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COMPARITIVE STUDY OF HYDROPHILLIC POLYMERS FOR SUSTAINED DRUG DELIVERY OF AN LAMIVUDINE

RESEARCH ARTICLE

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ABSTRACT

The objective of the present study was to formulate and evaluate Lamivudine matrix tablets using hydrophilic polymers like karayagum(K.R), kondagogu gum(K.G), and HPMC(K100) of different ratios 2.5%,5% and 7.5% were formulated by direct compression method. The formulated tablets were characterized for hardness, friability, drug content, tensile strength. In vitro drug release studies were carried out in pH 1.2 buffer for 2hrs and then in PH 6.8 phosphate buffer. The content uniformity was found to be within the compendial limits. FTIR revealed the absence of drug-polymer interaction. The rate of drug release was extended for more than 12 hours by the HPMC (K100).HPMC was able to sustain the drug release well when compared to gum karaya and gum kondagogu. The order of release for all the formulations fitted zero order except f7 formulation followed the first order release. Mechanism of drug release from all the formulations is non-fickian diffusion which refers to a combination of both diffusion and erosion controlled drug release.

Keywords: *Lamivudine, Direct compression, Natural polymers, Zero Order of release.*

INTRODUCTION

Lamivudine is a nucleoside reverse transcriptase inhibitor a type of retroviral drug used for the treatment of HIV/AIDS infection. it works by selectively inhibiting the reverse transcriptase enzyme responsible for the virus to make a DNA copy of its RNA[1,2]. Lamivudine has low therapeutic index, short biological half-life, poor bioavailability, due to short biological half life the patient need frequent administration of drug. It leads to an adverse side effect by inhibiting the DNA polymerase used by human cells to undergo cell division due to an accumulation of drug The reason behind in formulating sustained release dosage forms is to reduce the frequency of dosing, reducing the dose required, and better patient compliance. Due to the sustaining nature of drugs therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time. Tablets are the most widely used formulations available in the market preferred by patients and physicians. In the treatment of chronic diseases conventional tablets are to be administered in multiple doses, due to this drawback in conventional formulations there is a need to develop sustained release formulations for such chronic diseases [3,4].

Sustained release formulations can overcome some of the problems. Lamivudine is freely soluble in any PH so it is easily absorbed throughout gut. Hence selection of sustaining agent is important in achieving constant drug release.hydrophillic polymeric systems like HPMC, methylcellulose, sodium carboxy methyl cellulose, carbopols and polyvinyl alcohols [5, 6]. Majorly hydrophobic polymers are used mainly for highly soluble drugs. Matrix systems can be used to control the release of both water soluble and water insoluble drugs. Polysaccharide gums are naturally abundant, biocompatible, biodegradable, and non-immunogenic[7-8].Gum karayagum, called as sterculiagum is a complex water-soluble polysaccharide. It is a hydrophilic colloid prepared from the exudates of Sterculiaurens tree. Gum karayagum, Gum kondagogu (Cochlospermum gossypium) is a tree exudates gum [9,10]. Sustained drug delivery systems improve the thetherapeutic efficacy of drugs. Many natural, semi-synthetic and fully-synthetic polymers are used as drug release retarding materials.

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MATERIALS

Lamivudine was obtained as a gift sample from Hetero Drugs, Hyderabad. Kondagogu gum and karayagum gum was obtained as a sample from Girijan co-operative corporation Ltd, srisailam. All other ingredients are of analytical grade.

Methods

Matrix tablets were prepared by using direct compression method. 200mg of drug mixed with different ratios karayagum gum, kondagogu gum,HPMC(K100)(2.5%,5%,7.5%) of polymers and directly compressible lactose individually are triturated uniformly for 20 mts to ensure uniform mixing in geometric ratios. finally add lubricants to the mixture. The composition were given in table 1

Table-1: Composition of matrix tablets formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lamivudine(mg)	150	150	150	150	150	150	150	150	150
K.R(mg)	4	8	12	-	-	-	-	-	-
K.G(mg)				4	8	12	-	-	-
HPMC(mg)	-	-	-	-	-	-	4	8	12
Lactose(mg)	91	88	84	91	88	84	91	88	84
Mg state(mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc(mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight(mg)	250	250	250	250	250	250	250	250	250

