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Research Article

DESIGN AND DEVELOPMENT OF ORAL *IN SITU* GELS OF ACYCLOVIR

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Abstract

The present investigation deals with the development and optimization of an *In situ* gelling formulation of Acyclovir. It is an antiviral drug. *In situ* gels are capable of releasing drug in a sustained manner affording relatively constant plasma profiles. The study evaluates the potential of oral sustained delivery of Acyclovir with sodium alginate and xanthan gum as gelling agents. Calcium ions present in the formulation helps in formation of gel when administered oral aqueous solutions. Aqueous solutions of sodium alginate and xanthan gum form gels on warming to body temperature, in the presence of cations. Different solutions (sols) were prepared varying the concentrations from 0.5%w/v to 2%w/v using sodium alginate and xanthan gum. The sols were evaluated for rheological properties using brookfield viscometer. *In vitro* release studies were carried out using simulated gastric fluid (p^H 1.2) for 2 hrs followed by phosphate buffer (p^H 6.8) for 6 hrs respectively and cumulative amount of drug release was analyzed by UV spectrophotometry. The optimized formulation was able to release its contents up to 8 hrs. These *In situ* gels are, thus suitable for oral sustained release of Acyclovir.

Keywords: Acyclovir, *In situ* gels, sodium alginate, xanthan gum, sustained drug delivery.

Introduction

The antiviral drugs are mostly designed to suppress the replication of HIV, herpes viruses, the hepatitis B and C viruses, and influenza A and B viruses rather than killing them. cyclovir is a guanosine analog antiviral drug that acts as an antimetabolite. It is used to treat herpes simplex viral infections, varicella zoster(chicken pox) and herpes zoster(shingels). They inhibits viral DNA polymerase competitivelyand by termination of DNA synthesis by incorporation into DNA.

It is difficult to design safe and effective dosage forms of antiviral drugs because viruses use the host's cells to replicate. So it is hard to find targets for the drug that would interfere with the virus without also attacking the host organism's cells. Herpes simplex virus 1 and 2 (HSV-1 and HSV-2), also known as human herpes virus 1 and 2 (HHV-1 and HHV-2), are two members of the herpes virus family, Herpesviridae, that infect humans. Both HSV-1 (which produces most cold sores) and HSV-2 (which produces most genital herpes) are ubiquitous and contagious.

The antiviral drugs are thus interfere with viral replication, and suppress the physical severity of outbreak-associated lesions, and minimize the transmission to others. Studies of vulnerable patient populations have revealed that daily use of antivirals such as Acyclovir and Valacyclovir can reduce reactivation rates.

Treatment in Children: it decreases symptoms if oral Acyclovir is started within 24 hours of onset of symptoms. Use of acyclovir therefore is not currently recommended for immunocompetent individuals (i.e., otherwise healthy persons without known immunodeficiency or on immunosuppressive medication).It is not prescribed for Children younger than 12 years old and older than one month.

In adults treatment with antiviral drugs (e.g. Acyclovir or valacyclovir) are generally prescribed, as long as it is started within 24–48 hours from the onset symptoms. Antiviral medicines do not kill the virus, but stop it from multiplying [1].

An ample number of research works have been exploited in the development of *In situ* gelling systems. The development of *In situ* gels has attracted more attention over the past few decades. *In situ* gels are delivery systems which are capable of releasing drug in a sustained manner to maintain a constant plasma concentrations of drugs. These hydro gels are solutions at room temperature which undergo gelation when in contact with body fluids or change in pH. The gellation may occur due to changes in temperature , pH and ionic content[1]. *In situ* gels are drug delivery systems which possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, and improved patient compliance.[2-4]

In situ gels are resembling mucoadhesive drug delivery system in their mechanism of absorption in the GI tract. They swell to form a strong gel that is capable of prolonging the residence time of the drugs on the walls of GI tract. *In situ* gels can be administered by various routes such as oral[8], ocular [9], rectal[10], vaginal[11], injectable[12] and intra-peritoneal routes[12].

In the present work, two natural bio-degradable polymers namely sodium alginate and xanthan gum are used for this purpose at various concentrations. As a part of this study effect of polymer combination on pattern and duration of *In vitro* dissolution study was also carried out. The drug dissolution data were fitted with various kinetic equations such as zero order, first order, korsemeyer peppas, hixson-crowell and higuchi to find the best fit model for the drug release.

Materials and Methods

Materials

The drug Acyclovir was procured as gift sample from Orex pharma, Dombivali, India, Sodium alginate and xanthan gum were procured from SD fine chemicals, India. All other chemicals used in this study were of analytical grade.

Methods

Table 1. Acyclovir *In situ* gels with xanthan gum and sodium alginate (F1-F8)

Sr. no	Formulations	Acyclovir (mg)	Xanthan gum (mg)	Sodium alginate (mg)	Sodium citrate (%w/v)	Calcium Chloride (%w/v)
1	F1	1	0.5	-	0.17	0.016
2	F2	1	1	-	0.17	0.016
3	F3	1	1.5	-	0.17	0.016
4	F4	1	2	-	0.17	0.016
5	F5	1	-	0.5	0.25	0.075
6	F6	1	-	1	0.25	0.075
7	F7	1	-	1.5	0.25	0.075
8	F8	1	-	2	0.25	0.075

Compatibility Studies

Fourier transform infra-red spectroscopy (FTIR)

Drug and polymer compatibility studies were carried out using FTIR spectral studies to establish the possible interaction in the formulations. Samples about 5 mg was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 Psi for 3 minutes and then the FTIR spectra were recorded between 400 and 4000 cm-[1].

