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PREPARATION AND EVALUATION OF LOPINAVIR HOLLOW MICROBALLOONS BY NON-AQUEOUS SOLVENT EVAPORATION METHOD

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ABSTRACT

The aim of present study is an attempt to preparation and evaluation of floating hollow microballoons of Lopinavir by using Eudragit S-100 polymer for treating HIV & AIDS related conditions. There are five different formulations (FN1-FN5) are prepared by the Non-aqueous solvent evaporation method. Changing the polymer concentration ratio will significantly affect the *in vitro* drug release. The formulated hollow microballoons were evaluated for percentage yield, scanning electron microscopy (SEM), particle size, *in vitro* release and *in vitro* buoyancy. Among five formulations FN-3 was obtained as ideal formulation. The FTIR studies are indicates that there is no interaction between the drug and polymer. SEM is showing the surface pores and interior of the hollow microballoons. The short term stability studies on the formulations are indicates that there are no physical or chemical changes in the formulations during the study period time. According to the data obtained from Lopinavir hollow microballoons *in vitro* release showing sustained release over a period of 12 hrs. Thus reduce dose frequency, improve bioavailability which gives better patient compliance.

KEYWORDS: Eudragit S-100, Hollow Microballoons, Lopinavir, Non-aqueous solvent evaporation method.

INTRODUCTION

Any drug delivery system important goal is to achieve preferred concentration of the drug in the tissue or blood which is having great bioavailability, non-toxic and therapeutically

effective for a prolonged period of time.[1] The drugs having short half-life are quickly eliminated from the blood circulation and side effects hence need frequent dose administration and it reduces the patient compliance.

Oral sustained release (SR) formulations came into existence to overcome these problems. SR formulations are the attempt to maintain a constant plasma level of drug by prolongs drug release from the formulation and reduce side effects. A significant problem for these systems is the Gastric Retention Time (GRT). Hence, prolongation of GRT is very important for drugs which are having short half-life and poor bioavailability.

GRT can be prolonged by formulating gastroretentive drug delivery system dosage forms. This includes: (a) Mucoadhesive delivery systems, in which formulation adheres to the mucosal surface of GIT, (b) Swellable delivery systems, which swells after administration and prevents it pass through pylorus, (c) Floating or low density systems, in which formulation float over the gastric fluid (d) High density system, in which formulation sink they have density greater than that of gastric fluids.[2] Davis was first who described the gastroretentive floating system in 1968, they are low density systems having sufficient buoyancy to float over the gastric contents and it remain in the stomach for a prolonged period of time. Whereas the system floats over the gastric content the drug is released prolonged manner.[3]

The Lopinavir is an effective protease inhibitor used for the treatment of Human Immunodeficiency Virus (HIV) infection. This is effective component for the treatment of chemotherapy generally mentioned as Highly Active Antiretroviral Therapy (HAART). When administered orally the Lopinavir will shows poor bioavailability because of its poor drug solubility followed by it hepatic first pass metabolism.[4] The Lopinavir is suitable for gastro retentive floating dosage form, it is absorbed mainly in the stomach their by avoiding the first pass metabolism, improve drug bioavailability and achieve prolonged drug release.

MATERIALS AND METHODS

Lopinavir was obtained as gift sample Hetero drugs ltd, Hyderabad and Eudragit S-100 were purchased from Shreeji chemical, Mumbai. All other chemicals used were of analytical grade.

PREPARATION OF HOLLOW MICROBALLOONS[5]

Hollow microballoons containing antiretroviral drug Lopinavir were prepared by a Non-aqueous solvent evaporation method. The drug and different ratio of polymer Eudragit S-100 are used. Drug & polymer were mixed with acetone. This slurry was slowly introduced into the liquid paraffin while being stirred at 400 rpm by using a three bladed mechanical stirrer at room temperature. This solution was stirred for 2hrs to allow the solvent to evaporate completely. The obtained microballoons were collected by the filtration. Until free from oil microballoons were washed repeatedly with petroleum ether (40-60^{o}C). The hollow microballoons were dried 2hrs at room temperature and it stored in a desiccators over fused calcium chloride. The detailed composition of the formulation is shown in table 1.

EVALUATION OF HOLLOW MICROBALLOONS

The Lopinavir hollow microballoons were evaluated for the following parameters.

1) Fourier transforms infra-red spectroscopy (FT-IR)[6]

The drug-excipient compatibility studies were carried out using FT-IR spectrum. The spectra of pure drug Lopinavir, Eudragit S-100 and their physical mixture was obtained from FT-IR spectroscopy.

2) Percentage Yield[7]

The Percentage yield of hollow microballoons of FN1-FN5 formulations were calculated using initial total weight of the drug and polymer used for the preparation of microballoons and weight of final product after drying.

$$\text{Percentage yield} = \frac{\text{Practical mass}}{\text{Theoritical mass (polymer+drug)}} \times 100$$

3) Particle size determination[8]

The particle size of the hollow microballoons was determined with an optical microscope under regular polarized light, mean particle size was calculated and counting at least 150 microballoons per each batch.

