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Original Article

MUCOADHESIVE IN-SITU GEL FOR TRANSMUCOSAL DELIVERY OF CELECOXIB

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ABSTRACT

Objective: The main aim of the present study was development of mucoadhesive insitu gel for transmucosal delivery of celecoxib to increase its bioavailability by avoiding first pass metabolism. In the present study, transmucosal route was used for delivery of celecoxib so as to bypass the first pass metabolism seen in drug with oral route.

Methods: Temperature sensitive bio-adhesive in situ gel was prepared for the delivery of celecoxib in the rectal cavity. Optimization of the formulation was done using partial factorial ($2^{[4-1]}$) design considering the concentration all the excipients as independent variables.

Results: The optimized formulation containing 0.71% polymer, 3.5% NaCl, 9.12% PEG 400, 0.5% sodium lauryl sulfate was found to possess gelling temp 38°C, bio adhesion strength 4.05 g/cm^2 and 88.39% *in vitro* drug release in three hours. Pharmacokinetic study of the optimized batch was performed in male Wistar rats. It was found that the bioavailability of in situ formulation was increased by 1.54 folds as compared to that of the marketed formulation by same route.

Conclusion: It was concluded that development of mucoadhesive insitu gel for transmucosal delivery of celecoxib was found to be a promising approach to obtain celecoxib drug with increased in the bioavailability of the drug.

Keywords: Celecoxib, Transmucosal route, In-situ gel, Partial factorial study, Pharmacokinetic study.

INTRODUCTION

Celecoxib is BCS class2 drug having low solubility, celecoxib is a non steroidal anti inflammatory drug and a selective cox-2 inhibitor. It is used in treatment of rheumatoid arthritis, acute pain, osteoarthritis, painful menstruation, menstrual symptoms, and to reduce number of colon and rectum polyps in the people with familial adenomatous polyposis. It acts as an anti-inflammatory agent as it inhibits prostaglandin synthesis. It has been found that celecoxib drug is predominately eliminated by hepatic metabolism with little unchanged (< 3%) amount excreted in urine and faces [1- 3].

Its bioavailability is around 40%, which may be attributed to its lower solubility & first pass metabolism. Thus transmucosal route was assumed to improve the bioavailability of celecoxib. Mucosal surface are generally efficient absorption site because of the absence of stratum corneum epidermidis, which are considered to be a major barrier for drug absorption. Mucosal surfaces are rich in blood supply providing a better chance for the drug to transport in systemic circulation and avoiding, in most case, degradation of drug by first-pass hepatic metabolism [4-6]. Various routes for transmucosal drug delivery system are there which includes the following Nasal, buccal, ocular, rectal drug delivery system.[7]In the present study, rectal route was preferred because the volume required to be administered was higher than the volume that can be comfortably administered through other mucosal routes like nasal, buccal or ocular.

Bio adhesive *in situ* gel was prepared for ease of administration & retention at the site of absorption. '*In situ'* is Latin phrase that means 'in position'. In situ forming gels are drug delivery systems which are in sol form before administration in the body, after administration in the body [7,8].

Routes of administration include ocular, rectal, oral, vaginal, injectable & intraperitoneal. Various biodegradable polymers like gellan gum, Alginic acid, xyloglucan, Pectin, Chitosan, Poly (DL-lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone etc. are some of the examples used in the formation of *in situ* gel[9]. Gelling can take place due to pH [10]or change in temperature [11-17]. Development of temperature sensitive *in situ* gel was the aim of the present research work. Ease of administration, reduced dosing frequency, improved patient compliance and comfort, simple formulation, low manufacturing cost, improved retention at absorption site, sustained and controlled release are some of the advantages of insitu gelling system.[10]

MATERIALS AND METHODS

Materials

Celecoxib was a gift sample from Alembic Pharmaceuticals limited, Vadodara, India. Methyl cellulose was purchased from Aatur Instru Chem, Vadodara. Sodium chloride (NaCl), potassium chloride (KCl) and sodium bicarbonate ($NaHCO_3$) were purchased from S. D. Fine chemicals, Mumbai, India. Sodium lauryl sulfate (SLS), PEG 400 and HPLC grade methanol were procured from Loba Chemie, Mumbai, India.

