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Formulation Development, Evaluation and Optimization of Prednisolone Oral Gel

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ABSTRACT

Aphthous stomatitis (oral ulcers) is one of the oral mucosal diseases which is seen in 1-2% of general population. Gels are found to be the most suitable dosage for the treatment of ulcerative and inflammatory mucosal diseases as they can be spread easily as a thin layer on the lesion. Prednisolone, a poorly aqueous soluble corticosteroid, is found be very effective in relieving pain and inflammation caused by oral ulcers. The aim of this study is to formulate, evaluate and optimize prednisolone oral gel for the treatment of mouth ulcers. Prednisolone is converted into a solid dispersion to increase its solubility using beta-cyclodextrin and is incorporated into gel. Gels using different gelling agents like Methylcellulose, Carbopol 940p and Hydroxy propyl methyl cellulose (HPMC) were prepared and evaluated for physiochemical properties like drug content, pH, solubility, spreading coefficient, extrudability, *invitro* release study and *invitro* kinetics study. The study revealed that the gel made from Carbopol 940p had good mucoadhesive property than other polymers. Among the various formulations prepared, F5 exhibited good physiochemical parameters and maximum drug release. From the above investigations, it was concluded that prednisolone oral gel is a promising new dosage form for the improved treatment of oral ulcers.

1. INTRODUCTION

Many inflammatory and ulcerative diseases may occur at the mucous membrane lining in the oral cavity due to various environmental and genetic factors. Aphthous stomatitis (oral ulcers) is one such disease seen in 1 – 2% of general population. The treatment of aphthous stomatitis is based on empirical data. The goals of therapy include the management of pain and functional impairments by suppressing inflammatory responses as well as reducing the frequency of recurrence or avoiding the onset of new aphthae. Conventional ointments, creams, mouthwashes, and lozenges are the most widely available preparations for local treatment of oral ulcers. But the therapeutic drug level decreases on the mucosa when these conventional dosage forms are used as they get washed out easily from the applied region due to physiological removing mechanisms like washing effect of saliva, swallowing and tongue movement. Gels are found to be the most suitable dosage form as they can be easily spread on the lesions as a thin film layer and help to protect the lesions. Prednisolone, a corticosteroid with anti-inflammatory action, is found to be very effective in relieving pain and inflammation caused by oral ulcers. Although prednisolone is found to be effective in the treatment of oral ulcers, it has poor aqueous solubility and wettability which leads to difficulty in formulating the drug into oral or topical formulations. The formulation into solid dispersion is an effective method for increasing the dissolution rate of poorly soluble drugs, hence improving their bioavailability. Hence the work was undertaken to develop a solid dispersion incorporated oral gel of prednisolone and subject it to various evaluation studies in order to be used as a new dosage form for the treatment of oral ulcers.

2. MATERIALS AND METHODS

MATERIALS

Prednisolone, Beta cyclodextrin (β-cyclodextrin) and Hydroxy propyl methyl cellulose (HPMC) were obtained from Yarrow Chem Products, Mumbai. Carbopol 940p and Methyl cellulose were purchased from Oxford laboratory, Mumbai, Triethanolamine, Methyl paraben and Propyl paraben were obtained from Nice chemicals, Cochin.

METHODS

DRUG POLYMER COMPATIBILITY STUDIES

Drug polymer compatibility studies were carried out using Fourier transmission infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC).

FORMULATION AND EVALUATION OF PREDNISOLONE SOLID DISPERSION

Formulations were prepared with drug: β-cyclodextrin ratio of 1:2, 1:2.5 and 1:3 by kneading method. In this method, β-cyclodextrin was impregnated with a little quantity of hydro-alcoholic solution (water: ethanol in 1:1 ratio) to convert it into a paste. The drug was then added to the above paste and kneaded for sufficient time. The kneaded mixture was dried on a hot plate at 60-70° C. The solid dispersions were subjected to solubility studies and powder X ray diffraction analysis (PXRD). [1,2,3,5]

For the solubility studies, prednisolone solid dispersions (10mg) were added to 10ml of phosphate buffer pH 6.8 in a 10ml volumetric flask. The volumetric flasks were capped properly and shaken at room temperature for 24hours. Resultant samples containing undissolved solid dispersions were filtered through Whatman filter paper, suitably diluted with phosphate buffer pH 6.8 and analyzed by Ultraviolet (UV) spectrophotometer at 247nm.

