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Design and evaluation of controlled release matrix tablets of acyclovir

Ashok Kumar P[1] and Damodar Kumar S[2]

[1]*Department of Pharmaceutics, Sree Siddaganga College of Pharmacy, Tumkur, Karnataka, India*
[2]*Department of Chemistry Pachaiyappa's College, Chennai, India*

ABSTRACT

Acyclovir was formulated as oral controlled release matrix tablets using natural and synthetic polymers separately or in combinations. Tablets were prepared by direct compression method. The tablets were evaluated to thickness, weight variation test, drug content, hardness, friability and in vitro release studies. All the formulations showed compliance with pharmacopoeial standards. The results of dissolution studies indicated that formulation F3 was most successful of the study. The formulation F3 exhibited Anomalous (non-Fickian) diffusion mechanism. Based on the results of in-vitro studies it was concluded that the natural and synthetic polymers can be used as an efficient matrix former to provide controlled release of acyclovir. FT-IR study indicate the absence of interaction between acyclovir and excipients.

Key words: Acyclovir, Hydroxy propyl methylcellulose (HPMC K100), Locust bean gum (LBG), Xanthan gum (XG), Tamarind seed polysaccharide(TSP).

INTRODUCTION

Oral route of drug administration is oldest and safest mode of drug administration. It posses several advantage. It does not pose the sterility problem and minimal risk of damage at the site of administration. Most commonly used method of modulating the drug release is to include it in a matrix system because of their flexibility, cost effectiveness and broad regulatory acceptance. Use of hydrophilic polymers in matrix for controlled release of an active agent is known in the art. For controlled release solid dosage form comprising a drug dispersed uniformly in hydrophilic polymers, release of drug is controlled primarily by diffusion of the drug, or by surface erosion of the hydrophilic polymers in the surrounding medium, or by combination of the two processes. Hydroxy propyl methylcellulose is the dominant hydrophilic vehicle for the preparation of oral controlled drug delivery systems. Numerous studies have been reported in literature review[1, 2]

Natural gums are biodegradable and nontoxic, which hydrate and swell well on contact with aqueous media, and these have been used for the preparation of dosage form[3].

The hydrophilic polymer xanthan gum is a high molecular weight hetero polysaccharide gum produced by a pure culture fermentation of a carbohydrate with the microorganism *Xanthamonas campestris*. It has been widely used in oral and topical formulations, cosmetics and foods as suspending or stabilizing agent, and release control agent in hydrophilic matrix formulations[4].

Locust bean gum (LBG) is a plant seed galactomannan, composed of a 1-4 linked ß -D- mannan backbone with 1-6-linked a -D- galactose side groups. It is a nonionic molecule consisting of 2000 residues[5]. In LB the ratio of mannose to galactose is 4:1. It is not affected by the ionic strength or pH but will degrade at extreme (above pH 10) pH at higher temperature. LBG structure contains long stretches of bare mannose backbone (up to 80 D- mannose units long) which is responsible for synergistic interaction with other polymers and greater functionality[6, 7]. Tamarind seed polysaccharide is a galactoxylogulucan isolated from seed kernel of *Tamarindus indica.* It possesses properties like high viscosity, broad pH tolerance and adhesivity[8]

Acyclovir is a potent antiviral drug useful in the treatment of Herpes simplex, Herpes zoster, Chicken pox and HIV infection. Acyclovir has a short biological half life 2.5h and also dosing frequency of 200mg/400mg 5 times a day depending upon type of infection. An alternative dose of 800mg leads to plasma fluctuations. Controlled release formulation is need for acyclovir because of it short biological half life and also to overcome adverse side effects, poor patient compliance, reduce dose and maintain uniform drug levels[9].

The objective of present work is to develop a controlled release matrix tablets of acyclovir by using natural and synthetic matrix polymers alone or in combination and study on polymer concentration effect on release pattern.

MATERIALS AND METHODS

Materials

Acyclovir is obtained as gift sample from Arochem Industries (Mumbai). Xanthan gum, HPMC K 100, Locust bean gum and ethyl cellulose were purchased from Research Lab Fine Chem Industries (Mumbai),Micro crystalline cellulose was procured from Loba Chem PVT .LTD, (Mumbai). Starch 1500 was obtained from Strides Arco lab, (Bangalore).Magnesium stearate and Talc were obtained from Sd Fine Chem LTD (Mumbai). All the other ingredients used throughout the study were of analytical grade and were used as received.