Selection of ingredients

Methyl cellulose (MC) was used as the gelling polymer. Effect of different salts (NaCl, KCl, $NaHCO_3$) was studied on the gelation temperature of MC. As celecoxib has poor solubility in water, cosolvent was selected for the formulation out of ethanol, glycerine, propylene glycol & PEG400 by saturation solubility study. Surfactant SLS was also used to increase the wet-ability and reduce coarse precipitation of celecoxib.

Preparation of the formulation

The in-situ gel formulations were prepared by simple mixing of drug solution in polymer solution. [12-16]Briefly, weighed quantity of polymer, surfactant and salt were dissolved in water in one beaker. In another beaker drug was dissolved in PEG 400. The drug solution was added to the polymer solution with continuous stirring using magnetic stirrer for 30 minutes at 150-200 rpm.

Optimization of formulation

Gelling capacity (gelling time, gelling temperature), bio adhesion strength, viscosity, *In vitro* drug release were selected as dependent variables for the optimization study. Various independent variables selected were conc. of polymer (methyl cellulose), conc. of surfactant (SLS), conc. of PEG 400, conc. of salt (NaCl). Fractional factorial design of $2^{[4-1]}$ was used for the optimization of concentrations of all these 4 variables on the formulation. In the fractional factorial

design four factors were used and evaluated each at two levels and performing the experimental trials at all the eight possible combinations.

The model matrix design layout for $2^{[4-1]}$ for fractional factorial design was developed according to Gareth [18]. Compositions of all the formulations are given in Table 1.

Table 1: Compositions of Formulations F1-F8

Batches no	Drug (mg)	Methyl cellulose (mg)	PEG 400 (ml)	Sodium chloride (mg)	SLS (mg)	Water (q. s. ml)
F1	750	75	0.75	370	75	15
F2	750	225	1.5	370	75	15
F3	750	225	0.75	520	75	15
F4	750	75	1.5	520	75	15
F5	750	225	0.75	370	150	15
F6	750	75	1.5	370	150	15
F7	750	75	0.75	520	150	15
F8	750	75	1.5	520	150	15

Evaluation parameters of *in situ* gel formulation

Rheological property (viscosity)

In rheological studies, viscosity determination of sample was done using Brookfield (DVLV-I+ PRO) prime model viscometer using spindle no 62. At angular velocity of 30 rpm and constant temperature (37±1°C), viscosity of all the formulations were measured. The average of three readings was used for determining the viscosity. Viscosity of the formulations were measured at two points before gelling and after gelling[12].

Gelling Capacity

Gelling temperature

The prepared formulation was taken in transparent glass vial. It was kept in a water bath maintained at constant temperature (starting at 30 + 2°C). The glass vials were inverted and visually evaluated. If not gelled, the temperature of the water-bath was gradually increased till the sample started gelling[13].

Gelling time

The gelling time of the formulations were determined by taking 2 ml of the formulation into a glass vial, which was placed in the water bath maintained at temperature 37+2°C. The time taken for gel formation was noted[13].

Gel strength

Gel strength was performed by noting down the time up to which it remains in the form of gel at constant temperature of (37+2°C) using water bath. [13]

Drug content

Drug content was determined by dissolving 1 ml of formulation in methanol by shaking for few minutes. The concentration of celecoxib was determined at 248.5 λ_{max} using UV spectrophotometer after suitable dilution against blank formulation treated in same manner[12-15].

Bioadhesive strength

The bioadhesive strength was measured using a modified two arm balance with slight modification. [14-16] The biological membrane was fixed to the outer surface of the bottom of a 50 ml beaker with cynoacrylate adhesive and then placed in a 100 ml beaker. Accurately measured 1 ml formulation was converted into gel by exposing it to gelling temperature. The formed gel was transferred between the bottom of modified stainless steel pan and beaker. Initially, 50 gram preload was applied for the establishment of adhesion between gel and biological membrane. For all the formulations, preload time was kept constant. At the end of preload time another beaker was placed on the opposite pan. Water was added further drop by drop into the beaker until the membrane gets detached at the opposite end. The weight or mass in grams required to detach the pan from membrane gives the measure of bio-adhesive strength.

***In vitro* diffusion study**

In vitro diffusion study was performed using USP paddle II at 100 rpm, using 500 ml of Phosphate buffer pH 7.4 as the dissolution medium [12-14] and temperature was maintained at (37±1° C) throughout the study. In-situ gel formulation containing was inserted into dialysis bag. Both the sides of the dialysis bag were sealed to prevent leakage. The dialysis bag was then tied to the paddle, such that it remains immersed in the dissolution medium during the study.