Preparation of *in situ* gels of acyclovir

Preparation of xanthan gum *In situ* gels

Xanthan gum solutions of concentrations 0.5 -2.0 % w/v were prepared by adding the gum to ultrapure water containing 0.17 % w/v sodium citrate and heated to 90^{o}Cwhile stirring. After cooling to below 40^{o}C appropriate amounts of calcium chloride 0.016 % w/v was added while stirring. Acyclovir (50 mg) was then dissolved in 0.1N Hcl solution and added slowly to the above gum solution while stirring on a magnetic stirrer so that there was proper and homogeneous dispersion of the drug. The Hcl was neutralized with 0.1N NaOH.

Preparation of sodium alginate *In situ* gels

Sodium alginate suspensions were also prepared in a similar manner. Sodium alginate solutions of concentrations 0.5-2.0% w/v were prepared by adding the alginate to ultrapure water containing 0.25% w/v sodium citrate and heating to 60^{o}C. After cooling to below 40^{o}C appropriate amounts of calcium chloride 0.075 % w/v was added while stirring. Acyclovir (50mg) was then dissolved in 0.1N Hcl solution and added slowly to the above alginate solution while stirring on a magnetic stirrer so that there was proper and homogeneous dispersion of the drug. The HCl was neutralized with addition of 0.1N NaOH.(Table 1).

Evaluation of *In situ* gels

The prepared *In situ* gels were evaluated for the following parameters.

A) Drug content
B) Rheological properties
C) *In vitro* drug release studys
D) *In vitro* drug release kinetics.

A) Drug content

In situ gels of Acyclovir equivalent to 50mg was taken and dissolved in 10ml of 0.1N HCl buffer for 1 hr. Then that solution was filtered. From that 1ml is taken and diluted to 10ml and filtrate was analysed by UV Spectrophotometer at 255nm. .

B)Rheological properties of Sols and Gels

The viscosity of the sols and gels were determined at ambient condition using Brookfield viscometer using 2 ml aliquot of the sample.

C)*In vitro* drug release study

The drug release rate from gels were determined by using USP dissolution apparatus Type I (basket-type). A weighed amount of gels equivalent to 50 mg of drug (Acyclovir) was weighed and placed in the basket. Dissolution medium used was 0.1 N HCl (pH 1.2, 900 ml) for first 2 hours and maintained at 37 ± 0.5°C at a rotation speed of 100 rpm. 5 ml of sample was withdrawn at each 30mins interval, later this interval was extended to 2 hrs. Sample was then passed through a filter, and analyzed spectro photometrically at 255nm to determine the concentration of Acyclovir present in the dissolution medium . The initial volume of dissolution medium was maintained by adding 5 ml of fresh dissolution medium after each withdrawal. The dissolution study was continued using phosphate buffer (pH 6.8 ± 1, 900ml) for next 6 hrs. The cumulative % drug release was calculated using standard calibration curve.

D) IN VITRO DRUG RELEASE KINETICS

Zero order kinetics:

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_0 t$$

Where,Q_t is the amount of drug dissolved in time *t,*
Q_0 is the initial amount of drug in the solution (most times, Q_0= 0)

K_0 is the zero order release constant expressed in units of concentration/time.

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with slope equal to K_0.

First order kinetics

The release of the drug which followed first order kinetics can be expressed by the equation:

$$\log C = \log C_0 - K_t / 2.303$$

Where, C_0 is the initial concentration of drug,
K is the first order rate constant
t is the time.

The data obtained are plotted as log cumulative percentage of drug remaining *vs* time which would yield a straight line with a slope of -K/2.303.

Higuchi model:

The release of the drug which follows higuchi kinetics can be expressed by the equation:

$$Q = K_H * t_{1/2}$$

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

The data obtained were plotted as cumulative percentage drug release versus square root of time.

Hixson Crowell model:

Hixson Crowell recognized that the particle regular area is proportional to the cube root of its volume. Hixson Crowell equation is

$$Wo1/3 – Wt1/3 = Ks*t$$

Where,
Wo- initial amount of drug in pharmaceutical dosage form
Wt- remaining amount of drug in pharmaceutical dosage form at time t
Ks-constant incorporating the surface volume relation.

The data obtained are plotted as (percent drug release) 1/3 verses time.

Korsmeyer-Peppas model:

To find out the mechanism of drug release, drug release data were fitted in Korsmeyer-Peppas equation which is expressed as:

$$Q/Q_0 = k\ t^n$$

Where, K_0 to K_2 were release rate constants
Q/Q_0 was fraction of drug released at time t,

K was constant and n was diffusion constant that indicates general operating release mechanism. For Fickian (diffusion controlled) n ≤0.5; for non Fickian (anomalous/zero order) release ‘n’ value is in between 0.5 to 1.0; for zero order release n=1.0; for super case transport II, n >1.0.

To study the release kinetics, data obtained from *In vitro* drug release studies were plotted as log cumulative percentage drug release versus log time.

Results and Discussion

PREFORMULATION STUDIES

Compatibility Studies

Drug and polymer compatibility studies were carried out using FTIR spectral studies to establish the possible interaction in the formulations. The IR spectrum of Acyclovir, xanthan gum, sodium alginate & their physical mixture is shown in Fig .1-3.

