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Research Article

FORMULATION DEVELOPMENT AND I*N VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF LAMIVUDINE

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ABSTRACT
Two hydrophobic polymers Eudragit RL 100 and Eudragit RS 100 were used for preparing sustained release lamivudine tablet. In this study the effect of the thermal and solvent treatment on drug release, tensile strength was studied. Increasing the sintering duration increase in the sustained release and also increase in hardness of tablet. FTIR, XRD and DSC study shows no chemical interaction between drug and polymer and no polymorphic changes in drug due to sintering. SEM analysis conformed the redistribution of polymer and smoother tablet. The solvent treatment gives more sustained release of drug compare to thermal treatment.
KEYWORDS: Eudragit, Glass transition temperature, solvent sintering, Thermal sintering.

INTRODUCTION

Lamivudine is (-)- 4amino-1-[(2R,5S)-2-(hydroxyl methyl) 1,3-oxidation-5-yl]pyrimidine-2(1-H) –one. It has half life about 5-7 h. It is most commonly used antiretroviral drug in the treatment of AIDS and HBV infection and administered in dose of 150 mg twice a day. The main disadvantage of the antiretroviral drug in the long treatment is their adverse effect, huge cost and more frequency of administration[1,2].

For the long term treatment of any chronic disease condition the conventional release tablets have to be administered in multiple dose which presents problems like patient compliance, toxicity and therapeutic index[3].

Matrix sustained release (SR) tablets are easier to formulate and most popular system. In SR matrix tablets the drug is released at the predetermined rate and it depend on required therapeutic concentration and drugs pharmacokinetic parameters. Incorporating a drug within the insoluble matrix provides a conventional mean to controlled release. It offers many advantages like chemical inertness, drug embedding ability etc. Acrylic polymers are widely used as the plastic rate retarding matrix material. In these system the drug at the surface is released first and then dissolution medium penetrate into the tablet which is followed by the drug release. Dissolution of surface drug causes formation of depletion zone and is increased progressively.[4-7]

In the present study matrix tablets are prepared by sintering technique. Sintering is defined as bonding of adjacent particle surface in a mass of powder or in compact by the application of heat or by the use of suitable solvents. It causes the redistribution of polymer which covers the drug particle and gives sustained release. The temperature used for sintering should be above the glass transition temperature while solvent selected should be such that it partially solubilises the retarding polymer. [8,9,10]

The main objectives of present study is sustaining the drug action to reduce the dosing frequency and to study the effect of sintering technique, sintering time on release of lamivudine from the acrylic Polymer matrix tablets.

MATERIAL AND METHOD

Lamivudine is obtained as a gift sample from Hetro Labs, Andhrapradesh. Eudragit RS 100, Eudragit RL 100, Microcrystalline cellulose, Magnesium stearate, Talc. All chemicals were of analytical grade and used as received.

Calculation of dose[11,12]

The formulation involves the calculation of loading dose desired release rate, maintenance dose and total dose needed for lamivudine sustained release matrix tablets for once daily administration as follows:

Oral dose (Xo) – 150 mg, Elimination half life ($t_{1/2}$) – 6 h
Dosing interval (T) – 12 h, Time of peak concentration (t_p) – 1 h
Elimination rate constant (K_e) = $0.693/t_{1/2}$ = 0.1155/h
Initial dose – Di = Css.Vd/F , But Css= F.X0/Ke.Vd.T
Thus Di = Xo/Ke.T = 108.22 mg
Desired rate of drug release (Ks) = Di * Ke = 12.5 mg/h
Maintenance dose (Dm) = Ks * T = 150 mg
Corrected initial dose (Di*) = Di – (Ks * tp) = 89.47 mg
Total dose (Dt) = Dm + Di* = 239.47 mg = 240 mg

Preparation of Matrix Tablets of Lamivudine

Matrix tablets containing Lamivudine were prepared by direct compression technique.

