Research Article

DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE FORMULATION OF LAMIVUDINE BASED ON MICROPOROUS OSMOTIC TABLET TECHNOLOGY USING FRUCTOSE AS OSMOGEN

Chinmayakeshari saho^{1*}, Surepalli Ram Mohan Rao², Muvvala Sudhakar³

¹Pharmaceutics Department, Faculty of Pharmacy, University College of Technology, Osmania University, Hyderabad, Telangana-500007.

²Chemical Engineering, Mekelle Institute of Technology, Mekelle University, Mekelle Ethiopia, PO Box 231.

³Department of Pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Telangana-500014.

Submitted:02-05-2017

Revised:30-05-2017

Accepted:21-07-2017

*Corresponding author
Chinmayakesharisahoo

Email:sahoo.chinmaya83@gmail.com

ABSTRACT

The present study was undertaken to develop controlled release osmotic pump tablets of lamivudine a nucleoside reverse transcriptase inhibitor for the treatment of acquired immune deficiency syndrome (AIDS). The tablets were prepared by wet granulation method using controlled release polymer hydroxyl propyl methyl cellulose (HPMCE5 LV), MCC as a diluent, starch as binder and fructose as osmogen. The coating solution of core tablets was prepared by using cellulose acetate, poly ethylene glycol 400, 600, 4000, 6000 and acetone to a quantity sufficient with sorbitol for different batches. The prepared tablets were evaluated for pre compression parameters, post compression parameters, *in vitro* drug release study and scanning electron microscopy study. Among the prepared formulations LF4 batch show 97.78% drug release in 12h. The *in vitro* release kinetics were analyzed for different batches by different pharmacokinetic models such as zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell model. Short term stability study at 40±2°C/75±5% RH for three months on the best formulation was performed showing no significant changes in thickness, hardness, friability, drug content and *in vitro* drug release.

Keywords: AIDS, wet granulation, *in vitro* drug release, stability study

INTRODUCTION

Controlled release dosage forms offer prolong drug release of active ingredients at a predetermined rate and a predetermined time (Presscott, 1989). Among various controlled drug delivery systems osmotic controlled drug delivery system (OCDDS) utilizes the principle of osmotic pressure for controlled delivery of active ingredients. The drug released from OCDDS is independent of pH and hydrodynamic condition of the body and agitation intensity (Kaushal *et al.*, 2003). The present study is to develop controlled porosity osmotic pump (CPOP) tablets of lamivudine. The delivery system of the drug comprises a core with the drug surrounded by a semipermeable membrane (SPM) which is accomplished with different channeling agents of water soluble additives in the coating

membrane. The core is coated with cellulose acetate containing in situ micro pore former sorbitol. Further for increasing drug release fructose of 355atm was chosen as osmotic agent to generate high osmotic pressure gradient in CPOP. When CPOP tablets placed in a biological system of fluid low levels of water soluble additives are leached from polymer materials which form a sponge like structure in the controlled porosity walls. The rate of drug delivery depends upon the factors (Zenter *et al.*, 1985) such as water permeability of the SPM, osmotic pressure of core formulation, thickness and the total area of the coating.

Human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS) is a disease of the human immune system caused by infection with human immune deficiency virus. It is

called AIDS when a person infected with HIV has a CD4⁺ count of declines up to 200 cells/ μ L in the blood (Sahoo *et al.*, 2017). AIDS is transmitted by via unprotected sexual intercourse, contaminated blood transfusions, hypodermic needles and from mother to child during pregnancy, delivery or breastfeeding. The prevention of HIV infection primarily through safe sex using condoms, needle exchange programs awareness required to control the spread of disease and may lead to a near normal life expectancy (Sahoo *et al.*, 2015). The management of AIDS can be controlled by antiretroviral therapy, male circumcision, needle exchange program, use of diaphragms, topical protection, use of condoms and alternative medicine.

Lamivudine is a synthetic nucleoside analogue and is phosphorylated intra cellularly to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). This nucleoside analogue is incorporated into viral DNA by HIV reverse transcriptase resulting in DNA chain termination (Richman, 2001). The present research aimed to design CPOP tablets of lamivudine by wet granulation method containing a dose of 300mg once daily. Lamivudine has a bioavailability of 86%, protein binding of 36% and the biological half-life is between 5-7h. Hence it can be given to control the concentration of drug at the site of action. The main objective of the present study was to develop controlled porosity-based osmotically controlled release tablets of lamivudine

MATERIALS AND METHODS

Materials

Lamivudine was obtained from Hetero Drugs Pvt. Ltd. India., fructose and mannitol were obtained from Qualigens Fine Chemicals, India. Cellulose acetate (CA) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol, magnesium stearate, talc, HPMCE5LV and polyethylene glycol (PEG) 400, 600, 4000, 6000 were purchased from S.D. Fine Chemicals Ltd, Mumbai, India., Microcrystalline cellulose (MCC) and starch were purchased from Signet Pharma, Mumbai, India. All other solvents and reagents used were of analytical grade.