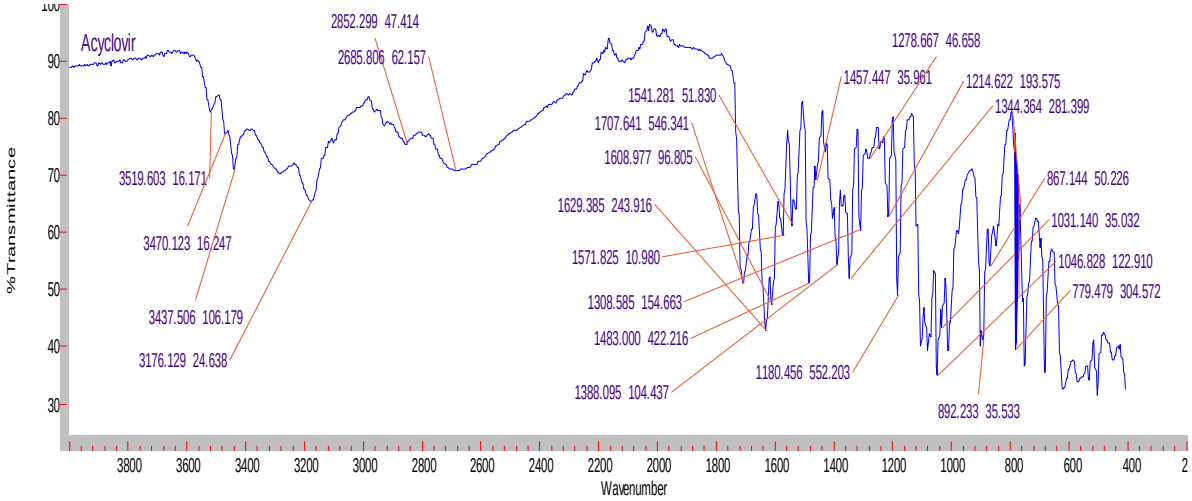

Fig.1 FT-IR spectrum of pure drug acyclovir

Table 2. Characteristic peaks of Acyclovir

Sr.No	Functional group	Theoretical value	Peak wave values of pure drug (Cm^{-1})
1	C=N	1670-1780	1707
2	NH	3300-3500	3438
3	C=0	1670-1780	1708
4	C-O	1050-1150	1082
5	C-N	1030-1230	1030

