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Original Article

Formulation and evaluation of controlled porosity osmotic pump for oral delivery of ketorolac

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ABSTRACT

Oral osmotic drug delivery systems that can deliver drug for extended period of time has been developed and characterized. This system contains semi-permeable membrane and water-soluble pore-former's in the coating membrane. The tablet has an orifice drilled on it by means of a laser beam or mechanical drill. The oral bio-availability of our drug (ketorolac) was 88- 92% and the biological half-life of 4-6 hours requires frequent administration to maintain the therapeutic effect. This drug delivery systems offer significant patient benefits by reducing the side effects, enhanced efficacy and also reduce the frequency or number of daily doses compared to conventional therapies. The aim of this study was to develop a controlled porosity osmotic pump based drug delivery system for controlled release of an NSAID agent, nonsteroidal anti-inflammatory, offer significant patient benefits by reducing the side effects, enhanced efficacy and also reduce the frequency or number of daily doses. This system was containing pore-forming water-soluble additives within the coating membrane, which after coming in touch with water, dissolve, leading to an in situ formation. The effect of various formulation variables, namely level of pore former (PVP), plasticizer (dibutyl phthalate) within the membrane, and membrane weight gain were studied. Drug release was inversely proportional to the membrane weight but directly associated with the initial concentration of pore former (PVP) within the membrane. Drug release was independent of pH and agitational intensity, but hooked in to the osmotic pressure of the discharge media. Based on the in vitro dissolution profile, formulation F3C1 (containing 0.5 g PVP and 1 g dibutyl phthalate in coating membrane) exhibited Peppas kinetic with Fickian diffusion-controlled release mechanism with a drug release of 93.67% in 12 hours and hence it had been selected as optimized formulation. SEM studies showed the formation of pores within the membrane. CPOP was designed for effective administration of medicine for prolonged period of your time.

Keywords: *Controlled porosity osmotic pump*, core tablet, *pore former*, coating solution, *peppas kinetics*, *scanning electron microscopy*, Accelerated stability study.

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INTRODUCTION

In recent years, considerable attention has been focused on the event of novel drug delivery systems (NDDS).[1] Conventional drug delivery systems haven't any control over the drug release and effective concentration at the target site. This type of dosing pattern may end in constantly changing, unpredictable plasma concentrations; hence once-daily controlled release preparation is usually desirable. Drug release from oral controlled release dosage forms could also be suffering from pH, gastrointestinal motility, and presence of food within the alimentary canal .[2] One practical approach with a possible to beat the abovesaid disadvantages is that the osmotic drug delivery system,[3,4] wherein drugs are often delivered during a controlled pattern over an extended period of your time by the method of osmosis.

The osmotic drug delivery systems suitable for oral administration typically contains a compressed tablet core that's coated with a membrane that has an orifice drilled thereon by means of a beam or mechanical drill.[5]

To obviate the necessity for sophisticated laser drilling, tablets coated with a membrane of controlled porosity are described. These membranes contains a leachable material which dissolves upon contact with water, leaving the pores through which the drug solution is pumped out. However, thanks to the relatively low permeability of the dense coatings, osmotic delivery of medicine with moderate to low solubility is restricted .[6,7]

Ketorolac may be a nonsteroidal agent with powerful analgesic and low anti-inflammatory activity, widely utilized in the management of both moderate and severe pain. The oral bioavailability of our drug was found to be 88 to 92% with very low hepatic first-pass elimination, the biological half-life of 4–6 hours requires frequent administration to take care of the therapeutic effect. The long-term use of currently available dosage sorts of ketorolac may end in gastrointestinal ulceration and acute kidney failure .[8]
In the present investigation, an effort are going to be made to style a simplified controlled porosity osmotic system of ketorolac and development of sustained release tablet dosage, which is predicted to enhance patient compliance thanks to reduced frequency;[9] it also eliminates the necessity for implicated and expensive laser drilling and maintain continuous therapeutic concentration.

MATERIALS AND METHODS

Materials: Ketorolac tromethamine (KT) was provided as a present sample from MSN Laboratories Ltd., Hyderabad, SymedPharma Ltd., Hyderabad; dextrose monohydrate and microcrystalline cellulose as a present sample from Micro labs Pvt. Ltd., Bangalore; polyvinylpyrollidone (PVP), talc, and magnesium stearate as a present sample from Elegant Drugs Pvt. Ltd., Hubli; and Lake Tartrazine as a present sample from Standardcon Pvt. Ltd., Mumbai. Following chemicals and excipients were purchased from commercial sources and used as such: ethyl cellulose (Thomas baker chemicals Pvt. Ltd., Mumbai), Dibutyl phthalate (DBP) (Himedia lab. Pvt. Ltd., Mumbai).