Release kinetics

The drug release data obtained were fitted to zero order, first order, Higuchi and Korsemeyer Peppas, Hixson– Crowell model to determine the mechanism and corresponding release rate from the *in situ* gel formulation. [14]

***Ex-vivo* permeation study**

Ex-vivo permeation study was done in Franz diffusion cell at 100 rpm at temp (37±1°C) using 40 ml of saline phosphate buffer as dissolution media.[15, 16] Buccal mucosa of goat was used as barrier membrane for the permeation study. The mucosa was stored overnight in saline phosphate buffer pH 7.4. The formulation (2 ml) was taken in donor compartment and 1 ml of sample was withdrawn at regular time interval and absorbance was measured at 248.5 λ_{max}.

***In vivo* pharmacokinetic study**

The *In vivo* pharmacokinetic study was carried out as per the guidelines compiled by the CPCSEA, Ministry of culture, Government of India (vide approval to protocol PIPH 30/13 by CPCSEA 921/AC/05/CPCSEA). Eighteen male Wistar rats weighing 250±10 gm were used for the bioavailability study. The rats were divided into 3 groups containing 6 animals in each group. In first group 6 animals were given normal saline, second group was given *in situ* gel formulation, and last group was administered with marketed formulation (converted into suspension of equivalent strength). During the experiment, the animals were anesthetized using diethyl ether orally before rectal administration of the formulation. On experiment day animals were kept in metabolic cage and dose of 10mg/kg was given rectally (n=8) in animal using Reyls tube. Animals were anaesthetized at time of blood collection from the retro orbital plexus using glass capillary. Control groups of rats were administered with normal saline. [19-21]

The collected animal blood samples were analysed by using Bio-analytical method at regular time intervals for time period of 8 hours. The blood samples were taken in micro centrifuge tube, in that 8 mg of EDTA was added as anticoagulant to prevent blood clotting. Collected blood samples were centrifuge in refrigerated centrifuge for separation of plasma from the blood. Separated plasma (500 µl) was collected through micropipette and 1.5 ml of methanol was added and mixed properly so that protein gets precipitated. The mixture was centrifuged at 5000 rpm for 20 min. After centrifugation supernatant was collected and analyzed by UV for determination of drug concentration. [19-21] Prior to sample analysis, a standard curve was prepared between 0.2-1.0 µg/ml by spiking plasma with known concentration of celecoxib.

Obtained plasma conc. was plotted against time. The maximum plasma concentration (C_{max}) and time of peak concentration (T_{max}) were directly determined from their respective plasma

concentration time profile. Non-compartment model was used for calculation of different pharmacokinetic parameters. Trapezoidal method was used to calculate the concentration time curve i. e. area under curve (AUC 0-t). [19]The total area under curve (AUC0-t) was calculated by:

$$\text{AUC } 0-t = 1/2 \times (C1 + C2)\,(t2 - t1)$$

Relative bioavailability (Fr) was calculated with reference to oral suspension using formula the relative bioavailability (Fr) at the same dose was calculated as

$$Fr = \frac{\text{AUC insitu gel } 0-t}{\text{AUC marketed formulation} 0-t}$$

RESULTS AND DISCUSSION

Temperature sensitive in-situ gel for drug delivery have been reported to be formed using polymers like Pluronic F68 [11, 12] or derived chitosan [13]. Methyl cellulose was selected as the polymer as it is widely available semi-synthetic polymer. Though methyl cellulose has a gelation temperature above 70°C, its gelling temperature can be modified using salts [22-24].

Selection of ingredients

In the screening studies carried out for selection of salt, NaCl was found to have reduced the gelling temperature of MC nearest to body temperature (Table 2).

