Preparation And Evaluation Of Lopinavir Hollow Microballoons By Solvent Evaporation Method

Sindhu.A.C.*1, J. Adlin Jino Nesalin *2
**1(Student of Bharathi College of Pharmacy Mandya, Karnataka, India -571422)*
**2(Professor of Bharathi College of Pharmacy Mandya, Karnataka, India -571422)*
*sindhukhushi0622k@gmail.com*1*

Abstract:

The present study involves the preparation and evaluation of floating hollow microballoons of Lopinavir for improving the drug bioavailability by prolongation of gastric residence time.A hollow microballoon of Lopinavir was prepared by solvent evaporation method by using ethyl cellulose as a polymer. Five different formulations were developed FS1 to FS5. The developed hollow microballoons were evaluated for percentage yield, particle size, entrapment efficiency, in vitro buoyancy, scanning electron microscopy (SEM) and in vitro drug release. The formulation FS-4 registered has optimized formulation. IR studies are indicates that no interaction between drug and polymer. The SEM shows the pores on the surface and interior of the microballoons. Short time stability studies on the formulation results shows there is no physical or chemical changes in the formulation during the study period. The hollow microballoons exhibits prolonged drug release for 12hrs.

Keywords : *Ethyl cellulose;Hollow Microballoons; Lopinavir; Solvent evaporation method.*

INTRODUCTION

The drug delivery systems main goal is to achieve desired concentration of the drug in the tissue or blood, which is non-toxic and therapeutically effective for a prolonged period of time [(1)]. Controlling the gastric residence time by using the gastro retentive dosage forms is one of the most suitable approaches for achieving a predictable and prolonged drug delivery in the gastro intestinal tract. A Gastro retentive dosage form are remains in the gastric region for several hours and hence prolongs the gastric residence time of the drug. It having several advantages over the immediate release dosage forms which including the minimization of fluctuations in plasma drug concentration and prolonged gastric residence time, resulting in reduced side effects and optimized therapeutic efficiencies, reduction of total dose administered and reduction of drug administration frequency leads to the improve patient compliances[(2,3)].The floating microspheres are gastro retentive drug delivery system based on the non-effervescent approach. These microspheres nature are free flowing, having a size less than 200µm and remain buoyant over gastric contents for prolonged period of time. As the system floats over gastric contents, the drug release slowly at desired rate which results in increased gastric retention with reduced fluctuation in the plasma drug concentration[(4,5)].Highly Active Antiretroviral Therapy has revolutionized the management of Human Immuno Virus (HIV)infection[(6)]. Most of the antiretroviral drugs are having low bioavailability due to its gastrointestinal degradation, extensive first pass metabolism, short half-life of the drug so frequent dose administration is necessary thereby increasing side effects due to peak through fluctuations. The current attempt is to overcome the all above limitations[(7)].Lopinavir is an HIV-1 protease inhibitor which works by interfering with the reproductive cycle of HIV. It inhibits HIV-1 protease result in

inhibiting the cleavage of HIV gag and gag-pol poly proteins, thereby preventing viral mutation. Lopinavir is absorbed mainly in stomach it is suitable for gastro retentive floating dosage form their by avoid first pass metabolism and achieve prolonged drug release[8, 9].

MATERIALS AND METHODS

Lopinavir was obtained as gift sample Hetero drugs ltd, Hyderabad and Ethyl cellulose were purchased from Rolex chemical industries, Mumbai. All other chemicals used were of analytical grade.

PREPARATION OF HOLLOW MICROBALLOONS[10]

Floating hollow micro balloons were prepared by the solvent evaporation method. Various concentration of polymer in dichloromethane were mixed well with Lopinavir this pasty, flowable mass was introduced into aqueous phase containing polyvinyl alcohol (PVA) and methanol. The system is stirred using propeller at 300 rpm at room temperature for 2-3 hr. The drug loaded hollow micro balloons formed were filtered, washed and dried in room temperature. The detailed composition of the formulation is shown in table 1.

EVALUATION OF HOLLOW MICROBALLOONS

The Lopinavir hollow micro balloons were evaluated for the following parameters.

1. Percentage yield of hollow microballoons :

The prepared hollow microballoons were collected, dried and weighed. The measured weight wasdivided by the total amount of all substances which were used for the preparation of the microballoons.

