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FORMULATION AND *IN VITRO* EVALUATION OF NELFINAVIR MESYLATE MICROCAPSULES USING HYDROXY PROPYL METHYL CELLULOSE

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ABSTRACT

Nelfinavir Mesylate is a protease inhibitor used in the treatment of human immunodeficiency virus infection. Microcapsules of Nelfinavir Mesylate were developed as sustained release dosage form and release kinetics were studied. The desired microencapsulation was achieved by solvent evaporation method using Hydroxy Propyl Methyl Cellulose in different drug: polymer ratios of 1:1,1:2,1:3,1:4 and 1:5.Characterization of five formulations FH-1, FH -2, FH-3, FH-4, FH-5 was performed by size, shape, entrapment efficiency, infrared spectroscopy and *in vitro* drug release analysis. The prepared microcapsules were free flowing, spherical in shape, with particle size in the range 85-100µm. FH-5 had maximum entrapment efficiency of 94.13%. The *in vitro* release profile of FH-5 was found to give 72.13% release of the drug which was more than the release of drug in FH-1, FH-2, FH-3 and FH-4. Release kinetics showed it followed zero-order kinetics and the correlation coefficient in Higuchi model indicated diffusion controlled mechanism.

KEYWORDS: Nelfinavir Mesylate, HPMC, Microcapsules, Release kinetics.

INTRODUCTION

Sustained release dosage forms have many advantages in comparison to conventional dosage forms. They maintain blood levels of the drug for long duration of time, minimize

undesirable side effects and reduce the dosing frequency.[1] Nelfinavir Mesylate is a protease inhibitor used in the treatment of human immunodeficiency virus (HIV) infection. Nelfinavir Mesylate is available as a conventional dosage form and the dosing frequency is three times a day.[2] Nelfinavir Mesylate was microencapsulated using Hydroxy Propyl Methyl Cellulose as polymer by solvent evaporation method to give a sustained release dosage form with increased bioavailability and to reduce dosing frequency with minimal side effects.[3]

MATERIAL AND METHODS

Nelfinavir Mesylate was obtained as a gift sample from Macleods Pharma, Daman, India and Hydroxy Propyl Methyl Cellulose from Loba Chemicals, Mumbai, India. All other chemicals were of analytical reagent grade.

Nelfinavir Mesylate microcapsules were prepared by solvent evaporation method. Formulations of FH-1, FH-2, FH-3, FH-4, FH-5 were prepared in the drug:polymer ratio of 1:1,1:2,1:3,1:4 and 1:5. Non-aqueous solvent evaporation method was employed for the preparation of microcapsules. Polymers of each category was dissolved in 25ml of dichloromethane and stirred until a homogenous solution was formed.[4] Core material, Nelfinavir Mesylate was added to the polymeric solution and mixed thoroughly.[5] The resulting mixture was then added in a thin stream to 100ml of light liquid paraffin contained in a 450ml beaker while stirring at 2000 rpm.The solution was stirred for 4 hours to allow the solvent to evaporate completely and the microcapsules were collected by filtration. The microcapsules were washed repeatedly with petroleum ether (40^{o}-60^{o}C) until free from oil. The collected microcapsules were dried at room temperature overnight and subsequently stored in desiccators over fused silica gel. Different proportions of core: coat ratio, (1:1, 1:2, 1:3, 1:4 1:5) from each polymer were prepared by the same methodology.[6][7]

The particle size of developed formulations was determined by microscopy method using calibrated eye piece micrometer. The particles were arranged on the basis of size ranges. The number of particles in each size range were then converted and tabulated. The percent number of particles in each interval and percent undersize were calculated. Histogram and cumulative undersize curve were plotted.[8]

Scanning electron microscopy was performed on the developed microcapsules to assess their surface and morphological characteristics using SEM (Philips/FEI XL30 ESEM). For drug entrapment efficiency 25mg of the microencapsulated product was crushed into powder and

