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Phamacokinetic Evaluation of Microcapsules Containing Fluvastatin Sodium Using Rats

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ABSTRACT

Microcapsules containing Fluvastatin Sodium having better drug retaining property. Most suitable for controlled release. Most satisfactory Fluvastatin Sodium microcapsules were subjected to pharmacokinetic evaluation with an objective to evaluate their drug release retarding and rate controlling efficiency *in vivo*. The rats were used for the in *vivo* bioavailability study. Ion exchange resins coated microcapsules of Fluvastatin Sodium was prepared by w/o/w emulsification technique. Fluvastatin Sodium release from Indion454 resins coated with eudragit RS100 microcapsules was slow and spread over 24 h. In the *in vivo* study, the absorption of fluvastatin sodium was slow over longer period of time with a rate constant (K_a) of 1.605 h^{-1}. The mean residence time was observed from 6.5 h. C_{max} was found to be 2.24µg/ml, t_{max} was found to be 6h, AUC was found to be 2.24µg/ml. From pharmacokinetic evaluation, Fluvastatin Sodium from resins coated microcapsules was released and absorbed slowly over longer period of time.

Keywords: Fluvastatin Sodium, Microcapsules, Pharmacokinetics, controlled release.

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INTRODUCTION

Now a day's obesity is more health concern in world wide. Obesity is a national epidemic[1]. Fluvastatin Sodium, a 3-hydroxy-3 methyl glutaryl co-enzyme (HMG COA) reductase inhibitor. It is a cholesterol lowering agents. It has shorter half life. It under goes first pass metabolism in the liver[3].

Ion exchange resins have been used widely in pharmaceutical industry as drug carrier in drug delivery systems. The cholestyramine resin is an insoluble strongly basic anion exchange resin in the chloride form supplied as dry fine powder. Cholestyramine resins (Indion454) as a drug carrier for anionic drug Fluvastatin Sodium. It complexes with the drug. Ion exchange resins alone without any barrier cannot achieve satisfactory controlled release. Thus resin complexes were coated with Eudragit RS100 for achieving controlled release in the small intestine [2,4]. Microencapsulation is an effective method to wrap liquid or solid materials are surrounded by coating with polymeric membrane. The purpose of the study is to formulate microcapsules by complexing Fluvastatin Sodium drug with anionic exchange resins and further coated with Eudragit RS100 polymer for achieving controlled release in the small intestine.

MATERIALS AND METHOD

Materials used:

Fluvastatin Sodium drug collected gift sample from Biocon Pvt Ltd, Bangalore. Indion454 ion exchange resins collected from Ion exchange resins India Pvt Ltd, Mumbai. Eudragit RS100 collected from Micro labs Pvt Ltd, Bangalore.

Preparation of Microcapsules*:*

Drug resinates were prepared by batch method. In 1:4 ratio maximum drug loading was observed. Dried drug resinates were coated with eudragit RS100 with different ratios. Microencapsulation was carried out by w/o/w double emulsion solvent evaporation technique. Drug resin complex 1.0 gram was poured in 20 ml of methylene chloride containing polymers. 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 solution to form w/o/w double emulsion. Continuously stirred at room temperature until methylene chloride gets evaporated to form solid microcapsules and evaluated [11].

Preparation of calibration curve by HPLC:

Accurately weighed 100mg of Fluvastatin sodium and transferred to 100ml volumetric flask and made up the volume up to 100 ml with methanol. From this solution 1ml was taken placed in 10

ml volumetric flask and the volume was made up to 10ml. The final concentration obtained is 100µg/ml. This was used as stock for calibration curve. A calibration curve was prepared by transferring 0.2, 0.4, 0.6, 0.8, 1, 1.2 ml aliquots into10 ml volumetric flask and the volume was made up to the mark. Final concentrations obtained for Fluvastatin Sodium were 2, 4, 6, 8, 10 and 12 µg/ml in methanol to get the linearity.

Pharmacokinetic study design and protocol [9, 10]:

In vivo study design and protocol was approved by institutional ethical committee. Ten healthy rats of either sex, weighing 200-220 g were used for the study, (n=3). A crossover experimental design with a wash out period of 1 month was followed for testing the formulation. Rats were kept for overnight fasting. No food or liquid other than water permitted until 24 h following the administration of the product. First Microcapsules were suspended in 0.1% Carboxy methyl cellulose solution. Sonicated for 5 minutes for uniform dispersion. Rat dose was calculated based on the weight of the rats.

