is less, it has low bioavailability. Thus an attempt has been made to develop sustain release microspheres of efavirenz so as to increase its bioavailability. Efavirenz microspheres were prepared by solvent evaporation method by employing polymers such as ethyl cellulose and Eudragit. The major objective of the present investigation is to study the influence of the formulation and process parameters, such as viscosity of the polymer solution and temperature besides the type of polymer, on the characteristics of microspheres, which in turn influence the release of drug. [2, 3]

MATERIALS AND METHODS

Materials: Efavirenz was obtained as a gift sample from Arch pharmalabs, India. Ethyl cellulose N-22 and Eutragit RS PO were purchased from Merck, Mumbai. Ethyl cellulose 100cps was obtained from S D Fine-Chem limited, Mumbai.

Methods:

Compatibility studies by FTIR:

The compatibility between drug and various polymers used was determined by using FTIR.

Preparation of microspheres by solvent evaporation method:[4,5]

Different ratios of efavirenz microspheres were prepared by solvent evaporation method using the polymers Ethyl cellulose N22, Ethyl cellulose 100cps and Eudragit RSPO. Initially, efavirenz and polymers were dissolved in acetone based on the drug and polymer ratio (1:0.5, 1:1, 1:2), then the resulted solution was dispersed slowly in heavy liquid paraffin under continuous agitation at two different temperature i.e. at room temperature and at 40 – 45°C for obtaining microspheres.

The mixture was vortexed for 15 to 30 minutes at high RPM by using mechanical stirrer. The obtained microspheres were separated from paraffin by filtration and washed with petroleum ether for three successive times, finally with water and then dried and collected.

Table.1: Formulation table for efavirenz microspheres

Ingredients / Formulation	Ratio	Efavirenz (g)	Ethyl Cellulose N-22 (g)	Ethyl Cellulose 100 CPS (g)	Eudragit RS PO (g)	Acetone	Temperature
F1	1:0.5	0.5	0.25	-	-	15 ml	-
F2	1:1	0.5	0.5	-	-	15 ml	-
F3	1:2	0.5	1.0	-	-	15 ml	-
F4	1:0.5	0.5	-	0.25	-	15 ml	-
F5	1:1	0.5	-	0.5	-	15 ml	-
F6	1:2	0.5	-	1.0	-	15 ml	-
F7	1:0.5	0.5	-	0.25	-	10 ml	40-45°C
F8	1:1	0.5	-	0.5	-	10 ml	40-45°C
F9	1:2	0.5	-	1.0	-	10 ml	40-45°C
F10	1:0.5	0.5	-	-	0.25	15 ml	-
F11	1:1	0.5	-	-	0.5	15 ml	-
F12	1:2	0.5	-	-	1g	15 ml	-
F13	1:0.5	0.5	-	-	0.25	10 ml	40-45°C
F14	1:1	0.5	-	-	0.5	10 ml	40-45°C
F15	1:2	0.5	-	-	1g	10 ml	40-45°C

Characterization of microspheres:

Determination of percentage yield of microspheres

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was than calculated using formula given.

$$\%\text{Yield} = \frac{\text{Mass of microspheres obatined}}{\text{Total weight of drug and polymer}} \times 100$$

Morphological characterization of microspheres [6]

The shape and surface characterization of microspheres were observed under a Scanning Electron Microscope (ZEOL JSM–5610). The dry microspheres were mounted directly on the SEM sample stub, using double-sided sticking tape, and coated with ion sputter (thickness 200 nm) under reduced pressure (0.001 torr) and photographed. Picture of microspheres were taken by random scanning of the stub.