Precompression parameters

Angle of repose was determined by funnel method, bulk density and tapped density were determined by cylinder method.carrs index and Hausner ratios are calculated by the following equations

Angle of repose

$tan\theta = h/r$

where, h = height of the granule heap formed
r = radius of the heap,
θ = angle of repose

The bulk density and the tapped density were calculated using the following formulae.

$$Bulk\ density = \frac{W}{V_0}$$

$$Tapped\ density = \frac{W}{V_f}$$

where, W= Weight of the granules
V_0 = Initial volume
V_f = final volume

$$Hausner\ ratio = TD/BD$$

where, TD = tapped density and
BD = bulk density

.

$$\%CI = (TD - BD)/TD\ X\ 100$$

Table-2: Pre compression parameters of formulation blends (mean±S.D:n=3)

formulation	Angle of repose	Bulk density	Tapped density	Cars index	Hausner ratio
F1	29.59±1.973	0.570±0.004	0.605±0.011	5.83±1.215	1.05±0.015
F2	27.4±1.25	0.565±0.001	0.619±0.008	6.01±1.147	1.06±0.001
F3	28.76±0.647	0.595±0.002	0.638±0.004	6.04±0.141	1.048±0.007
F4	29.59±0.121	0.601±0.004	0.646±0.009	5.07±0.08	1.06±0.007
F5	24.61±0.563	0.625±0.004	0.681±0.024	5.45±0.791	1.08±0.005
F6	22.41±0.143	0.654±0.009	0.688±0.005	5.52±0.702	1.05±0.017
F7	27.51±0.645	0.585±0.008	0.627±0.004	4.76±0.745	1.032±0.001
F8	28.2±0.540	0.611±0.007	0.601±0.001	5.30±0.046	1.042±0.015
F9	26.45±0.134	0.599±0.021	0.688±0.003	5.9±0.763	1.05±0.01

Post compression parameters

After evaluation of Precompression parameters the blend was compressed using tablet compression machine equipped with beveled 8mm flat faced punches. The obtained tablets are evaluated for hardness, friability, drug content, tensile strength. Hardness was determined by using Pfizer hardness tester, friability was determined by using Roche friability apparater.content uniformity was determined by using I.P method. Tensile strength can be applied once load required to fracture the tablet has been determined and calculated from the following formula [11,12]

Tensile strength of the following tablets was measured by using the formula

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

where Cs is the crushing strength

T is the tensile strength

D is the diameter

T is the thickness

Table-3: Physical characteristics and drug content of matrix tablets(mean±S. D: n=3)

Formulation	Hardness (Kg/cm^2)	Friability (%)	%Drug content	Tensile strength
F1	5.93±0.23	0.43	96.5±1.501	5.72±0.611
F2	5.6±0.2	0.67	96.2±1.735	14.84±0.53
F3	5.93±0.23	0.82	99.5.±1.322	13.46±0.525
F4	6.33±0.11	0.48	98.8±1.616	16.78±0.305
F5	6.46±0.11	0.25	99.6±2.193	17.13±0.305
F6	6.4±0.2	0.36	97.8±1.014	14.52±0.455
F7	6.26±0.11	0.61	97.5±2.151	16.60±0.305
F8	5.93±0.23	0.54	99.9±1.882	15.72±0.611
F9	5.86±0.11	0.39	98.6±1.442	13.31±0.265

Invitro drug release study

Drug release studies were Carried out on a eight stage USP type II apparatus (paddle method) at 37.5± 0.5 and 50 rpm for a period of 12h were conducted. The dissolution studies were carried out using 900 ml 0.1N HCL for 2 hrs followed by phosphate buffer (PH6.8) for 12 hrs.5ml of sample was withdrawn from the dissolution for every one hour and then replaced with fresh dissolution medium to maintain sink conditionsthe samples withdrawn were filtered through whitmans filterpaper(No:1). After filtration and appropriate dilution the samples were analyzed for drug content by UV. the dissolution experiments were conducted in triplicate and average values were taken[13,14]

Fig-1: Comparative invitro drug release from the sustained release tablets of lamivudine using karaya gum (2.5%,5% &7.5%) of F1,F2,F3 formulations