Blood samples were collected from retro-orbital Plexus vein from rat eye. After collecting the 'zero' hour blood sample (blank), 1 ml sample was administered orally by using syringe. Two ml of blood samples were collected at 0.5, 1, 2, 4, 6, 8, 12 and 24 h after administration. The blood samples were centrifuged at 6000 rpm and serum separated was collected into dry test tubes and all the samples were stored under defreeze maintained temperature -40°C.

Fluvastatin sodium drug from serum concentrations were determined by a known HPLC method as follows: Methanol 1 ml were added to 0.5 ml of serum and agitated for cyclomix for 2 to 3 minutes. Followed by using cooling centrifuge at 4ºC maintained 5000 rpm speed for 10 minutes. In this supernatant was removed and placed in ependroff tube.

Then the supernatant was diluted with mobile phase Acetonitrile: 1 octane sulphonic acid at pH 2.5:: 60:40, Flow rate 1ml/min, injection volume 20µLof solution was injected in to HPLC column (column dimension ID: 250×4.6 mm, particle size: 5µm, High pressure gradient, Detector : UV Wavelength:230nm).

From the time v/s serum drug concentration data various pharmacokinetic parameters such as peak plasma concentration (C_{max}), time at which peak occurred (t_{max}), area under the curve (AUC), elimination rate constant (K_{el}), biological half life ($t_{1/2}$), absorption rate constant(ka) and volume of distribution(Vd) were calculated as per known calculation methods. Highest concentration of drug in plasma attained by the administrated dose is C_{max}. Time taken to reach maximum concentration of drug in plasma is t_{max}. Area under the curve was calculated by using

trapezoidal rule. Vd was calculated by using formula: Administrated dose/Initial plasma drug concentration. Biological half life was calculated by using formula $0.693/K_e$.

Absorption rate constant was calculated by using method of residuals. Clearance (Cl) was calculated by using formula: Administered dose/ AUC. Mean residence time was calculated based on 63.2% of drug eliminated from the body.

RESULTS AND DISCUSSION:

From HPLC method standard calibration data was prepared (table1) and linearity was constructed as shown in the (figure 1). Standard chromatogram of Fluvastatin Sodium pure drug as shown in the (figure 2). Highest sharp peak at 4.315 in the chromatogram was observed. Resin coated microcapsules of Fluvastatin Sodium prepared by w/o/w double emulsion solvent evaporation technique.

Table1: Calibration of standard data of Fuvastatin Sodium by HPLC

Sl no	Drug Conc.(µg/ml)	Peak Area
1	2	34254.949
2	4	66189.299
3	6	97164.935
4	8	129429.632
5	10	161460.015
6	12	190450.781