Flow Properties of Microspheres [7]

- **Bulk density:**

Bulk density is determined by pouring microspheres into a graduated cylinder via a large funnel and measure the volume and weight.

$$\text{Bulk density} = \frac{\text{Weight of microspheres}}{\text{Bulk volume of microspheres}}$$

- **Tapped density:**

Tapped density is determined by placing a graduated cylinder containing a known mass of microspheres and mechanical tapper apparatus, which is operated for a fixed number of taps using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

$$\text{Tapped density} = \frac{\text{Weight of microspheres}}{\text{Tapped volume of microspheres}}$$

- **Carr's index:**

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index

$$\text{Carr}'\text{s Index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

- **Hausner's Ratio:**

Hausner's ratio is measured by using by using the values of tapped density and bulk density.

$$\text{Hausner}'\text{s Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

- **Angle of repose:**

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder ion a conical heat on a level, flat surface and measure the included angle with the horizontal.

$$\tan\theta = \frac{h}{r}$$

Where, h = height, r = Radius, θ = Angle of Repose

Swelling studies[8]

A known weight of microspheres was placed in a glass vial containing 10ml of distilled water at 37-±0.5°C in incubator with occasional shaking. The microspheres were removed, blotted with filter paper and their changes in weights were measured during the swelling until equilibrium was attained.

Finally, the weight of the swollen microspheres was recorded after a period of 24 hours, and the swelling ratio (SR) was then calculated from the formula. The studies were carried out in triplicate.

$$\text{Swelling Ratio} = \frac{W_e - W_0}{W_o}$$

Where,

W_0 = Initial weight of the dry microspheres,

We = weight of the swollen microspheres at equilibrium swelling in the media.

Encapsulation efficiency[8]

Encapsulation efficiency was calculated using the following formula

$$\text{Encapsulation efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

In vitro dissolution studies[9]

The release rate of Efavirenz microspheres was determined by employing USP type 2 apparatus by rotating paddle method. The dissolution test was performed using 900 ml SLS phosphate buffer pH 7.0, in 37 ± 0.5°C at 50 rpm. Efavirenz microspheres equivalent to 500 mg were placed in a basket. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus for every 30 minutes for 12 hrs, and the samples were replaced with 5 ml of fresh dissolution medium. The samples absorbance of these solutions was measured at 248 nm. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot. Data obtained was also subjected to kinetic treatment to understand release mechanism.

Release Kinetics

The dosage forms most commonly release the drug either in the zero order or in the first order pattern. Efavirenz was prepared and studied for their dissolution behavior. The behavior of drug release from the formulations is determined by using various kinetic models such as first order, zero order, Higuchi and Krosmeyer Peppas model.

RESULTS AND DISCUSSION

Compatibility Studies: IR spectra of pure Efavirenz and the physical mixtures of drug and polymers were showed in figure 1-4. As the identical principle peaks were observed in all the cases, it was confirmed that there is no interaction between the drug and polymers.