All ingredients except magnesium stearate mixed together by geometric mixing for the period of 10 min. Magnesium stearate was added prior to compression. Tablets were compressed using KBr press. The composition of various formulation were given in table 1.

Sintering of Matrix Tablets

The two methods were used for the sintering solvent and thermal sintering.

Thermal treatment

The prepared tablets were placed on aluminium foil and subjected to heating at temperature 70^0 C for 6, 12, 18, 24 h in hot air oven

Solvent treatment

The tablets were also subjected to solvent sintering by exposing them to acetone vapours for 1.5, 3, 4.5 h. Acetone was used in sintering because the polymers used are partially soluble in the acetone. The bottom of desicater is filled with the acetone and it is allowed to equilibrate with acetone vapours for 24 h. After treatment the tablets were kept in desicater for 24 h.

Release test

For *in vitro* release of Lamivudine from sintered matrix tablet, a Veego Dissolution apparatus VD-6 was used at 50

rpm in 900 ml dissolution medium at 37^0 C. Buffer solution of pH 1.5 for first 2 h and pH 6.8 for 22 h were employed as the dissolution media. Samples were withdrawn at appropriate time intervals, filtered and assayed for lamivudine using a UV- 1800 shimadzu spectrophotometer at 280 and 271 nm for pH 1.2 and pH 6.8 respectively.

Surface Morphology

SEM was used to study the morphological changes in tablet surface before and after sintering. Tablets were coated with gold palladium alloy using Jeol/EO fine coat sputter. The samples were then observed under 100X, 200X and 300X magnification using Jeol JSM 6360A.

Differential Scanning Calorimetric (DSC)

DSC analysis was performed on Eudragit RS 100, lamivudine and optimized formulation using Nanotechnology, DSC 6220 SII. Accurately weighed 10 mg of sample was heated in closed aluminium pan from 30^0 to 300^0 C at heating rate 10^0/min.

IR absorption spectroscopy

FTIR spectra of lamivudine, Eudragit RS 100, optimized formulation were investigated using shimadzu IR affinity -1-CE.

XRD study

Diffraction pattern of lamivudine and formulation were recorded with Philip's diffractometer.

Percent erosion study

For erosion measurement dissolution apparatus was used at 50 rpm speed, 900 ml phosphate buffer pH 6.8 at 37^0C. Initially weighed tablets were placed in buffer for 24 h. After 24 h tablets were removed and kept for drying. The percent erosion was calculated using formula as

$$\text{Percent erosion} = \frac{\text{Initial wt} - \text{Remaining Dry wt}}{\text{Initial wt}} * 100$$

Percent water uptake study

Initially weighed tablets were placed in phosphate buffer pH 6.8 for 24 h. After 24 h these wet tablets are again weighed and kept for drying. Percent water uptake was calculated using formula as

$$\text{Percent water uptake} = \frac{\text{Wet wt} - \text{Remaining Dry wt}}{\text{Remaining Dry wt}} * 100$$

Table 1: Composition of Lamivudine matrix tablet

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lamivudine	240	240	240	240	240	240	240	240	240
Eudragit RL 100	100	150	200	_	_	_	50	75	100
Eudragit RS 100	_	_	_	100	150	200	50	75	100
Talc	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Magnesium stearate	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
MCC	148.5	98.5	48.5	148.5	98.5	48.5	148.5	98.5	48.5

Total weight of tablet 497.57 mg.
*All ingredients are in mg per tablet.