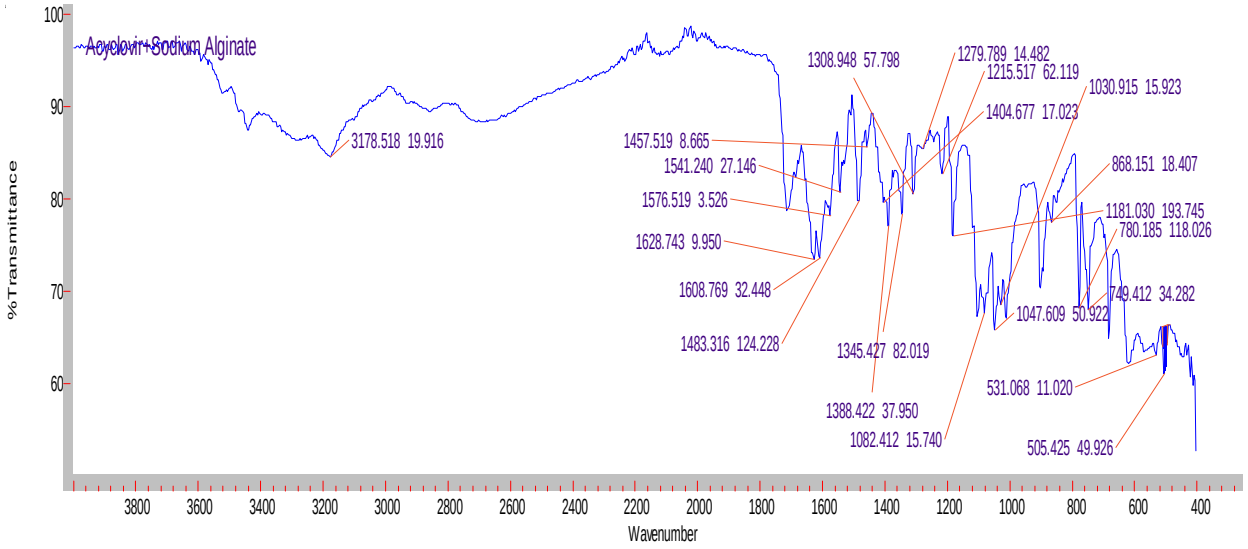

Fig .2 FT-IR Spectrum of acyclovir + sodium alginate

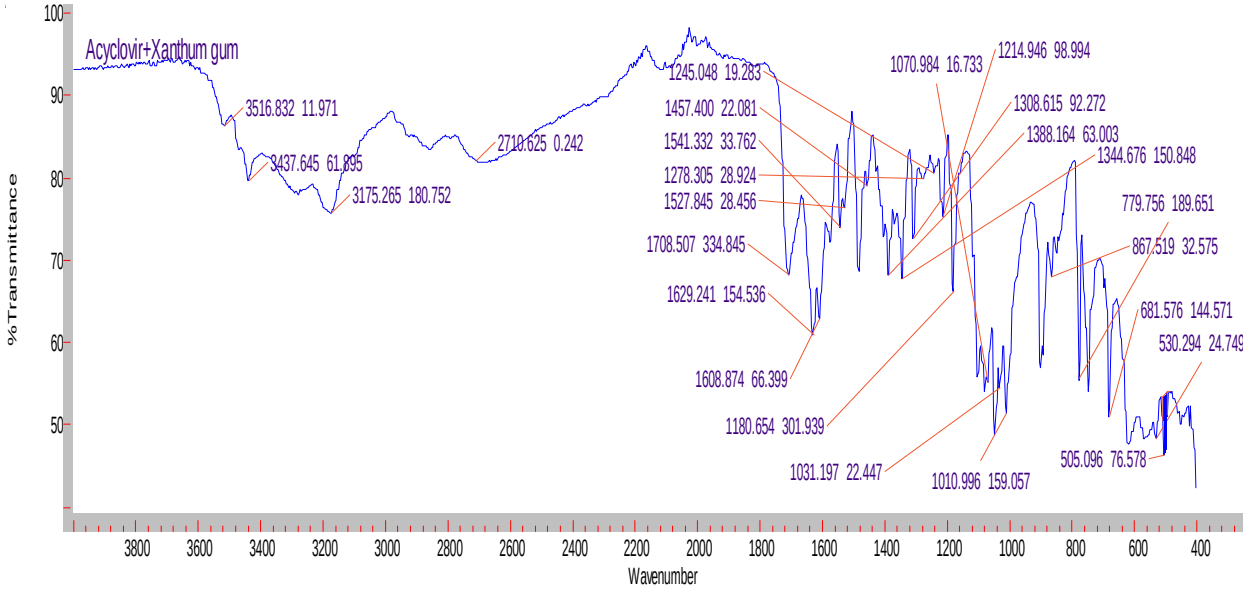

Fig.3 FT-IR Spectrum of acyclovir + xanthan gum

Table 3. Comparative FTIR Interpretation of Acyclovir with Excipients

Sl.No	Functional Group	Theoretical value	pure drug(Cm^{-1})	Pure drug+sodium alginate	Pure drug +xanthan gum
1	-C=N	1670-1780	1707	1686	1708
2	-NH	3300-3500	3438	3436	3470
3	-C=O	1670-1780	1708	1686	1708

From the above table 2 the peak values of mixture of drug with excipients is within the range of peak values of pure drug.This implies that the excipients are compatible with the drug since their combination did not alter the functional groups of pure drug.

Drug content determination

In situ gel of Acyclovir equivalent to 50mg was taken and dissolved in 10ml of 0.1N Hcl buffer for 1 hr and then that solution was filtered. From that 1ml is taken diluted to 10ml and filtrate was analysed by UV Spectrophotometer at 255 nm.

Table 4:Drug Content determination of Acyclovir *In situ* gels with Xanthan gum and sodium alginate F1-F8

FORMULATION	DRUG CONTENT (%)±SD
F1	70±0.62
F2	73±0.85
F3	69.7±0.60
F4	68.9±0.58
F5	71.34±0.72
F6	**95.2±0.40**
F7	84.2±0.92
F8	79.2±0.54

UV spectroscopic analysis of one ml of all the formulation diluted with 0.1N Hcl revealed that all the formulations contains from 68.9±0.58(F4) to **95.2±0.40** %(F6) of the drug the results are triplicate of analysis.

Rheological properties

Table 5. Rheological properties of acyclovir *In situ* gels

Formulation Code	Drug : polymer	Concentration (%)	Speed (RPM)	Viscosity (CP)
F1	1:0.5	0.5	150	260
F2	1:1.0	1	150	325
F3	1:1.5	1.5	150	350
F4	1:2	2	150	370
F5	1:0.5	0.5	150	175
F6	**1:1.0**	**1**	**150**	**255**
F7	1:1.5	1.5	150	272
F8	1:2	2	150	270

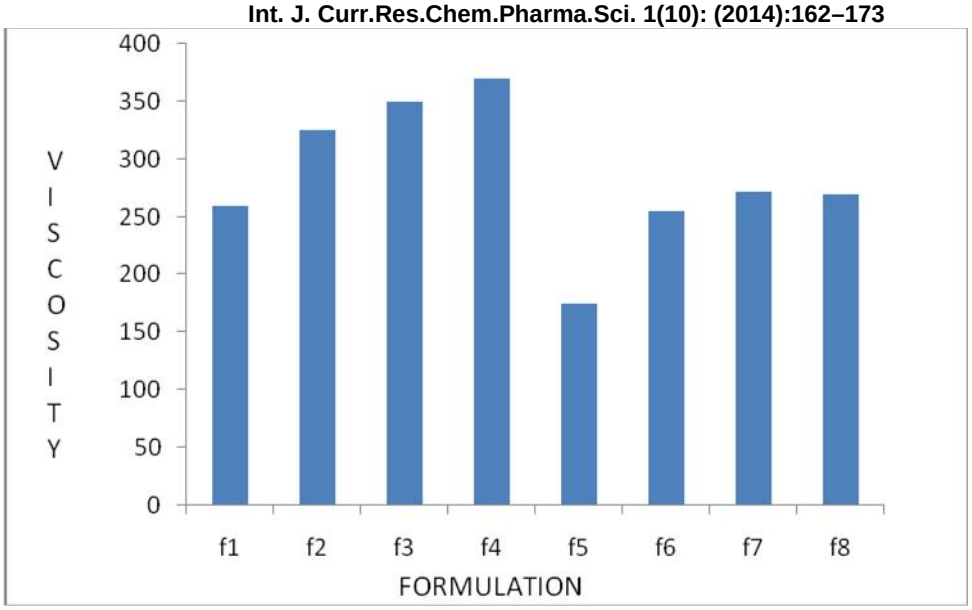

Fig .4. viscosity of acyclovir *In situ* gels (F1-F8) at 150 RPM

Dissolution studies of *in situ* gels

The *In vitro* drug release studies were carried out by using USP type I dissolution apparatus. The *In situ* gels were placed in a basket. The dissolution medium used was 900ml of 1.2 pH buffers at 37°C for first 2 hours followed by 6.8 pH phosphate buffers at 37°C for the rest of the study.

The cumulative present drug release of F1 to F8 formulations at various time intervals was calculated. The cumulative percent drug release in all formulations was plotted against time in fig.5-8. The maximum percent of drug release was found in F6 formulation.