Compatibility studies

DSC

Physical mixtures of drug and individual excipients in the ratio of 1:1 were taken and examined in DSC. Individual samples as well as a physical mixture of drug and excipients were weighed to about 5mg in DSC pan (Shimadzu DSC-50, Japan). The sample in the pan was scanned (Kumaravelrajan *et al.*, 2011) in the temperature range of 50-300°C. The heating rate of 20°C min⁻¹ was used and the thermogram obtained was reviewed for evidence of any interactions. Then the thermograms were compared with pure samples versus optimized formulation.

Preparation of lamivudine CPOP tablets

The tablets were prepared by wet granulation technique (Sahoo *et al.*, 2016). Accurately weighed quantities of ingredients (Table Ia) were passed through sieve No. 30. Lubricant (magnesium stearate), a glidant (talc) were passed through sieve No. 80. The ingredients were manually blended homogeneously in a mortar by way of geometric dilution without the addition of except lubricant and glidant. The mixture was moistened with an aqueous solution and granulated through sieve No.30 and dried in a hot air oven at 60°C for sufficient time (3-4h). The dried granules were passed through sieve No.30 and blended with talc and magnesium stearate. The homogeneous blend was then compressed into round tablets with standard concave punches using 10 station rotary compression machine (Minipress, Karnavati, India).

Coating of core tablets

Table Ib summarizes the components of the coating solution. The coatings of tablets were performed by spray pan coating (Sahoo *et al.*, 2012) in a perforated pan (GAC-205, Gansons Ltd, Mumbai, India). Initially tablets were pre heated by passing hot air through the tablet bed and by rotating at a lower speed of 5-8rpm. The coating process was started with a rotation speed of 10-12 rpm. The spray rate and atomizing air pressure were 4-6mL/min and 1.75 kg/cm² respectively. Inlet and outlet air temperature were 50°C and 40°C respectively, coated tablets were dried at 50°C for 12h.

Table Ia. Composition of lamivudine CPOP tablets

Formulation code	LM (mg)	MCC (mg)	Starch (mg)	HPMC E5LV(mg)	Fructose (mg)	Magnesium stearate (mg)	Talc (mg)	Total wt. (mg)
LF1	300	190	25	100	25	5	5	650
LF2	300	165	25	100	50	5	5	650
LF3	300	140	25	100	75	5	5	650
LF4	300	115	25	100	100	5	5	650

Table I b. Coating composition for CPOP tablets

Formulation code	CA (g)	PEG 400 (g)	PEG 600 (g)	PEG 4000(g)	PEG 6000 (g)	Sorbitol (g)	Acetone (mL)
LF1	6	2	0	0	0	0	300
LF2	6	0	2	0	0	0.4	300
LF3	6	0	0	2	0	0.8	300
LF4	6	0	0	0	2	1.2	300

Evaluation of CPOP tablets**Pre compression parameters of CPOP granules (Sahoo *et al.*, 2015)****Angle of repose (θ)**

The flow property of granules was determined by measuring the angle of repose where the granules were allowed to flow through funnel freely onto the clean surface. The funnel was fixed at such a height that bottom tip of the funnel should not touch apex of the heap of granules. The angle of repose is calculated using the following equation:

$$\tan \theta = h/r \dots\dots\dots (1)$$

$$\theta = \tan^{-1}(h/r) \dots\dots\dots (2)$$

Where θ is the angle of repose, h is the height of heap in cm and r is the radius of the circular support (cone) in cm. According to the specifications the angle of repose value less than 25°C indicates excellent flow whereas angle greater than 40°C indicates poor flow.