4) Surface Analysis[9]

The surface morphology of the hollow microballoons was examined by using the Scanning electron microscopy (SEM).

5) Percentage drug entrapment efficiency (%DEE)[10]

The amount of drug entrapped was estimated by taking microballoons equivalent to 10mg of the Lopinavir drug for evaluation. Crushing the microballoons and dissolved in 5ml methanol and transferred into 100 ml volumetric flask and the volume was made up using 0.1N HCL. This solution was filtered, 10ml was taken and the absorbance was measured in UV at 234nm against appropriate blank (0.1N HCL).

$$\%\text{Drug Entrapment Efficiency} = \frac{\text{Practical drug loading}}{\text{Theoretical drug loading}} \times 100$$

6) Floating behavior (Buoyancy)[11]

The *in vitro* floating behavior (buoyancy) of the hollow microballoons was determined by taking 50mg of microballoons and dispersed in 100ml of 0.1 N HCL solution (pH 1.2) containing tween 80 (0.01 W/V %) at 37^{o}C. The mixture was stirred with a paddle at 100 rpm. After 12hrs the layer of floating microballoons was pipetted and separated by filtration and sinking microballoons was also separated. Both microballoons type were dried at 40^{o}C overnight. Each weight was measured and buoyancy was determined by the weight ratio of the floating microballoons to the sum of floating and sinking microballoons.

$$\%\ \text{Buoyancy} = \frac{\text{Microballoons remaining floating}}{\text{Total mass of microballoons}} \times 100$$

7) *In vitro* release studies[12]

The *In vitro* release studies of Lopinavir microballoons were carried out in a USP type I (basket) dissolution test apparatus. 75mg Lopinavir drug loaded hollow microballoons was introduced into 900ml of the dissolution medium and stirred at 100 rpm at 37^{o}C. At different time intervals, the solution was withdrawn and absorbance was read at 234nm. An equal volume of the medium was replaced into the container after each withdrawal to maintain sink condition.

8) Drug Release Kinetics Data Analysis [13]

The release kinetic study of Lopinavir from the hollow microballoons the release data was fitted to these equations.

Zero-order equation: (cumulative % release vs. time)

$Qt = k0.t$

Where Qt is the percentage of drug released at time t and k0 is the release rate constant

First order equation: (log % drug remaining vs. time)

In (100-Qt) = In 100- kI.t

Where kI is the release rate constant

Higuchi's equation: (cumulative % drug release vs. square root of time)

Qt = kH.t1/2

Where kH is the Higuchi release rate constant

Peppas: (log of cumulative % drug release vs. log time)

$Qt/Q\infty = kKP.tn$

Where $Qt/ Q\infty$ is the fraction of drug released at time t, kKP a constant compromising the structural and geometric characteristics of the device and n is the release exponent.

9) Stability Study[14]

From the prepared hollow microballoons FN3 which showed an appropriate balance between the buoyancy and the percentage release was selected for stability studies. FN3 were placed at 5^{o}C, room temperature 30 ^{o}C and $40^{0} \pm 2^{0}$C/75%RH for 3 month, the microballoons were analysed for their drug content and *in vitro* dissolution studies.

RESULT AND DISCUSSION

Evaluation of hollow microballoons

By using the Eudragit S-100 spherical hallow microballoons are formed by using three bladed mechanical stirrer. Hollow microballoons are obtained by the Non- aqueous solvent evaporation method. The FTIR spectrum shows no significant changes in the chemical integrity of the drug and also they indicate drug and polymer are compatible with each other. The prepared microballoons morphology were analysed by SEM (fig.1 A&B), their mean size distribution was found to be 152µm. Microballoons particle size are less than 200µm, so this drug delivery system can be used for the parenteral formulations. The drug administered by the parenteral route will achieve direct systemic drug delivery their by reduction in dose and avoiding first pass metabolism.

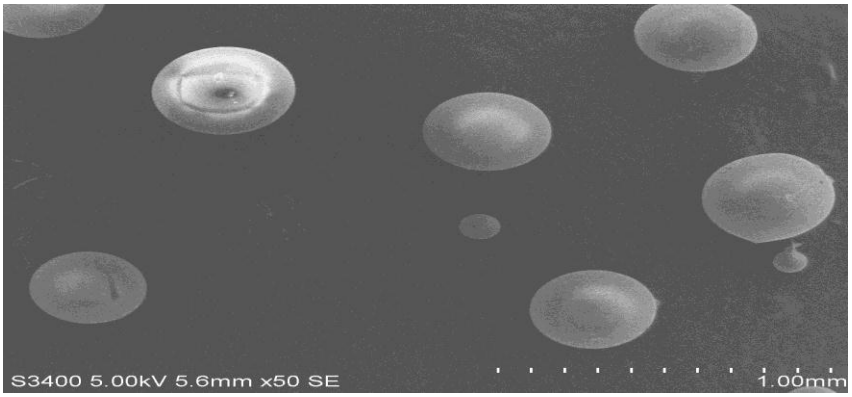

Fig.1 A: SEM of FN-3.