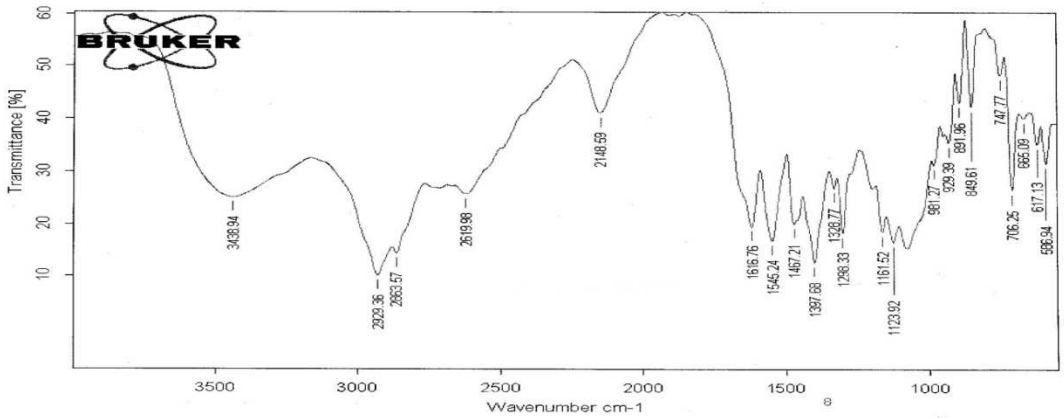

Fig 1: FT – IR spectra of pure Drug

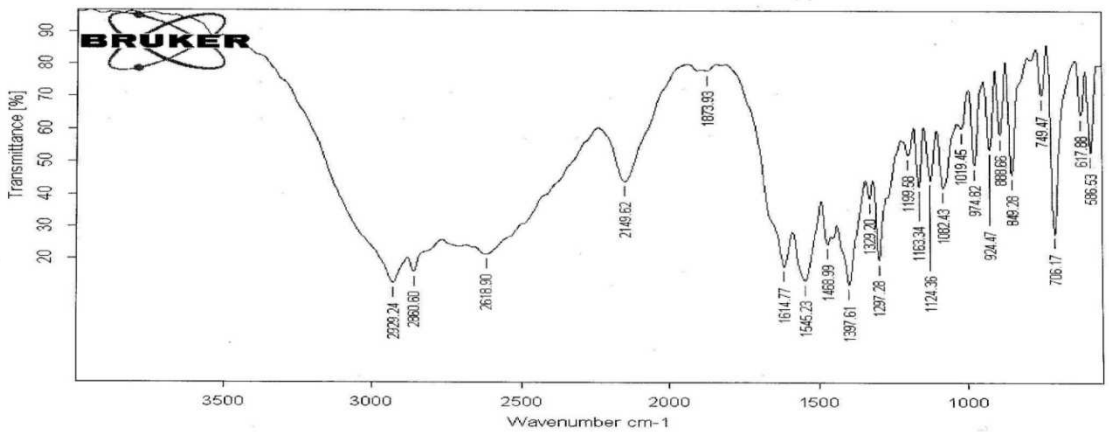

Fig 2: FT – IR spectra of physical mixture of Drug + Eudragit RS PO

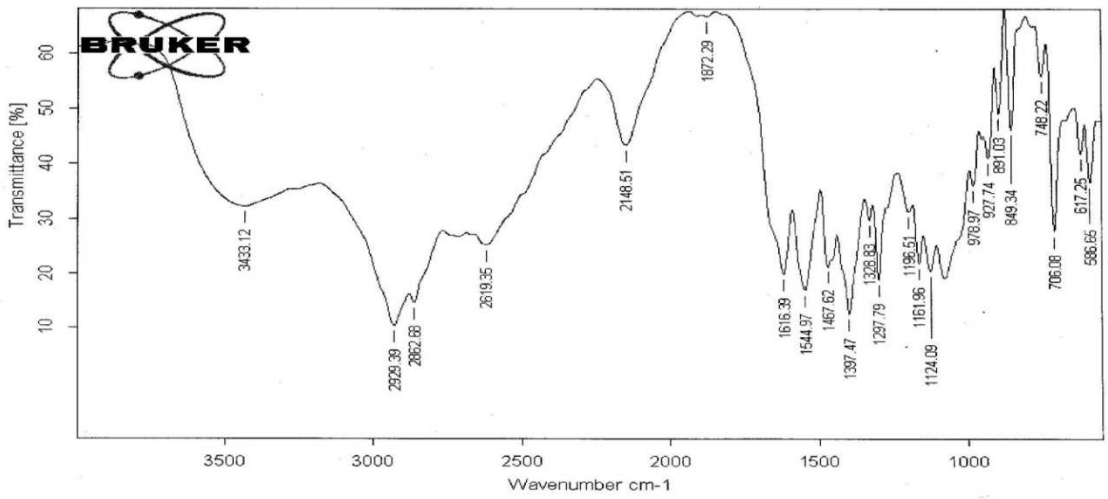

Fig 3: FT – IR spectra of physical mixture of Efavirenz + Ethyl cellulose N22

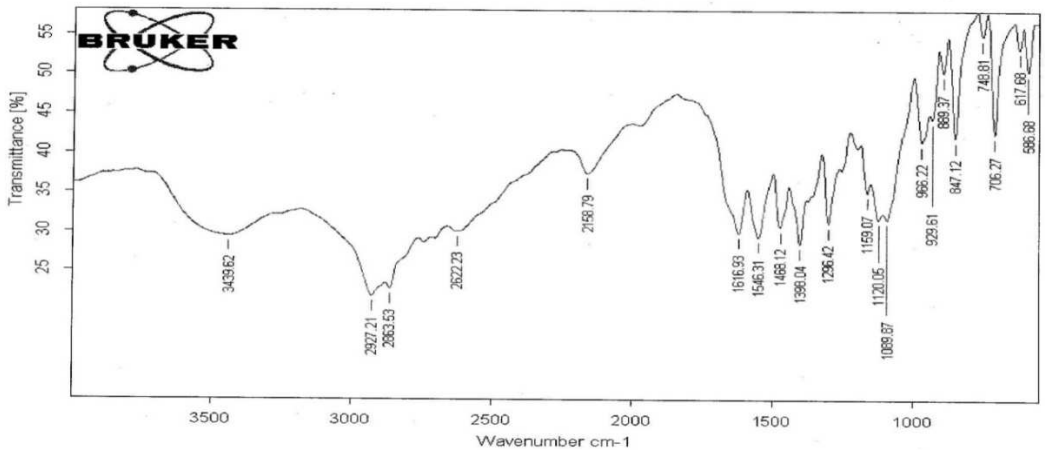

Fig 4: FT – IR spectra of physical mixture of Efavirenz + Ethyl cellulose100 cps

Studies on flow properties

The microspheres were evaluated for various derived properties such as bulk density, tapped density and flow properties such as angle of repose, Hausner's ratio and Carr's index, all the results were shown in table 2.

The change in the bulk densities, before and after a suitable tapping procedure, indicated that the granules were having good compressibility and package ability. The results of the flow ability studies indicated that the microspheres of all the formulations were having well to excellent flow ability. These studies combinely indicated that the microspheres of all formulations were efficient for either compression or filling into capsule.

Table 2: Flow Properties of Efavirenz Microspheres