Bulk density (e_{bulk})

Bulk density is determined by pouring the granules into a graduated cylinder of bulk density apparatus (Sisco, India). The bulk volume (V_{bulk}) and mass (m) of the granules are determined. The bulk density is calculated by using the following formula.

$$e_{\text{bulk}} = \frac{m}{V_{\text{bulk}}} \dots\dots\dots (3)$$

Tapped density (e_{tap})

The measuring cylinder containing a known mass of granules blend is tapped 1000 times for a fixed time in tap density tester (Sisco, India). The minimum volume occupied in the cylinder (V_{tap}) and mass of the granules (m) are measured. The tapped density is measured by using the following formula.

$$e_{\text{tap}} = \frac{m}{V_{\text{tap}}} \dots\dots\dots (4)$$

Compressibility index (Carr's index)

The compressibility index determines the flow property characteristics (Patel *et al.*, 2012) of granules developed by Carr. The Carr's index can be calculated by the following formula.

$$\% \text{ Carr's index} = \frac{e_{\text{tap}} - e_{\text{bulk}}}{e_{\text{tap}}} \times 100 \dots\dots\dots (5)$$

Where e_{tap} is the tapped density of granules and e_{bulk} is the bulk density of granules.

According to the specifications the Carr's index values between 5-15 indicates excellent flow whereas between 12-16 indicates good flow. Values between 18-21 indicate fair passable whereas between 23-35 indicates poor and values between 33-38 indicates very poor and greater than 40 indicates extremely poor.

Hausner's ratio (H_R)

Hausner's ratio is used for the determination of flow properties of granules.

The Hausner's ratio can be calculated by the following formula

$$H_R = \frac{e_{tap}}{e_{bulk}} \dots \dots \dots (6)$$

According to specifications values less than 1.25 indicate good flow (= 20% of Carr's index) whereas greater than 1.25 indicates poor flow (=33% of Carr's index).

Post compression parameters of CPOP tablets (Sahoo *et al.*, 2015)

Thickness

The thickness of individual tablets is measured by using Vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan) which gives the accurate measurement of thickness in mm. The limit of the thickness deviation of each tablet is $\pm 5\%$.

Coat thickness

After dissolution the film was isolated from the tablets and dried at 40°C for 1hr. Thickness was measured by using electronic digital calipers (Absolute digimatic, Mitutoyo Corp. Japan) and mean values were taken.

Hardness test

The hardness of tablets can be determined by using Monsanto hardness tester (Sisco, India) and measured in terms of kg/cm².

Friability test

Friability of tablets was performed in a Roche friabilator (Sisco, India). Ten tablets (Edavalath *et al.*, 2011) were initially weighed ($W_{initial}$) together and then placed in the chamber. The friabilator was operated for 25 revolutions for 4mins and the tablets are then dusted and reweighed (W_{final}). The percentage of friability was calculated using the following equation.

$$\% \text{Friability} = F = \left(1 - \frac{W_{final}}{W_{initial}} \right) \times 100 \dots (7)$$

Where, $W_{initial}$ and W_{final} are the weight of the tablets before and after the test respectively.

Weight variation test

The weight variation test is done by weighing 20 tablets individually in weighing balance (Shimadzu, Japan) calculating the average weight (Maheswari *et al.*, 2012) and comparing the individual tablet weights to the average. The percentage weight deviation was

calculated and then compared with USP specifications.

Uniformity of drug content test

Ten tablets were weighed and powdered by mortar. Drug content (USP, 2003, Pragathi *et al.*, 2015) for tablets was done by the assay method. An accurately weighed equivalent weighed quantity of powdered tablet was dissolved in 0.1N HCl using magnetic stirrer (Ricon, Hyderabad, India) in a volumetric flask for 24h. The solution was filtered through Whatman filter paper No.1 and analyzed spectrophotometrically at 280nm (Shimadzu UV-1800, Japan).

Diameter of tablet

The diameter of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan) in mm.

In vitro dissolution studies

In vitro dissolution test (Kanagale *et al.*, 2007) was carried out by using USP type II (paddle) apparatus at 75 rpm in 900mL of dissolution fluid of 0.1N HCl for first 2 hours and phosphate buffer pH 6.8 from 3 to 12h maintained at $37 \pm 0.5^\circ\text{C}$. At specified time intervals 5mL aliquot of the solution was withdrawn through 0.45- μm cellulose acetate filter from the dissolution apparatus (Sahoo *et al.*, 2017) with the replacement of fresh fluid to dissolution medium. The filtered solution is diluted and analyzed spectrophotometrically at 280nm for 0.1N HCl (pH 1.2) and 270nm for phosphate buffer pH 6.8.

Mathematical modeling of *in vitro* drug release (IVDR) kinetics

For the determination of the drug release kinetics (Sahoo *et al.*, 2015) from the porous osmotic pump tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi, Korsmeyer and Peppas and Hixson-Crowell equations.

Zero order kinetics can be expressed by the equation

$$Q_t = Q_0 - K_0 t \dots \dots \dots (8)$$

Where

Q_t is the amount of drug dissolved in time t , Q_0 is the initial amount of drug in the solution and K_0 is the zero order release constant.