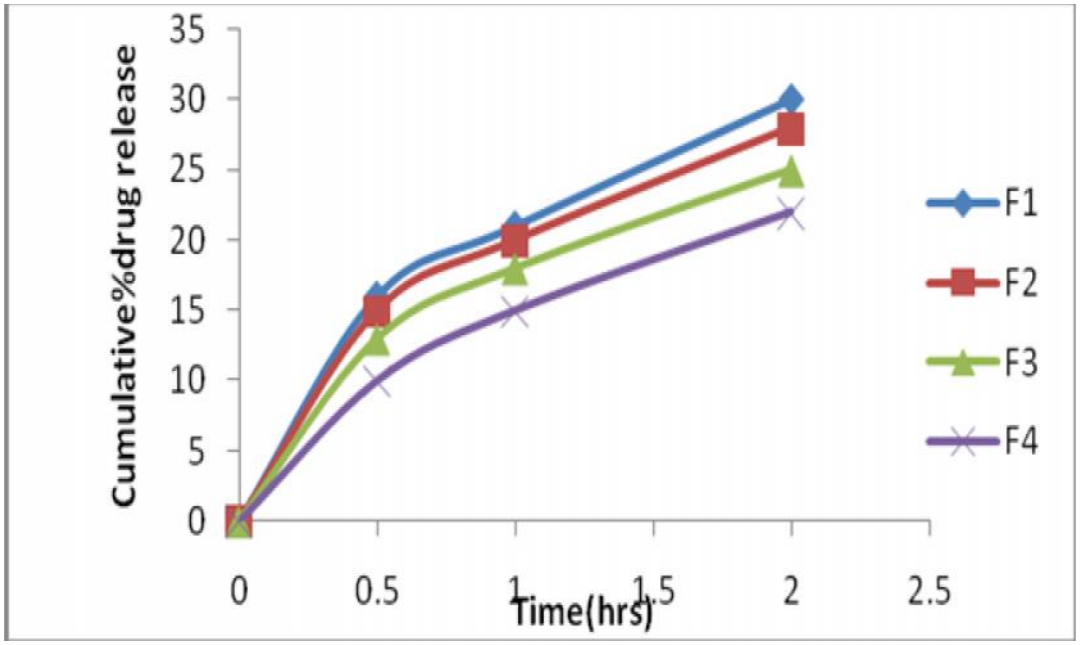

Fig. 5 *In vitro* cumulative% drug release of Acyclovir *In situ* gels with xanthan gum in p^H1.2

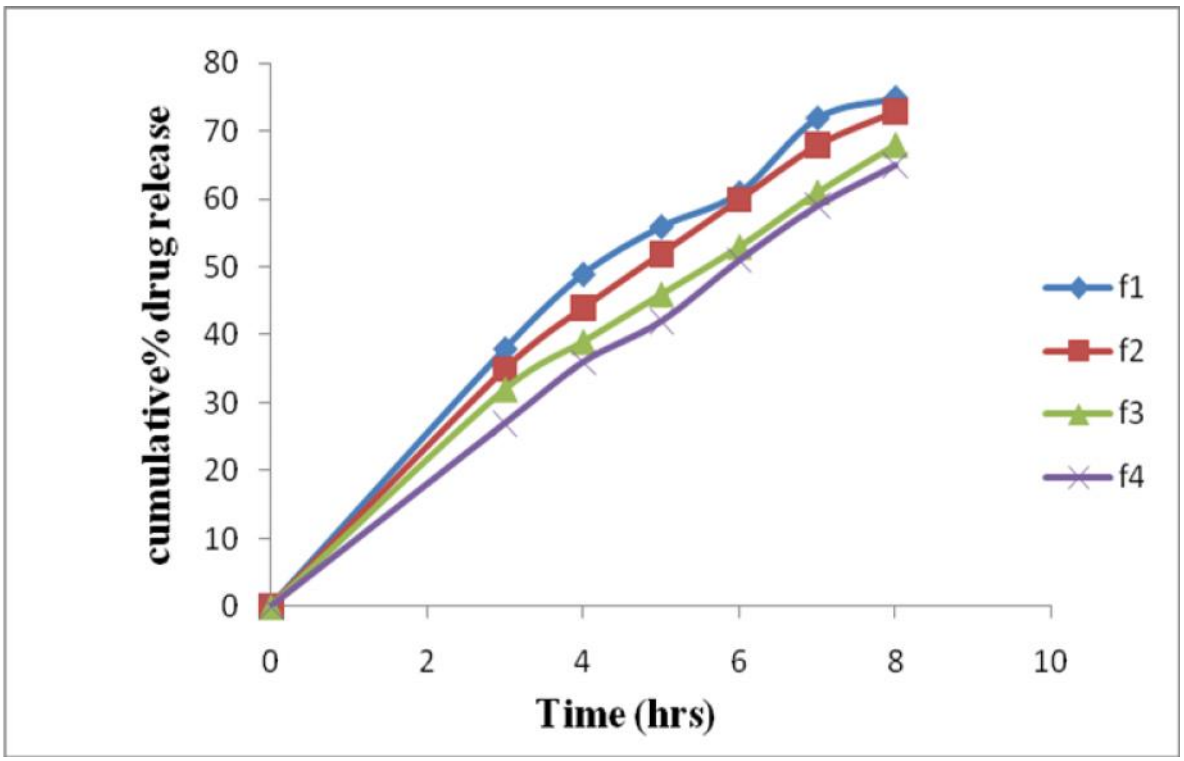

Fig.6 *In vitro* cumulative% drug release of Acyclovir *In situ* gels with xanthan gum in p^H6.8

