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Formulation and Evaluation of Microspheres Containing Fluvastatin Sodium

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Abstract

Fluvastatin sodium is a cholesterol lowering agent. It has shorter half life (1.2).It undergoes extensive first pass metabolism. Frequent dosing is required in case of conventional dosage form. The purpose of the study is to formulate microcapsules containing Fluvastatin sodium by complexing with anionic exchange cholestyramine resin Indion-454 by coating with ethyl cellulose, eudragit-RS100 polymers for achieving controlled release in the small intestine. Complexation of drug on the resins by batch method. Compatibility studies were carried out using FTIR, DSC and X-ray diffraction studies. Microencapsulation was carried out by w/o/w double emulsion solvent evaporation technique. Characterization of various physicochemical properties like % Yield, % DEE, % Polymer coating and particle size were evaluated. *In vitro* drug release studies were carried out in USP type I dissolution test apparatus. The accelerated stability studies were carried out on the most satisfactory formulations. FTIR, X-Ray diffraction and DSC spectra of drug, ion-exchange resin and drug-polymers revealed that no chemical interaction. Drug loading was observed in 4 hrs 1:4 ratio. Percentage yield for the formulations observed that for F1 to F8 is varied from 93.4±5.84 to 98.7±6.30. Percentage drug entrapment efficiency was observed for the formulations of F1 to F8 are varied from 96±0% to 98.3±0.1%. Microcapsules of F4 and F5 prepared with EudragitRS100 and Ethyl cellulose using ion-exchange resins provide a convenient dosage forms for achieving best performance regarding release study, there is no changes in % DEE and %CDR was observed after stability studies.

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Key words:
Ion exchange resin, Fluvastatin sodium, drug-resinates, SEM

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Introduction:

Now a day's obesity is more health concern in world wide. Obesity is a national epidemic (1). A controlled release drug delivery system is usually designed to deliver the drug at particular rate controlled release properties can also be imparted to oral dosage

formulations through the formation of resin-drug complexes coated with polymers(2).

Fluvastatin sodium, a 3-hydroxy-3 methyl glutaryl co-enzyme (HMG COA) reductase inhibitor, is a lipid regulating drug with actions on plasma lipids, inhibits the HMG-COA reductase leads to reduced cholesterol synthesis in the liver and lower intracellular cholesterol concentrations. The drug has a relatively short half life (1.2) hours and it undergoes extensively first metabolism in the liver (3).

The cholestyramine resin is an insoluble strongly basic anion exchange resin in the chloride form supplied as a dry fine powder. Cholestyramine resin is suitable for pharmaceutical applications as carrier for anionic drug substances. When used as an active ingredient, cholestyramine resins a strong pharmacological bile salt-binding agent binds bile acid, this leads to replenishment of the bile acids through increased catabolism of serum cholesterol resulting in lowered serum cholesterol levels (4).

Anionic exchange cholestyramine resin Indion-454 as a drug carrier, it complexes with anionic drug. Ion exchange process alone, without any barrier cannot achieve satisfactory controlled release. Thus the resin complexes were coated with ethyl cellulose, eudragitRS100 polymers for achieving controlled release in the small intestine.

The drug is released from the resin *in vivo* as the drug resinates reaches equilibrium with the high electrolyte concentrations typically found in the gastrointestinal tract (2).

The drug release from the drug-resin complex occurs by replacement of drug molecule by sodium, potassium and chloride ions in the GI tract and diffusion of drug molecule from the resin (8).

Materials & Methods:

Fluvastain sodium was gift sample from Biocon Company, Bangalore and Ion exchange resins gift sample from Ion exchange resins Ltd Mumbai. Ethyl cellulose from central drug house Pvt. Ltd, New Delhi. EudragitRS 100 from Micro Labs, Bangalore.

Preformulation studies:

Drug polymer compatibility studies were carried out using FTIR, DSC and X-ray diffraction studies.

Complexation of drug on the resin (preparation of drug-resinate complex):

Preparation of drug-resinate was tried by batch method (9). Accurately weighed drug and cholestyramine resins in 1:4 ratios. Then slurry of resin was made by using 100 mL distilled water and stirred half an hour at 500 rpm, in order to allow the polymer structure to swell uniformly. Drug solution was made by using 2 mL 0.1N NaOH, then slowly drug solution was added to resin slurry under stirred condition, The mixture was stirred for 4hrs continuously on magnetic stirrer till equilibrium was established. Drug loading of Fluvastatin sodium was determined spectrophotometrically by at 304nm.