Study of interexcipients and drug compatibility study: A compatibility study was performed for Acular and together with different polymer and excipients within the ratio of 1:1. The sample was exposed to 40°C/75% RH (stability chamber, TH 50S Thermolab, Mumbai) for 3 months and was analyzed by differential scanning calorimetric (DSC).[3]

Formulation of core tablets: Core tablets of Acular were prepared by direct compression,[10] and therefore the batch size was kept as 50 tablets. Required amounts of Acular , dextrose monohydrate, microcrystalline cellulose were weighed and transferred into mortar pastel. The dry powders were blended for five minutes. The mixture was skilled 44-mesh sieve. The blend was dried at 45°C for 20 minutes, then blended with magnesium stearate and talc (all 60-mesh passed) and compressed into tablets having a mean weight of 100 mg employing a multistation tablet-punching machine (Rimek mini press I) fitted with 9.5 mm round standard concave punches. The formula of core formulation of Acular is listed in Table 1.

Table 1: Formulation of ketorolac tromethamine coretablets

Sr No.	Ingredient (s)	Formulation		
		F1 (mg)	F2(mg)	F3(mg)
1	Ketorolac tromethamine	20	20	20
2	Dextrose monohydrate	12	22	32
3	Microcrystalline cellulose	75	65	55
4	Magnesium steçarate	1	1	1
5	Talc	2	2	2

	Total weight	110	110	110

Coating of core tablets: The composition of the coating solution used for coating of Acular tablets is given in Table 2. Various components of the coating solution were added to the solvent mixture during a sequential manner. The component added first was allowed to dissolve before addition of subsequent component and mixed until a homogeneous mixture was formed.

Table 2: Formula of coating solutions

Sr No.	Ingredient (s)	Formulation		
		C1 (mg)	C2(mg)	C3(mg)
1	Ethyl cellulose	5	5	5
2	Dibutyl phthalate ♯	1	1	1
3	PVP K30	10	20	30
4	Lake tartrazine	0.1	0.1	0.1
	Coat weight gain (CWG)	5	5	5

All quantities were taken in %, Toluene:ethanol [8:2] ratio was used as a coating solvent*

Materials: The core tablets were loaded into the pan and spray nozzle was adjusted to spray on the upper half the tablet bed. The operating condition was maintained as follows: pan speed 12 rpm, spray rate 02 ml/min, air temperature 35–40°C, atomization atmospheric pressure 6–10 psig, and distance from the tablet bed to the applicator 15–20 cm. The coating was performed during a conventional coating pan of 12 inch (internal) diameter rotated on its horizontal axis at 45° inclination with a pilot applicator type 68-S and drier fitted to coating pan. The tablets were sprayed by solution within the reservoir of the applicator . The coating process was administered till tablets attained a desired weight gain.[11] Composition of the tablets along side codes is tabulated Table 3.

Table 3: Composition of ketorolac tromethamine tablets (All quantities are in mg Except (#) in g, Toluene:ethanol [8:2] ratio was used as a coating solvent)

Ingredients (%)	Ingredients (%) Formulation codes								
	F1C1	F1C2	F1C3	F2C1	F2C2	F2C3	F3C1	F3C2	F3C3
Ketorolac tromethamine	20	20	20	20	20	20	20	20	20
Dextrose monohydrate	12	22	32	12	22	32	12	22	32
Microcrystalline cellulose	75	65	55	75	65	55	75	65	55
Magnesium steçarate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Total weight of core tablet	**110**	**110**	**110**	**110**	**110**	**110**	**110**	**110**	**110**
Ethyl cellulose	5	5	5	5	5	5	5	5	5
Dibutyl phthalate ♯	1	1	1	1	1	1	1	1	1
PVP K30	10	20	30	10	20	30	10	20	30
Lake tartrazine	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Coat weight gain (CWG)	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**

Evaluation Test:

Content uniformity test: Ten tablets were finely powdered; quantity of the powder equivalent to 100 mg of ketorolac tromethamine was accurately weighed and diluted with distilled water to make concentration of 10 mcg/ml and measure the absorbance at 323 nm.[2,12]

Dimensions; Six tablets randomly picked from formulations were subjected for individual thickness and diameter measurements using dial-caliper (Mitutoyo, Japan).[11]

