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Fabrication and Characterization of Lamivudine Matrix Tablets using Gum Damar and HPMC

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ABSTRACT

The aim of the study was to formulate and evaluate matrix tablets of a water soluble antiretroviral drug using hydrophobic and hydrophilic polymers. Matrix tablets of Lamivudine were prepared by direct compression method using gum damar (GD) and HPMCK100 (HPMC) as release retardants. Different concentrations of polymers GD (5%, 10% and 15%), HPMC (2.5%, 5% and 7.5%) were examined to know their effect on in vitro drug release. Tablets were characterized for their pre compression and post compression parameters. The in vitro drug release studies were carried out in pH 1.2 buffer for 2 hours and then in pH 6.8 phosphate buffer. The content uniformity was found to be within the compendial requirements. Though the release was extended for more than 8hrs by both the polymers, HPMC was able to sustain the drug release well when compared to gum damar. The drug release of F_1, F_2, F_4 and F_5 formulations fitted zero order kinetics where F_3 and F_6 which fitted first order kinetics. Mechanism of release for all the formulations is by non fickian release (anomalous) which refers to a combination of both diffusion and erosion controlled drug release.

Key words: *Gum damar, HPMC, Lamivudine, Sustained drug release.*

INTRODUCTION

Controlled Drug delivery is the phasing of the drug administration to needs of a condition at hand so that an optimal amount of drug is used to cure or control the condition in minimum time. The term 'controlled release' includes not only the notion of prolonged duration as implied by the term 'sustained release' but goes further in denoting predictability and reproducibility of release kinetics. These novel drug delivery systems are gaining popularity since they have surpassed the drawbacks of the conventional dosage form of increased frequency of dosing, prompt drug release etc., by controlling and sustaining the duration of the therapeutic activity [1]. In pharmaceutical CRDDS, matrix based systems are the most commonly used type of release controlling methodology owing to their simple manufacturing process, level of reproducibility, stability of the raw materials and dosage forms as well as ease of up operation and also resistant to dose dumping. These systems improve patient compliance and decreased adverse drug reactions [2].

Acquired immune deficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). Lamivudine is approved for clinical use and used widely in treatment of Hepatitis B and AIDS either alone or in combination with another antiviral drugs because of its water solubility and shorter half -life (5-7 hours) drug requires frequent dosing by oral route, of various recent techniques for controlling drug release, matrix system offer various advantages of ease of formulation better control on release profile of drug and better patient compliance [3].

Many plant derived natural materials are studied for use in novel drug delivery systems, out of which polysaccharides, resins and tannins are most extensively studied and used. Ability to produce a wide range of material based on their properties and molecular weight, natural polymers became a thrust area in majority of investigations in drug delivery systems [4]. Gum damr is a hard resin collected by tapping trees from *Shorea spp. (including S.javanica, S.lamellata, S.retinodes,)* dipterocarp forests From South-East Asia, including Malay & Indonesian archipelagos. Dammar gum is a triterpenoid resin, containing a large number of triterpenes and their oxidation products. Many of them are low molecular weight compounds (Dammarane, Dammarenolic acid, Oleanane, Oleanonic acid, etc), but dammar also contains a polymeric fraction, composed of polycadinene. Their main use is in the manufacture of paper or wood varnishes and lacquers, particularly as a varnish for the fine art, and some paints. It is a water- resistant coating, sometimes also used for its glazing functionality, and found in the indigenous system of medicine [5]. A few works were reported on gum dammar using it as a matrixing agent for sustained release [6, 7]. Considering the scope and availability of the natural polymers the present research work was planned with GD and HPMC as matrixing agents for the sustaining the drug release.

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MATERIALS AND METHODS

Materials:

Lamivudine was obtailned was obtained as a sample from Hetero drugs, Hyderabad. Gum Damar is procured from Girijan co-operative corporations, Vizag and HPMC were procured form drugs India, Hyderabad. All other ingredients are of analytical grade.

Methods:

All the matrix tablets, each containing Lamivudine 150 mg, were prepared by direct compression method. Drug is mixed with appropriate quantities of GD (5%, 10%, 15%), HPMC (2.5%, 5%, 7.5%) and directly compressible lactose for 20min to ensure uniform mixing in geometrical ratio. Powder mixture was evaluated for angle of repose bulk density (BD) and tapped density (TD). Carr's index (CI) and Hausner ratio were calculated using following equations [8]. After evaluation this powder mixture was blended with lubricating agents (1% w/w magnesium stearate and 1% w/w talc) and compressed using 16 station rotary punching machine, equipped with flat-faced, round punches of 8-mm diameter. Composition of the floating tablets and precompression data of the powder mixture were given in the **Table 1 & 2** respectively.

$$\text{Hausner ratio} = \frac{TD}{BD} \qquad \%CI = \frac{TD - BD}{TD} \times 100$$

Determination Of Hardness, Friability And Drug Content:

The prepared matrix tablets were evaluated for hardness, friability, thickness, uniformity of the weight and content uniformity. Hardness was determined by using Pfizer hardness

tester. Friability was determined using Roche friability testing apparatus. Thickness was measured using vernier calipers. Uniformity of the weight and content uniformity were performed according to the I.P method [9, 10]. The tensile strength of the tablets was measured by using the following formula and the values were given in the **Table 3**.

$$T = \frac{2C_s}{\pi Dt}$$

Where, C_S = crushing strength, D= diameter, t = thickness, T = tensile strength.