25ml water was added. The resulting mixture was kept for 24 hours and the solution was filtered. The drug entrapped was determined by measuring the absorbance at 254.6 nm after appropriate dilution with water.[9] Infrared spectra of the pure drug and the formulations were obtained by potassium bromide pellet method using Shimadzu FTIR-8400S spectrophotometer in order to rule out drug-carrier interactions.[10]

Standard calibration curve was determined in pH 1.2 and phosphate buffer pH 6.8. *In vitro* release studies of the formulated microcapsules was studied in USP XXIII type-2 dissolution apparatus (Electrolab Dissolution Tester TDT-08L) employing a paddle stirrer at 50 rpm using 900ml of 0.1 N HCl pH 1.2 for 2 hours and phosphate buffer pH 6.8 for 6 hours at 37 ± 0.5°c as dissolution medium.[11] 100mg of microcapsules from each formulation was used in each test. Aliquots of dissolution medium were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 250nm.The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.[12] Cumulative percent of drug released was calculated and plotted against time. The release kinetics of Nelfinavir Mesylate from various formulations was determined by comparing respective correlation coefficients of zero-order,first-order and Higuchi model.[13]

RESULTS AND DISCUSSION

The percentage yield of the microcapsules for FH-1, FH-2, FH-3, FH-4 and FH-5 was 70.10%, 87.53%, 75.09%, 93.64% and 93.92% respectively. The particle size of the formulation was in the range of 80-100µm. Scanning electron microscopy (SEM) studies revealed that the microcapsules are almost spherical in shape as shown in Fig1.The drug entrapment efficiency of microcapsules in formulations FH-1, FH-2, FH-3, FH-4 and FH-5 was 38.22%, 43.50%, 55.18%, 73.56% and 94.03% respectively. The maximum drug entrapment was seen in formulation FH-5.

The IR spectrum of the formulations showed all the characteristic peaks of pure drug Nelfinavir Mesylate thus confirming that no interaction of drug occurred with the polymer. *In vitro* drug release studies of the microcapsules at the end of 8 hours showed release profiles which are graphically presented. Release of Nelfinavir Mesylate from the polymeric microcapsules was slow and spread over a longer period of time.[14][15] The release profiles of microcapsules in phosphate buffer pH 6.8 was better than the release profiles in pH 1.2.The percentage cumulative release profile of formulation FH-5 was 81.68% which gave

maximum release compared to other formulations .So FH-5 was taken as the best formulation. The release kinetics of microcapsules from FH-5 was determined by comparing their correlation coefficients.[16][17][18] It followed zero-order kinetics and it was diffusion controlled as in Table 2.

Table 1: Ingredients used for the formulation of Nelfinavir Mesylate microcapsules

Ingredients	FH-1	FH-2	FH-3	FH-4	FH-5
Nelfinavir Mesylate (mg)	1000	1000	1000	1000	1000
HPMC (mg)	1000	500	333.33	250	200
Dichloromethane (ml)	25	25	25	25	25
Liquid paraffin (ml)	100	100	100	100	100
Speed (r.p.m)	2000	2000	2000	2000	2000

Table 2: Coefficient coefficient (R^2) of different kinetic models for Nelfinavir mesylate microcapsules

Microcapsules	Zero order R^2	First order R^2	Higuchi equation R^2
FH-5	0.9986	0.9672	0.9723

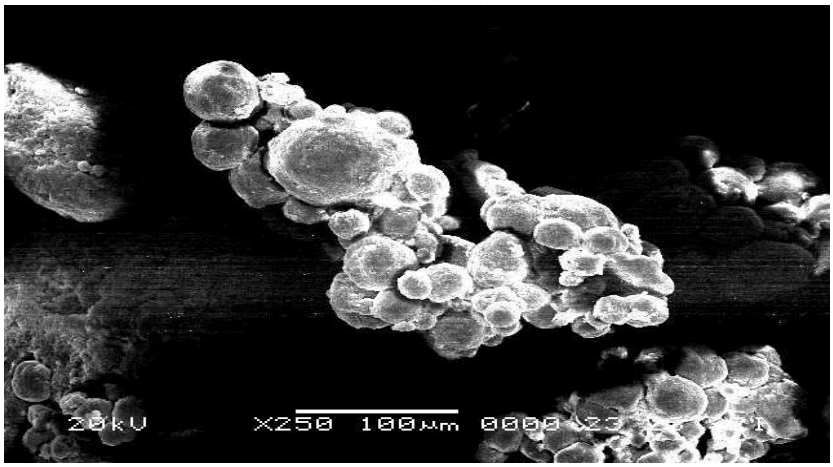

Photo-1 S.E.M Analysis of FH -5 (250x, 100µm)