Formulation code	Bulk Density (Avg. ± S.D.)	Tapped Density (Avg. ± S.D.)	Angle of repose (Avg. ± S.D.)	Carr's Index (Avg. ± S.D.)	Hausners's ratio (Avg. ± S.D.)
F1	0.372 ± 0.01	0.387 ± 0.01	17.103 ± 0.12	3.875 ± 0.01	1.040 ± 0.01
F2	0.416 ± 0.02	0.430 ± 0.02	16.921 ± 0.11	3.258 ± 0.02	1.034 ± 0.01
F3	0.327 ± 0.01	0.339 ± 0.01	16.537 ± 0.09	3.539 ± 0.01	1.037 ± 0.01
F4	0.383 ± 0.01	0.397 ± 0.01	16.909 ± 0.13	3.429 ± 0.02	1.036 ± 0.01
F5	0.406 ± 0.02	0.419 ± 0.02	16.812 ± 0.12	3.102 ± 0.02	1.032 ± 0.01
F6	0.307 ± 0.01	0.318 ± 0.01	21.170 ± 0.12	3.611 ± 0.01	1.037 ± 0.01
F7	0.386 ± 0.01	0.398 ± 0.01	17.181 ± 0.13	2.917 ± 0.02	1.031 ± 0.01
F8	0.417 ± 0.02	0.428 ± 0.02	16.926 ± 0.13	2.570 ± 0.01	1.026 ± 0.01
F9	0.318 ± 0.01	0.329 ± 0.01	17.108 ± 0.15	3.459 ± 0.02	1.034 ± 0.01
F10	0.373 ± 0.01	0.383 ± 0.01	20.120 ± 0.12	2.610 ± 0.01	1.026 ± 0.01
F11	0.291 ± 0.01	0.304 ± 0.01	23.942 ± 0.15	4.309 ± 0.03	1.045 ± 0.01
F12	0.351 ± 0.01	0.364 ± 0.01	20.321 ± 0.16	3.571 ± 0.02	1.037 ± 0.01
F13	0.363 ± 0.01	0.375 ± 0.01	20.162 ± 0.11	3.210 ± 0.01	1.033 ± 0.01
F14	0.290 ± 0.01	0.304 ± 0.01	22.371 ± 0.13	4.309 ± 0.02	1.048 ± 0.01
F15	0.282 ± 0.01	0.295 ± 0.01	22.461 ± 0.15	4.406 ± 0.01	1.046 ± 0.01