The X-ray diffraction analysis was carried out to evaluate possible reduction in the crystallinity of drug after formulation into solid dispersion using β- cyclodextrin as carrier. The formulation was subjected to Powder X-ray diffraction (PXRD) using Copper radiation generated at 30mA and 40 kV potential. The diffracted X-rays were then detected in the 2-theta range of 20 - 80° and the result were processed by a pre-loaded program. [12]

PREPARATION OF PREDNISOLONE GEL

10g of each gel was formulated using different gel forming polymers like Carbopol 940, HPMC and Methyl cellulose as given in table 1. All the formulations were prepared at room temperature by hydrating the gelling agents in water and stirring until clear gels were formed. In the case of Carbopol 940p gel, the polymer was dispersed in a mixture of 2ml glycerol and 5ml of water. The mixture was allowed to stand for air bubbles to separate and then gelled by neutralization with triethanolamine. After full swelling of the gel, the prepared solid dispersions were dissolved in remaining water and were incorporated into the gel base. In

case of HPMC and Methyl cellulose, gels were prepared by dispersing each polymer in hot water, followed by addition of cold water to dissolve the gelling agents. After full swelling was obtained, the prepared solid dispersions were dissolved in remaining water and were incorporated into each gel. Then methyl paraben and propyl paraben are dissolved in alcohol, incorporated into the gels and mixed well. [13]

Table 1. Formulation of prednisolone oral gel

INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Prednisolone (mg)	100	100	100	100	100	100	100	100	100	100	100
Beta Cyclodextrin(mg)	300	300	200	250	300	200	250	300	200	250	300
Methyl Cellulose (%)	0.5	-	-	-	-	-	-	-	-	-	-
HPMC (%)	-	0.5	-	-	-	-	-	-	-	-	-
Carbopol 940(%)			0.5	0.5	0.5	1	1	1	2	2	2
Glycerin (ml)			2	2	2	2	2	2	2	2	2
Alcohol (%)	5	5	5	5	5	5	5	5	5	5	5
Methyl Paraben (%)	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Propyl Paraben (%)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

EVALUATION OF PREDNISOLONE GEL

The gel formulations were assessed for the following physiochemical parameter.

Invitro mucoadhesive measurement

The experiment was performed following the published guideline by Nakamura et al with slight modification.[13] An agar plate which contained agar at 1.5%w/v was prepared by weighing 1.5g of agar powder, then phosphate buffer (pH 6.8) was added into the agar, and finally gently the mixture was heated gently in a water bath. The hot solution was poured into a Petri dish with a diameter of 9cm. The agar was then allowed to cool to setting point. At the centre of each agar plate, a circle with diameter of 1cm was made. Equal quantities of each

gel were placed on it. The longest movement distance of the sample at room temperature was determined by slanting the plate at 30°.At 1, 2, 3 and 4hours, the movement distance of each gel was measured and recorded.

Appearance

Gel formulations were visually inspected for color, homogeneity, presence of particles and fibers.

Drug content

Drug content was determined by taking 1g of gel in a 100ml of standard flask. Phosphate buffer, pH 6.8 was added, mixed well and the volume was made up. It was then sonicated for 2hours and then filtered. From this solution 1ml of aliquot was pipetted out and diluted to 10 ml. The content of drug was determined by UV spectrophotometer at 247nm. Further calculations were done to obtain the drug content.

Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. Initially, the pH meter was calibrated using standard buffers of pH 4 and 9.2. 1g of gel was weighed accurately and dispersed in 10ml of purified water and the pH was noted. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Measurement of viscosity

The viscosity of the formulated gel was determined using Brookfield viscometer. The sample holder taken for the viscosity measurement was filled with the sample and then inserted into a flow jacket mounted on the viscometer. Spindle number 6 was used for gel and the spindle speed was 2 r/min at 28°C. [8,9]

Spreadability

Spreadability of the formulations was determined by an apparatus suggested by Mutimer e t al [14] which was suitably modified in the laboratory and used for the study. It consists of a wooden block which was provided by a pulley at one end. A rectangular ground glass plate was fixed on the block. An excess of gel (500mg) under study was placed on this ground plate. The gel was then sandwiched between the plate and another plate having the same

dimension of the ground plate and was provided with a hook. A 50g weight was placed on the top of the two plates. Excess of the gel was scrapped off from the edges. The top plate was then subjected to a pull of 30g with the help of a string attached to the hook and time (in seconds) required by the top plate to cover 5cm was noted. A shorter time interval indicates better spreadability.