Table 2: Effect of different salts on gelling temperature of MC

Batches no.	Conc. of methyl cellulose (%)	Conc. of salt (%)	Gelling temperature (°C)
M8	1%	NaCl (3%)	37 °C
M9	1%	KCl (4%)	40 °C
M10	1%	$NaHCO_3$ (6%)	39 °C
M11	0.5%	NaCl (3%)	39 °C
M12	0.5%	KCl (4%)	42 °C
M13	0.5%	$NaHCO_3$ (6%)	40 °C

The solubility of celecoxib was checked in different solvent. Among these different solvents, solubility of celecoxib was found to be maximum in PEG 400. Thus PEG 400 was selected as co solvent to enhance the solubility of drug. In the screening study Effect of different conc. of co-solvent (PEG 400) on the gelling temperature of the polymer with milliequivalents (0.0595) 3% NaCl salt was studied. Significant effect of different conc. of PEG 400 with same salt was observed on the gelling temperature of polymer (Table 3). Thus, 10% PEG 400 was used as co-solvent.

Table 3: Effect of co-solvent on gelling temp of MC-salt mixture

B. No.	MC (%)	Conc. of PEG 400	Gelling temperature
A1	0.5%	10%	41°C
A2	0.5%	5%	39 °C
A3	1%	10%	38°C
A4	1%	5%	36°C
A5	1.5 %	10%	38°C
A6	1.5%	5%	33°C

* 3% NaCl in each formulation

Optimization study

For an *in situ* gel preparation, Gelling capacity (gelling time, gelling temperature), bio-adhesion strength, viscosity, and *In vitro* drug release are critical quality attributes. So, these were selected as dependent variables. These variables were dependent upon the concentration of various ingredients such as polymer (methyl cellulose), salt (NaCl), surfactant (SLS), and co-solvent (PEG 400). Hence, they were selected as independent variables due to their significant effect on formulation. Since the number of independent factors is 4, only 2 levels were selected for optimization study. However, the full factorial design 2^4 gives rise to requirement of 16 batches. In order to reduce the requirements of experimental batches, fractional factorial design (2[4-1]) was used. In the fractional factorial design 4 factors were used and evaluated each at 2 levels and performing the experimental trials at all the 8 possible combinations.

Rheological properties

The viscosity of all the formulations from F1 to F8 were measured at angular velocity of 20 RPM using spindle no 62 at constant temperature (Table 4).

Table 4: Viscosity of formulations at room temperature before and after gelling

Formulation batches	Viscosity in cps (n=3) ± S. D before gelling at 25ºC	Viscosity in cps (n=3) ± S.(D after gelling at 37ºC
F1	95±1.58	945±2.0
F2	232±2.78	3006±3.04
F3	201±2.51	2875.1±2.56
F4	103±1.52	1284±2.64
F5	212±2.51	2586±2.51
F6	86.5±2.08	645±1.18
F7	62.8±2.25	322±2.21
F8	202±1.52	2385±2.08

ANOVA (Table 5) using DOE software suggested following equation for viscosity:

$$\textbf{Viscosity} = +679.74 + 1920.53 * \textbf{conc. of methyl cellulose} + 28.35 * \textbf{conc. of PEG} * - 84.73 * \textbf{conc. of NaCl} - 1074.05 * \textbf{conc. of surfactant}$$

Table 5: ANOVA table for viscosity

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob> F	
Model	8.008	4	2.002	67.49	0.0029	Significant
Conc. of methyl cellulose	7.377	1	7.377	248.70	0.0006	
Conc. of PEG400	40171.95	1	40171.95	1.35	0.3287	
Conc. .of salt	14356.65	1	14356.65	0.48	0.5367	
Conc. of surfactant	5.768	1	5.768	19.45	0.0216	
Residual	88986.10	3	29662.03			
Cor Total	8.09	7				

It was found that conc. of polymer and conc. of surfactant have P value 0.0006 and 0.0216, respectively (i. e. $p<0.05$), which gives indication that there is significant effect of conc. of polymer and conc. of surfactant on viscosity of the formulation. Therefore, by eliminating non-significant terms, the reduced equation become.

$$\text{Viscosity} = +679.74 + 1920.53 * \text{conc. of methyl cellulose} - 1074.05 * \text{conc. of surfactant}$$

The positive value of coefficient indicates that viscosity of the formulation increases with increase in the concentration of methyl cellulose.

Whereas, with the increase in surfactant-conc., viscosity of the formulation decreases.

Gelling temperature

Gelling temperature of all the formulations was between 34-43°C (Table 6).