Table 2: *In-vitro* dissolution kinetic models for F6 formulation

	Unsin	Thermal sintering				Solvent sintering				
Kinetic Model		6 h	12 h	18 h	24 h	1.5 h	3 h	3.5 h	4 h	4.5 h
Zero order	0.888	0.899	0.944	0.970	0.947	0.953	0.984	0.947	0.985	0.986
Matrix	0.974	0.983	0.992	0.987	0.995	0.993	0.990	0.998	0.978	0.990
First order	0.766	0.794	0.847	0.885	0.849	0.859	0.924	0.801	0.879	0.918
Peppas	0.986	0.997	0.990	0.977	0.993	0.989	0.97	0.992	0.959	0.976

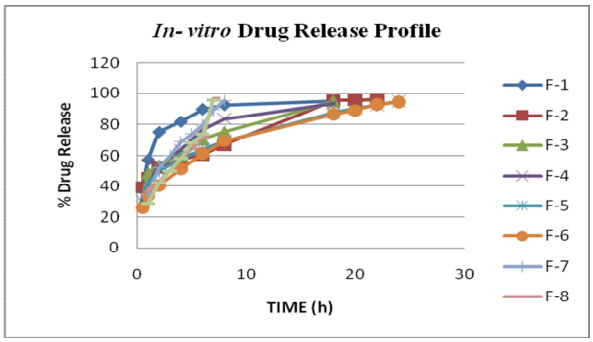

Figure 1: *In- vitro* Dissolution profile of 6 h Thermal sintered formulation F-1to F-9

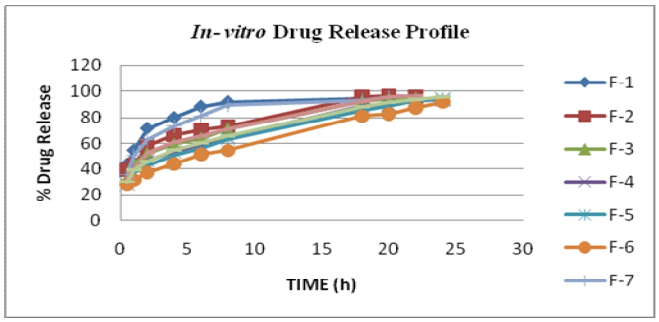

Figure 2: *In- vitro* Dissolution profile of 3 h Solvent sintered formulation F-1to F-9

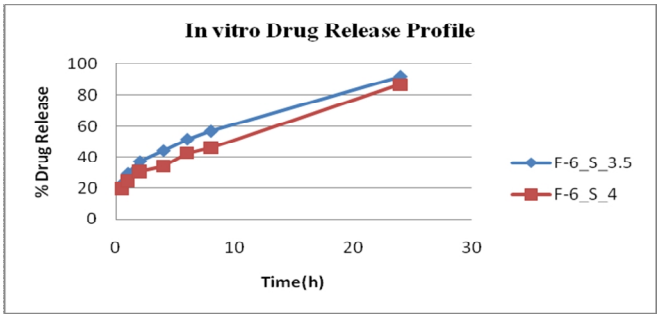

Figure 3: *In- vitro* Dissolution profile of 3.5 and 4 h Solvent sintered F-6 formulation

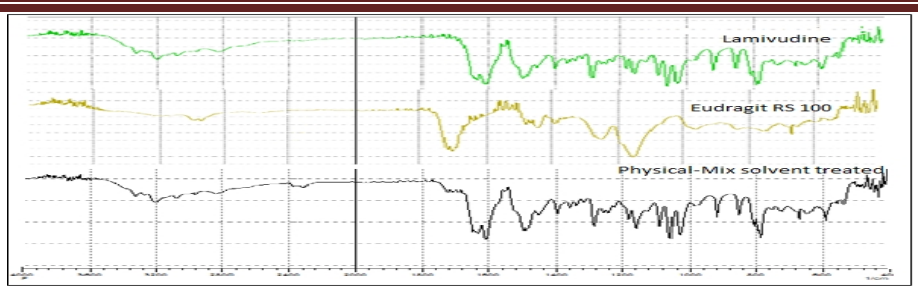

Figure 4: FTIR of lamivudine, Eudragit RS 100, physical-mix solvent treated samples