The spreadability was calculated using equation 1.

$$S = ML/t \text{----------1}$$

where, S is the spreadability (g.cm/sec), M is the weight tied to the upper plate (g), L is the distance moved by the glass plate (cm) and t is the time taken (sec).

Extrudability

The gel formulations were filled in standard capped collapsible Aluminum tubes and sealed by crimping the end. The weights of the tubes were recorded. The tubes were placed between two glass slides and were clamped. A 1kg weight was placed over the slides and then the cap was removed. The amount of extruded gel was collected and weighed. The percent of the extruded gel was calculated (>90% extrudability: excellent, >80% extrudability: good, >70% extrudability: fair)[8].

***In vitro* release studies**

The release studies of the prepared gels were carried out in a 100ml beaker. Gel sample (2.5mg) was placed in beaker and the release studies were done in 50ml of phosphate buffer (pH 6.8) at 37°C±0.5. 1ml of each solution was withdrawn periodically at 5, 10, 20, 30, 45 and 60 minutes and replacing each time with equal volume of fresh dissolution medium. Then the samples were analyzed for the drug content by using phosphate buffer as blank spectrophotometrically at 247 nm. From the calibration plot, corresponding concentrations were determined and further calculations were made to find out the release of drug. [10]

***In vitro* release kinetic studies**

The result of *invitro* release profiles obtained for the optimized formulation was fitted into four models of data treatment as follows. [15]

1. Cumulative percentage drug released versus time. (Zero-order kinetic model)

2. Log cumulative percent drug remaining versus time. (First-order kinetic model)

3. Cumulative percent drug released versus square root of time. (Higuchi's model)

4. Log cumulative percent drug released versus log time (Korsemeyer - Peppas equation)

Zero Order Kinetics

A zero-order release would be predicted by the following equation 2.

$$At = Ao - Kot \text{----------2}$$

Where:

A_t = drug release at time 't'

A_0 = initial drug concentration

K_0 = zero-order rate constant (hr^{-1})

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 a slope equal to K_0.

First order kinetics

A first-order release would be predicted by the following equation 3.

$$logC = logCo - 2.303Kt \text{----------3}$$

Where:

C = Amount of drug remaining at time 't',

C_0 = Initial amount of drug

K = First-order rate constant (hr^{-1})

When the data is plotted as log cumulative percent drug remaining versus time, it yields a straight line, indicating that the release follows first-order kinetics. The constant 'K' can be obtained by multiplying 2.303 with slope values.

Higuchi's Model

Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.[7]

$$Q = [\frac{D€}{\tau(2A - €Cs)Cst}] \quad \text{---------- 4}$$

Where,

Q = Amount of drug released at time 't'

D = Diffusion coefficient of the drug in the matrix,

A = total amount of drug in unit volume of matrix

Cs = the solubility of the drug in the diffusion medium

€ = porosity of the matrix

τ = tortuosity

t = time (hours) at which 'Q' amount of drug is released

Equation 4 may be simplified if one assumes that D, Cs and A are constant. Then equation 4 becomes

$$Q = Kt^{1/2} \text{----------} \quad 5$$

When the data is plotted according to equation 4 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism and the slope is equal to 'K'.

Korsemeyer and peppas model:

The release rates from controlled release polymeric matrices can be described by the following equation 6 proposed by the Korsemeyer et al.

$$Q = Kt^{n} \text{----------6}$$

Where,

Q = the percentage of drug released at time 't'

K = a kinetic constant incorporating structural and geometric characteristics of tablets

n = the diffusion exponent indicative of release mechanism

For fickian release, n is equal to 0.45 while for anomalous (Non fickian transport), n ranges between 0.45 and 0.89 and for zero order release, n is equal to 0.8980.