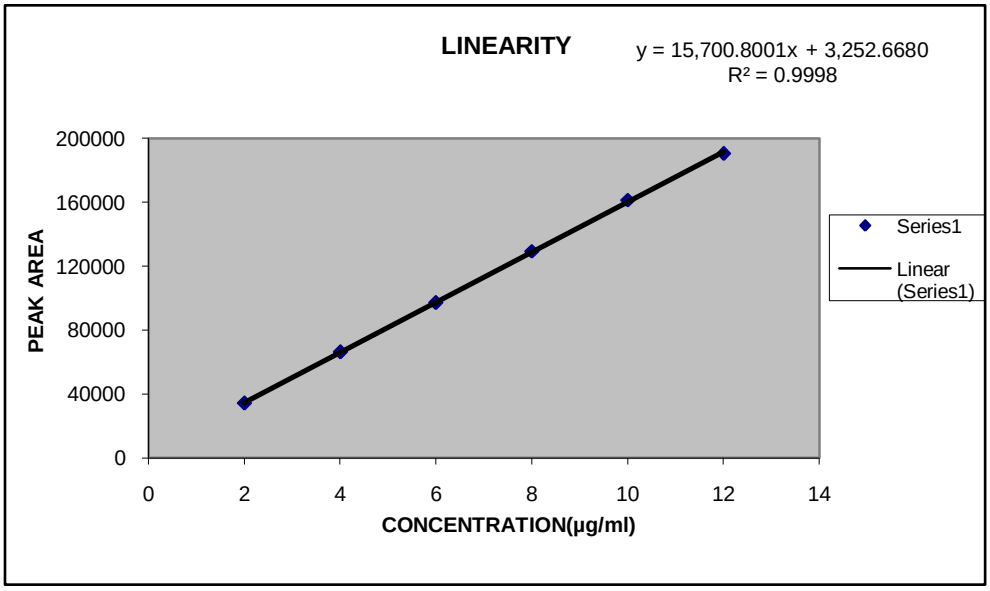

Figure1: Standard Linearity Curve by HPLC

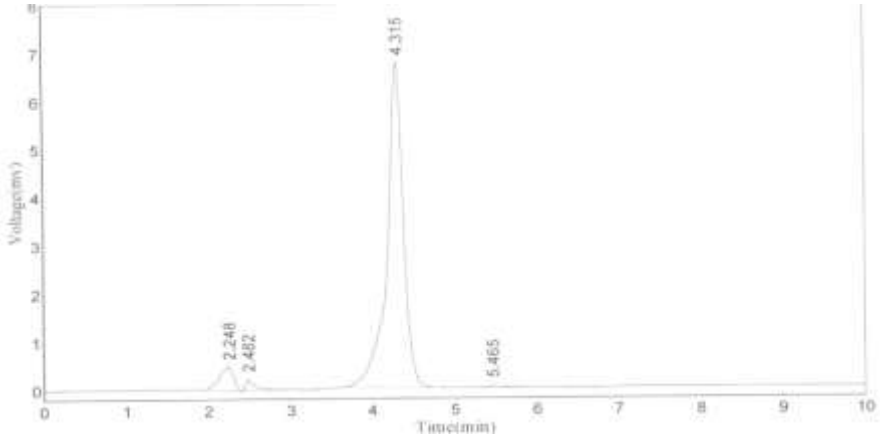

Figure2: Standard chromatogram for Fluvastatin Sodium by HPLC

Table2: System evaluation parameters from chromatogram

Peak no	Retention time	H eight	Area	Concentration
1	2.248	468. 373	5899.350	5.8246
2	2.482	213.674	1600.000	1.5797
3	4.315	6732.044	93315.102	92.132
4	5.465	30.629	469.200	0.4633

Table3: Integrated System parameters

Peak no	Half peak width	Resolution	Tail factor	Asymmetry
1	0.202	0.000	0.756	0.503
2	0.110	0.749	2.471	3.469
3	0.182	6.286	0.779	0.578
4	0.203	2.987	1.801	2.579

Table 4: Plasma concentration of Fluvastatin Sodium microcapsules following the oral administration in Rats.

Time(h)	Average plasma drug concentration(µg/ml)
0	0
0.5	0.022±0.0005
1	0.0607±0.0001
2	0.081±0.001
4	0.143±0.0015
6	0.2±0.02
8	0.095±0.0011
12	0.067±0.0005
24	0.012±0.001

Fluvastatin Sodium drug peak at 4.003 was observed in rat plasma as shown in the (figure4). Time v/s Average plasma drug concentration profiles of Fluvastatin Sodium microcapsules AUC were plotted as shown in the (figure3). From AUC pharmacokinetic parameters was calculated as shown in the (table 5).