First order kinetics can be expressed by the equation:

$$\log C = \log C_0 - K_1 t / 2 \dots \dots \dots (9)$$

Where C_0 is the initial concentration of the drug, C is the amount of drug remaining to be released in time t , K_1 is the first order release constant.

Higuchi's classical diffusion equation (Higuchi, 1963) can be expressed as

$$Q = K_H \sqrt{t} \dots \dots \dots (10)$$

Where Q is the amount of drug release in time t , K_H is the Higuchi dissolution constant.

Korsmeyer-Peppas model (KP Model) for the drug release (Korsmeyer *et al.*, 1983) for this model is expressed as

$$\log (M_t / M_\infty) = \log K + n \log t \dots \dots \dots (11)$$

Where M_t is the amount of drug release at time t , M_∞ is the amount of drug release after an infinite time, K is the release rate constant incorporating structural and geometric characteristics of the tablet and n is the release exponent indicative of mechanism of drug release.

Hixson and Crowell model (Hixson, 1931) is expressed by the equation

$$W_0^{1/3} - W_t^{1/3} = \kappa t \dots \dots \dots (12)$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is remaining amount of drug in the pharmaceutical dosage form at time t and κ is proportionality constant incorporating the surface volume relation.

Effect of osmogen concentration

To check the effect of osmogen (Shah *et al.*, 2013) concentration on drug release formulations were prepared with the different concentration of osmotic agents (Sahoo *et al.*, 2017) and all other parameters of tablet kept constant. The drug release was compared with the different osmogen concentration of formulated batches by using USP-II dissolution apparatus.

Effect of pore former concentration

Different concentrations of pore former (Dasankoppa *et al.*, 2013) are used in SPM formation. In order to compare the effect

of different concentrations of pore formers *in vitro* release profiles as well as a number of formation of micro pores are compared.

Effect of coating thickness

The tablet is kept in 900mL of dissolution fluid 0.1N HCl for first 2h and next followed by 3 to 12h in phosphate buffer pH 6.8 of USP type II dissolution apparatus at 75 rpm and maintaining the temperature $37 \pm 0.5^\circ\text{C}$ of dissolution media to check the effect of membrane thickness (Sahoo *et al.*, 2017). The sample 5mL was withdrawn through 0.45- μm cellulose acetate filter at different time intervals replaced with fresh medium and analyzed in UV-Visible spectrophotometer.

Effect of osmotic pressure

The effect on osmotic pressure (Rani *et al.*, 2004) on the optimized formulation was studied in media of different osmotic pressure and the release profile with varying osmotic pressure is compared. To increase the osmotic pressure of the release media mannitol (Sahoo *et al.*, 2017) was added to produce 30 atm, 60 atm and 90 atm respectively.

Effect of pH

In order to study the effect of pH of release medium in the drug release of optimized formulation, the *in vitro* release study was carried in dissolution media having different pH media (Patel *et al.*, 2012). Dissolution can be carried in 900mL of 0.1 N HCl (pH 1.2), pH 6.8 and phosphate buffer pH 7.4 in USP type II dissolution apparatus at 75rpm with maintaining the temperature at $37 \pm 0.5^\circ\text{C}$. The sample (5mL) was withdrawn at predetermined intervals and analyzed after filtration through 0.45- μm cellulose acetate filter.

Effect of agitation intensity

The drug release of optimized formulation was subjected to dissolution at various rotation speeds (Verma *et al.*, 2004) to demonstrate the effect of agitation intensity. Dissolution was carried out in USP-II (Paddle) at 50, 100 and 150rpm. The samples were withdrawn at predetermined intervals through 0.45- μm cellulose acetate filter and analyzed by UV-Visible spectrophotometer.

Figure 1a. DSC thermogram of lamivudine

Figure 1b. DSC thermogram of LF4

Scanning electron microscopy study

In order to observe the mechanism of drug release and surface morphology (Rao *et al.*, 2009) from the developed formulations surface coated tablets before and after dissolution studies was examined using scanning electron microscope (Leica, Bensheim, Switzerland).

Accelerated stability studies

The formulation was subjected to accelerated stability studies (Sharma *et al.*, 2014) as per ICH (The International Conference of Harmonization) guidelines. The packed tablets in air tight container were placed in stability chambers (Thermo lab Scientific equipment Pvt. Ltd., Mumbai, India) maintained at $40 \pm 2^\circ\text{C}$, $75 \pm 5\%$ RH for 3 months. Tablets were periodically removed and evaluated for physical characteristics, drug content, *in vitro* drug release etc.