Studies on other physical properties

The results of the swelling index were shown in table 3. These results indicated that upon increase in the concentration of the polymer, the swelling capacity was found to be reduced. This might be because of the more strengthened polymer network in the microspheres of higher concentration which made the water difficult to absorb into the microsphere. This behavior was observed in all the three polymers. There is no significant difference was observed in the swelling index among these polymers, which might be because all these polymers are water insoluble.

The percentage yield results were shown in table 3. All the microspheres of different formulations were prepared by solvent evaporation technique and from the results; more than 80% yield in any case, indicated that the solvent evaporation technique was highly effective for the preparation of microspheres.

The results of entrapment efficiency were shown in table 3. These results indicated that upon increase in concentration of the polymer, the entrapment efficiency was found to be improved as the higher amount of polymer allows more amount of drug to be entrapped in its matrix. The increase in the viscosity of the drug and polymer solution also resulted in increased entrapment efficiency. Again the entrapment efficiency of the microspheres of different polymers indicated that it was improved upon increase in the molecular weight of the polymer. The increasing order of efficiency of the polymers was observed as

Ethyl Cellulose N22 < Ethyl Cellulose 100 cps < Eudragit RS PO

Table 3: Physical evaluation parameters of Efavirenz Microspheres

Formulation code	% Yield (Avg. ± S.D.)	% Entrapment Efficiency (Avg. ± S.D.)	Swelling Index (Avg. ± S.D.)
F1	90.13 ± 0.31	62.35 ± 0.21	1.1
F2	92.56 ± 0.43	65.81 ± 0.28	0.9
F3	86.30 ± 0.34	69.32 ± 0.32	0.2
F4	76.88 ± 0.32	78.43 ± 0.33	1.4
F5	83.01 ± 0.31	83.41 ± 0.37	0.7
F6	80.23 ± 0.33	88.52 ± 0.42	0.1
F7	93.21 ± 0.42	85.98 ± 0.40	1.2
F8	86.37 ± 0.34	86.41 ± 0.41	0.5
F9	88.15 ± 0.31	96.03 ± 0.43	0.1
F10	90.42 ± 0.41	77.83 ± 0.34	1.3
F11	88.34 ± 0.38	81.75 ± 0.37	0.8
F12	89.10 ± 0.35	97.53 ± 0.42	0.3
F13	88.91 ± 0.38	79.05 ± 0.30	1.2
F14	94.12 ± 0.33	98.78 ± 0.36	0.7
F15	82.66 ± 0.32	90.54 ± 0.42	0.2

Studies on Scanning Electron Microscopy (SEM) Analysis

The results of the SEM analysis were shown in fig 5-7. The pictures of microspheres of formulation F6 (Ethyl Cellulose 100 cps at 1:2 ratio, 15 ml acetone) showed that the texture was not uniform and also small pits were also present. The pictures of microspheres of formulation F9 (Ethyl Cellulose 100 cps at 1:2 ratio, 10 ml acetone) showed that the texture was more uniform and smooth, and no pits were present on the surface. And the size of the microspheres was also less when compared to that of the microspheres of formulation F6.This might be attributed to the higher viscosity of the polymer phase, which allowed formation of small and compact droplets upon emulsification under high speed rotation and the higher temperature also aided the strengthening of the polymer matrix.

The texture of the microspheres of formulation F14 (Eudragit RS PO at 1:2 ratio, 10 ml acetone) was jagged and uneven, the matrix of the polymer strands was clearly observed and it was more complex. This might be because of the long chain length and high molecular weight of the polymer molecules of Eudragit RS PO.