Determination of amount of uncomplexed drug by UV:

The mixture to be kept aside to allow the particles to sediment and then filtered. From the filtrate 1mL was transferred into volumetric flask and volume was adjusted with 0.1N NaOH. After suitable dilution, drug was determined spectrophotometrically at 304nm (10).

Microencapsulation of drug-resinates:

To further retard the drug release, the resinate particles were coated with ethyl cellulose, eudragit RS100 with different ratios. Microencapsulation was carried out by w/o/w technique.

Drug resin complex 1.0 gram was poured in 20 mL of methylene chloride containing polymers (As shown in the table1). The solution was mixed for 30 sec, using vertex mixer. To make w/o emulsion first by added 1 ml of water. Then added 100mL of 0.01%w/w cold poly vinyl alcohol (PVA) solution to form w/o/w double emulsion. Continuously stirred at room temperature until methylene chloride gets evaporated to form solid microcapsules.

Table 1: Microencapsulation formulation chart

Formulation code	Drug-resinates taken(g)	Eudragit RS100 Polymer coating ratios (%)	Formulation code	Drug-resinates taken(g)	Ethyl Cellulose Polymer coating ratios(mg)
F1	1	5	F5	1	5
F2	1	10	F6	1	10
F3	1	15	F7	1	15
F4	1	20	F8	1	20

Evaluation of microspheres:

Microscopic examination:

Particle size and shape of microspheres was observed using compound microscope.

Scanning Electron Microscopy (SEM):

Dried microspheres were mounted into stubs by using double sided adhesive tape. The microspheres were coated with gold and observed under scanning electron microscope for surface characteristics.

Particle size analysis:

Particle size analysis was determined using compound microscope with the help of stage micrometer and eye piece micrometer, counted at least 100 microspheres per batch.

Yield of microspheres:

Yield of microspheres was calculated by actual weight of microspheres divided by total weight of copolymers and drug.

Percentage Yield = (Actual weight of microspheres / total weight of copolymers and drug) × 100

Percentage drug entrapment efficiency (%DEE)

Accurately weighed drug resinates equivalent to 10 mg of drug was stirred with 100mL of PH 6.8 for 2hours.The solution was filtered and after suitable dilution drug content was determined spectrophotometrically at 304nm.

Percentage DEE = (Amount of drug actually present / theoretical drug load expected) × 100

Determination of coating polymer on microspheres

One gram of the microcapsules was accurately weighed and washed 3 times with 20mL dichloromethane to remove polymer coating. The remaining drug-resinate core were dried at room temperature for 12 hrs and weighed.

Percentage coating polymer =Microcapsules weight - Dried complex weight/Microcapsules weight × 100

***In-vitro* drug release study:**

In vitro drug release studies were carried out in Type: USP type I dissolution test apparatus. Microspheres equivalent to 80 mg of the drug were used for dissolution study. The dissolution test was carried out using 870 ml of dissolution medium at pH 1.2 for first 2 h and volume was made up to 900ml by adjusting the pH 6.8 for remaining 6h, a speed of 100 rpm and temperature 37 ± 0.5°C was employed. The amount of dissolved drug was determined using UV spectrophotometer method at 304 nm.

Stability studies:

The accelerated stability studies were carried out on the most satisfactory formulations. The formulations sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 °C / 65 ± 5 % RH and 40 ± 2 °C / 75 ± 5% RH for three months. At the end of studies, samples were analyzed for the drug content, *in-vitro* dissolution and other physicochemical parameters.

Results & Discussion:

Drug-resinates were prepared by batch method, it was stirred for 4 h continuously in which optimum drug loading was observed in 1:4 ratio because increase in the amount of resins increases the amount of drug complexed from the solution but decreases in the drug content/gram of resinates.

FTIR spectra of pure drug shows the peaks at 1587cm^{-1} due to C=O streching, 970 cm^{-1} due to aryl-F functional group, 3335cm^{-1} due to aryl-H , 3247 cm^{-1} due to C=C stretching, 3878 cm^{-1} due to O-H bending which are characteristic band for pure drug Fluvastatin Sodium. After complex with resins,

same pure drug considerable peak was observed from the drug resin complex(Fig1).