Extraction of Tamarind Seed Polysaccharide[10].:

To 20 g of tamarind kernel powder, 200 ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800 ml of boiling distilled water. The solution was boiled for 20 mints under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The solution was then centrifuged at 5000 rpm for 20 minutes. The supernatant was separated and poured into twice the volume of absolute ethanol by continuous stirring. The precipitate was washed with absolute ethanol, diethyl ether and petroleum ether and then dried at 50-60º C under vacuum. The dried material was ground and sieved to obtain granules of different particle size range. The particle size range of 150-75 microns was used for preparation of tablets.

Fourier Transform Infrared (FT-IR)Studies:

FT-IR spectra of pure acyclovir and their respective physical mixture were taken to assure the compatibility between pure acyclovir and its physical mixtures. Infrared spectrum was taken (Shimadzu FT-IR system,Japan) by scanning the sample in KBr discs .

Preparation of Matrix Tablets:

Matrix tablets were prepared by direct compression method. The composition of various formulations is given in Table 1. All the ingredients were sieved by mesh (no.40) and mixed with other ingredients and the powder mixture was compressed with 9 mm flat shaped punches on a 10-station mini rotary tableting machine(Shakti Pharmatech Pvt.Ltd) at 750mg weight. Ten different formulas having different concentrations of hydroxy propyl methylcellulose, tamarind seed polysaccharide ,locust bean gum , xanthan gum and ethyl cellulose were developed to study the effect of polymer concentration on drug release.

Evaluation of Tablets:

Prepared tablets were evaluated for thickness, weight variation, drug content, hardness and friability according to official methods .

In-vitro drug relase studies:

In-vitro dissolution studies of acyclovir tablets were carried out in USP XXIII tablet dissolution test apparatus-II(Electrolab) employing a paddle stirrer rotating at 50 rpm. The dissolution medium consisted of 750 ml of 0.1 N

Hcl (pH 1.2) for 2hours and then the pH was changed to 6.8 by adding 250 ml of 0.2 M tri sodium phosphate for the rest of the dissolution duration. The temperature of the dissolution medium was maintained at 37± 0.5^0 C throughout the experiment . 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter and drug content in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 255 nm, and cumulative percent drug release was calculated. The study was performed in triplicate. The results of dissolution studies were shown in Figure 1

Data Analysis:
To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in zero order, first order, Higuchi matrix and Korsmeyer- Peppas models. The best-fit model was selected by comparing the R^2 values obtained are presented in Table 3[11].

RESULTS AND DISCUSSION

The FT-IR Spectrum of pure Acyclovir and its physical mixture with polymers and different excipients are shown in Figure 2A to 2E and 3F to 3J. Pure acyclovir showed peaks at 3522.02cm^{-1}(O-H stretching),1608.63cm^{-1} (O-H deformation),3471.87 cm^{-1} (1^0 N-H stretching) , 2927.94 cm^{-1} (aliphatic C-H stretching anti symmetric), 2854.65 cm^{-1} (aliphatic C-H stretching symmetric), 1485.19 cm^{-1} (aliphatic C-H deformation), 1712.79 cm^{-1} (C=O stretching) and 1105.21 cm^{-1} (C-O stretching). Infrared absorption spectrum of formulation F5 shows peaks at 3522cm^{-1}(O-H stretching),1600cm^{-1} (O-H deformation),3400 cm^{-1} (1^0 N-H stretching) , 2950 cm^{-1} (aliphatic C-H stretching anti symmetric), 2800 cm^{-1} (aliphatic C-H stretching symmetric), 1450 cm^{-1} (aliphatic C-H deformation), 1720 cm^{-1} (C=O stretching) and 1105 cm^{-1} (C-O stretching). As the sharp characteristic peaks of acyclovir did not change in physical mixture with polymer and different excipients , indicating no possible interaction.

The prepared tablets were evaluated for parameters such as weight variation, drug content, hardness , friability, thickness and were found to be in the range of 747±0.26 to 751±0.48, 98.12±0.36 to 101.28±0.10, 4.2±0.08 to 6.0±0.12, 0.32±0.12 to 0.64±.04, 5.54±0.04 to 6.00±.02. The formulated matrix tablets met the pharmacopoieal requirement of uniformity of weight. All tablets conformed to the requirement of drug content, hardness , friability and thickness. Results are provided in Table 2.