% Yield = (Actual weight of product / Total weight of the excipient and drug) x 100

2. Particle size analysis :

Size distribution was determined by optical microscopy using stage micrometer slide and calibrated eyepiece by counting at least 150 microballoons per batch[11].

3. Percentage drug entrapment efficiency (%DEE) :

Microballoons equivalent to 50mg of the Lopinavir drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microballoons and were dissolved in methanol (5ml) was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCL. This solution was filtered, made suitable dilution and the absorbance was measured in UV at 243nmagainst appropriate blank. By using the following formula the amount of the drug entrapment in microballoons was calculated.

%Drug Entrapment Efficiency = (% drug content / % Theoretical content) x 100

4. Surface Topography :

The surface morphology of the microballoons was examined by the Scanning Electron Microscopy (SEM) [12].

5. *In vitro* Buoyancy :

Floating hollow microballoons (equivalent to 100mg) were dispersed in 900ml 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 12 hrs the layer of floating microballoons (W_f) was pipetted and separated by filtration and simultaneously sinking microballoons (W_s) 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[13].

$$(\%)\ \text{Buoyancy} = \frac{W_f}{W_f + W_s} X100$$

6. *In vitro* dissolution studies :

In vitro dissolution studies 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 100rev/min at 37^{o}C. At different time intervals, the solution was withdrawn and absorbance was read at 243nm. An equal volume of the medium was replaced into the container after each withdrawal to maintain sink condition. The dissolution studies were repeated three times in simulated gastric fluid (0.1N HCL). The mean values are plotted as percent cumulative release versus time[14].

7. Kinetic modeling :

The result of the *in vitro* drug release study of hollow microballoons wasfixed with various kinetic equations to understand the kinetics and mechanism of the drug release. The kinetics equations like Zero order (cumulative % release vs. time), First order (log% drug remaining vs. time), Higuchi model (cumulative % drug release vs. square root of time), Peppas plot (log of cumulative % drug release vs. log time). R2 (coefficient of correlation) and k (release rate constant) values were calculated for the linear curve obtained by regression analysis of the above plots.

8. Stability study :

The hollow microballoons was taken in a crucible and placed at 5^{o}C, room temperature 30^{o}C and 40^{0} ± 2^{0}C/75%RH for 3 month, the microballoons were analysed for their drug content and *in vitro*dissolution studies[15].

RESULT AND DISCUSSION

Physicochemical characterization of hollow microballoons

By using the ethyl cellulose spherical hallow microballoons are formed spontaneously by using mechanical stirrer. Hollow microballoons are obtained by the solvent evaporation method. FTIR spectrum shows no significant changes in the chemical integrity of the drug and also they indicate drug and polymer are

compatible. Theprepared microballoons morphology were analysed by SEM (fig.1 A&B), their mean size distribution was found to be 155µm. Hollow 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.

The entrapment efficiency of the hollow microballoons containing drug: polymer in the various ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 were found to be 92.62%, 82.45%, 90.04%, 94.12% and 80.32% respectively (Table 2). The zeta potential of the hollow microballoons FS-4 was found to be -12.1 mV, which indicates they are stable.

Fig.1 A: SEM of FS-4

Fig.1 B: SEM of FS-4

***In vitro* release of hollow microballoons**

The cumulative drug release of the formulations FS1-FS5 is shown in (fig.2). The formulation FS1, FS2, FS3, FS4 & FS5 showed the percentage drug release 93.41%, 88.94%, 91.29%, 96.23% and 82.11%at the end of 12hrs respectively. Among all the formulations FS4 formulation was found to be best formulation, as it release Lopinavir in sustained manner.