In vitro drug release: In vitro drug release of the formulations was carried out in a USP dissolution apparatus (paddle type) set at a rotating speed of 100 rpm and temperature of 37 ± 0.5°C. The dissolution medium (900 ml) was simulated gastric fluid (SGF IP 2007, pH 1.2) for the first 2 hours and simulated intestinal fluid (SIF IP 2007, pH 6.8) thereafter. Samples (5 ml) were withdrawn at 1 hour time intervals over a 12-hour period and the medium was replenished with fresh dissolution fluid. The samples were suitably diluted, analyzed spectrophotometrically at 323 nm, and drug release was computed.[4]

Measurement of the film thickness: Following the completion of dissolution, the film was isolated from the tablets and dried at 40°C for 1 hour. The thickness was measured at three different points on

the film using dial-caliper (Mitutoyo, Japan) and the mean values were taken.[4]

Mechanism of drug release: The drug release mechanism from coated tablets was studied by the following tests:

i. Effect of % coat weight gain: The different % coat weight gain in the coating formulation was verified and its effect on the drug release of optimized formulation was evaluated.[3]

ii. Effect of pH: In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were carried out at pH 1.2 in simulated gastric fluid (SGF) and pH 6.8 in simulated intestinal fluid (SIF) and distilled water.[3]

iii. Effect of agitational intensity: To study the effect of agitation intensity (rpm) of the dissolution medium, the release study was carried out using USP-type II dissolution apparatus (paddle type) at rotational speeds of 50, 100, and 150 using the dissolution medium (900 ml) of SGF of pH 1.2 for the first 2 hours and SIF of pH 6.8 thereafter.[3]

iv. Effect of osmotic pressure: Optimized formulation were subjected to release studies in dissolution media containing dextrose monohydrate (osmotically effective solute) of varying strengths, to confirm the release mechanism by osmosis. Release studies were performed in 900 ml of osmotically active medium using USP-II dissolution apparatus at 100 rpm.[13]

Scanning electron microscopy (SEM) study; In order to elucidate the mechanism of drug release, optimized A2 coating membranes of tablets were subjected to scanning electron microscopy (SEM) studies before and after dissolution studies.[14,15]

Accelerated stability study: Optimized formulation (F3C1) was sealed in aluminum packaging coated inside with polyethylene. The packed tablets were placed in stability chambers maintained at 40 + 2°C and 75 + 5 % RH for 3 months in a stability chamber. The samples were withdrawn after 3 months and were evaluated for drug content and for in vitro drug release.[11]

RESULTS AND DISCUSSION

Differential scanning calorimetric study: Figure 1 indicates that the melting of drug is at 168.89°C and is concordant with the literature value. In Figure 2, two endotherms were observed at 163.49°C and 94.15°C, endotherm at 163.49°C of drug and at 94.15°C of dextrose monohydrate and other excipients present in the physical mixture. Hence, ketorolac tromethamine was compatible with other excipients that are intended to be added into the formulation.