3. RESULTS AND DISCUSSION

DRUG EXCIPIENT COMPATIBILITY STUDIES'

Differential Scanning Calorimetry (DSC)

DSC results revealed that the physical mixture of prednisolone with excipient did not show significant change in the melting endotherm when compared with that of pure drug. This indicated no drug –excipient incompatibility.[6]

FTIR Spectroscopy

The Infra-red (IR) spectrum of drug – excipient mixture did not show significant changes in the principal peaks of drug when compared with the IR spectrum of pure drug as shown in Fig. 1 indicating no drug excipient incompatibility.[6]

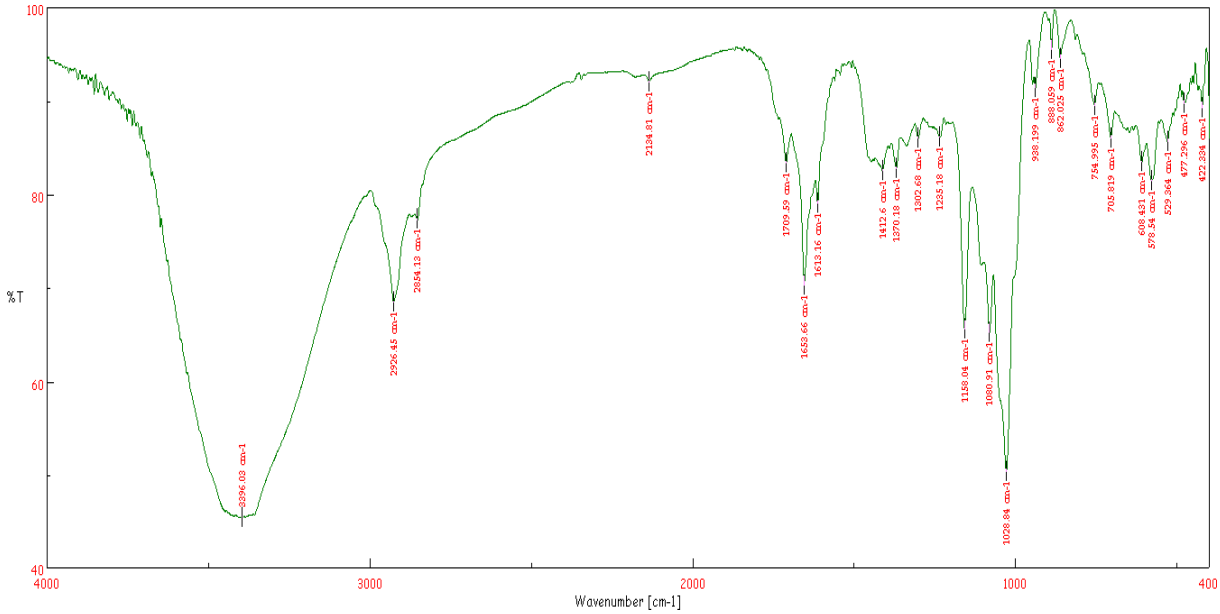

Fig 1. Fourier transmission infrared spectra of drug- excipient mixture

FORMULATION OF PREDNISOLONE SOLID DISPERSION

Preparation of drug –β-cyclodextrin complex by kneading method.

Solid dispersion of prednisolone and β-cyclodextrin were prepared at different ratios by kneading method.

EVALUATION OF SOLID DISPERSION

Determination of solubility of solid dispersions

All the prepared solid dispersions exhibited better solubility when compared to pure drug (table 2). This may be attributed to the fact that β-cyclodextrin formed inclusions complex with lipophilic prednisolone and enhanced the solubility of drug.[14]

Table 2. Solubility of solid dispersions

Drug: betacyclodextrin ratio	Solubility (mg/ml)
Pure drug	5.53±0.001
1:1	52.38±0.010
1:2	78.62±0.004
1:2.5	83.68±0.005
1:3	87.61±0.007

Powder X-ray diffraction analysis

The characteristic peaks for PXRD of pure drug sample is shown at 2 theta range of 21.1°, 22.58°, 25.18°, 26.1° and 31.92°. In solid dispersion of prednisolone with β- cyclodextrin the intensity of drug peak was reduced indicating a decrease in crystallinity as shown in Fig. 2 and Fig. 3. Amorphous nature had been established in the solid dispersion in the diffractogram. Crystallinity of drug was reduced because of complex formation with carrier. [15]