RESULTS AND DISCUSSION

DSC thermograms

DSC thermo gram showed an endothermic peak at 162.2°C which is the corresponding melting point of drug (Figure 1a). DSC thermo gram showed an

endothermic peak at 161.2°C in the LF4 formulation (Figure 1b). From the above DSC studies it was observed that the formulation is thermodynamically stable. No shifting of peaks from endothermic to exothermic was also noticed. Hence physical mixture showed that there was compatibility with the drug.

Pre compression parameters

The angle of repose of pre-compression blends of various batches was in the range of 25.01 ± 0.12 to 28.78 ± 0.14 . The bulk density of pre-compression blends was found to be in the range of 0.524 ± 0.14 to $0.528 \pm 0.12 \text{ g/mL}$, tapped density in the range of 0.558 ± 0.06 to $0.571 \pm 0.12 \text{ g/mL}$, the Carr's index values were in the range of 5.73 ± 0.05 to 8.05 ± 0.14 , and Hausner's ratio values were ranges of 1.06 ± 0.03 to 1.08 ± 0.11 . So the results of pre compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio indicated that the dry granules of all the formulations of lamivudine showed excellent flow properties which favor easy manufacturing of CPOP tablets under study (Table IIa).

Table IIa. Pre compression parameters of CPOP granules

Formulation code	Angle of repose (degree) ^a ± S.D	Bulk density (g/mL) ^a ± S.D	Tapped density (g/mL) ^a ± S.D	Carr's Index (%) ^a ± S.D	Hausner's Ratio ^a ± S.D
LF1	28.78±0.14	0.528±0.12	0.562±0.11	6.05±0.14	1.06±0.09
LF2	27.82±0.12	0.524±0.14	0.567±0.12	7.58±0.12	1.08±0.11
LF3	26.19±0.11	0.525±0.11	0.571±0.12	8.05±0.14	1.08±0.09
LF4	25.01±0.12	0.526±0.04	0.558±0.06	5.73±0.05	1.06±0.03

N.B.-All values are expressed as mean ± S.D, ^a n = 3

Table IIb. Post compression parameters of lamivudine CPOP tablets

Formulation code	Thickness (mm) ^a ± S.D	Coat thickness (μm) ^a ± S.D	Hardness (kg/cm ²) ^a ± S.D	% Friability (%) ^b ± S.D	Average wt.of tablet (mg) ^b ± S.D	%Drug content(%) ^a ± S.D	Diameter (mm) ^a ± S.D
LF1	3.571±0.02	251.1±3.2	7.6±0.12	0.17±0.05	649.09±1.03	99.219±1.15	12.13±0.05
LF2	3.567±0.03	200.8±3.1	7.9±0.01	0.19±0.04	651.08±1.04	98.69±1.03	11.98±0.06
LF3	3.509±0.01	150.5±2.6	8.0±0.02	0.12±0.12	650.07±1.03	98.958±1.06	12.29±0.03
LF4	3.503±0.02	100.3±2.4	8.1±0.04	0.11±0.13	650.04±1.1	99.47±1.25	12.2±0.07

N.B.-All values are expressed as mean ± S.D, ^a n = 10, ^b n = 20

Table III. Fitting of IVDR data in various mathematical models

Models	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
Batches	R ²	K ₀	R ₁ ²	K ₁	R _H ²	K _H	R _K ²	K _{KP}	n	R ²	K _s
LF1	0.946	6.324	0.927	0.1658	0.972	24.77	0.941	26.061	0.458	0.961	0.181
LF2	0.920	6.229	0.950	0.1727	0.986	24.90	0.963	29.922	0.419	0.971	0.184
LF3	0.903	6.274	0.954	0.1888	0.987	25.33	0.964	32.885	0.394	0.973	0.195
LF4	0.886	6.446	0.884	0.2487	0.982	26.21	0.953	36.728	0.368	0.956	0.229

Post compression parameters

The thickness of formulated tablets was found to be in the range of 3.503±0.02 to 3.571±0.02mm, coat thickness in the range of 100.3±2.4 to 251.1±3.2μm, the hardness values were in the range of 7.6±0.12 to 8.1±0.04kg/cm², the friability values were in range of 0.11±0.13 to 0.19±0.04, average weight of tablet was in the range of 649.09±1.03 to 651.08±1.04 mg, drug content of tablet was in the range of 98.69±1.03 to 99.47±1.25 and diameter of tablets values were ranges of 11.98±0.06 to 12.29±0.03 mm. Post compression parameters of all the formulation of lamivudine showed satisfied results according to the Pharmacopoeias specifications (Table IIb).