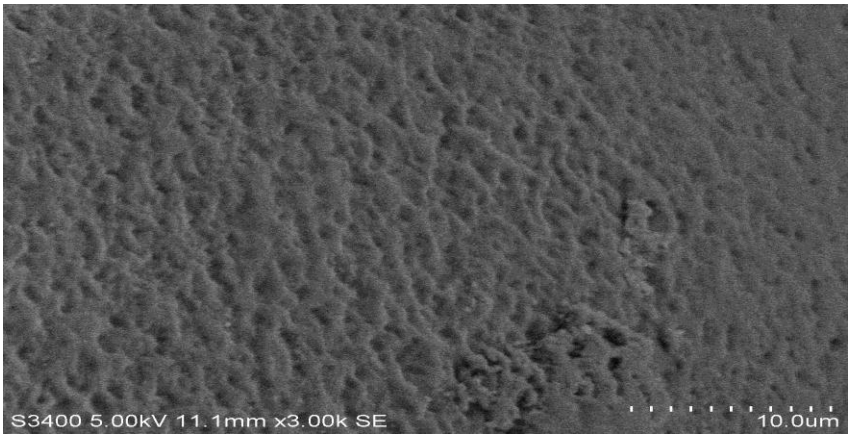

Fig.1 B: SEM of FN-3

The entrapment efficiency of the hollow microballoons FN1-FN5 containing drug: polymer in the various ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 were found to be 78.52%, 80.42%, 91.82%, 85.85% and 76.95% respectively and in vitro buoyancy of the hollow microballoons was found to be (Table 2). The zeta potential of the hollow microballoons FN-3 was found to be -41.1 mV, which indicates they are stable.

***In vitro* release of microballoons**

The cumulative drug release of the formulations FN1-FN5 is shown in (fig.2). The formulation FN1, FN2, FN3, FN4 & FN5 showed the percentage drug release 83.52%, 76.23%, 90.11%, 86.35% and 80.23% at the end of 12hrs respectively. Among all the formulations FN-3 formulation was found to be best formulation, as it release Lopinavir in sustained manner.

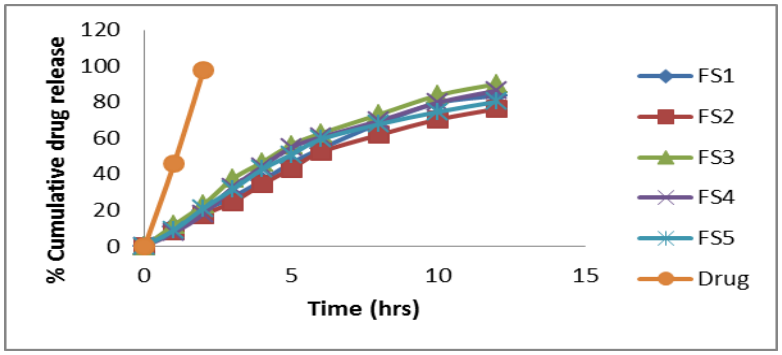

Fig.2: Cumulative release of hollow microballoons.

Kinetics studies

The release kinetics of FN1-FN5 formulations the dissolution data were fitted in the various kinetic dissolution models like zero order, first order, higuchi and peppas respectively (Table 3). As indicated by the higher R2 (coefficient and correlation) values, the drug release from FN1-FN5 formulations are follows first order release and higuchi model. Since it was confirmed as higuchi model, swelling and diffusion controlled was the release mechanism. Peppas model used to confirm whether the release mechanism is zero order, fickian diffusion or non-fickian diffusion. 'n' (release exponent of korsmeyer peppas model) the value used to describe different release mechanism. 'n' values for the FN1-FN5 formulations are found to be more than 0.50. It specifies the release approximately the non-fickian diffusion mechanism.

Stability studies

The drug content result of the optimized formulation FN-3 after 3 month of stability testing period at different storage conditions were shown in fig. 3. The *in vitro* release profile for the FN-3 formulation stored at the different storage conditions were shown in fig. 4.