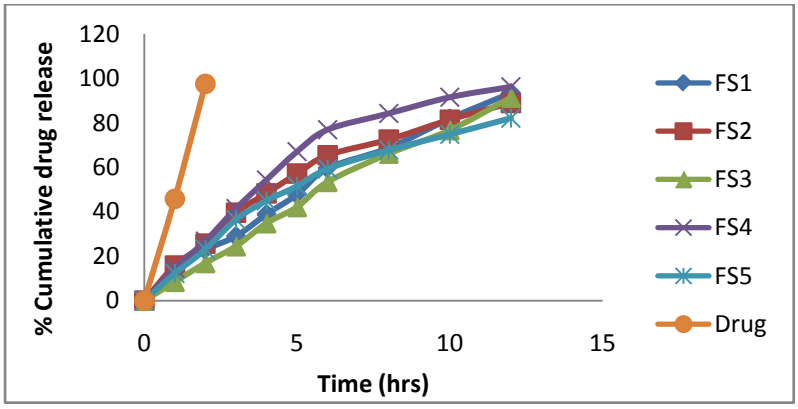

Fig.2: Cumulative release of hollow microballoons

Kinetics studies

The release kinetics of FS1-FS5 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 FS1-FS5 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 FS1-FS5 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 FS-4 after 3 month of stability testing period at different storage conditions were shown in fig. 3. The *in vitro* release profile for the FS-4 formulation stored at the different storage conditions were shown infig.4.

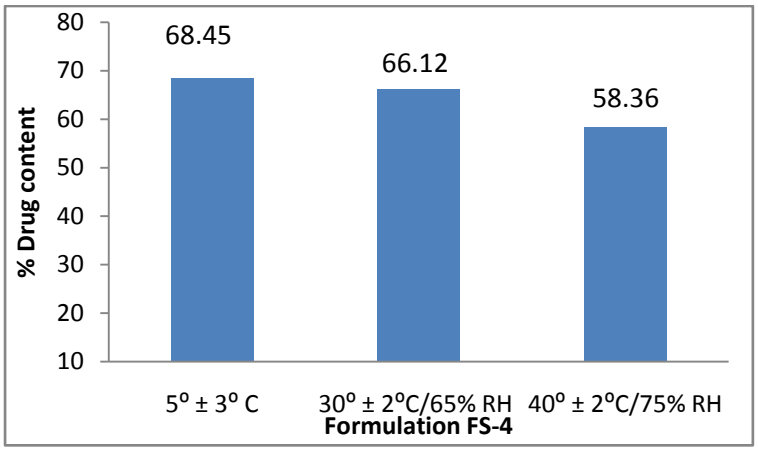

Fig.3: Stability study: comparison of drug content of formulation FS-4 at 5°C, room temperature 30 °C and 40° ± 2°C/75%RH

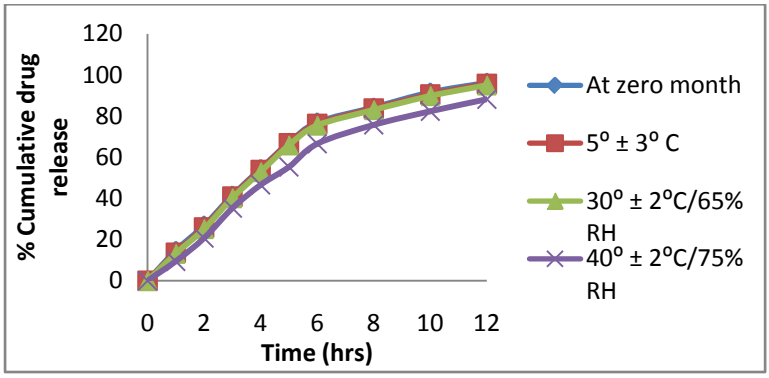

Fig.4: Stability study: comparison of *in vitro* drug release profile for formulation FS-4 at zero month, 5°C, room temperature 30 °C and 40° ± 2°C/75%RH after 3 month storage

By comparing this data with the earlier data of the FS-4it observed there is minor decrease in the drug content when the formulation FS-4 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	F1	F2	F3	F4	F5
1	Lopinavir (mg)	300	300	300	300	300
2	Ethyl cellulose (mg)	300	600	900	1200	1500
3	Dichloromethane(ml)	10	10	10	10	10
4	PVA (mg)	20	20	20	20	20
5	Methanol(ml)	10	10	10	10	10

Table 2: Physicochemical characterization of Lopinavir hollow microballoon

SI.NO	Batch code	Drug:carrier ratio	Entrapment efficiency (%)	Particle size (µm)	*In vitro* buoyancy
1	FS-1	1:1	92.62	126	84%
2	FS-2	1:2	82.45	142	76%
3	FS-3	1:3	90.04	164	88%