In vitro drug release study

The *in vitro* drug release characteristics were studied in 900mL of 0.1N HCl (pH1.2) for a period of the first 2h and 3 to 12h in phosphate buffer pH 6.8 using USP type II dissolution apparatus (Paddle type). The cumulative percentage drug release for LF1, LF2, LF3 and LF4 were 90.54, 91.26, 92.43 and 97.78% respectively of lamivudine at the end of 12h. It was observed that the drug release is more in LF4 batch as it contains 100mg of polymer and 100mg of fructose. Hence it was confirmed that the drug release depends upon osmotic pressure of osmogen (Figure 2).

Figure 2. *In vitro* release profiles showing lamivudine release from various fabricated formulations LF1-LF4

IVDR kinetics

From the kinetic it is observed that LF1 follows non-Fickian transport mechanism and LF2, LF3 and LF4 show Fickian diffusion mechanism. The regression values of LF1 to LF4 for zero order were 0.946, 0.920, 0.903 and 0.886 respectively. The regression values of LF1 to LF4 for first order were found to be 0.927, 0.950, 0.954 and 0.884 respectively. All the formulations showed to be best expressed by Higuchi equation as the plots showed high linearity with regression values closer to unity. The optimized formulation LF4 is showing highest regression values (R^2) in Higuchi model than zero order and first order. Hence the drug release follows Higuchi kinetics. The n value for optimized formulation is 0.368 ($n < 0.45$). Hence it follows Fickian diffusion mechanism (Table III).

Effect of osmogene concentration

It is observed that osmogene enhances the drug release of drug and thus had a direct effect on drug release. The concentrations of osmogen were 25, 50, 75 and 100mg/tablet for LF1, LF2, LF3 and LF4 respectively. The cumulative percentage drug release for LF1, LF2, LF3 and LF4 were 90.54, 91.26, 92.43 and 97.78% respectively of lamivudine at the end of 12h. It was observed that the drug release is more in LF4 batch comparing to other batches due to more concentration of osmotic agent (Figure 2).

Effect of pore former

To study the effect of pore forming agent core formulations of lamivudine were coated with varying coating compositions of pore forming agent containing 0%, 6.6%,

13.3% and 20% w/w of CA of sorbitol for LF1, LF2, LF3 and LF4 respectively. The drug release order for LF1 to LF4 batch is $LF4 > LF3 > LF2 > LF1$. The optimized lamivudine CPOP tablets LF4 contain fructose 100mg/tab and pore former concentration 20% w/w of CA of sorbitol releases drug 97.78% up to end of 12h. It is clearly evident that the level of sorbitol had a direct effect on drug release. As the level of pore former increases the membrane becomes more porous after coming contact with aqueous environment resulting in faster drug release. Statistical analysis (t -test) of drug release data gives t value of 0.03 for an LF4 formulation which is much less compared to the table value of 2.353 ($p < 0.05$). Hence it can be concluded that osmogen concentration as well as porogen concentration both have a direct relation to drug release of lamivudine (Figure 2).

Effect of membrane thickness

The coating thickness for LF1, LF2, LF3 and LF4 were 251.1, 200.8, 150.5 and 100.3 μ m respectively. The drug release is highest (97.78%) at the end of 12h in LF4 because the thickness of coat is less. Similarly, the drug release is minimum at the end of 12h in LF1(90.54%) as the thickness of coat is more. It is clearly evident that drug release decreases with increase in a coating thickness of the semi permeable membrane. Release profile of lamivudine from these formulations (Figure 2).

Figure 3. *In vitro* release profiles showing lamivudine release from best LF4 in different osmotic pressures

Effect of osmotic pressure

The results of release studies of optimized formulation in media of different osmotic pressure indicated that the drug release is highly dependent on the osmotic pressure of the release media. The release was inversely

related to the osmotic pressure of release media. This finding confirms that the mechanism of drug release is by osmotic pressure. The drug release for LF4 was found to be 89.36% for 30atm, 79.24% for 60atm and 70.98% for 90atm respectively (Figure 3).