Marketed formulation (Herperax 200mg, Micro labs limited) released 100% of drug in 10 minutes. The amount of acyclovir released from formulation F1 to F10 at first hour ranged between 23.64 to 30.16 (Figure 1). Polymer HPMC K100 has been well known to retard the drug release by swelling in aqueous media. A polymer's ability to retard the drug release rate is related to its viscosity. Processing factors including particle size, hardness, porosity and compressibility index etc. also can affect the release rate of drug from tablets[12]. The hydration rate of HPMC depends on the nature of the substituents like hydroxypropyl group content. Hence, HPMC K100 was used because it forms a strong viscous gel in contact with aqueous media which may be useful in controlled delivery of drug [13].

Formulation F1(70% of TSP),F2 (60% of TSP), F4(60% of HPMC K 100 and 10% of EC), F5(60% of TSP and 10% of EC) and F6(50% of TSP and 20% of EC) were able to sustain release for 10 to12 hours .A lesser amount of drug release rate was obtained with more concentration of tamarind seed polysaccharide. Among the different formulation, matrix tablets containing blend of HPMC K100 and tamarind seed polysaccharide in the ratio 60%:10%,could sustain the release up to 12 hours. The release from formulationF3 was found to be slower and more controlled when compared to other formulations.It is possibly due to the arrangement of more concentrated ,viscous gel layer and increased gel tortuosity.

Formulation F7(70% of XG),F8 (60% of XG and 10% of LBG), F9 (50% of XG and 20% of LBG) and F10(35% of XG and 35% of LBG) were able to sustain release for 8 to 11 hours. A reduced amount of drug release was obtained when xanthan gum combined with locust bean gum than xanthan gum alone . Formulation 10 illustrated much more controlled drug release compared to other formulations (F7 to F9) is probably due to synergistic interaction between two polymers , burly and elastic gel around the matrix.

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all the formulations F1 to F10 could be best expressed by zero order equation as the plots showed highest linearity (R^2: 0.985 to 0.999), than first order release kinetics(R^2: 0.674 to 0.850). The n values

obtained from Korsmeyer Peppas plots ranges from (0.5376 to 0.5861) indicate that mechanism of release of formulations F1to F10 was Anomalous (non-Fickian)diffusion.

Table 1: Tablet composition of different formulations of acyclovir controlled release matrix tablets (mg/tablet).

INGREDIENDS	FORMULATION CODE									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Acyclovir	200	200	200	200	200	200	200	200	200	200
Tamarind seed polysaccharide	525	450	450	375	450	375	-	-	-	-
HPMC K 100	-	-	75	150	-	-	-	-	-	-
Ethyl cellulose	-	-	-	-	75	150	-	-	-	-
Xanthan gum	-	-	-	-	-	-	525	450	375	262.5
Locust bean gum	-	-	-	-	-	-	-	75	150	262.5
Microcrystalline cellulose	2.5	77.5	2.5	2.5	2.5	2.5	-	-	-	-
Starch 1500	-	-	-	-	-	-	2.5	2.5	2.5	2.5
Magnessium stearate	15	15	15	15	15	15	15	15	15	15
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5

Table 2: Tablet properties of the different formulations of acyclovir controlled release matrix tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Thickness(mm)	5.58 ±0.06	5.76 ±0.08	5.67 ±0.05	5.73 ±0.04	5.85 ±0.07	6.00 ±0.02	5.54 ±0.04	5.62 ±0.07	5.71 ±0.02	5.68 ±0.08
Hardness(kg/cm^2)	4.2 ±0.08	4.6 ±0.02	4.8 ±0.16	4.9 ±0.06	5.4 ±0.10	5.8 ± 0.18	5.2 ±0.08	5.6 ±0.06	5.8± 0.14	6.0 ±0.12
Friability (%)	0.62	0.58	0.54	0.42	0.38	0.32	0.58	0.63	0.61	0.64
Drug content(%)	99.92 ±0.28	101.26 ±0.10	99.64 ±0.20	98.12 ±0.36	101.18 ±0.24	100.60 ±0.30	98.62 ±0.18	99.84 ±0.36	101.28 ±0.10	100.22 ±0.12