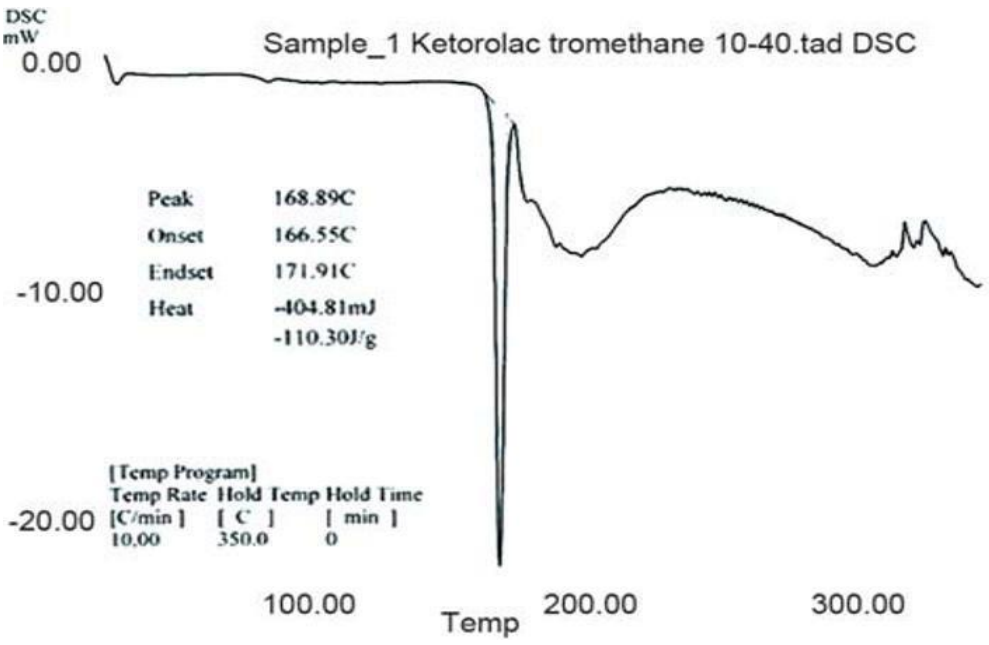


Figure 1: DSC thermogram of ketorolac tromethamine.

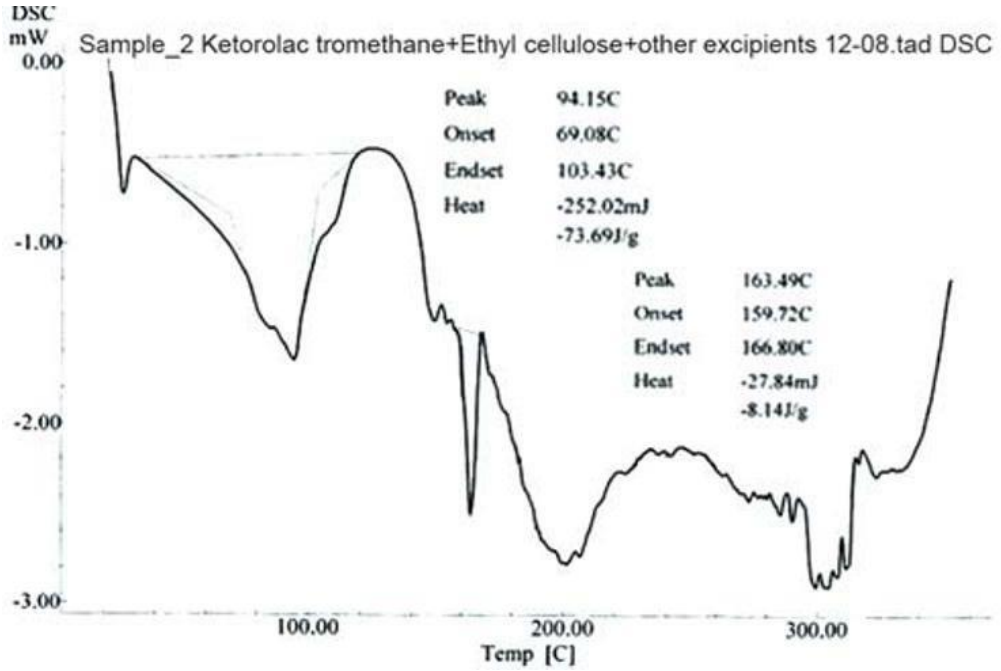


Figure 2: DSC thermogram of physical mixture of drug and other excipients after 3 months of storage at 40±20C/75±5% RH

Core formulation of ketorolac tromethamine: The coated tablets were subjected to various physicochemical properties. All the batches exhibit good physicochemical properties and are to be used for further coating [Table 4].

Table 4: The Physicochemical properties of the controlled porosity osmotic pump.

Formulation code	Weight variation (mg ± S.D.) (n=20)	Hardness (kg/cm 2) (n=5)	Thickness (mm ± S.D.) (n=10)	Friability (%)	Drug content (%)	Film thickness (% ± S.D.) (n=3)
F1C1	110.30 ± 1.32	5.20 ± 0.10	3.228 ± 0.01	0.059	98.62	0.130 ± 0.005
F1C2	110.40 ± 1.40	5.10 ± 0.10	3.128 ± 0.01	0.064	99.55	0.126 ± 0.005
F1C3	110.50 ± 1.53	5.05 ± 0.10	3.142 ± 0.01	0.095	98.75	0.142 ± 0.005
F2C1	110.25 ± 1.20	5.25 ± 0.10	3.210 ± 0.01	0.085	99.55	0.135 ± 0.005
F2C2	110.50 ± 1.52	5.08 ± 0.10	3.132 ± 0.01	0.076	98.96	0.122 ± 0.005
F2C3	110.40 ± 1.41	5.06 ± 0.10	3.152 ± 0.01	0.054	99.20	0.134 ± 0.005
F3C1	110.50 ± 1.52	5.14 ± 0.10	3.125 ± 0.01	0.098	100.20	0.125 ± 0.005
F3C2	110.20 ± 1.20	5.10 ± 0.10	3.218 ± 0.01	0.099	99.86	0.140 ± 0.005
F3C3	110.30 ± 1.32	5.20 ± 0.10	3.122 ± 0.01	0.089	99.78	0.123 ± 0.005