The X-Ray diffraction shows that crystalline characteristics with drug alone. After complexing with resins diffused peak was observed due to amorphous characteristic (Fig2).

DSC spectrum of pure drug, exhibited a sharp exothermic peak at 375.1°C, resinates 381.4 °C and resinates coated with Eudragit RS100 402.4°C & Ethyl cellulose 434.9 °C due to complexation, it deviates from pure drug Fluvastain Sodium (Fig 3). Since it can be revealed that there is no interaction between drug resinates and polymers.

Morphology of microcapsules observed from compound microscope and SEM as shown in the figure 5&6. In SEM, Number of micropores present on the surface.

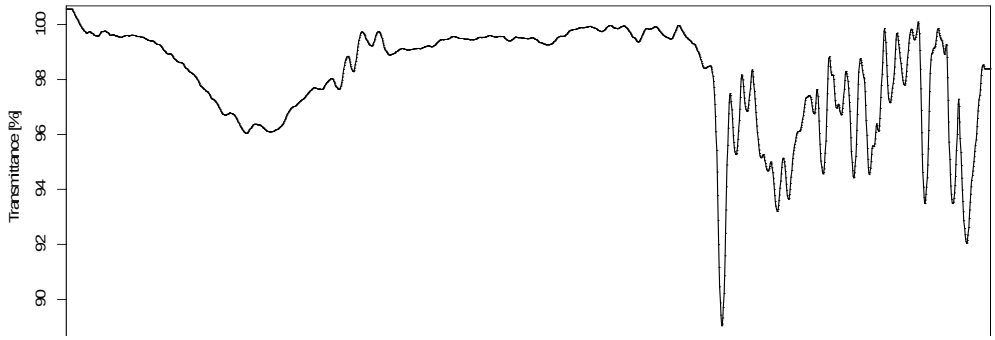
Various physicochemical properties like % Yield, % Drug entrapment, % Polymer coating and particle size were evaluated as shown in the table 1. Percentage yield for the formulations of F1 to F8 varied from 93.4±5.84 to 98.7±6.30 due to increase in polymers thickness. Percentage drug entrapment efficiency for the formulations of F1 to F8 varied from 96±0.8% to 98.7±0.1%. *In-vitro* drug dissolution was carried out for all the formulations as shown in the figure 8 & 9.

The drug release in acidic medium (pH1.2) is low due to drug is weak acid and its pKa value is 5.5, but when drug resinates comes in contact with alkali medium (pH 6.8), drug release rate is faster because of due to phosphate ions. The drug release rate from the Eudragit RS100 and Ethyl cellulose coated microcapsules was slower than that from the uncoated resinates.

The drug release from microcapsules data were fitted into drug release kinetic models such as zero order, first order, higuchi and korsmeyers-peppa's equation. The exchange of drug from the uncoated resinate was found to follow the particle diffusion process accordance with the equation proposed by Reichenberg in 1953. However coated resinates was deviated from particle diffusion mechanism. The release of drug across the thin layer around the particle (membrane diffusion control) was predominant mechanism involved in this drug release system. Hence data was fitted into korsmeyer-peppa's equation $Mt/M_a = Kt^n$, where K is a constant; n is the release exponent, indicates the drug mechanism and Mt/M_a fraction of drug released at time t. The values of n varied from 0.07 to 0.31. This indicates that fickian type of mechanism. The release data from the Higuchi equation yielded comparable linearity. Eudragit RS100 and Ethyl cellulose coated microcapsules obeyed diffusion controlled process as shown in the table3.

Based on drug release kinetics data microcapsules of F4 and F5 formulations provide a convenient dosage form for achieved controlled release, percentage yield, percentage DEE and obeyed diffusion controlled process.

There was negligible change in % DEE and *in-vitro drug* release was observed after stability studies.