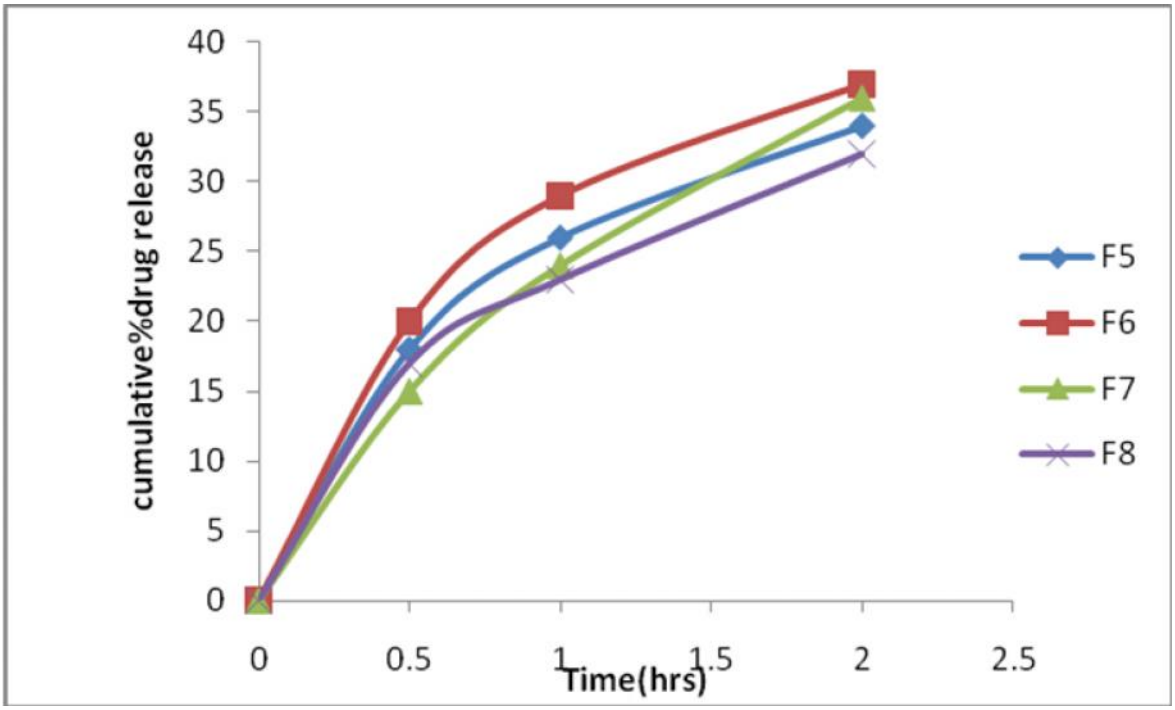

Fig .7 *In vitro* cumulative% drug release of Acyclovir *In situ* gels with sodium alginate in p^H1.2

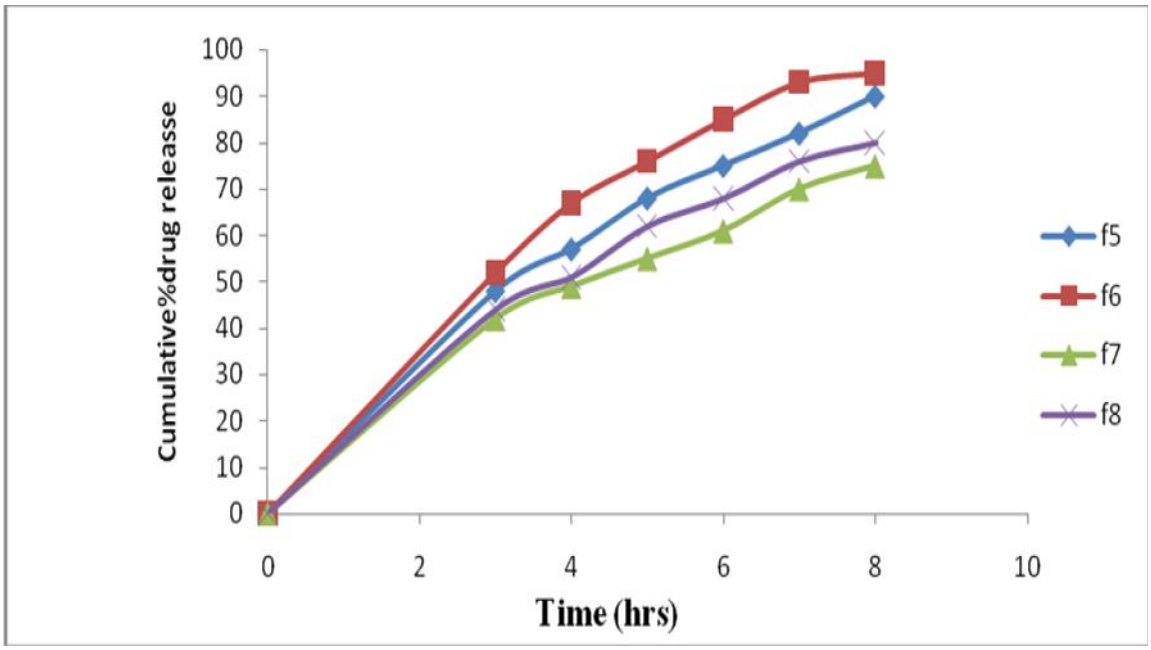

Fig. 8 *In vitro* cumulative% drug release of Acyclovir *In situ* gels with sodium alginate in p^H 6.8

The *In-vitro* drug release study was performed using dissolution rate test apparatus in phosphate buffer (pH 6.8). The dissolution profiles of acyclovir are given in Fig.5-8.

The *In-vitro* cumulative percentage drug release was observed in the range of 95 to 65 percent. The formulations F1, F2, F3, F4, F5, F6, F7, F8 containing xanthan gum and sodium alginate respectively showed a release of 75, 73, 68, 65,90,95,75 and 80% after 8 hours. This shows that more sustained release was observed with the increase in percentage of xanthan gum and sodium alginate. The best formulation was observed as F6, by the observation of all results of the eight formulations acyclovir *In situ* gels.