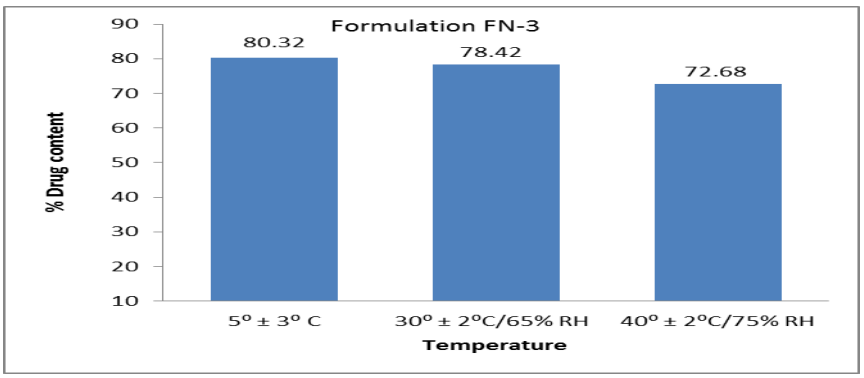

Fig. 3: Stability study: comparison of drug content of formulation FN-3 at 5°C, room temperature 30 °C and 40° ± 2°C/75%RH.

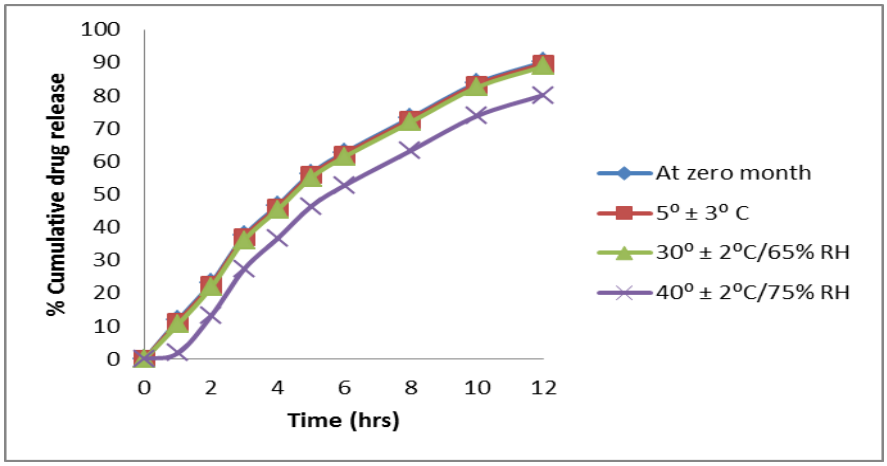

Fig.4: Stability study: comparison of *in vitro* drug release profile for formulation FN-3 at zero month, 5°C, room temperature 30 °C and 40° ± 2°C/75%RH after 3 month storage.

By comparing this data with the earlier data of the FN-3 it observed there is minor decrease in the drug content when the formulation FN-3 was stored at the 5°C and at room temperature. But the formulation stored at 40° ± 2°C/75% RH shows significant decrease in the drug content. It was because at the higher temperature there may be a chances of the drug degradation so that will decreases the drug release.

Table 1: Formulation details of hollow microballoons of Lopinavir.

SI.NO	INGREDIENTS	FN1	FN2	FN3	FN4	FN5
1	Lopinavir (mg)	300	300	300	300	300
2	Eudragit S-100 (mg)	300	600	900	1200	1500
3	Acetone (ml)	30	30	30	30	30
4	Liquid paraffin (ml)	30	30	30	30	30

Table 2: Physicochemical characterization of Lopinavir hollow microballoon.

SI.NO	Batch code	Drug:carrier ratio	Entrapment efficiency (%)	Particle size (µm)	*In vitro* buoyancy
1	FN-1	1:1	78.52	120	75%
2	FN-2	1:2	80.42	137	71%
3	FN-3	1:3	91.82	178	89%
4	FN-4	1:4	85.85	156	83%
5	FN-5	1:5	76.95	164	72%

Table 3: Correlation and coefficients according to the different kinetic equations.

Formulation code	% CDR	Zero order	First order	Higuchi plot	Peppas plot	'n' values
FN-1	83.52	0.9748	0.9897	0.953	0.9947	1.0426
FN-2	76.23	0.9666	0.9972	0.9533	0.9875	0.9645
FN-3	90.11	0.9463	0.9856	0.972	0.9775	1.1283
FN-4	86.35	0.9415	0.9967	0.9542	0.9568	0.9739
FN-5	80.23	0.9339	0.9947	0.964	0.9642	1.0407

CONCLUSION

The present study demonstrated the successful preparation of hollow microballoon of the Lopinavir with Eudragit S-100 polymer was prepared by the Non-aqueous solvent evaporation method. Based on the drug entrapment efficiency, drug content, zeta potential, particle size morphology, *in vitro* buoyancy and *in vitro* release formulation FN-3 was selected as an ideal formulation. Hence the hollow microballoons of Lopinavir (FN-3) were considered to be good microballoons formulation with high bioavailability and side effect found to be suitable for sustain drug delivery.

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