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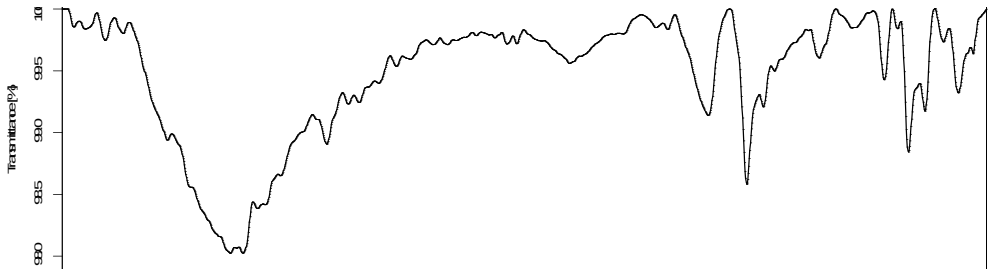

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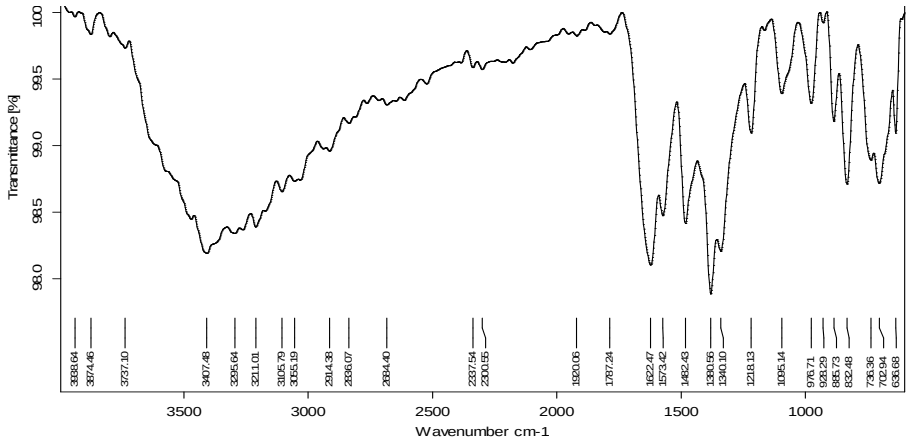
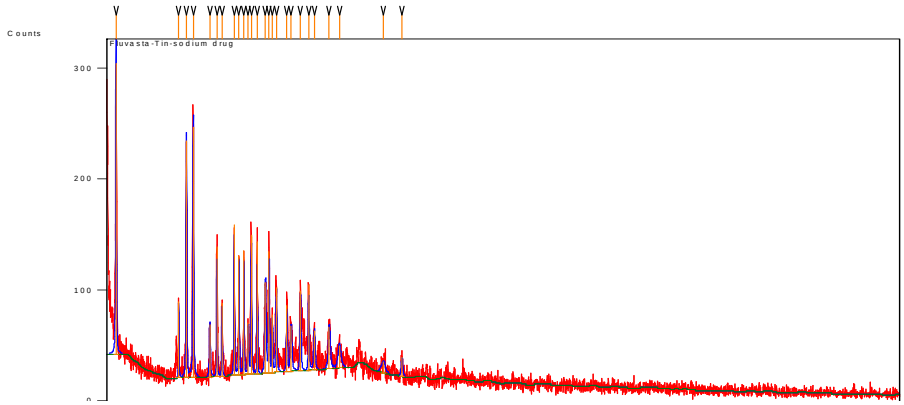


(c)

Figure 1: FTIR Spectra of a) Fluvastatin drug b) Indion 454 resin and c) Drug resonates



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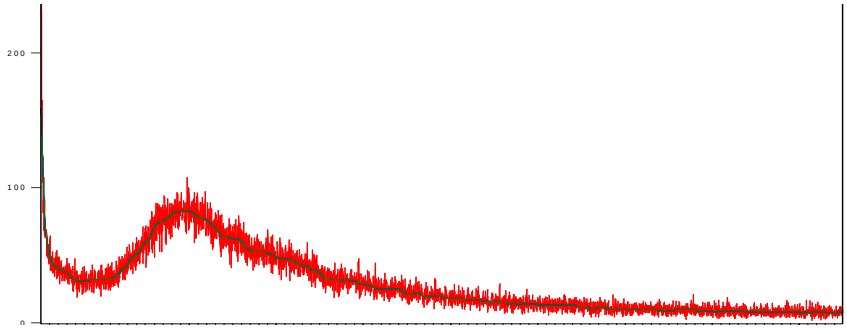