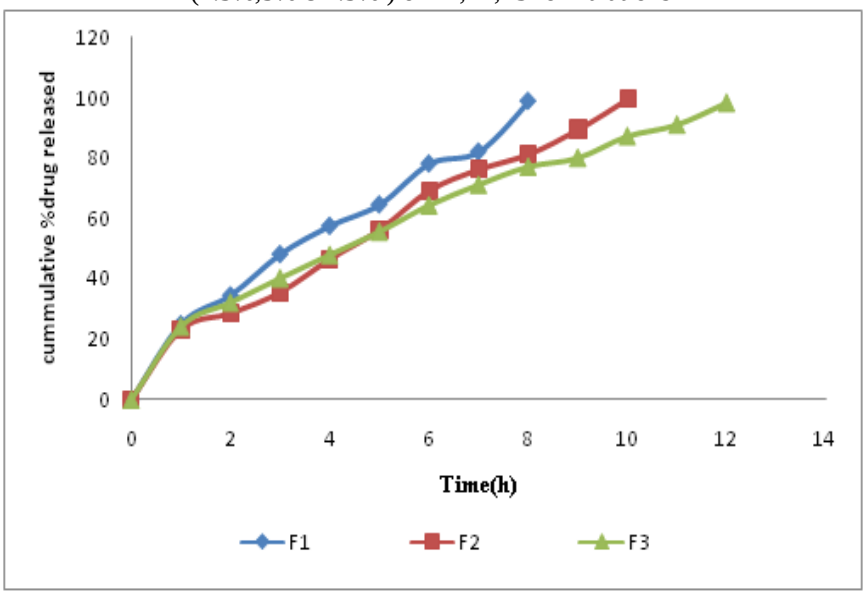


Fig-2: Comparative invitro drug release from the sustained release tablets of lamivudine using kondagogu gum (2.5%,5% &7.5%) of F4, F5, F6 formulations

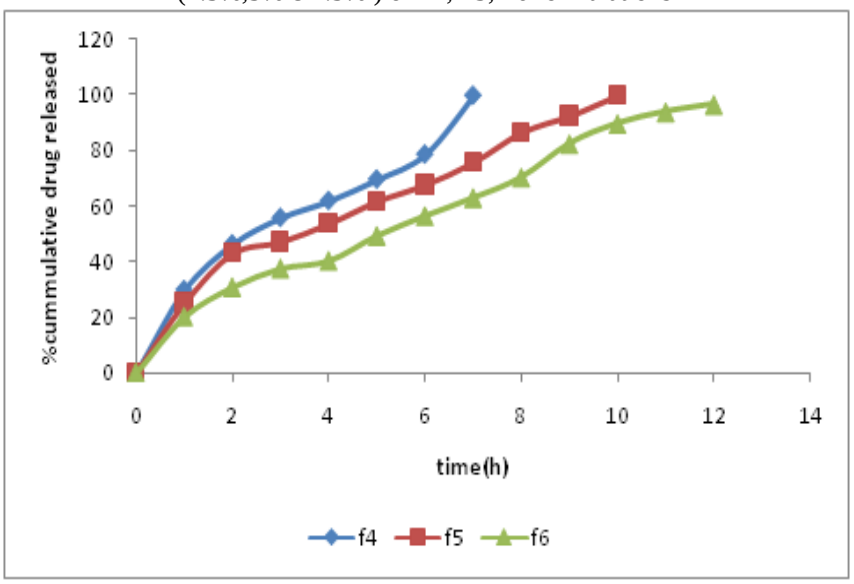
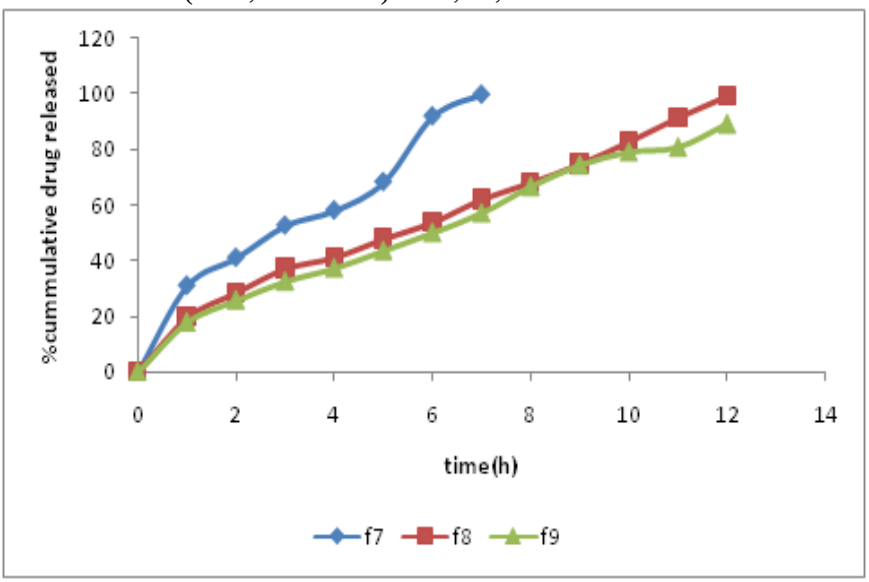