The polynomial equation obtained from the model was

$$\text{Gelling temp.} = 29.56 - 1.38 * \text{conc. of methyl cellulose} + 0.58 * \text{conc. of PEG} - 0.63 * \text{conc. of NaCl} + 10.25 * \text{conc. of surfactan}$$

Table 6: Gelling temperature & bio-adhesion strength of the optimization batches

Formulation batches	Gelling temperature (°C) (mean±S. D, n=3)	Bioadhesion strength (g/cm²) ±S. D (n=3)
F1	37±1.0	4.7±1.2
F2	36±2.2	5.8±2.2
F3	34±1.5	6.5±2.3
F4	39±2.5	4.3±1.0
F5	38±2.0	5.58±1.2
F6	43±2.1	2.14±3.1
F7	40±1.8	2.91±2.9
F8	38±1.1	5.12±1.2

The statistical study of the data of response gelling temperature was analyzed by design expert and DOE software 9.0. Result of the ANOVA (Table 7) was obtained using DOE software

Table 7: ANOVA table for gelling temperature

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob> F	
Model	73.63	4	18.41	65.44	0.0030	Significant
Conc. of methyl cellulose	3.78	1	3.78	13.44	0.0351	
Conc. of PEG400	16.53	1	16.53	58.78	0.0046	
Conc. .of salt	0.78	1	0.78	2.78	0.1942	
Conc. of surfactant	52.53	1	52.53	186.78	0.0008	
Residual	0.84	3	0.28			
Cor Total	74.47	7				

The conc. of polymer, conc. of PEG and conc. of surfactant showed significant impact on gelling temperature. Thus, the reduced equation for gelling temp. can be represented as:

$$\text{Gelling temp.} = 29.56 - 1.38 * \text{conc. of methyl cellulose} + 0.58 * \text{conc. of PEG} + 10.25 * \text{conc. of surfactant}$$

Gelling temperature of the formulation increased with increase in the concentration of PEG400 and Conc. of surfactant. The conc. of surfactant was found to have greater impact on gelling temp. The negative sign of coefficient of polymer conc. indicates gelling temp. of the formulation decreased with increase in conc. of MC.

Bioadhesion strength

Bio adhesion strength was measured of all the formulation from F1 to F8 and results of the bio adhesion strength are given in Table 6. Table 8 depicts the results of ANOVA rom the obtained data. Relationship between the independent variables and bioadhesion strength was generated using DOE software

$$\text{Bio} - \text{adhesion strength} = 4.55 + 2.32 * \text{conc. of methyl cellulose} - 0.11 * \text{conc. of PEG 400} + 0.19 * \text{conc. of NaCl} - 2.64 * \text{conc. of surfactant}$$

P values of conc. of MC & conc. of surfactant were found to be <0.05, indicating that there is significant effect of conc. of polymer & surfactant on bio-adhesion strength. Thus, bio-adhesion strength can be expressed as

$$\text{Bio} - \text{adhesion strength} = 4.55 + 2.32 * \text{conc. of MC} - 2.64 * \text{conc. of surfactant}$$

Bio-adhesion strength of the formulations were found to have increased with the increase in concentration of methyl cellulose and decreased with increase in conc. of surfactant.

Table 8: ANOVA table of bio-adhesion strength

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob> F	
Model	14.96	4	3.74	21.70	0.0150	Significant
Conc. of methyl cellulose	10.76	1	10.76	62.48	0.0042	
Conc. of PEG 400	0.64	1	0.64	3.71	0.1499	
Conc. of salt	0.068	1	0.068	0.40	0.5732	
Conc. of surfactant	3.48	1	3.48	20.23	0.0205	
Residual	0.52	3	0.17			
Cor Total	15.47	7				

Table 9: *In vitro* drug release profile of Batches F1 to F8

Time (Hour)	In-vitro diffusion study							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	43.42	21.12	30.79	44.27	23.33	45.52	38.55	27.61
1	64.91	43.16	47.32	69.32	39.41	62.29	61.28	43.69
2	80.18	57.81	60.32	83.12	57.81	80.69	83.64	57.77
3	96.20	68.16	76.16	97.69	68.16	97.20	94.20	72.34
4		80.98	85.12		78.69			88.80
5		94.23	92.18		85.82			95.14

In vitro drug release for at 3 hours was taken as a parameter for comparison and results of ANOVA for the response are given in Table 10 using DOE software.