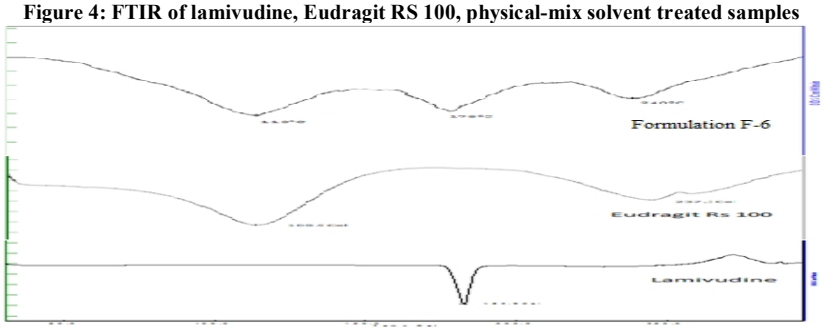

Figure 5: DSC of Lamivudine, Eudragit RS 100 and Optimized formulation F-6

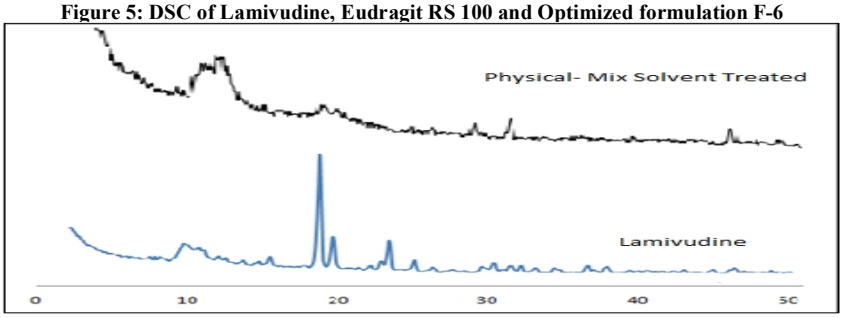

Figure 6: X-ray spectra of lamivudine and solvent treated sample

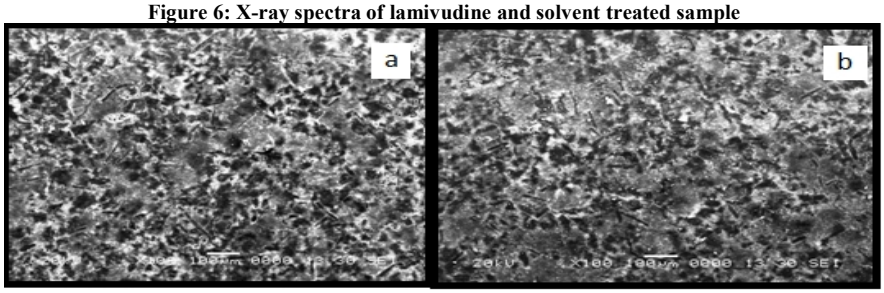

Figure 7: Scanning electron micrographs of prepared tablet (a) unsintered tablet (b) sintered tablet

RESULT AND DISCUSSION

In the present study sintering was carried out at 70^0 C for 6, 12, 18 and 24 h. This temperature is slightly above Tg (glass transition temperature) of EudragitRL100 and Eudragit RS100 and well below the melting point of lamivudine (182.9^oC) to avoid drug instability. Coalescence of Eudragit particles is influenced by minimum film forming temperature.[13] At this temperature, coalescence takes place but may require different time period. Exposure to this temperature made the structural changes in the tablet compacts resulted in matrix tablet structure. Similarly exposure to the good solvent vapours i.e. solvent in which polymer has solubility solubilise the polymer at the surface and if expose for more time fusion of polymer particles in the bulk of tablet takes place thus bringing about sintering.[14,15] If we compare the release of drug from RL100 and RS 100 and the combination of RL100 and RS100 unsintered tablets maximum sustaining action was found with RS100 polymer with concentration ranging between 150-200mg.This might be due to the difference in extent of quaternary ammonium substitutions between RL100 and RS 100. RL 100 polymer is relatively more hydrophilic than RS100 polymer.[13] On sintering these formulations for solvent as well as thermal it was found that F6 formulation gave better results compared to F5 and other formulations. Our aim was to release the loading dose 87.47mg in first 2h and release the remaining amount in next 22 h which was achieved by F6 formulation were as F5 formulation released 119.32mg which was more than F6 formulation (97.39mg) for 6h oven sintering and also sustained the drug release for more than 24h. For Solvent Sintering for 3h F5 formulation released 101.95mg drug in first two hours and F6 released 89.13mg in 2h whereas for 4.5 h the release for F5 was 96.67 mg and F6 was 70.03mg (figure 1,2)