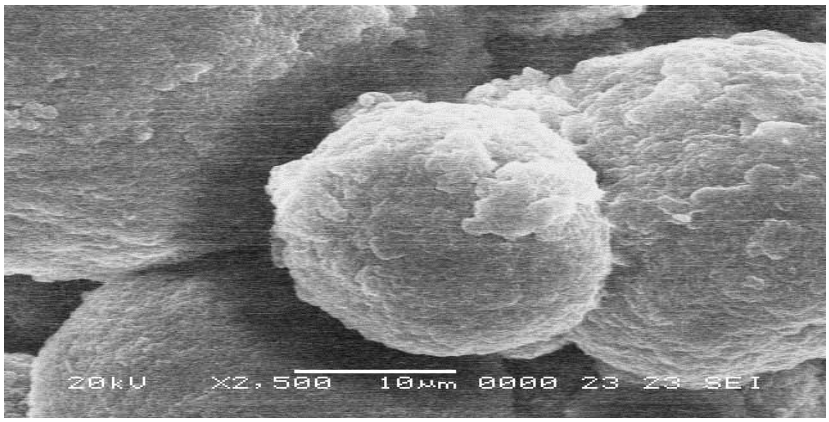

Photo 2- S.E.M Analysis of FH -5 (2500x, 10µm)