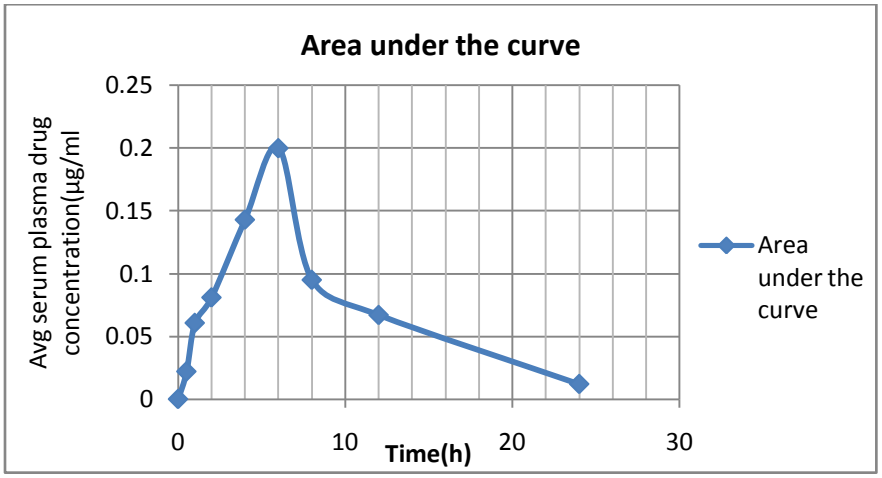

Figure 3. Time v/s Plasma drug concentration area under the curve

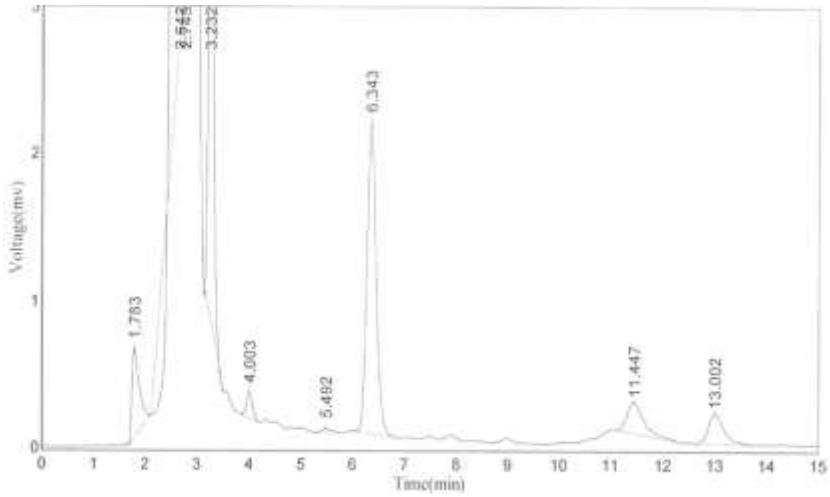

Figure4: Determination of Fluvastatin Sodium in rat Plasma by HPLC

From Area under the curve we can calculate the extent of drug absorption after 24 hours. C_{max} was found to be 0.2µg/ml, t_{max} was found to be 6 hours. The elimination rate constant K_{el} for Fluvastatin microcapsules was found to be 0.143 h and the corresponding biological half life was found to be 4.8 h. The half life value of pure Fluvastain Sodium drug was 1.2 h. The mean residence time was found to be 6.5 h. The absorption rate constant Ka was found to be 1.605 h^{-1}.

Parameters for HPLC method development was given below

- Mobile phase: Acetonitrile:1octane sulphonic acid at pH 2.5 (60:40)
- Detector : UV detector, nm: 230
- Flow rate: 1mL/minute
- Injection volume; 20µL
- Diluent: Acetonitrile
- Column dimension: 250x4.6 mm, 5µ

Table 5: Pharmacokinetic parameters

C_{max}	t_{max}	AUC	Elimination rate constant	Biological half life	Vd	Ka	MRT	Cl
0.2µg/ml	6 hrs	2.24µg/ml	0.143 hr	4.8 h	14.5 L	1.60 h^{-1}	6.5 h	0.142

Table6: System evaluation parameters from chromatogram

Peak no	Retention time	Height	Area	Concentration
1	1.783	604.633	5862.400	1.4856
2	2.642	23099.277	181644.031	46.0311
3	2.743	20581.758	147467.188	37.3702
4	3.232	3179.597	22921.201	5.8085
5	4.003	170.289	1388.750	0.3519
6	5.492	28.420	370.200	0.0938
7	6.343	2119.382	25915.451	6.5673
8	11.447	209.648	4828.800	1.2237
9	13.002	203.103	4213.500	1.0678

Table7: Integrated evaluation parameters

Peak no	Half peak width	Resolution	Theoretical levels	Tail factor	Asymmetry
1	0.145	0.000	844.266	2.120	3.065
2	0.128	3.140	2359.112	0.654	0.488
3	0.117	0.408	3074.167	2.714	4.000
4	0.117	2.071	4250.745	1.373	1.681
5	0.128	3.197	5422.529	1.080	1.167
6	0.185	7.447	6523.576	1.243	1.396
7	0.185	7.447	6523.576	1.243	1.396
8	0.318	10.149	7175.664	1.639	1.942
9	0.310	2.480	9765.056	1.407	1.679

CONCLUSION:

Fluvastatin Sodium microcapsules was released the drug prolonged period of time. The mean residence time was found to be 6.5 h, indicates that more residence time was observed. From pharmacokinetic evaluation, thus, indicated that Fluvastatin Sodium microcapsules was released and absorbed slowly over a prolonged period of time.

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