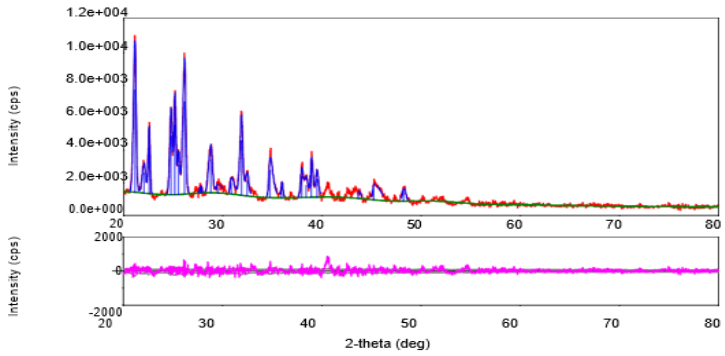

Fig 2. Powder X-ray diffraction pattern of pure drug

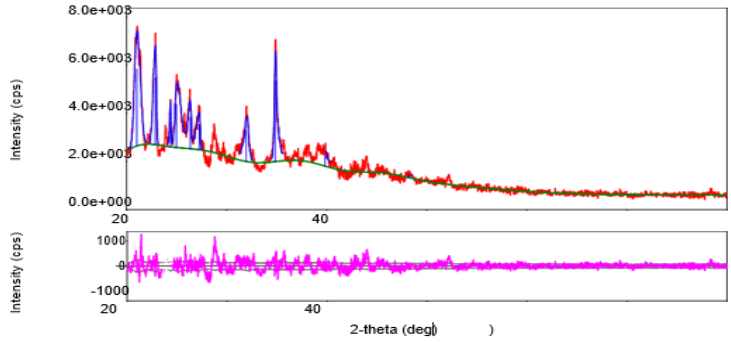

Fig 3. Powder X-ray diffraction pattern of Solid dispersion of the drug

PREPARATION OF PREDNISOLONE GEL

The prepared solid dispersions were formulated into gels using 3 gelling agents - Carbopol 940, HPMC and methyl cellulose.

EVALUATION OF PREDNISOLONE GEL

Appearance

All the formulations were inspected for its appearance and the observations are shown in table.3.

Drug content

The percentage drug content of the gels was found to be in the range of 94% to 99%.

Measurement of pH

The normal range of oral mucosal pH is reported to be between 6.8 to 7.4. Therefore, the

effects of pH of the formulations on oral tissue should be considered. It was found that the pH values of all the formulations were comparable to the oral mucosal pH (table. 3) and therefore, do not cause any irritation and damage to the hard and soft oral tissues.

Measurement of viscosity

Based on the results as shown in table. 3, the viscosities of the formulations were found to be influenced by the concentration of the polymer used. It was found that the viscosity of the formulations significantly increased with the increase in the polymer concentration. [5,7]

Table 3. Evaluation of prednisolone oral gel based on appearance, drug content, pH, viscosity.

Formulation code	color	homogeneity	Presence of particulate matter	Drug content	pH	Viscosity(cps)
F3	whtie	+++	no	94.07 ± 1.19	7.14 ± .041	18590
F4	whtie	+++	no	97.57 ± 0.53	7.06 ±0.026	18730
F5	whtie	+++	no	98.53 ± 0.46	7.16 ±0.05	18840
F6	whtie	+++	no	95.91± 1.32	7.22 ±0.026	22910
F7	whtie	+++	no	96.68 ± 1.24	7.32 ±0.032	23420
F8	whtie	+++	no	96.66 ± 1.52	7.25 ±0.032	23589
F9	whtie	+	no	94.89 ± 0.78	7.21 ±0.045	31348
F10	whtie	+	no	94.60 ± 2.69	7.16 ±0.061	31980
F11	whtie	+	no	94.45 ± 1.21	7.10 ±0.031	32210

***In vitro* mucoadhesion measurement**

The shorter the movement distance, better the adhesion between the polymer and the agar plate. Except for formulations made out of Carbopol 940, there was a movement of all formulations on the agar plate at 1hour. The movement distance of the formulation of Carbopol did not increase after the completion of 3hours of experiment. There is a possibility that there may be hydrogen bond formation between the hydrophilic functional groups of the polymers and the corresponding functional groups of the agar. Apart from this, viscosities of

the gel formulations tended to affect the residence time of the polymers on the agar plate. Again, the effect of viscosity was more obvious in the case of anionic polymers, Carbopol 940p as shown in table. 4. Therefore, F1 and F2 were discarded.