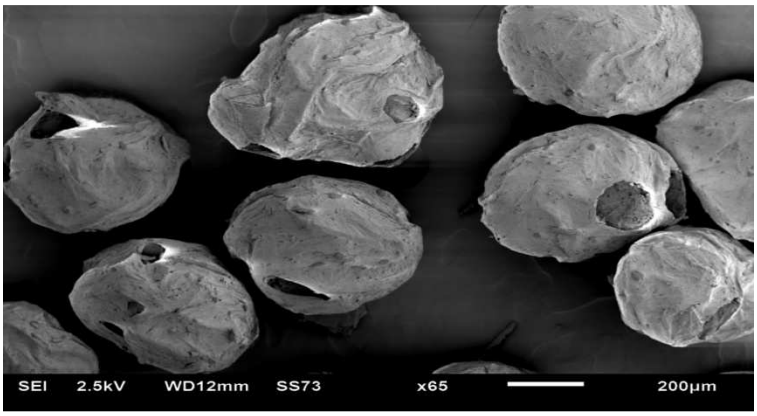

Fig 5: SEM pictures of Efavirenz microspheres of formulation F6

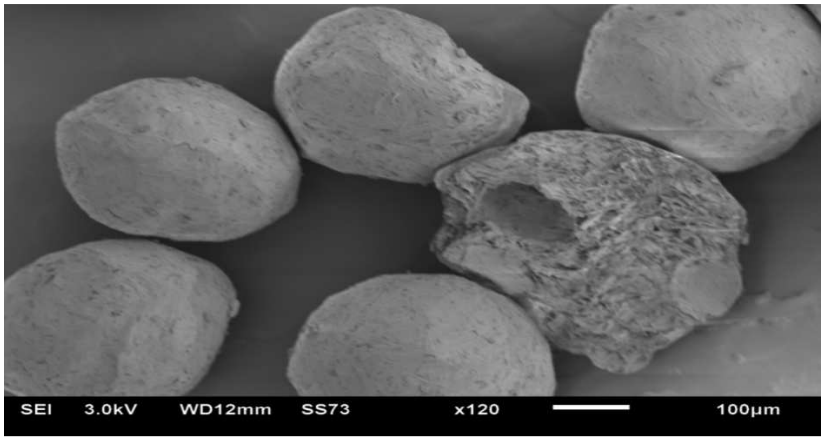

Fig 6: SEM pictures of Efavirenz microspheres of formulation F9

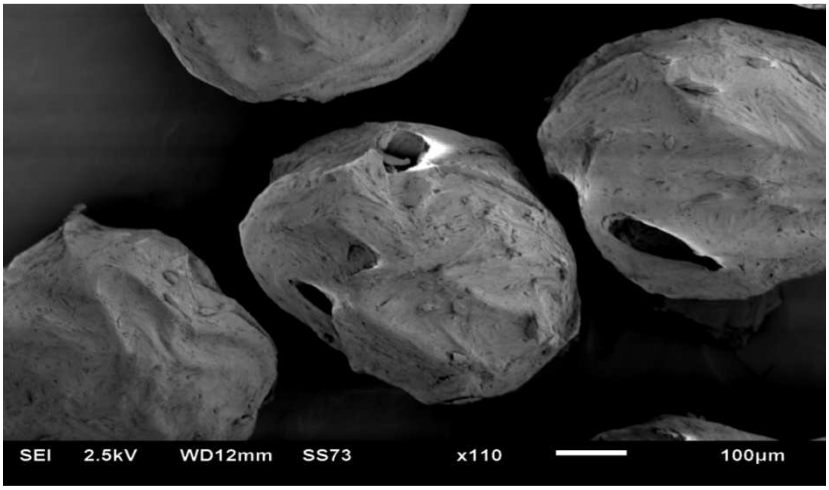

Fig 7: SEM pictures of Efavirenz microspheres of formulation F14

Studies on Dissolution Test of Efavirenz Microspheres

The results of the dissolution studies of microspheres of formulations F1 to F3 were shown in table 4. The results indicated that upon increasing the concentration of Ethyl Cellulose N 22, the drug release rate was more controlled. The results of the dissolution studies of microspheres of formulations F4 to F15 were shown in table 5 and 6. These results indicated that upon increasing the concentration of Ethyl Cellulose 100 cps, the drug release rate was found to be decreased. The comparison between F9 & F10, F11 & F14 and F15 indicated that the drug release rate was more controlled at higher viscosity of the polymer phase. This might be attributed to the formation of more compact polymer matrix without any surface defections, because of high viscosity of polymer phase and high processing temperature, which was evidenced by swelling index studies and SEM analysis.