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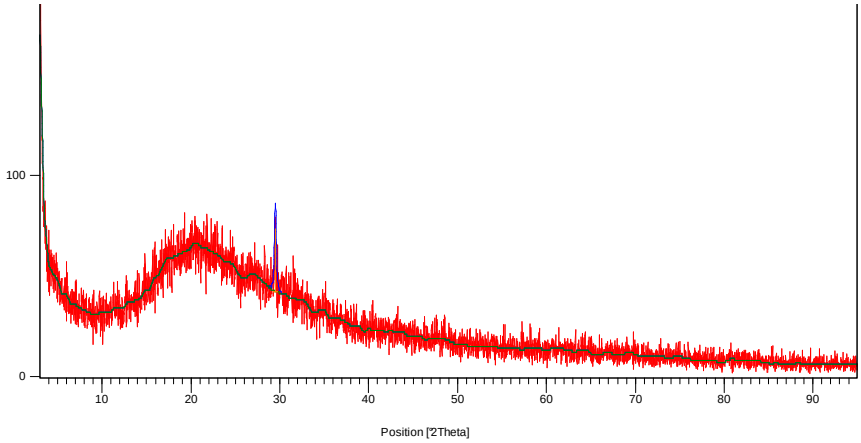
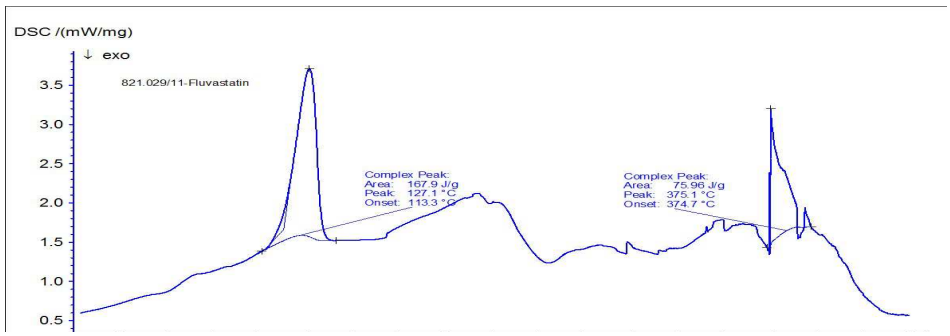


(c)

Figure 2 : X-Ray diffraction spectra of a) Fluvastatin Sodium b) Indion 454 resin c) Drug- resinates



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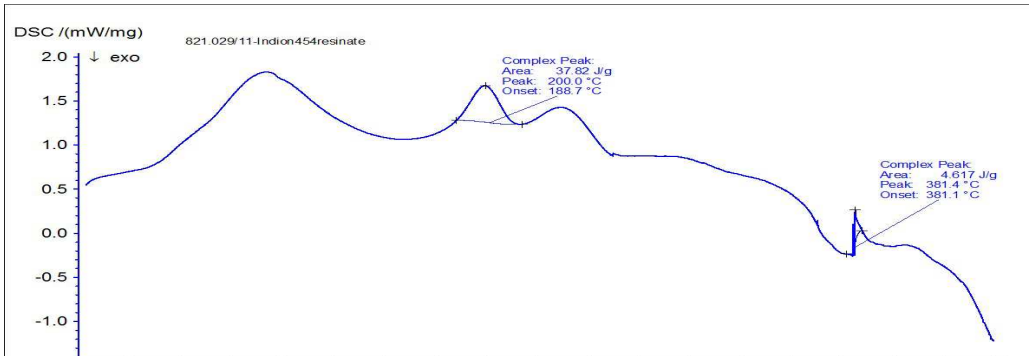