Therefore solvent sintering was optimized based on loading dose release and sustain action. Further the time for solvent sintering was kept between 3 to 4.5 i.e. 3.5and 4h in an attempt to get the exact loading dose release in first 2h and it was observed that on sintering for 4 h the loading dose was exactly released (88mg) and then sustained for 24 h (figure 3).

On applying various models on the dissolution release all the formulation showed matrix diffusion model. The regression coefficient values are shown in table 2.

As the tablets are sintered by thermal and solvent exposure. The sustained release of drug may be due to the chemical

interaction with polymer. To determine the any possible chemical interaction FTIR study was carried out. The FTIR spectra of lamivudine, Eudragit RS 100 and optimized formulation were shown in figure 4. In the lamivudine spectrum two peaks at 1286.52 cm^{-1}, 1559.52 cm^{-1} for symmetric and asymmetric –C-C- stretching , 1651.1 cm^{-1} for carbonyl group, 3326.8 cm^{-1} for $–NH_2$ stretch, 3194.12 cm^{-1} -OH stretch , 1452.4 cm^{-1} for aromatic C=C stretch are seen. Other important peaks are 918.12 cm^{-1} and 850.65 cm^{-1}. Important peaks in Eudragit RS 100 spectrum are 1393.51 cm^{-1} (asymmetric CH_3 bending), 1448.49 cm^{-1} (symmetric CH_3 bending), 1740.32 cm^{-1}(C=O stretching), 1147.68 cm^{-1} (C-CO-C stretch).[16,17] The comparison FTIR spectra of Drug-RS 100 mixture after sintering shows no difference in the absorption band position. This shows there is no chemical interaction between lamivudine and Eudragit polymers.

The thermogram of lamivudine, Eudragit and their physical mixture after curing is shown in Figure 5. Lamivudine spectrum showed a very sharp endothermic melting peak at 182.9^0C which show characteristic of lamivudine form II. [18] Eudragit RL 100 and RS 100shows the amorphous nature, graph shows the inclination between 55- 60^0C for RS100 and 60-65^0C for RL 100.It is related T_g of polymer.[13] In the physical mixture of polymer and drug after sintering shows endothermic peak near 180^0C. This indicate that there is no polymorphic change in the drug due to sintering.

Lamivudine exist in three polymorphic forms i.e. Form I, II and III which have different thermal stability. The X-ray diffraction peaks of pure lamivudine powder occurred at 2θ values 14.36, 17.6, 20.69, 21.6, 26.56 which show that lamivudine is in stable Form II.[19,20] The diffraction peaks in the physical mixture after sintering are located in the same position(figure 6). This indicates that there is no chemical change in crystalline form of drug by sintering.

The SEM micrographs of tablet surface both before and after sintering were studied. (figure 7) The sintered tablet surface appeared smoother and sintering causes the decrease in the porosity of tablet. This is due to coalescence of Eudragit particle due to sintering and there is uniform redistribution of the polymer in the pores of tablet.[21]

The percent water uptake and percent erosion of tablet was maximum with unsintered tablets. With increase in sintering duration both water uptake and erosion decreases indicating redistribution of polymer to increase in hydrophobicity of tablet

CONCLUSION

During sintering of tablets, polymer particle transform from glassy state to rubbery state and redistributed to entangled the drug particles , leading to drug release retardation. By electing proper polymer concentration, sintering condition and duration we formulated effective sustained release formulation of lamivudine. The drug did not undergo degradation during sintering.

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