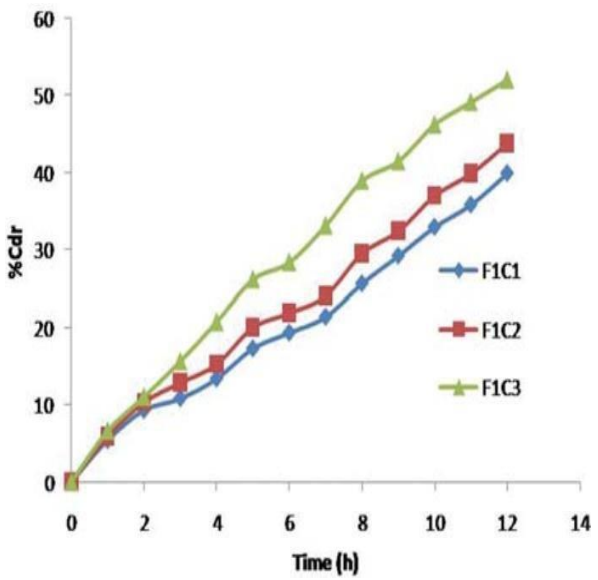
Dissolution profile of the CPOP: F1C1, F1C2, and F1C3 formulations exhibited 39.95%, 43.86%, and 52.02% drug release. F2C1, F2C2, and F2C3 formulations exhibited 61.54%, 65.28%, and 81.43% drug release at 12 hours respectively. F3C1, F3C2, and F3C3 formulations exhibited 93.67% drug release after 12 hours, 93.84% drug release after 10 hours and 94.18% drug release after 7 hours respectively [Figures 3–5].

Kinetics and mechanism of drug release

Dissolution data of the formulations were fitted to various mathematical models (zero-order, first-order, Peppas, and Hixon–Crowel) in order to describe the kinetics of drug release. The smallest value of the sum of squared residuals (SSR) and the highest value of the correlation coefficient (r) were taken as criteria for selecting the most appropriate model. It is clear that optimized formulas have n value 0.4499, indicating Fickian diffusion-controlled release Figure 6 and Table 5.

The aim of current study was to develop a 12-hour controlled release formulation. Based on the in vitro dissolution profile, formulation F3C1 shows the prominent % drug release, i.e., 93.67, in 12

hours and hence it was selected as optimized formulation.



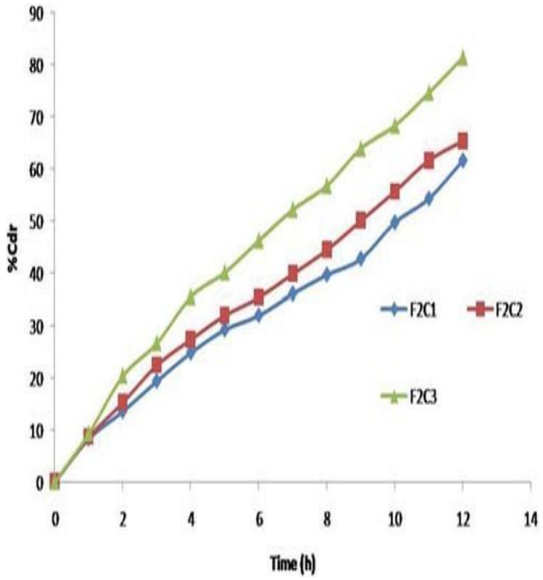
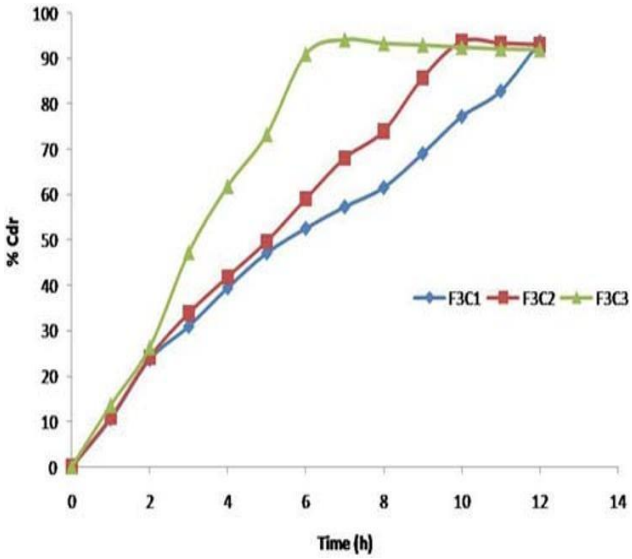