Fig-3: Comparative invitro drug release from the sustained release tablets of lamivudine using HPMC(k100) (2.5%,5% &7.5%) of F7, F8, F9 formulations



Determination of swelling index

The swelling properties of the matrix tablets were determined by weight basis method. The swelling behavior was studied in buffer solutions, P^H 1.2, 6.8 phosphate buffers. Tablets of known weight were placed in Petri dish containing 25ml of swelling medium and allowed to swell at room temp. The swollen tablets were removed and weighed periodically. The wet weight of swollen tablets was determined by blotting them with filter paper to remove moisture adhering on the surface immediately followed by weighing on a electronic balance. The percent swelling of tablets was calculated from the following formula.

$$\text{Swelling index} = \frac{W_t - W_i}{W_i}$$

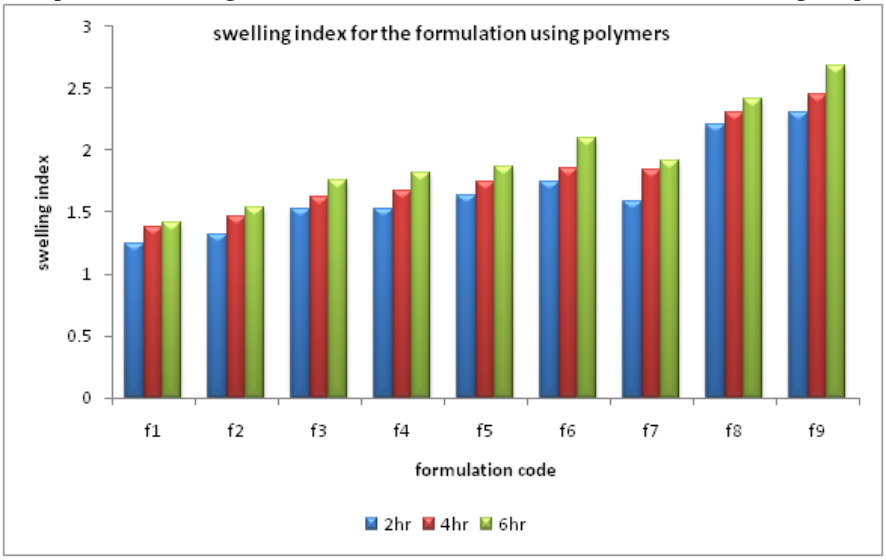
where W_i = initial weight
Wt = final weight

The results of swelling index for all the formulations were given in Table 4 and the comparative swelling index were depicted in Fig. 4.

Table-4: Swelling index for the formulations using polymers (mean ± S.D; n=3)

CODE	TIME IN H		
	2	4	6
F_1	1.24	1.38	1.41
F_2	1.32	1.47	1.54
F_3	1.53	1.62	1.76
F_4	1.52	1.67	1.82
F_5	1.64	1.75	1.86
F_6	1.74	1.85	2.1
F_7	1.59	1.84	1.91
F_8	2.203	2.305	2.408
F_9	2.305	2.454	2.684

Fig-4: Comparative swelling index for lamivudine matrix tablets formulated using the polymers