Table 10: ANOVA table for Response surface of *In vitro* drug release

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	1453.30	4	363.33	15.52	0.0241	Significant
Conc. of methyl cellulose	1412.46	1	1412.46	60.35	0.0044	
Conc. of PEG 400	4.18	1	4.18	0.18	0.7012	
Conc. of salt	36.64	1	36.64	1.57	0.2996	
Conc. of surfactant	0.029	1	0.029	1.23	0.9742	
Residual	70.22	3	23.41			
Cor Total	1523.52	7				

Concentration of polymer, PEG & surfactant caused decrease in the release rate, as evident from the following equation

In-Vitro drug release

In vitro drug release of all the formulation was performed using saline phosphate buffer pH 7.4. Formulation F6 showed fastest *In vitro* release (97.2% in 3h) where as Formulation F5 followed slowest release pattern, releasing only 85.82% drug in 5h (Table 9).

$$\text{In vitro drug release} = 99.12 - 26.58 * \text{conc. of methyl cellulose} - 0.29 * \text{conc. of PEG} + 4.28 * \text{conc. of NaCl} - 0.24 * \text{conc. of surfactant}$$

But, only conc. of polymer showed p<0.05, implying that only MC concentration significantly guides the *In vitro* drug release. As expected, the release rate decreased with increase in polymer concentration. Thus, the reduced equation become

$$\text{In vitro drug release} = +99.12 - 26.58 * \text{conc. of methyl cellulose}$$

Validation of optimization model

The validation of the optimization model was carried out by preparing a checkpoint batch from the results of the overlay plot (Fig. 1) for the confirmation of the optimization of the formulation.

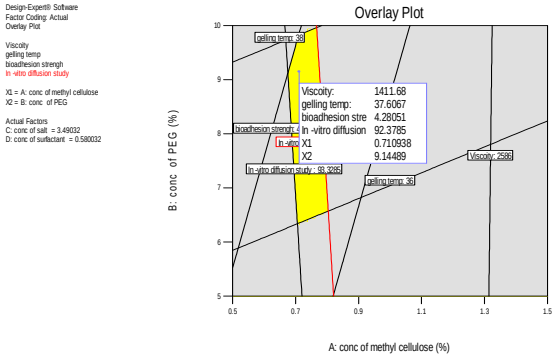


Fig. 1: Overlay plot for formulation batches for validation of model

The prepared checkpoint was further evaluated for all the responses for which equations have been generated. The experimental values of responses of the prepared checkpoint batch were near to the predicted values (Table 11) obtained from the overlay plot generated using 9.0. version of design expert software. Thus the model can be concluded as validated.

Table 11: Characterization of check point (optimized) batch

S. No.	Responses	Experimental value	Predicted value
1	Gelling temperature	38.0 °C	37.6 °C
2	Bio adhesion strength	4.05 g/cm^2	4.28g/cm^2
3	*In vitro* drug release	89.33 %	92%
4.	Viscosity cps	1389.50 cps	1411.12 cps

Table 12: Release kinetics of optimized formulation

Zero order release		First order release		Hixon Crowell		Higuchi model		Korsmeyer-Peppas model		Release mechanism
K_0	R^2	K_1	R^2	K_{HC}	R^2	K_H	R^2	N	R^2	Fickian diffusion
9.34	0.961	0.076	0.905	0.284	0.869	25.19	0.970	0.244	0.892	

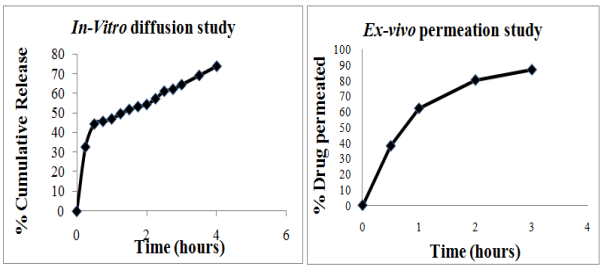
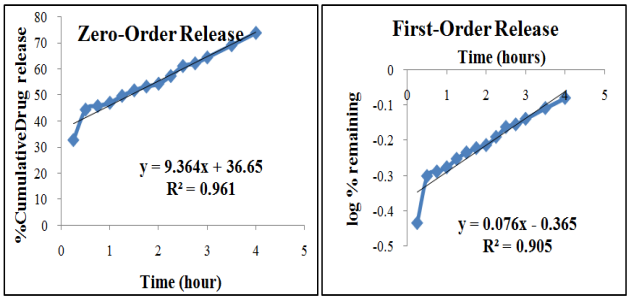


Fig. 2: *In vitro* diffusion and *ex-vivo* permeation profile of optimized batch

According to the kinetic model fit analysis (Fig. 3), the formulation follows **Higuchi model** as it has highest R^2 value among the other models (Table 12).