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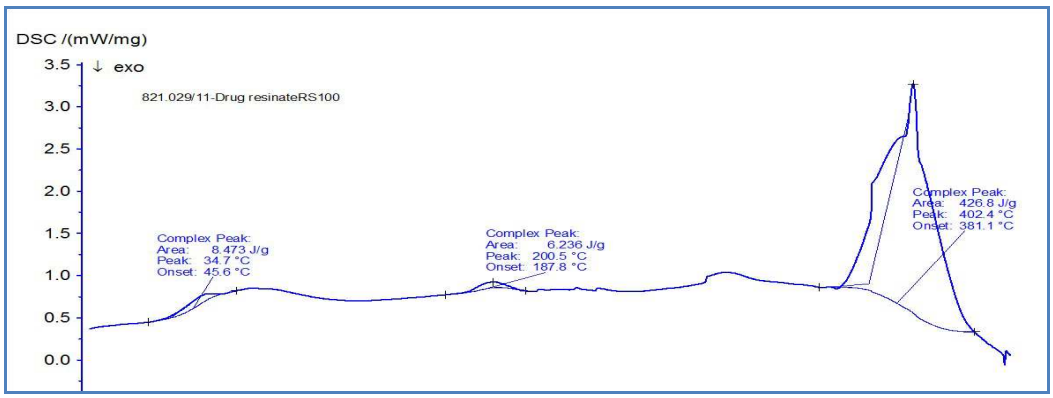

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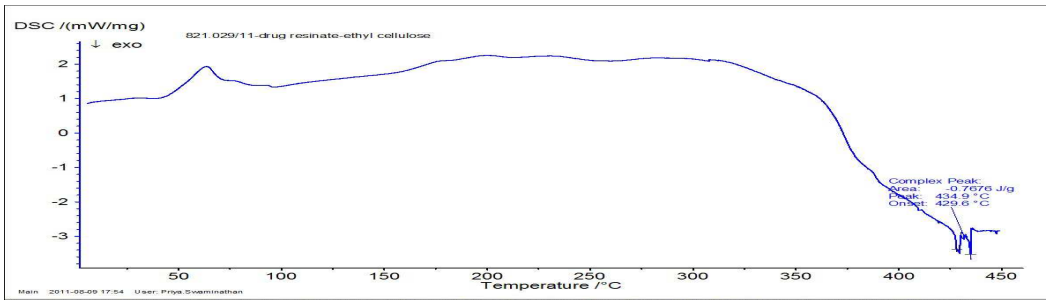
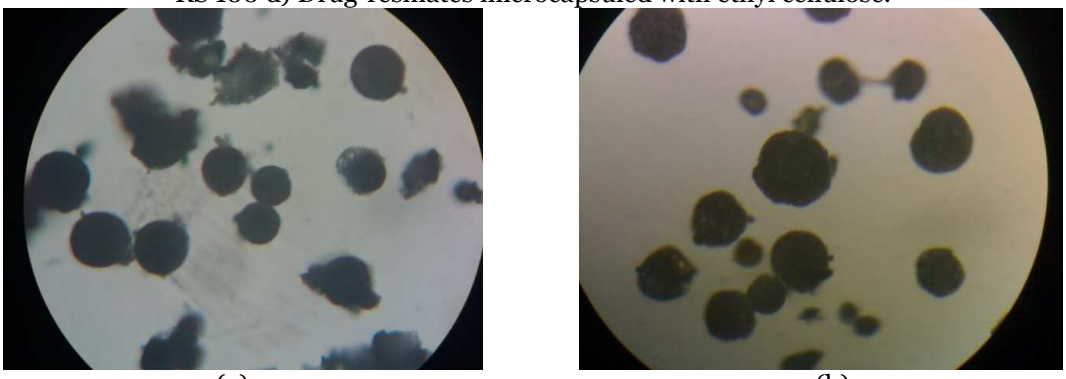


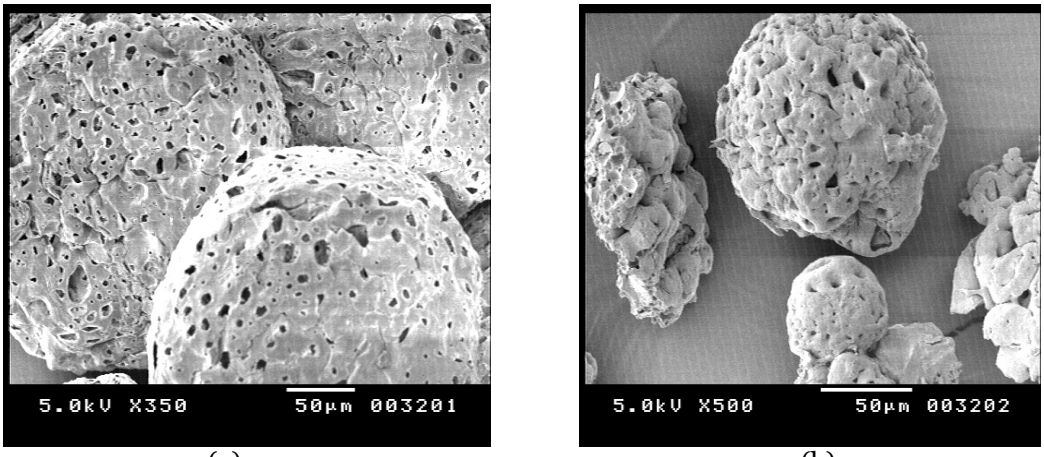
(d)