When the dissolution profiles of the Efavirenz microspheres of three different polymers were compared, the order of efficiency of controlling the drug release was found to be Ethyl Cellulose N22 < Ethyl Cellulose 100 cps < Eudragit RS PO

Table 4: Results of dissolution test performed on Efavirenz microspheres of F1 to F3

Time(Mins)	% Drug release		
	F1	F2	F3
0	0	0	0
15	91.87 ± 0.41	47.03 ± 0.21	18.71 ± 0.11
30	98.48 ± 0.46	76.98 ± 0.24	42.45 ± 0.20
45	-	82.21 ± 0.42	46.04 ± 0.26
60	-	92.67 ± 0.51	62.93 ± 0.32
90	-	97.88 ± 0.48	77.76 ± 0.38
120	-	-	84.72 ± 0.45

Table 5: Results of dissolution test performed on Efavirenz microspheres of F4 to F9

Time (mins)	%Drug release					
	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0
30	43.24 ± 0.22	36.75 ± 0.12	22.19 ± 0.12	48.71 ± 0.23	27.72 ± 0.12	13.9 ± 0.10
60	67.72 ± 0.21	52.24 ± 0.23	44.41 ± 0.14	73.21 ± 0.32	40.97 ± 0.17	21.83 ± 0.14
90	82.42 ± 0.48	69.45 ± 0.32	52.68 ± 0.21	83.93 ± 0.29	44.79 ± 0.21	39.32 ± 0.16
120	94.01 ± 0.51	80.23 ± 0.45	67.03 ± 0.25	91.39 ± 0.43	49.53 ± 0.26	44.79 ± 0.23
150	-	89.06 ± 0.23	73.93 ± 0.38	94.69 ± 0.42	57.53 ± 0.30	49.06 ± 0.29
180	-	92.16 ± 0.37	81.03 ± 0.43	96.58 ± 0.43	70.07 ± 0.43	50.9 ± 0.25
240	-	97.47 ± 0.43	90.92 ± 0.21	98.35 ± 0.44	83.48 ± 0.25	54.71 ± 0.27
300	-	98.41 ± 0.33	95.41 ± 0.33	-	87.83 ± 0.42	66.96 ± 0.33
360	-	-	96.36 ± 0.45	-	92.9 ± 0.45	71.88 ± 0.35
420	-	-	97.91 ± 0.46	-	95.78 ± 0.46	82.09 ± 0.40
480	-	-	98.79	-	97.88 ± 0.46	85.67 ± 0.43
540	-	-	-	-	98.74 ± 0.47	87.83 ± 0.42
600	-	-	-	-	-	90.77 ± 0.46
660	-	-	-	-	-	94.67 ± 0.47
720	-	-	-	-	-	95.68 ± 0.42

Table 6: Results of dissolution test performed on Efavirenz microspheres of F10 to F15