The **'n' value** obtained from **Korsemeyer-Peppas model** was found to be around 0.244, which suggest that the formulation follows Fickian diffusion.



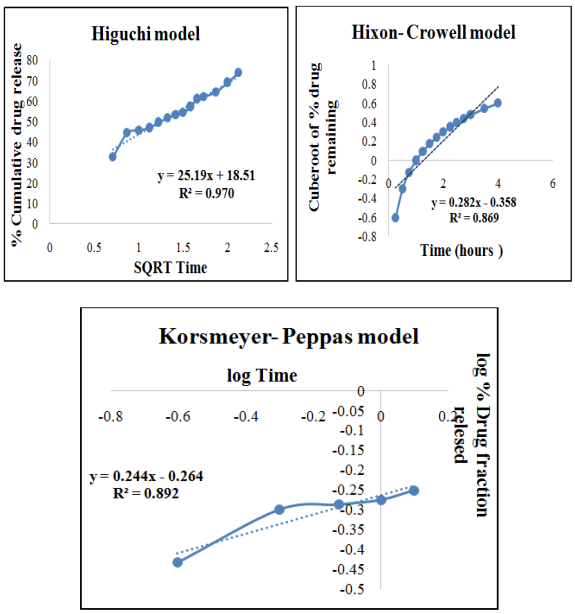


Fig. 3: Release kinetics study of optimized batch

Ex-vivo permeation

Exvivo permeation of the optimized batch was performed using Franz diffusion cell in saline phosphate buffer pH 7.4. The % Cumulative drug permeation was found to be 86.98% after 3 hours, which suggest similarity with the in-vitro release pattern (Fig. 2).

In vivo study of the optimized batch

In vivo study was carried out for confirming our concept that rectal administration of the prepared in-situ gel may improve bioavailability of celecoxib. For this, a comparative study was done between the prepared formulation & marketed formulation given by same route in same concentration. Spectrophotometric bioanalytical method was developed for analyzing celecoxib in plasma having linearity (r^2= 0.992) within 0.5-1.0 mcg/ml. Results (Fig. 4, Table 13) showed that the AUC of celecoxib (370.63 µg/ml. hr) was found to be more than AUC of the marketed formulation (215.47 µg/ml. hr).

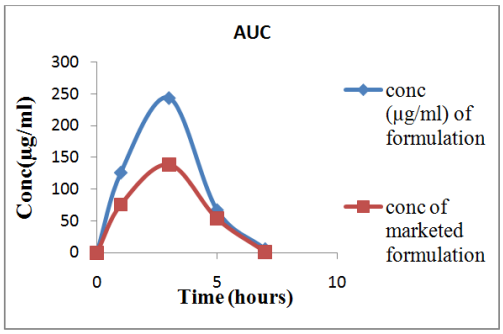


Fig. 4: Comparative Plasma profile of *in situ* gel and marketed formulation

Thus, a 1.54 folds increase in bioavailability could be achieved with the formulated *in situ* gel formulation in comparison with the marketed formulation.

Table 13: Comparative *in-vivo* performance of formulation marketed formulation

Formulation	C_{max} (µg/ml)	T_{max} (hour)	AUC (µg/ml. hr)	Fr (Relative bioavailability)
In situ gel	244.05	3	370.63	
Marketed formulation	139.24	3	215.47	1.54

CONCLUSION

Development of the *in situ* gel for transmucosal delivery of celecoxib by rectal route was attempted for the increasing the bioavailability of drug. The optimized batch, containing methyl cellulose (0.72%), PEG400 (9.14%), NaCl (3.49%) and surfactant (0.51%), showed gelling temperature near to body temperature with adequate bioadhesion strength and *In vitro* drug release profile. *In vivo* study of the optimized batch in male Wistar rat showed both AUC and C_{max} of the *in situ* gel was more than those of the marketed formulation, with 1.54 folds increase in bioavailability by rectal route. Thus, the developed formulation can prove to be a better delivery option in critical pains.

CONFLICT OF INTERESTS

Declared None

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