Figure 3: Drug release profiles of F1C1, F1C2, F1C3 formulations
Figure 4:Drug release profiles of F2C1, F2C2, F2C3 formulations.



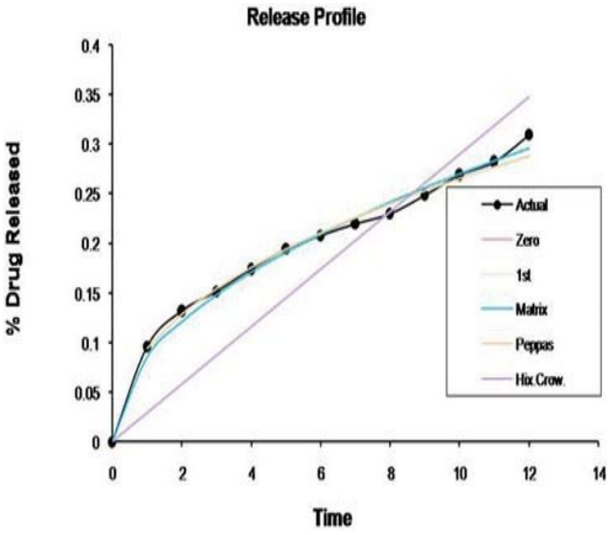


Figure 5:Drug release profiles of F3C1, F3C2, F3C3 formulations.
Figure 6: Kinetics of the drug release profile of the controlled porosity osmotic pump

Table 5: Fitting of drug release data of the optimized formulation according to various mathematical models

Sr no.	**Model**	**Parameters used to asses the fit of model**	
		r	**K**
1.	Zero order 0.8416 0.0290	0.8416	0.0290
2.	First order	0.8152	- 0.0002
3.	Peppas	0.9855	0.0004
4.	Hixon-Crowel	0.9688	0.8522
5.	N	0.4425	- 0.0004

Effect of different level of osmogent

The amount of osmogent in the core formulation was varied and its effect on the drug release of the formulations was studied using osmogent, i.e., dextrose monohydrate, and the concentration was varied at three levels namely 10 mg, 20 mg, and 30 mg with coat weight gain of 5% [Figure 7].

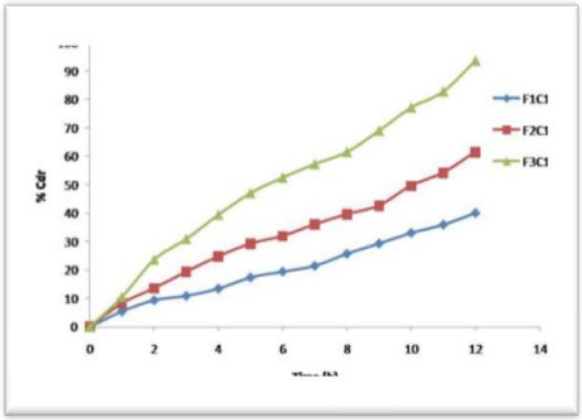


Figure 7: In vitro release from CPOP F1C1, F2C1, and F3C1 formulations with different level of osmogent

Formulations F1C1, F2C1, and F3C1 containing 10 mg, 20 mg, and 30 mg of dextrose monohydrate exhibited 39.95%, 61.54%, and 93.67% drug release after 12 hours. Drug release is higher in the formulation F3C1 compared to F2C1 and F1C1 due to higher concentration of osmogent level, owing to greater osmotic pressure.

Effect of the different type and level of pore former: The amount of pore former in the coating formulation was varied and its effect on the drug release of the formulations was studied using a pore former, i.e., PVP, and the concentration was varied at three levels namely 0.5 g, 1 g, and 1.5 g with coat weight gain of 5%. The in vitro release profiles are shown in Figure 8.