Effect of pH

The optimized formulation LF4 was subjected to *in vitro* drug release studies in buffers with different pH media like 0.1N HCl (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer pH7.4 in USP type II dissolution apparatus in 75rpm. The drug release of optimized formulation was observed in 0.1N HCl (pH 1.2) for drug release, it was found that the drug release was nearly same for the end of 11h. But at the end of 12h the drug release was same with optimized formulation 97.78%. The drug release of the LF4 formulation was observed in phosphate buffer pH 6.8 for drug release, it was found that the drug release was nearly same for the end of 11h. But at the end of 12h the drug release was same with optimized formulation 97.78%. The drug release of the LF4 formulation was observed in phosphate buffer pH 7.4 for drug release, it was found that the drug release was nearly same for the end of 11h. But at the end of 12h the drug release was same with optimized formulation 97.78%. It is observed that there is no significant difference in the release profile, demonstrating that the developed formulation shows pH independent release (Figure 4).

Figure 4. *In vitro* dissolution study of best formulation LF4 in various pH media

Effect of agitation intensity

The optimized formulation of the LF4 batch was carried out in USP dissolution apparatus type-II at varying rotational speeds (50,100 and 150rpm). The drug releases of the

optimized formulation were observed in 50, 100 and 150rpm for drug release, it was found that the drug release was nearly same for the end of 11h. But at the end of 12h the drug release was same with optimized formulation 97.78%. It shows that the release of lamivudine from CPOP is independent of agitation intensity. Hence it is expected that the release from the developed formulation will be independent of the hydrodynamic conditions of the absorption site (Figure 5).

Figure 5. *In vitro* dissolution study of best formulation LF4 in various agitation speeds

SEM analysis

SEM study indicates before dissolution fewer pores were found in the coating membrane. But after dissolution comparatively more numbers of pores were found in the membrane might be due to leaching or removal of the entrapped drug from the formulation as well as the presence of pore forming agent sorbitol in the formulation (Figure 6 a and 6 b).

Figure 6a. SEM image of LF4 before dissolution, 6b. SEM image of LF4 after dissolution

Stability studies

From short term stability studies of optimized formulation LF4, it was confirmed that there was no significance changes in

physical appearance, thickness, hardness, friability, weight variation and drug content and % drug release.

CONCLUSION

Lamivudine CPOP tablets were successfully developed. Out of several formulations LF4 containing 100mg of fructose per core tablet, 100mg of HPMC E5LV and 1.2 gm of sorbitol in SPM as pore former was successfully complied with the rate of drug release of CPOP tablets. Thus LF4 can provide more prolong, control and pH independent drug release and expected to perform therapeutically better with improved patient compliance.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contributions of Pharmaceutics department, Faculty of Pharmacy, University College of Technology, Osmania University, Hyderabad, India for providing necessary facilities to carry out the review work. This study was part of a Ph.D thesis under Osmania University, Hyderabad.

REFERENCES

- Dasankoppa FS., Ningangowdar M., Sholapur H., 2013. Formulation and evaluation of controlled porosity osmotic pump for oral delivery of ketorolac. *J Basic and Clin Pharmacy*.4(1):2-9.
- Edavalath S., Shivanand K., Prakasam K., Rao BP., Divakar G. 2011. Formulation development and optimization of controlled porosity osmotic pump tablets of diclofenac sodium. *Int. J. Pharm. Pharm. Sci.* 3(1):80-87.
- Higuchi T., 1963. Mechanism of sustained action medication theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci*52:1145-1149
- Hixson AW., Crowell JH., 1931. Dependence of reaction velocity upon surface and agitation, *Ind.Eng.Chem.* 23:923-931.
- Kaushal AM., Garg S., 2003. An update on osmotic drug delivery patents. *Pharm. Tech.*, 27: 38-44
- Kumaravelrajan R., Narayanan N., Suba V., 2011. Development and evaluation of controlled porosity osmotic pump for Nifedipine and Metoprolol combination. *Lipids in Health and Disease*.10:51
- Kanagale P., Lohray BB., Misra A., Davadra P., Kini R., 2007. Formulation and Optimization of Porous Osmotic Pump based Controlled Release System of Oxybutynin. *AAPS Pharm SciTech.* 8(3): E1-E7
- Korsmeyer RW., Gunny R., Docler E., Buri P., Peppas NA., 1983. Mechanism of solute release from porous hydrophilic polymers *Int.J.Pharm.*15:25-35
- Maheswari U., Elango K., Chellakumari D., Saravanan K., Samy AJ., 2012. Formulation and evaluation of controlled porosity osmotic tablets of lornoxicam. *Int. J. Pharm Scie Res* 3(6):1625-1631.
- Pragathi NA *et al.*, 2015. Effect of different diluents on release profile of Lamivudine from sustained release matrix tablet using kollidon SR as release retardant, *Int.J.Res. Pharm. and Nano Sciences*, 4(2): 50-59.
- Presscott LF., 1989. The need for improved drug delivery in clinical practice in Novel Drug Delivery and its Therapeutic applications. West Sussex, UK: John Wiley and Sons; 1-11.
- Patel H., Patel UD., Kadikar H., Bhimani B., Daslaniya D., Patel G., 2012. Formulation and evaluation of controlled porosity osmotic pump tablets of glimepiride. *Inter J Drg Del*4(1):113-24.
- Patel H., Patel MM., 2012. Formulation and evaluation of controlled porosity osmotic drug delivery system of carvedilol phosphate. *J PharmScie Bioscie Res*2(2):77-82.
- Rani M., Mishra B., 2004. Comparative in vitro and in vivo evaluation of matrix, osmotic matrix and osmotic pump tablets for controlled delivery of diclofenac sodium. *AAPS Pharm. Sci Tech.*5(4):1-7.
- Rao BP., Geetha M., Purushothama N., Sanki U., 2009. Optimization and development of swellable controlled porosity osmotic pump tablet for theophylline. *Trop. J. Pharm Res.* 8(3):247-255.
- Richman DD., 2001. HIV chemotherapy. *Nature* 410, 995-1001, 2001