***IN VITRO* DRUG RELEASE KINETICS**

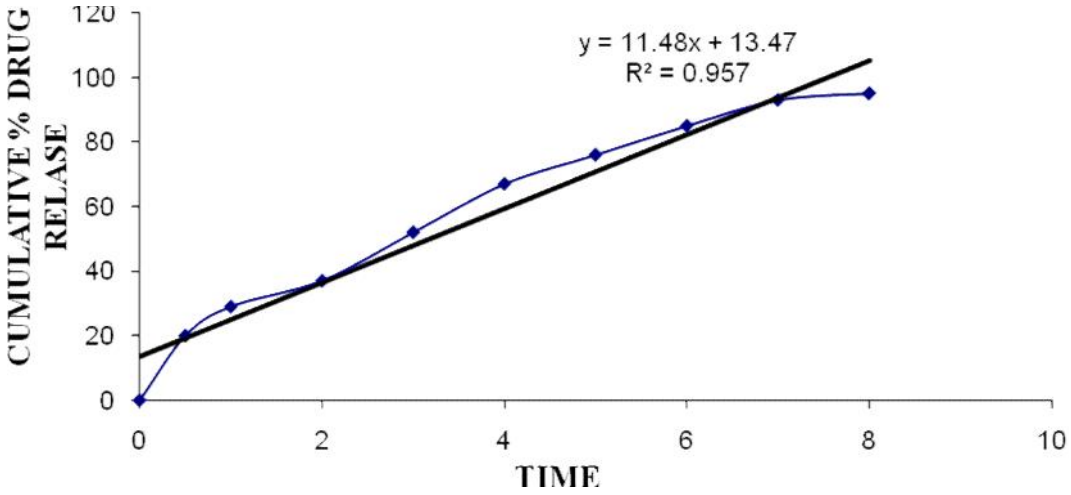

Fig.9 Zero order release kinetics of optimized formulation F6

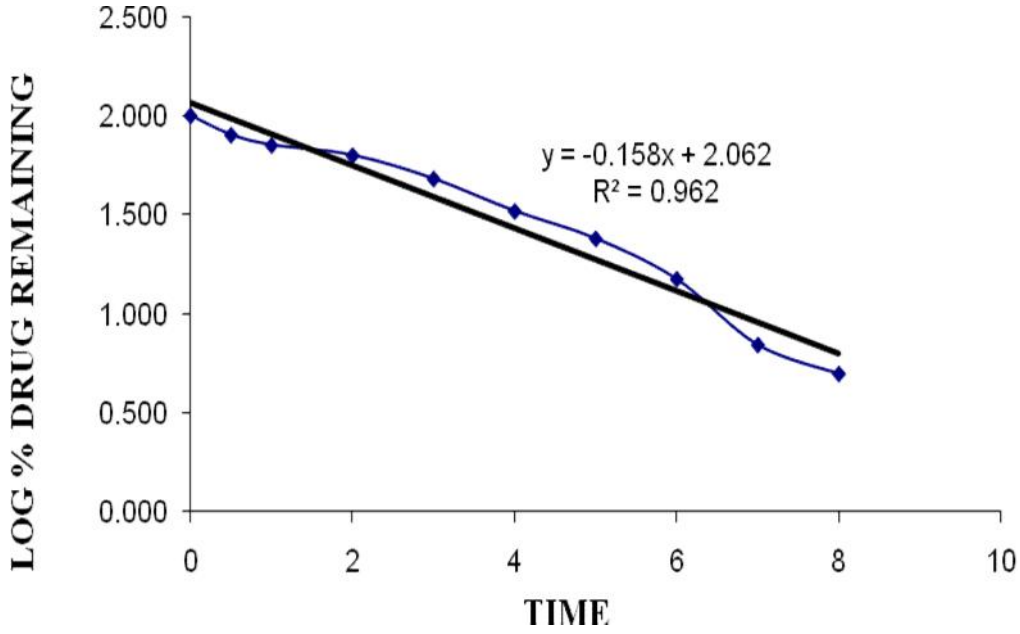

Fig .10 First order release kinetics of optimized formulation F6

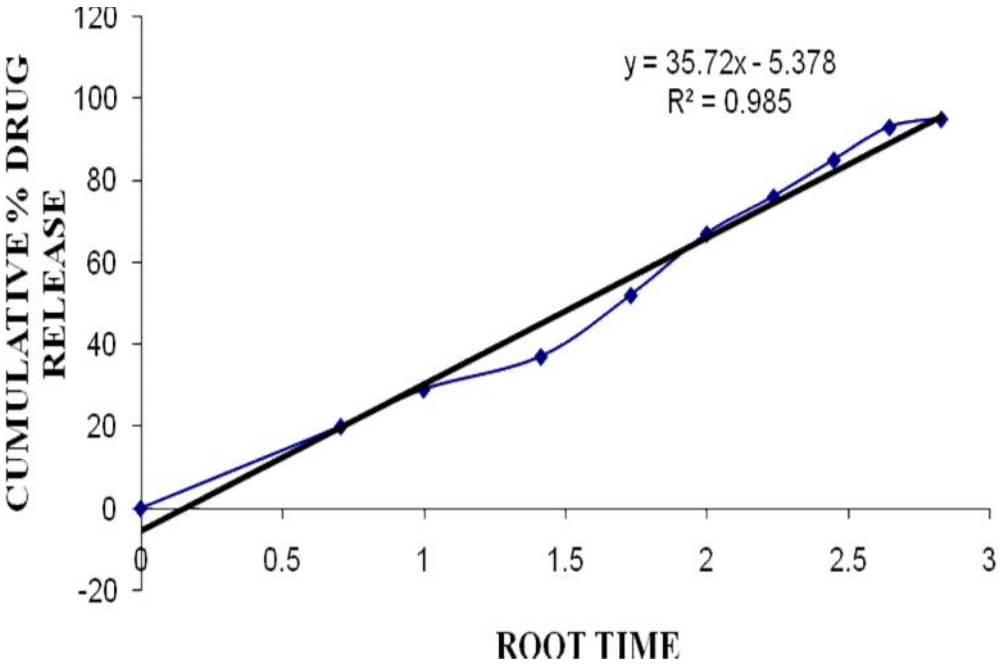

Fig .11Higuchi release kinetics of optimized formulation F6

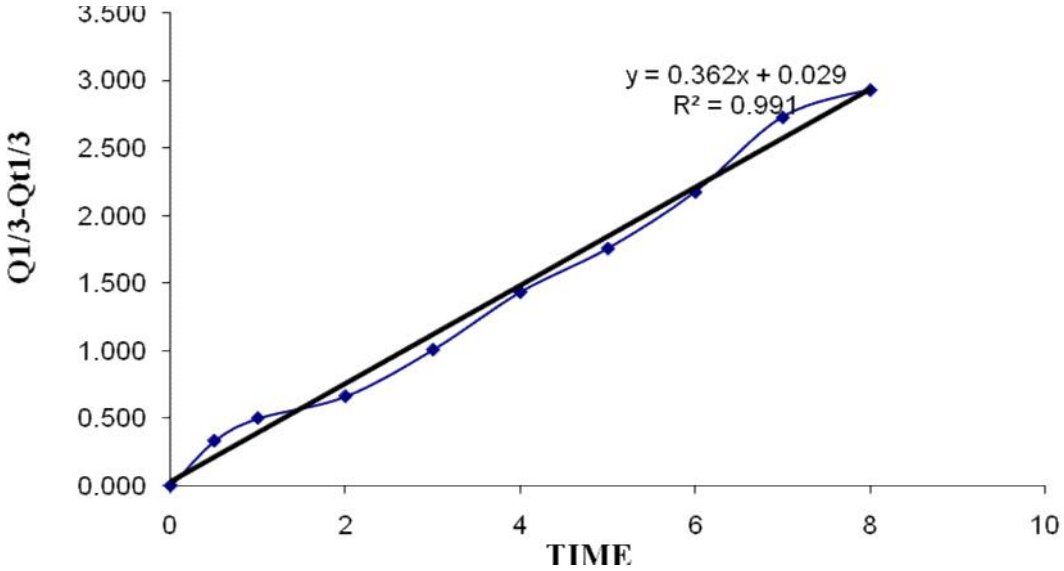

Fig .13 Hixson Crowell release kinetics of optimized formulation F6

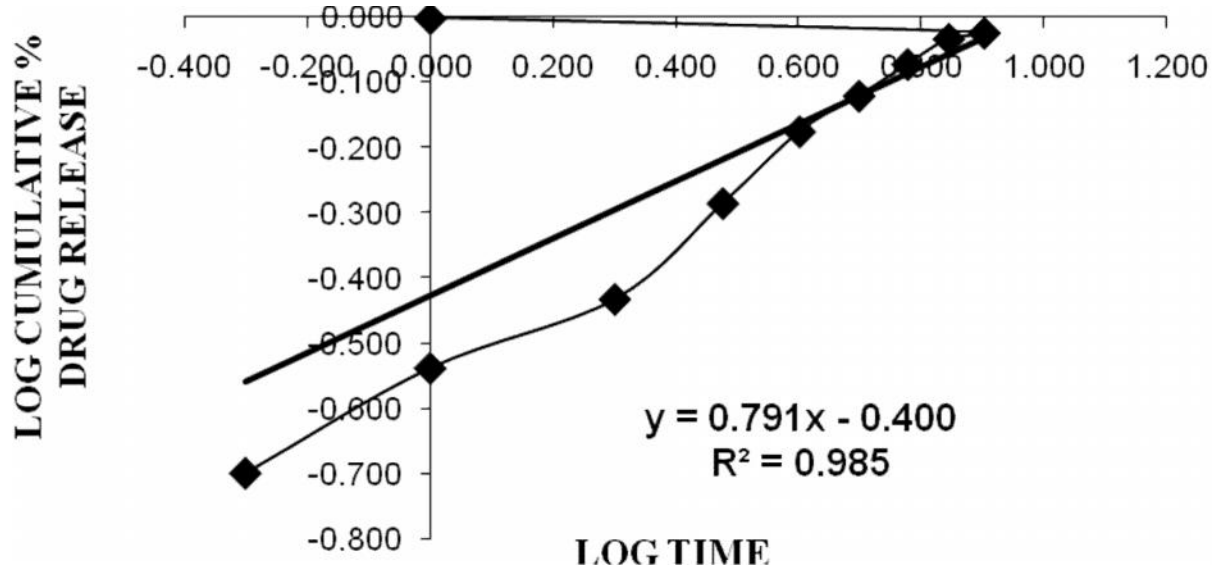

Fig .14 Korse meyer peppas release kinetics of optimized formulation F6

r^2 values of different kinetic models of *In situ* gels

Table 6. r^2 values of different kinetic models of optimized formulations F6

Formulation	Zero order	First order	Higuchi model	Korsemeyer peppas model		Hixson Crowell model
				r^2	n	
F6	0.9577	0.8724	0.9853	0.9822	0.588	0.9911

Where, r^2 = regression coefficient
n = slope

Based on the mathematical data revealed from kinetic models, it was concluded that the release data of F6 formulation was best fitted with Hixson Crowell model. The diffusion exponent 'n' values were found to be more than 0.5 indicating non-Fickian diffusion.

Conclusion

In the present research work we have prepared oral in situ gels of acyclovir. Under the preformulation studies, API (Active Pharmaceutical Ingredient) characterization and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics. This study was demonstrated that *In situ* gels formed by oral administration of solutions of sodium alginate and that release of Acyclovir is sustained over a period of at least 8 hrs when compared to xanthan gum.

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