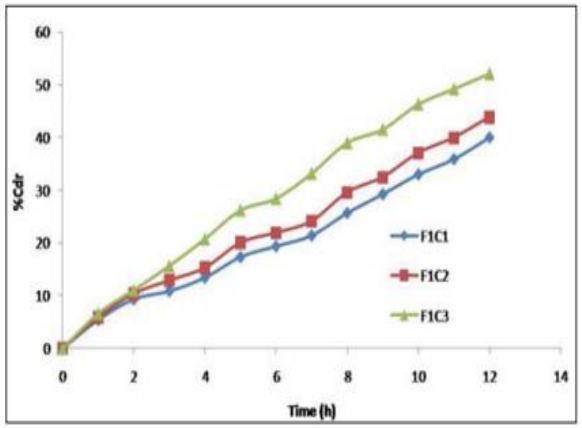


Figure 8: In vitro release from CPOP F1C1, F1C2, and F1C3 formulation with different level of pore former

Formulations F1C1, F1C2, and F1C3 containing 0.5 g, 01 g, and 1.5 g of PVP exhibited 39.95%, 43.86%, and 52.02% drug release respectively at the end of 12 hours. Drug release is higher in the formulation containing PVP 1.5 g; as the level of pore former increases, the membrane becomes more porous after coming in contact with the aqueous environment, resulting in faster drug release.

Effect of % weight gain: To study the effect of weight gain by coating on drug release, core tablets of ketorolac tromethamine were coated with coating composition C1 so as to get tablets with different weight gain (04%, 05%, and 06%). It is evident that drug release decreases with an increase in weight gain of the coating membrane and no burst effect was observed during the dissolution [Figure 9].

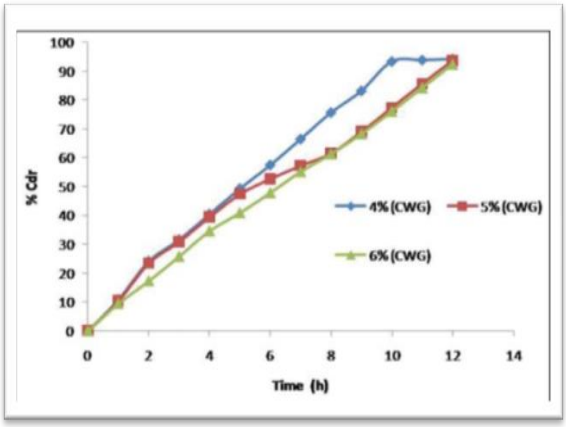


Figure 9: Effect of coat weight gain on release of ketorolac tromethamine from F3C1 optimized formulation

Effect of pH: In order to study the effect of pH and to assure a reliable in vivo performance, release studies of the optimized formulations F3C1 were conducted in media of different pH (SGF, pH 1.2, and SIF, pH 6.8), SIF, and water. Drug release profiles are superimposing [Figure 10]. Therefore the variations in pH of gastrointestinal tract had no effect on ketorolac tromethamine release.

Effect of agitational intensity (RPM): The release profile of ketorolac tromethamine from the F3C1 was fairly independent of the agitational intensity 50, 100, and 150 rpm of the release media, and hence, it can be concluded that the release was independent of the hydrodynamic conditions of the body [Figure 11].

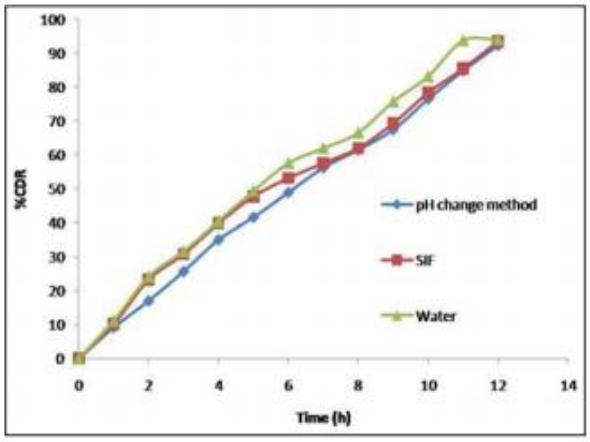


Figure 10: Effect of pH on ketorolac tromethamine release from CPOP

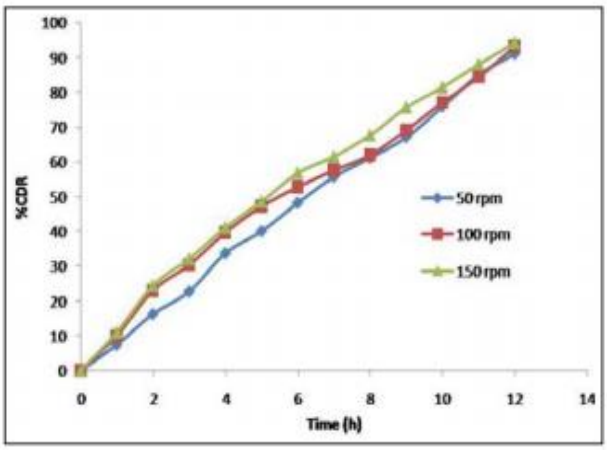


Figure 11: Effect of agitational intensity of the release media on ketorolac tromethamine release from CPOP