Drug Release Studies:

The *in vitro* drug release studies were carried out on a eight stationed USP type II dissolution apparatus (paddle method) at 37°C ± 0.5°C and 50 rpm for a period of 8h. The dissolution studies were carried in triplicate in 900 ml of 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 8 hours. An aliquot (5ml) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 265 nm. The amount of drug present in the sample was calculated with the help of appropriate calibration curve constructed from reference standards.

Release Kinetics:

To analyze the mechanism of drug release from the matrix tablets, the release data was fitted into various mathematical models viz., Zero order, first order and Highuchi equation [11]. The dissolution data was also fitted to the well known experimental equation (Koresmeyer's Peppas equation), which is often used to describe the drug release behavior from polymer systems [12].

$$\log\left(\frac{Mt}{Mf}\right) = \log K + n\log t$$

Where, M_t is the amount of drug release at time t, M_f is the amount of drug release after infinite time; K is a release rate constant incorporating structural and geometrical characteristics of the tablet and n is the differential exponent indicative of the mechanism of drug release. To clarify the release exponent for the different batches of matrix tablets, the log value of %drug was plotted against log time for each batch according to the equation 4. A value of n=0.45 indicates Fickian (case I) release; >0.45 but <0.85 for non Fickian (anomalous) release; > 0.89 indicates super case II type of release. Case II gradually refers to the erosion of the polymeric chain and anomalous transport (non- Fickian) refers to a combination of both diffusion and erosion controlled drug release [13]. Mean dissolution time (MDI) was calculated for dissolution data using the following equation [14].

$$MDI = \left(\frac{n}{n+1}\right) \times K^{-1/n}$$

Where n= release exponent and K= release rate constant.

RESULTS AND DISCUSSIONS

Lamivudine matrix tablets were prepared by direct compression method using gum damar and HPMC as retarding agents. The aqueous medium on contact with polymer matrix gradually begins to hydrate from the periphery toward the centre, forming a gelatinous swollen mass. The hydrated gel layer thickness determines the diffusional path length of the drug.

The micromeritic parameters of the powder blend of different formulation batches are shown in **Table 2**. The angle of repose was less than 29° indicates satisfactory flow behavior. The tablets of all formulations were found to be white, smooth, flat faced circular with no visible cracks. The matrix tablets were evaluated for hardness, friability, content uniformity, uniformity of weight, tensile strength and *in vitro* drug release studies. The hardness of the tablets in all the batches was found to be in the range of 5.96 – 7.46 Kg/cm^2. The friability of all the formulations was less than 1%. The drug content was found to be uniform for all the batches of tablets prepared and was found to be within range of labeled claim. The tensile strength of the tablet ranges from 15.83 – 19.28. Evaluation data of the matrix tablets were given in **Table 3**. The hardness and friability values indicated good handling properties of the prepared matrix tablets.

In vitro drug release studies were also carried out for the prepared matrix tablets. From the release profile of different formulations it was observed that the drug release is inversely proportional to the polymer concentration as formulations with GD 5% and HPMC 2.5% showed higher drug release when compared to other concentrations. **Fig. 1** depicts the release profile of lamivudine from the matrix tablets of different concentrations of gum Dammar and HPMC respectively. The order of release was F_1>F_2>F_3 in case of GD and F_4>F_5>F_6 in case of HPMC. Among the two hydrophilic and hydrophobic polymers used, tablets prepared with gum dammar though hydrophobic in nature have shown greater release rate when compared to tablets prepared using HPMC. An increase in the polymer concentration causes increase in the viscosity of the gel as well as the formation of the gel layer with longer diffusion path. This could cause a decrease in effective diffusion coefficient of drug and therefore a reduction in drug release rate.

The *in vitro* release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi and Korsemeyer's models in order to determine the mechanism of drug release. **Table 4** indicates the data analysis of release profiles according to different kinetic models. The drug release of F_1, F_2, F_4 and F_5 formulations fitted zero order kinetics where F_3 and F_6 which fitted first order kinetics. Mechanism of release for all the formulations is by non fickian release (anomalous) which refers to a combination of both diffusion and erosion controlled drug release.