All the values are expressed as mean ±SD, n=6

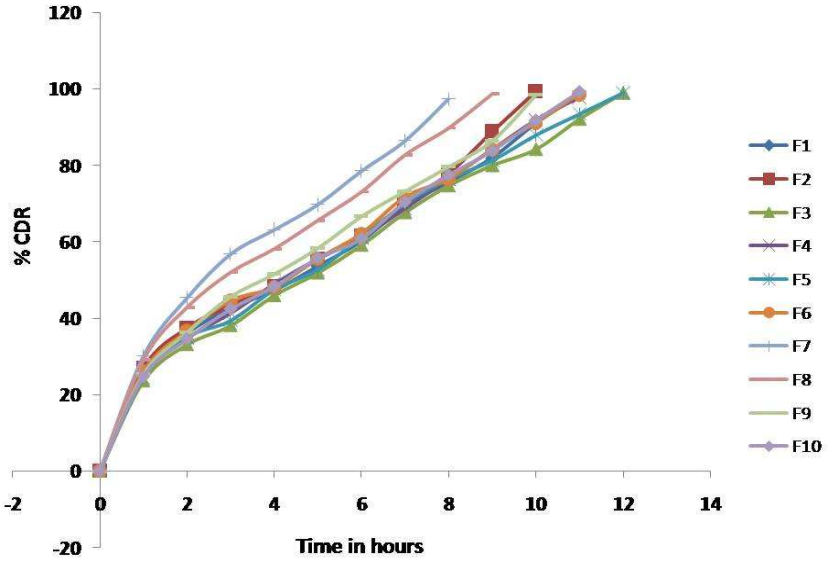

Figure 1: *In vitro* dissolution profile of F1to F10 formulations.

Table 3: Kinetics of drug release from acyclovir controlled release matrix tablets.

Formulation code	Zero order regression coefficient(R^2)	First order regression coefficient(R^2)	Higuchi equation regression coefficient(R^2)	Korsmeyer et al's plots	
				Regression coefficient (R^2)	Slope (n)
F1	0.996	0.754	0.970	0.979	0.5559
F2	0.988	0.714	0.949	0.965	0.5441
F3	0.997	0.723	0.982	0.985	0.5861
F4	0.999	0.674	0.975	0.978	0.5524
F5	0.995	0.850	0.984	0.986	0.5748
F6	0.996	0.765	0.977	0.983	0.5490
F7	0.985	0.745	0.989	0.994	0.5383
F8	0.993	0.755	0.987	0.993	0.5376
F9	0.994	0.776	0.981	0.992	0.5701
F10	0.998	0.729	0.979	0.987	0.5785

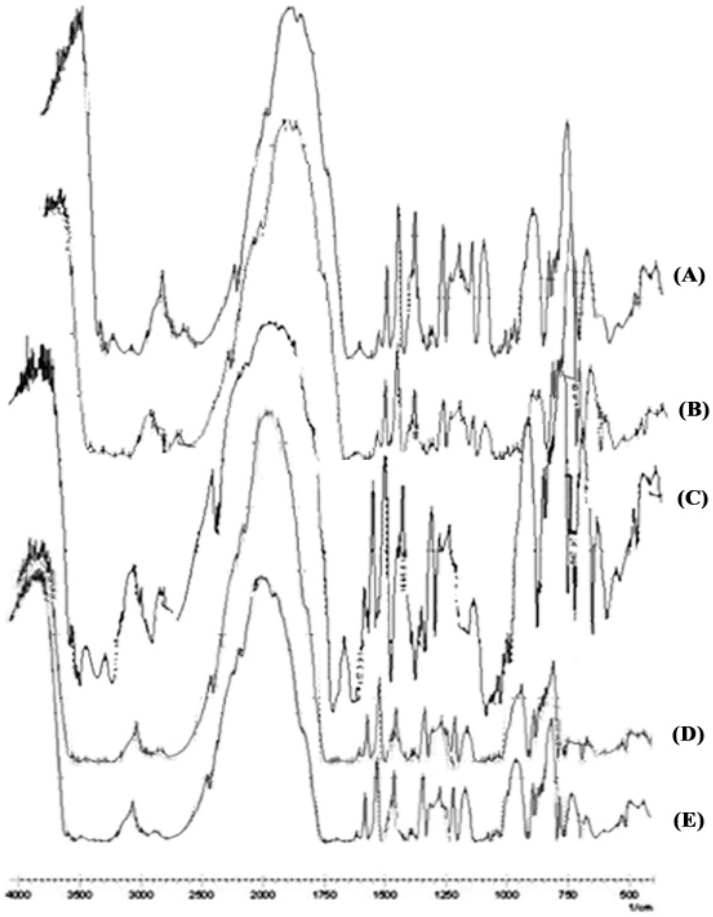

Figure 2: The FT-IR spectra of pure acyclovir(A), acyclovir with HPMC K100(B), acyclovir with ethyl cellulose (C),acyclovir with locust bean gum(D) , acyclovir with xanthan gum (E) .