Table 4. *In vitro* mucoadhesion data

POLYMER	Movement distance(cm)			
	1hour	2hour	3hour	4hour
Carbopol 940	0.2± 0.1	0.3±0.2	0.4±0.2	0.4±04
Methyl cellulose	>4	-	-	-
HPMC	>4	-	-	-

Spreadability

The spreadability of gel was evaluated to test the ease of applicability of gels on oral mucosa. From the results as shown in table. 5, it was concluded that as the concentration of polymer increased, the spreadability decreased. Good spreadability was seen in the formulations F3, F4 and F5.

Extrudability studies

When the polymer concentration was increased, extrudability was found to be decreased due to increase in viscosity.

***Invitro* release study**

The *invitro* release study was carried out for all formulations and the amount of drug released at each time interval and percentage cumulative drug release (CDR) obtained are shown in table.5, It was recognized that if the active substance is held firmly by the vehicle (polymer), the release of the active substance is slow. In the case of Carbopol 940p, the formulations F3, F4 and F5 which contained the lowest concentration of Carbopol 940p (0.5%) showed the highest release of prednisolone in comparison with the formulations F6, F7, F8 and F9, F10, F11which contained higher concentration of Carbopol 940 (1% and 2% respectively). As the release of the active substance generally occurs through the spaces or channels within the hydrogel network, it was likely that at higher polymer concentrations, the drug was trapped in the dense polymer network, resulting in an increased diffusional resistance. The increase in polymer concentration could increase the density of chain structure, thereby limiting the

movement area of the drug. *In vitro* drug release studies showed formulation F5 with drug: β-cyclodextrin ratio of 1:3 which was incorporated into 0.5% Carbopol 940p exhibited maximum percentage drug release when compared to other formulations. [7]

Table 5. Evaluation of prednisolone gel based on spreading coefficient, extrudability and cumulative drug release.

Formulation code	Spreadability coefficient (g cm/sec)	Extrudability	Cumulative drug release (%)
F3	26.43±2.31	+++	90.446±0.78
F4	26.40±2.16	+++	91.622±0.83
F5	26.55±0.02	+++	93.563±0.19
F6	20.61±0.03	++	82.564±0.57
F7	20.41±1.19	++	82.584±0.07
F8	21.17±0.01	++	86.406±1.09
F9	15.02±0.73	-	67.797±0.13
F10	14.98±0.007	-	71.827±2.08
F11	15.48±0.71	-	76.022±0.87

***In vitro* release kinetics**

The result of linear regression analysis of data including regression coefficient are shown in fig.4 and summarized in table.6. When the regression coefficient 'R'-values of zero order and first order plots were compared, it was observed that the 'R^2' value of zero order was 0.715 and first order was 0.962(R^2 value close to '1', indicating more linearity). Therefore, the drug release from the formulation was assumed to follow first order kinetics. Good fit of the Higuchi's model (highest regression coefficient) to the dissolution profile of the formulation F5 suggested that diffusion is the predominant mechanism limiting the drug release from the gel. The *In vitro* release data as log cumulative versus time were fitted to Korsemeyer equation to understand the mechanism by which prednisolone was released from this formulation. Values of the exponent 'n' were found to be 0.324 indicating that the drug release mechanism is fickian where n is the diffusion exponent indicative of release mechanism. For fickian release n is 0.45 while for anomalous (Non fickian transport), n ranges between 0.45 and 0.89 and for zero order release n is 0.8980.[15]