Effect of osmotic pressure: F3C1 formulation when exposed to media of different osmotic pressure showed that the drug release is highly dependent on the osmotic pressure of the release media. Ketorolac tromethamine release from the formulation decreased as the osmotic pressure of the media increased; hence the delivery system is dependent on osmotic pressure [Figure 12].

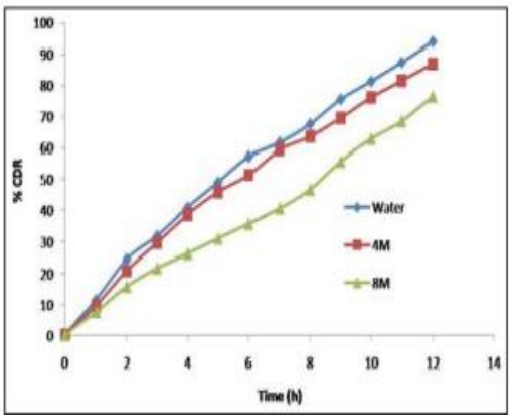


Figure 12: Effect of osmotic pressure of the release media on ketorolac tromethamine release from CPOP

Scanning electron microscopy (SEM): In order to elucidate the changes in the membrane structure, SEM studies were conducted (both before and after dissolution studies). Figure 13 shows SEM micrographs of coating membrane before and after dissolution of F3C1 optimized formulation containing 500 mg of PVP. The surface of the tablet was smooth before dissolution and after dissolution, the pores formed were in large number, and were visible, and a rough surface was observed on account of leaching [Figure 13]. Finally, it can be concluded that leaching of the pore former from the membrane had made membrane porous, through which drug release took place and designed drug delivery was controlled porosity osmotic pumps.

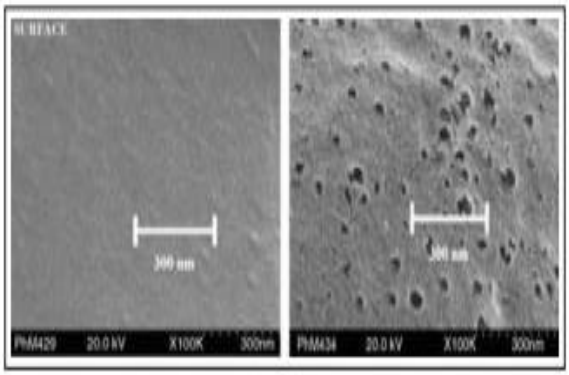


Figure 13: SEM micrograph of F3C1 formulation containing 500 mg of PVP, before and after dissolution

Accelerated stability study: After a period of 3 months, the formulations were found to be stable in terms of drug content and dissolution [Table 6 and Figure 14].

Sr. No.	accelerated stability studies	Content uniformity
1.	**At zero days**	98.2312%
2.	**After 1 month**	97.4523
3.	**After 3 months**	97.5233

Conclusion

The formulation F3C1 was the optimized formulation. A CPOP tablet coated with ethyl cellulose as a semipermeable membrane containing different types of pore former agent has been developed for drug ketorolac tromethamine. The release profile was obtained by using different concentration of controlled release polymer concentration, flux regulating agent level, and plasticizer concentration. The drug release mechanism of optimized formulation was mainly depends on the osmotic pressure since, release rate was significantly affected by the concentration of osmotic agent in the dissolution medium, directly proportional to the concentration of pore former,

but inversely related to the coating weight gain or membrane weight. Drug release from the CPOP Tablet was found to be independent of pH and hydrodynamic conditions. Drug release of developed formulations was follows Peppas release kinetics and Fickian diffusion mechanism. SEM studies showed formation of pores within the membrane in the dissolution medium. After 3 months of storage under accelerated stability conditions the optimized formulation was found to be stable . CPOP was designed for effective administration of medicine for a prolonged period of time.

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