Time (min)	% drug dissolved (Avg. ± S.D.)					
	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0
30	31.29 ± 0.14	29.10 ± 0.12	16.44 ± 0.13	29.53 ± 0.15	18.71 ± 0.10	14.68 ± 0.11
60	51.01 ± 0.21	37.34 ± 0.17	25.53 ± 0.12	42.05 ± 0.20	29.04 ± 0.15	22.19 ± 0.10
90	54.58 ± 0.22	38.63 ± 0.20	26.54 ± 0.14	44.79 ± 0.21	40.84 ± 0.18	31.29 ± 0.15
120	70.34 ± 0.34	41.12 ± 0.20	33.85 ± 0.12	53.44 ± 0.22	43.5 ± 0.25	36.61 ± 0.23
150	71.42 ± 0.34	47.38 ± 0.22	37.63 ± 0.18	62.58 ± 0.35	54.91 ± 0.27	41.65 ± 0.24
180	85.54 ± 0.40	62.59 ± 0.31	47.35 ± 0.22	71.75 ± 0.38	60.91 ± 0.33	48.71 ± 0.27
240	89.67 ± 0.39	68.74 ± 0.34	54.5 ± 0.25	83.48 ± 0.42	67.93 ± 0.34	56.84 ± 0.39
300	94.87 ± 0.46	73.33 ± 0.34	67.34 ± 0.33	89.23 ± 0.46	78.17 ± 0.32	61.36 ± 0.36
360	96.84 ± 0.47	81.25 ± 0.40	73.93 ± 0.34	94.37 ± 0.42	80.85 ± 0.41	62.76 ± 0.37
420	-	87.12 ± 0.43	75.51 ± 0.32	95.96 ± 0.43	86.81 ± 0.44	67.86 ± 0.39
480	-	91.68 ± 0.41	82.03 ± 0.41	98.31 ± 0.41	91.81 ± 0.43	74.17 ± 0.35
540	-	93.97 ± 0.44	86.82 ± 0.44	-	93.39 ± 0.46	79.62 ± 0.38
600	-	95.43 ± 0.51	90.45 ± 0.41	-	94.81 ± 0.41	83.78 ± 0.40
660	-	97.18 ± 0.47	93.39 ± 0.45	-	96.45 ± 0.45	85.54 ± 0.43
720	-	-	95.53 ± 0.41	-	96.82 ± 0.41	88.51 ± 0.46

Release kinetics: Different models like zero order, first order, higuchi's, and peppas plots were drawn for formulation F14. The regression coefficient (r^2) value for zero order, first order, higuchi's, and peppas plots for formulation F14 was found to be and (0.9198, 0.996, 0.968, 0.9751) respectively. The formulation F14 follows first order release and peppas plot and slope 'n' value is less than 0.5 which confirms that the drug release through the matrix was fickian diffusion.

CONCLUSION

Studies have been carried out on the study of influence of formulation and process parameters on drug release rate from Efavirenz microspheres. The research was undertaken to study the influence of viscosity of the polymer phase and temperature as process parameters and, and concentration of the polymer as the formulation parameters. The drug was found to be compatible with all the three polymers based on IR spectral studies. At higher concentration of polymer phase, temperature was required for the rigidization of the microspheres after formation. Another interesting finding was the microspheres prepared from the high viscosity polymer phase were smaller in size than those prepared from the lower viscosity polymer phase. The packaging ability, compressibility and flow properties were found to be good. Swelling capacity was found to be reduced upon increase in the concentration of polymer in microsphere matrix. From the percentage yield and entrapment efficiency studies, it was observed that emulsion solvent evaporation method was found to be more successful. Surface morphology studies (SEM analysis) indicated that at lower viscosity of the polymer (Ethyl Cellulose 100 cps) phase, microspheres of irregular surface with small pits were formed. A more uniform and smooth surfaced microspheres were formed at higher viscosity of the polymer phase. SEM analysis of the microspheres prepared from Eudragit RS PO showed the surface of the microspheres was completely uneven and the rich complex network of the polymer chains was also observed. From the dissolution studies an interesting finding was observed that the drug release rate was found to be reduced upon increase in the viscosity of the polymer phase even at the same amount of the polymer. The drug release was more controlled from the microspheres prepared with Eudragit RS PO than those prepared with Ethyl Cellulose. The drug

release from the microspheres was able to be controlled until 12 hrs at a drug to polymer ratio of 1:2 with both Ethyl Cellulose 100 cps and Eudragit RS PO.Thus the major objectives of the present investigation were achieved and the results were appropriately placed. Optimized formulation is F14 as is shows good results. Formulation F14 contains Drug & Eudragit in the ratio of 1:1, which has a % yield of 94.12%,% Entrapment efficiency of 98.78% & the drug release of 96.82% at the end of 12 hrs when compared to other formulations.

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