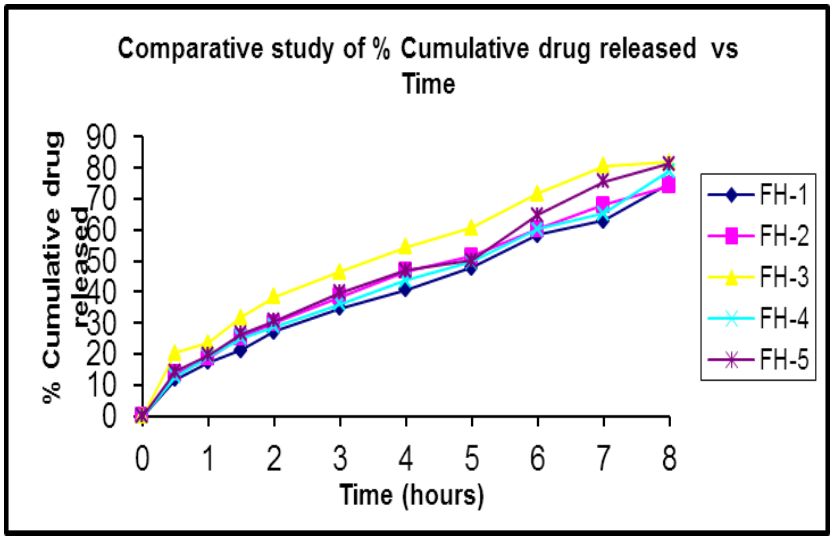

Figure 1 Comparative study of percentage drug released vs Time

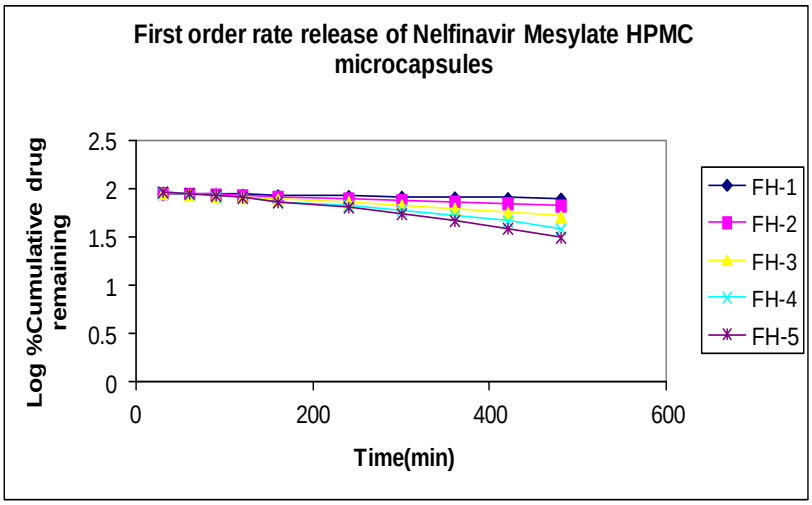

Figure 2 First order rate release of Microcapsule

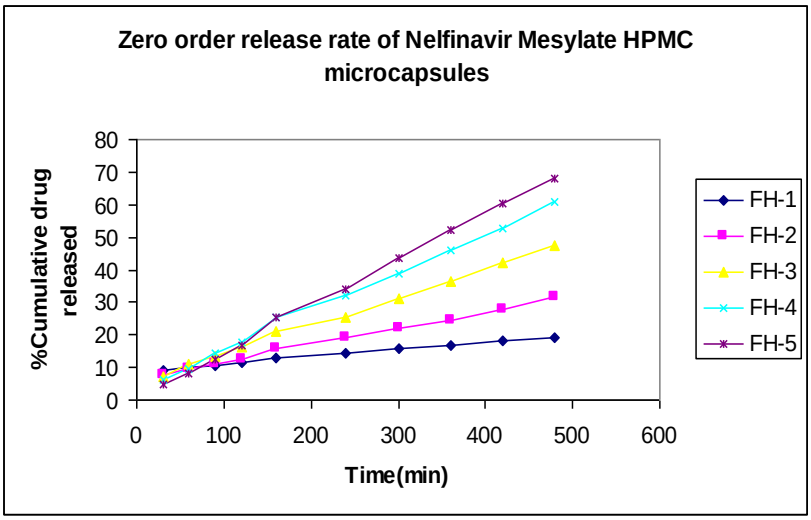

Figure 3 Zero order rate release of Microcapsule

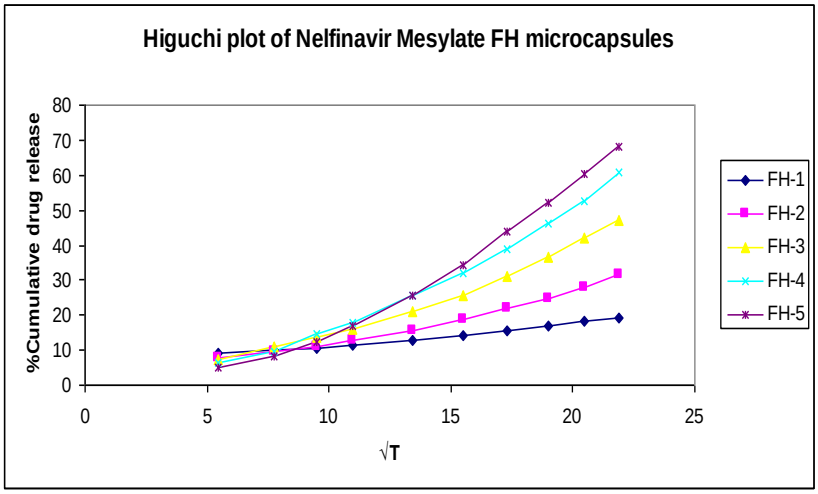

Figure 4 Higuchi plot of Microcapsule

CONCLUSION

It can be concluded that the solvent evaporation technique is a simple and reproducible method for the preparation of Nelfinavir Mesylate microcapsules. The prepared microcapsules of FH-5 were spherical with high entrapment efficiency and *in vitro* release using HPMC as the retardant material. *In vivo* studies have to be done to confirm enhanced bioavailability and reduced dosing frequency with lesser side effects.

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