Release kinetics

To analyze the mechanism of drug release from the matrix tablets the release data was fitted in to various mathematical models like zero order, first order, Higuchi, koresmeyer-peppas equations which is often used to discuss the drug release mechanism from the formulation

$\log (Mt/Mf) = logK + nlogt$

Where, Mt is the amount of drug release at time t, M_f is the amount of drug release at infinite time, k is the release rate constant, n is the exponent used to determine the drug release mechanism. 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 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.[15,16]

Table-5: Mathematical modeling for drug release data obtained from lamivudine matrix tablet

Formula	Zero order		First order		Higuchi		Peppas			t1/2
	K_0 (mg/h)	R	$K_1(h^{-1})$	R	$k_H (\%h^{-0.5})$	r	$k_p (h^{-n})$	r	n	h
F1	11.18	0.987	0.195	0.934	74.28	0.989	16.595	0.993	0.82	8.944
F2	9.318	0.991	0.163	0.981	56.61	0.926	26.363	0.983	0.482	10.731
F3	7.359	0.98	0.163	0.956	59.46	0.972	12.133	0.983	0.701	13.888
F4	12.11	0.97	0.262	0.985	76.15	0.977	29.785	0.987	0.563	8.257
F5	8.801	0.977	0.172	0.95	64.12	0.991	17.378	0.992	0.717	11.362
F6	7.646	0.989	0.147	0.927	51.34	0.938	14.757	0.977	0.677	13.078
F7	13	0.98	0.241	0.99	67.18	0.971	28.641	0.975	0.594	2.875
F8	7.436	0.991	0.145	0.983	54.62	0.964	14.791	0.985	0.724	13.448
F9	6.939	0.991	0.184	0.988	48.65	0.964	13.899	0.985	0.69	14.411

RESULTS AND DISCUSSION

Lamivudine matrix tablets were prepared by direct compression method using karayagum gum, kondagogu gum HPMC (K100) hydrophilic polymers. Composition of the formula is given in table 1. The Micromeritic parameters of the formulations of different batches were characterized with respect to angle of repose, bulk density and tapped density were shown in table 2. The angle of repose was less than 30º indicates satisfactory flow behavior .the tablets of all the formulations was found to be smooth, round white, no visible cracks. After the formulation of tablets they were evaluated for hardness, friability, content uniformity, uniformity of weight and in vitro drug release studies. The hardness of the tablets in all the batches was found to be in the range of from5.86 to 6.46 kg/cm2 .The friability of the tablets was in the range of 1.0%. The tensile strength was found to be within the5.72-17.34. The drug content was found to be uniform for all the tablets and was found to be within the limits. Evaluation parameters of tablets are listed in the table 3.

Invitro drug release studies were conducted on matrix tablets. From the drug release profile it is concluded that increase in polymer is inversely proportional to the drug release. From the figure 1 concluded that karayagum gum highest concentration retatarded for more hours.fig 2 kondagogu gum (7.5%) retarded for more than 12 hours. Karayagum and kondagogu gum could not efficiently controlled the drug release compared to HPMC (K100) has higher retarding ability. Retarding effect of polymers in formulations are HPMC(k100)>K.G>K.R.invitro release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order,. higuchi. korseymeyer equation are used to determine the mechanism of drug release from the tablets all. Table 4 indicates swelling index of different formulations of matrix tablets using polymers. Table 5 indicates the data analysis of release profiles of kinetic models. The drug release of all the formulations followed zero order except F7 formulation first order kinetics. Mechanism of drug release from all the profiles is non fickian diffusion, where both diffusion and erosion controlled drug release.

CONCLUSION

Lamivudine sustained release matrix tablets were formulated using hydrophilic polymers, the formulated tablets showed acceptable weight variation, drug content, friability, hardness. Results showed that the drug release is retarded if the concentration of the polymer is increased. Among all the formulations F8 HPMC (K100) was selected as a best formulation with 95% of drug release and F9 formulation showed retarding for more than 12hrs but our target is 12hours. HPMCk100 (F8) formulation showed satisfactory results when compared to karayagum gum and kondagogu gum

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ABBREVIATIONS

K.R = Karaya gum. K.G = Kondagogu gum. HPMC= Hydroxy propyl methyl cellulose. BD = Bulk density. TD = Tapped density. CI = Carr's index.

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