Table No. 1: Composition of Lamivudine matrix tablets

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6
Lamivudine (mg)	150	150	150	150	150	150
GD (%)	5	10	15	-	-	-
HPMC (%)	-	-	-	2.5	5	7.5
DCL (mg)	38.5	31	23.5	42.25	38.5	34.75
Ms (%)	1	1	1	1	1	1
Talc (%)	1	1	1	1	1	1
Total weight (mg)	200	200	200	200	200	200

Table No. 2: Pre compression parameters of formulation blends (mean ± S.D; n=3)

Formulation code	Angle of repose (°)	Bulk density (g/cc)	Tapped density(g/cc)	Carr's index (%)	Hausner's ratio
F_1	26.91 ± 0.513	0.505 ± 0.005	0.567 ± 0.006	11.03 ± 0.794	1.12 ± 0.001
F_2	25.90 ± 0.727	0.498 ± 0.006	0.527 ± 0.005	5.504 ± 0.358	1.05 ± 0.004
F_3	28.25 ± 0.517	0.433 ± 0.007	0.466 ± 0.007	7.006 ± 0.551	1.10 ± 0.006
F_4	27.49 ± 0.56	0.399 ± 0.005	0.440 ± 0.006	9.302 ± 0.372	1.10 ± 0.004
F_5	28.87 ± 0.534	0.397 ± 0.003	0.425 ± 0.005	6.426 ± 0.837	1.06 ± 0.009
F_6	26.89 ± 0.522	0.424 ± 0.007	0.461 ± 0.010	8.018 ± 0.468	1.08 ± 0.005

Table No. 3: Physical characteristics and drug content of the matrix tablets (mean ± S.D; n=3)

Formulation code	Hardness (Kg/cm²)	Friability (%)	Drug content (%)	Tensile strength	Weight variation
F_1	6.5 ± 0.10	0.49	96.55 ± 0.585	17.24 ± 0.265	200 ± 0.001
F_2	7.46 ± 0.05	0.40	96.81 ± 1.330	19.28 ± 0.402	198 ± 0.001
F_3	5.96 ± 0.20	0.54	97.47 ± 0.688	15.83 ± 0.552	202 ± 0.001
F_4	7.06 ± 0.15	0.61	99.55 ± 0.785	18.75 ± 0.402	199 ± 0.001
F_5	6.73 ± 0.15	0.55	98.81 ± 1.01	17.86 ± 0.406	200 ± 0.001
F_6	6.43 ± 0.15	0.54	99.15 ± 1.13	17.06 ± 0.406	200 ± 0.001

Table No. 4: Mathematical modelling of matrix tablets

Code	Zero order		First order		Higuchi		Korse meyer peppas			$T_{50\%}$ (h)
	K_0(mg/h)	R	$K_1(h^{-1})$	r	K_0(mg/h)	r	$K_1(h^{-1})$	r	n	
F_1	18.98	0.975	0.723	0.942	63.99	0.993	35.727	0.997	0.643	3.951
F_2	13.07	0.975	0.488	0.937	53.38	0.993	29.991	0.998	0.61	5.738
F_3	10.92	0.97	0.276	0.991	46.14	0.984	20.137	0.984	0.759	2.51
F_4	15.16	0.975	0.564	0.907	56.46	0.991	31.117	0.993	0.635	4.947
F_5	11.54	0.99	0.375	0.929	46.37	0.977	20.137	0.998	0.756	6.499
F_6	9.83	0.981	0.204	0.994	41.04	0.984	18.578	0.991	0.734	3.397

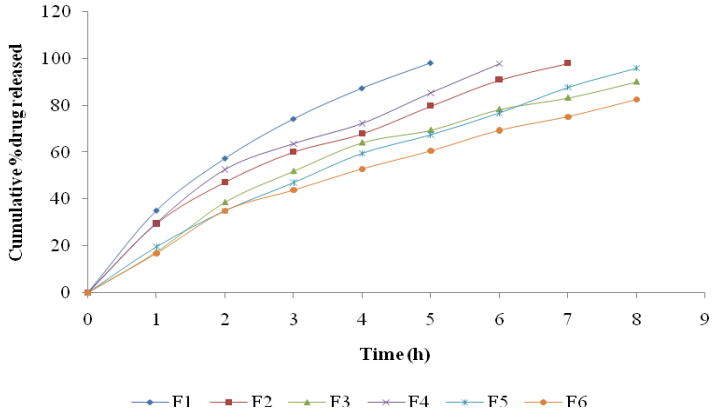

Fig. 1: *In vitro* drug release profile of matrix tablets containing GD and HPMC as release retardants

CONCLUSION

Lamivudine sustained release matrix tablets were successfully prepared using hydrophobic and hydrophilic polymers. Fabricated tablets showed acceptable weight variation, hardness and uniformity of drug content. Study indicated that increase in amount of the polymers in the tablets resulted in a reduction in the release rate. Formulation F_6 containing HPMC 7.5% was selected as the best formulation as it was able to produce satisfactory results when compared to gum Dammar and other formulations.

ABBREVIATIONS

DCL = directly compressible lactose, HPMC – Hydroxy propyl methyl cellulose, GD- Gum Dammar, MS – Magnesium state.

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