4	FS-4	1:4	94.12	186	91%
5	FS-5	1:5	80.32	158	74%

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

Formulation code	% CDR	Zero order	First order	Higuchi plot	Peppas plot	'n' values
FS-1	93.41	0.9840	0.9326	0.9554	0.9955	1.1122
FS-2	88.94	0.9304	0.9927	0.9811	0.9822	1.2262
FS-3	91.29	0.9926	0.9328	0.9327	0.9966	0.9405
FS-4	96.23	0.9049	0.9938	0.9628	0.9645	1.2175
FS-5	82.11	0.9321	0.9972	0.9778	0.9741	1.1457

CONCLUSION

The hollow microballoon of the Lopinavir with ethyl cellulose polymer was successfully prepared by the solvent evaporation method. Based on the drug entrapment efficiency, drug content, zeta potential, particle size morphology, *in vitro* buoyancy and *in vitro* release formulation FS-4 was selected as an optimized formulation. The stability studies were carried for this optimized formulation FS-4 shows that maximum drug content and closest *in vitro* release as the earlier data was found for the FS-4 stored at the 5^{o}C and room temperature. Hence the hollow microballoons of Lopinavir (FS-4) were found to be suitable for sustain release.

AKNOWLEDGEMENT

The authors are thankful to the Hetero drugs ltd, Hyderabad for proving the drugas gift sample for this work. We also thankful to the principal, Bharathi college of pharmacy, Bharathinagar, Mandya (D), Karnataka, India for their kind support for this research work.

REFERENCES

1) *Chiao CS, Robinson JR. Sustained-Release Drug Delivery Systems. In: Longer MA, Robinson JR editors. Remington: The science and practice of pharmacy. 19th ed. Easton Pennsylvania; Mack Publication Company; 1995: (II), 1660-75.*
2) *Chien Y.W, Noval drug delivery system. 2nd edi, Vol. 50, Marcel Dekker Inc, New York, 1992, 161- 72.*
3) *Khar R. K, Vyas S. P, Targeted and controlled drug delivery novel carrier system, 1st ed, CBS Publishers and Distributors, New Delhi, 2002, 417-41.*
4) *Tanwar Y. S.; www.pharmainfo.net, 4(3), 2006.*

5) *Arora S, Ali J, Ahuja A, Khar R.K, Baboota S. Floating drug deliverysystem: a review, AAPS Pharm SciTech, 2005;6(3):372-90.*
6) *Chandwani A, Shuter J.Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. Therapeutics and Clinical Risk Management 2008;4(5):1023-33.*
7) *Nesalin JA, Smith AA. Preparation and evaluation of chitosan nanoparticles containing zidovudine. Asian J Pharm Sci. 2012;7(1):80-4.*
8) *Hunziker ME, Suehs BT, Bettinger TL, Crismon ML. Duloxetine hydrochloride: a new dual-acting medication for the treatment of major depressive disorder. Clinical therapeutics. 2005;27(8):1126-43.*
9) *Patel DS, Deshpande SS, Patel CG. Duloxetine: a dual action antidepressant. Indo Glob J Pharm Sci.2011;1:63-76.*
10) *Patil C, Bakliwal S, Pawar S, Rane B, Gujrathi N. Preparation and evaluation of hollow microsphere drug delivery system of Zidovudine. Int J Pharma Sci Res. 2011;2(10):2669-74.*
11) *Gandhi S. Optimization of floating microspheres of captopril using full factorial design. Asian J Biomed Pharma Sci. 2012;2(15) :69-94.*
12) *Patel A, Ray S, Thakur RA. Invitro evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride. Volume 14, No. 2, 2006;57-64.*
13) *Najmuddin M, Ahmed A, Shelar S, Patel V, Khan T. Floating microspheres of Ketoprofen: formulation and evaluation. Int J Pharma Pharma Sci. 2010;2(2):83-7.*
14) *Joseph NJ, Lakshmi S, Jayakrishnan A. A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits. J Cont Rel. 2002;79(1-3):71-9.*
15) *Ahmed AB.Design, development and evaluation of hollow microspheres of Repaglinide.J Chem Pharma Res. 2014;6(9):267-77.*