- Sahoo CK., Sahoo TK., Moharana AK., Panda KC., 2012. Formulation and optimization of porous osmotic pump based controlled release system of Residronate sodium for the treatment of postmenopausal osteoporosis. *Int. J PharmSci Rev Res* 12(1):118-122.
- Sahoo CK., Sahoo NK., Rao SRM., Sudhakar M., Satyanarayana K., 2015. A review on controlled porosity osmotic pump tablets and its evaluation. *Bulletin of Faculty of Pharmacy, Cairo University*, 53(2):195-205.
- Sahoo CK., Rao SRM., Sudhakar M., 2015. Evaluation of controlled porosity osmotic pump tablets a review. *Research J. Pharm. And Tech.* 8(12):119-125.
- Sahoo CK., Rao SRM., Sudhakar M., Kokkula S., 2015. The kinetic modeling of drug dissolution for drug delivery systems: an overview. *Der Pharmacia Lettre* 7(9):186-194.
- Sahoo CK., Sahoo NK., Rao SRM., Sudhakar M., 2017. A review on prevention and treatment of AIDS. *Pharm Pharmacol Int J*, 5(1):00108.
- Sahoo CK., Rao SRM., Sudhakar M., 2015. A review on human immunity system and HIV infection. *Int. J. Current Pharmaceutical Review and research* 6(6):262-268.
- Sahoo CK., Rao SRM., Sudhakar M., 2017. Formulation and optimization of controlled porosity osmotic pump tablets of zidovudine using mannitol as osmogen for the treatment of AIDS. *International J. Chem. Tech. Research.* 10(5): 216-235.
- Sahoo CK., Rao SR., Sudhakar M., Shashikala P., 2017. Formulation and optimization of controlled porosity osmotic pump tablets of ritonavir. *J. of Chemical and Pharmaceutical Sciences*, 10(3):1345-1352.
- Sahoo CK., Rao SRM., Sudhakar M., 2017. Formulation and optimization of controlled porosity osmotic pump tablets of zidovudine and lamivudine combination using fructose as osmogen. *Journal of Drug Delivery and Therapeutics*, 7(4):41-50.
- Sahoo CK., Rao SRM., Sudhakar M., Satyanarayana K., 2017. Development and evaluation of controlled release formulation of zidovudine based on microporous osmotic tablet technology using fructose as osmogen. *Research J. Pharm. and Tech.* 10(5):1459-1470.
- Sahoo CK., Rao SRM., Sudhakar M., Bhaskar J., 2016. Advances in granulation technology. *Research J. Pharm. and Tech.* 9(5):571-580.
- Sharma F., Jain H., Kanzariya V., Upadhyay U., 2014. Formulation and evaluation of controlled release osmotic tablet of metoprolol succinate. *Asian J. Pharm Clin Res* 7(3):38-43.
- Shah N., Patel K., 2013. Design and development of controlled porosity osmotic tablets of captopril. *J. Pharm Sci Bioscientific Research*, 3(4):145-150.
- The USP 26-National Formulary 21 Rockville MD US Pharmacopoeial Convention 2003.
- Verma RK., Garg S., 2004. Development and evaluation of osmotically controlled oral drug delivery system of glipizide. *Euro. J. Pharm. Biopharm.* 57:513-525.
- Zenter GM., Rork GS., Himmelstein KJ., 1985. The controlled porosity osmotic pump. *J control release*, 1:269-282.