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Formulation and Evaluation of Ketorolac Tromethamine Push Pull Osmotic Pump Tablets

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ABSTRACT

The present study aimed to prepare and evaluate the elementary osmotic pump tablets (OPT) of ketorolac tromethamine (KT). Because of its high potency, short half-life, and excellent water solubility, it would appear to be the drug of choice for these formulations. A compatibility study between KT and the used excipients was carried out. Twenty osmotic pump tablets were prepared and subjected to release-rate study and the release data were analyzed to determine the drug release order. All the physicochemical tests were carried out and all were within the pharmacopeial limits. It was found that the optimal OPT formula was able to deliver KT at a zero-order for up to 12 h.

INTRODUCTION:

The oral route has been a commonly adopted and most convenient route for drug delivery. This route of administration has been received more attention in the pharmaceutical field, because of the more flexibility in designing the dosage forms (1). Conventional drug delivery systems have no control over the drug release and effective concentration at the target site. In recent years, pharmaceutical research has led to the development of several novel drug delivery systems. One practical approach with the potential to overcome the above-said disadvantages is the osmotic drug delivery system, wherein drugs can be delivered in a controlled pattern over a long period by the process of osmosis (2). The osmotic drug delivery system is an oral controlled release and novel drug delivery system.

The osmotic drug delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane that has an orifice drilled on it utilizing a laser beam or mechanical drill.

Ketorolac is a nonsteroidal agent with powerful analgesic and low anti-inflammatory activity, widely used in the management of both moderate and severe pain (3). The present study aimed to prepare and evaluate elementary osmotic pump tablets (OPT) of ketorolac tromethamine (KT). Because of its high potency, short half-life, and excellent water solubility, it would appear to be the drug of choice for these formulations (4-5).

MATERIALS AND METHODS:

MATERIALS:

Ketorolac tromethamine (KT) was provided as a gift sample from Dr.Reddy's Laboratories Ltd., Hyderabad, Dicalcium phosphate and microcrystalline cellulose as a gift sample from Micro Labs Pvt. Ltd., Bangalore; HPMC K4M, HPMC K15M, Sodium chloride, Polyvinylpyrrolidone (PVP), talc, and magnesium stearate obtained from SD Fine chemicals.

METHODS:

Formulation development: Preparation of ketorolac tromethamine core tablets: Core tablets of ketorolac tromethamine were formulated by wet granulation technique by using different ratios of polymers (HPMC K4M, HPMC K15M) in Push layer. Then semipermeable coating was done with different levels of a pore-forming agent (6-8). Pull layer is formulated by accurately weighed quantities of the drug (ketorolac tromethamine), polymer (HPMC),

osmogen (sodium chloride) and diluent MCC pH 101 were mixed in a mortar. The required quantity of binder (PVP K 30 in IPA as 5% solution) was added and the same was mixed thoroughly to form a mass suitable for granulation. The dough mass was passed through sieve # 16 to form granules which were dried in an oven at 50^0c for 30 minutes. The dried granules were passed through sieve #22 and mixed with required quantities of lubricant (talc) and glidant (Magnesium stearate) (9-12).

The push layer was formulated by accurately weighed quantities of polymer (HPMC K4M, HPMC K15M), osmogen (sodium chloride), diluents MCC PH 101 were mixed in a mortar. Required quantities of binder (PVP K30 in IPA 5% solution) were added and mixed thoroughly to form a wet mass suitable for granulation. The dough mass was passed through sieve #16 to form granules which were dried in an oven at 50ºC for 30 minutes. The dried granules were passed through sieve #22 and mixed with the required quantities of lubricant and glidant. The pull layer and Push layer were compressed separately and then compressed together to form bilayer tablets in a 16 station rotary tablet machine (Riddi, Ahmedabad) using 8mm round concave punches. Six formulations of 50 tablets each were prepared with varying polymer concentrations. The total weight of each tablet was 200mg of which the Pull layer was 120mg and the Push layer was 80mg which contains 35mg of ketorolac tromethamine in the pull layer. Formulae of different core formulations of ketorolac tromethamine are shown in table 1.