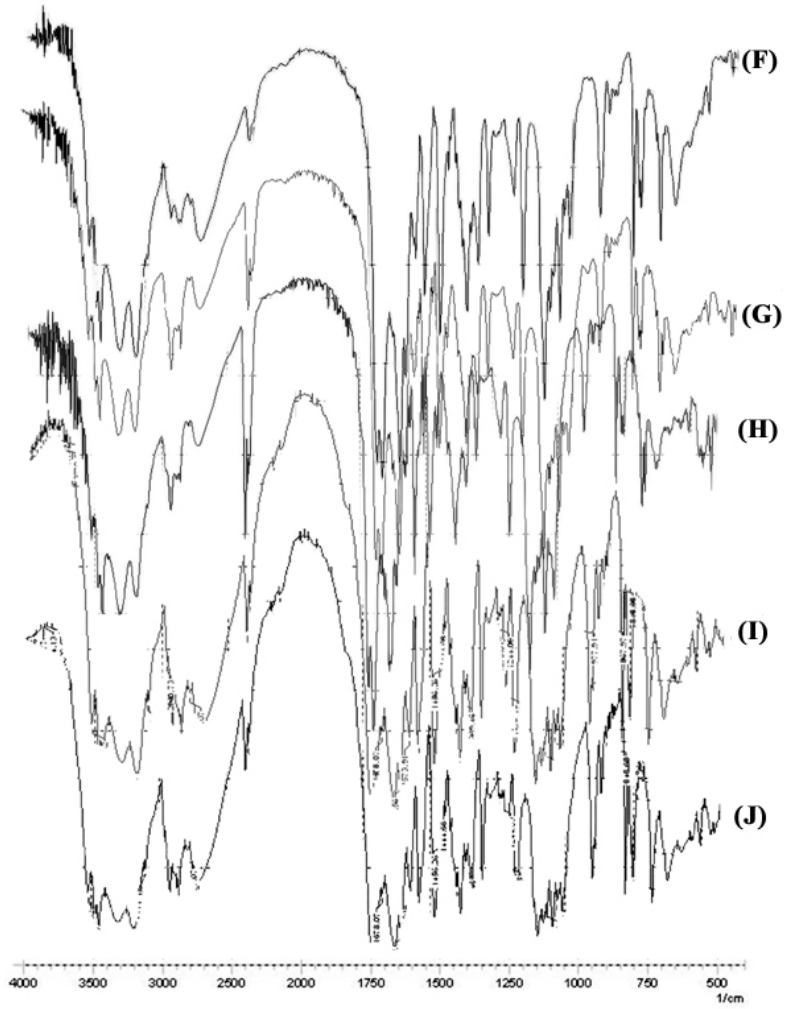

FIGURE 3: The FT-IR spectra of acyclovir with tamarind seed polysaccharide (F), Acyclovir+ tamarind seed polysaccharide + hyrdoxy propyl methyl cellulose K100 + microcrystalline cellulose + magnesium stearate + talc (formulation)F3(G), Acyclovir+ tamarind seed polysaccharide + ethyl cellulose + microcrystalline cellulose + magnesium stearate + talc (formulation)F5(H) , acyclovir+ xanthan gum+ starch 1500 + magnessium stearate + talc (formulation)F7(I), acyclovir+ xanthan gum+ locust bean gum + starch 1500 + magnessium stearate + talc (formulation)F10(J).

CONCLUSION

From the study it was concluded that the finest controlled release of tablet might be produced using tamarind seed polysaccharide and HPMC K 100. Addition of HPMC K100 was found to be helpful to control drug release. Slow, controlled and complete release of acyclovir for a period of 12 hours was obtained from matrix tablet formulated with blends of HPMC K100 and TSP in of 60%:10%. The mechanism of drug release from formulation F3 was diffusion coupled with erosion. Suitable combination and concentrations of polymers provided fairly good controlled drug release.

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