Figure 4: DSC Spectra a) Fluvastatin Sodium drug b) Drug-resinates c) Drug-resinates microcapsuled with E-RS 100 d) Drug-resinates microcapsuled with ethyl cellulose.



(a) (b)

Figure 5: Microscopic examination a) Ethyl cellulose coated b) Eudragit RS100 coated microspheres.



(a) (b)

Figure 6: Surface electron microscopy (SEM) of a) Ethyl cellulose coated b) EudragitRS100 coated microspheres.

Table 2: Physicochemical parameters of developed formulations

Batch	Drug-resinates to polymer ratio (%w/w)	Nature	Percentage Yield*	Percentage DEE*	Percentage Coating of Polymer*	Particle size (µm)
F1	5	Free flowing	97.6±3.25	98.7±0.1	98.2 ± 5.6	45-120
F2	10	Free flowing	98.7±6.30	98.6±0.3	98.1 ± 7.8	54-164
F3	15	Free flowing	95.6± 7.5	96.9±0.8	97.4 ± 8.9	77-176
F4	20	Cohesive	96.9± 6.75	98.7±0.5	96.9 ± 7.6	85-201
F5	5	Free flowing	97.8± 8.9	98.5±0.1	98.7 ± 8.8	43-105
F6	10	Free flowing	93.4±5.84	97.7±1.2	98.6 ± 9.7	59-140
F7	15	Free flowing	95.9±3.89	97.1±0.6	98.5 ± 9.6	71-170
F8	20	Cohesive, lumpy	94.8±3.71	96.0±0.8	97.9 ± 7.1	86-230

*All readings are mean of three ± SD

Table 3: Effect of formulation factors on Fluvastatin Sodium release kinetics data from microcapsules

Batch	Zero order r^2	First order r^2	Higuchi equation r^2	Higuchi equation K_H	Korsmeyer-peppa's equation r^2	Korsmeyer-peppa's equation n
F1	0.6292	0.736	0.737	55.0	0.592	0.07
F2	0.973	0.931	0.931	53.5	0.974	0.09
F3	0.453	0.950	0.950	52.1	0.988	0.10
F4	0.391	0.968	0.969	48.7	0.914	0.10
F5	0.8297	0.921	0.922	81.4	0.7202	0.26
F6	0.7845	0.888	0.888	75.7	0.669	0.27
F7	0.8509	0.893	0.894	74.0	0.682	0.29
F8	0.779	0.889	0.893	71.2	0.691	0.31