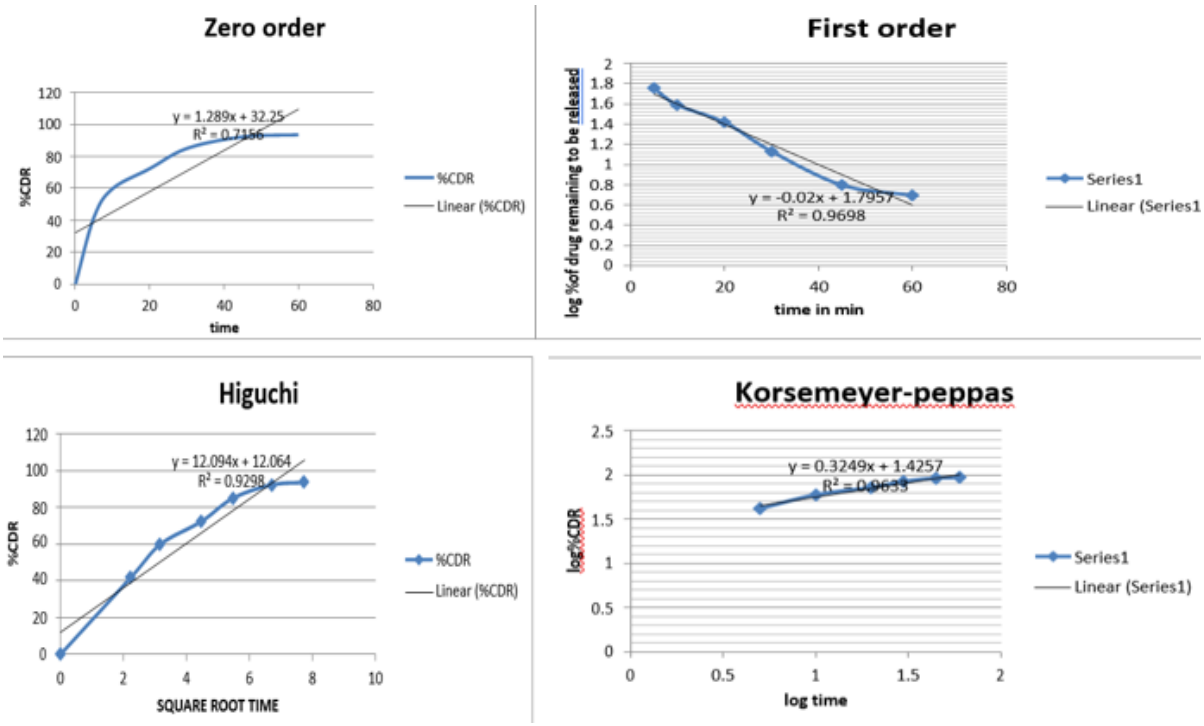

Figure 4 *In vitro* release kinetics

Table 6 Regression coefficients of various kinetic studies

ZERO ORDER	FIRST ORDER	HIGUCHI MATRIX	KORSMEYER PEPPAS	
R^2	R^2	R^2	R^2	n
0.715	0.962	0.929	0.963	0.324

4. CONCLUSION

Solid dispersions of prednisolone were prepared using different concentrations of β-cyclodextrin (1:2, 1:2.5 and 1:3) by kneading method. These were then subjected to solubility analysis and the results showed that the prednisolone solid dispersions exhibited 15 times more solubility than the pure drug. These solid dispersions were formulated into gels using different polymers like Carbopol 940p, HPMC, and Methylcellulose. It was concluded that gel prepared from Carbopol 940p had better mucoadhesion than the gels prepared from HPMC and methylcellulose. Therefore, nine formulations using different concentrations of Carbopol 940p and β-cyclodextrin were prepared. These formulated gels were then evaluated for drug content, viscosity, spreadability, extrudability and *invitro* drug release studies. The evaluation studies revealed that the formulation F5 exhibited good parameters and maximum

drug release when compared to other formulations. Thus, it was considered as the optimized formulation. Regression analysis showed that the optimized formulation follows first order release pattern, and the release was mainly by diffusion. Therefore, it seemed that a prednisolone oral gel is a promising new dosage form for the improved treatment of oral ulcers. It must be pointed out that further investigations like *in vivo* animal studies and clinical trials should be conducted to prove the efficacy of the formulation and also to establish the possibility of increased therapeutic outcome in the treatment of oral ulcers.

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