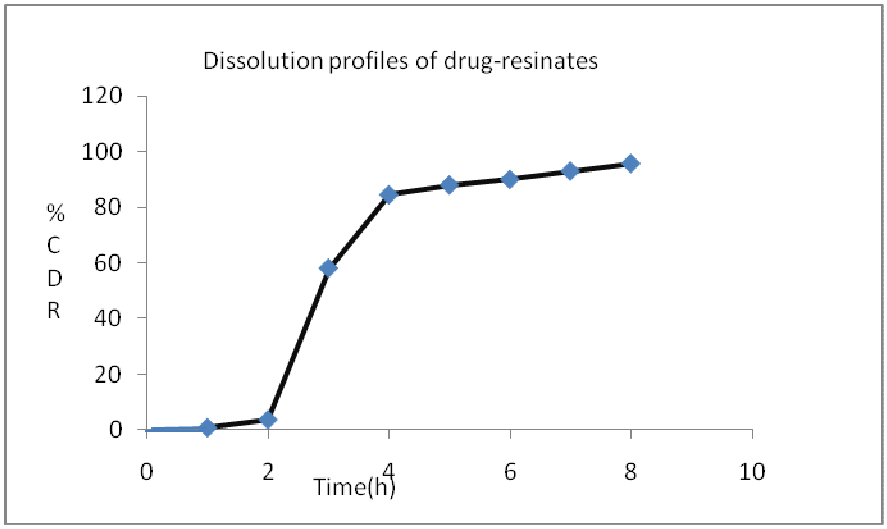


Figure 7: Dissolution profiles of drug-resinates

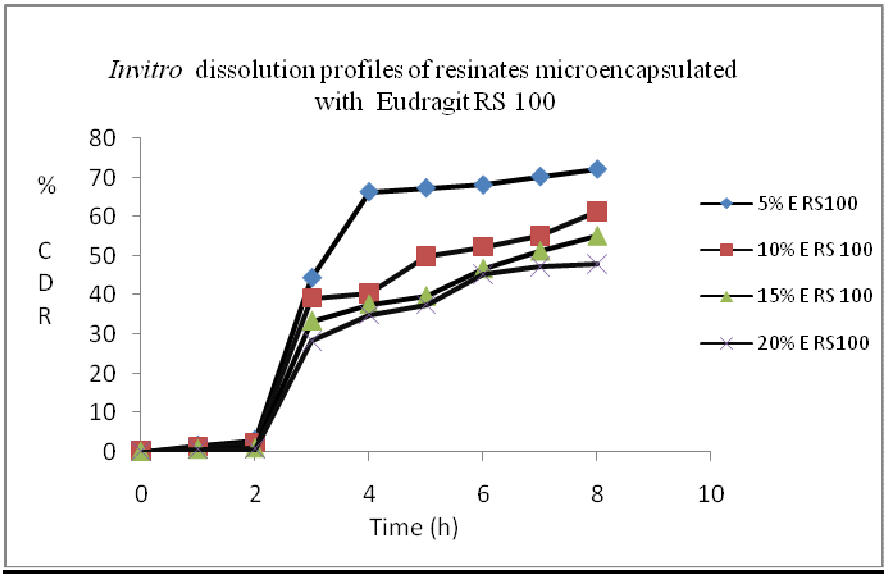


Figure 8: *In vitro* drug release of resinates microencapsulated with Eudragit RS 100

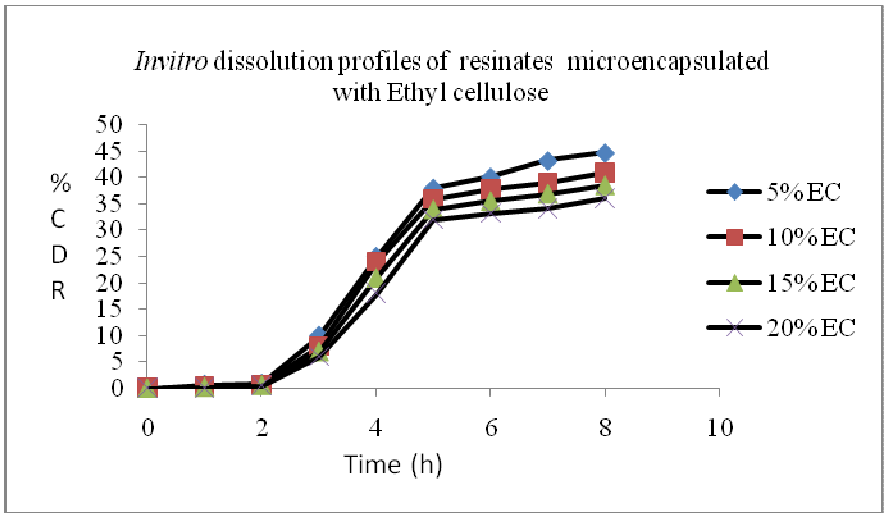


Figure 9: *Invitro* drug release of resinates microencapsulated with Ethyl cellulose

Conclusion: Thus drug-resinates coated with Ethyl cellulose and EudragitRS100 has proved to be efficient carrier for diffusion controlled release microspheres of Fluvastatin sodium.

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