Preparation of coating solutions: The coating solution was prepared by taking the solvent in a glass beaker and adding the pre-weighed quantities of polymer cellulose acetate (semipermeable coating), in small quantities at a time. Mixing was ensured by utilizing a mechanical stirrer. After complete solubilization of the polymer then plasticizer, pore-forming agent (i.e., D-sorbitol) and kept for overnight stirring.

Coating of core tablets: Initially, the pan was rotated at low speed and heated air was passed and when the pan gets heated, core tablets were placed in the coating pan along with filler tablets (tablets made using 10mm round deep concave punches and containing microcrystalline cellulose/dibasic calcium phosphate, magnesium stearate, and talc). The heated air was passed through the tablet bed and pan speed was increased to 20-30rpm. Coating solution was sprayed.

Characterization of semi-permeable membrane coated tablets

The prepared ketorolac tromethamine tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability, and drug content.

A. Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance.

B. Tablet hardness

The hardness of the tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. For each formulation, the hardness of 6 tablets was determined using Monsanto hardness tester and the average is calculated.

C. Tablet thickness

Twenty tablets were taken and their thickness was recorded using a digital micrometer.

D. Friability

It is measured by the mechanical strength of tablets. Roche friabilator (Electrolab, Mumbai, India) was used to determine the friability by the following procedure. Preweighed tablets (20 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

E. Determination of drug content

Ten tablets were finely powdered; quantities of the powder equivalent to 40mg of ketorolac tromethamine were accurately weighed, transferred to a 100ml volumetric flask containing 50ml of pH 7.4 phosphate buffer. The mixture was made up to volume with pH 7.4 phosphate buffer. The solution was suitably diluted and the absorption was determined by UV-Visible spectrophotometer at 352.6 nm. The drug concentration was calculated from the calibration curve (13-15).

F. *In-vitro* drug release studies

Drug release studies of semipermeable membrane coated tablets

The *in-vitro* evaluation was carried out by USP type I (basket) apparatus. The test was carried over 12 hours using pH 7.4 phosphate buffer (16-18).

RESULTS AND DISCUSSION:

Drug-excipient compatibility studies: Differential Scanning Calorimetry (DSC)

The thermal properties of the drug and the mixture of drug and excipients are of important interest since this can help to assess the interaction among different components of the formulations. The DSC thermogram of pure ketorolac tromethamine showed an endothermic peak at a temperature of 171.26°C (fig1-2).

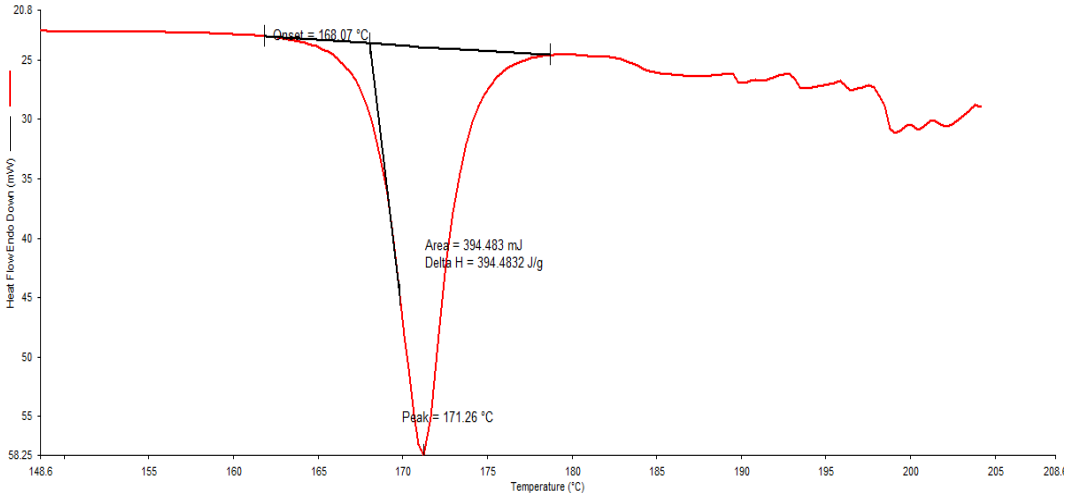

Figure No. 1: DSC thermogram of pure drug

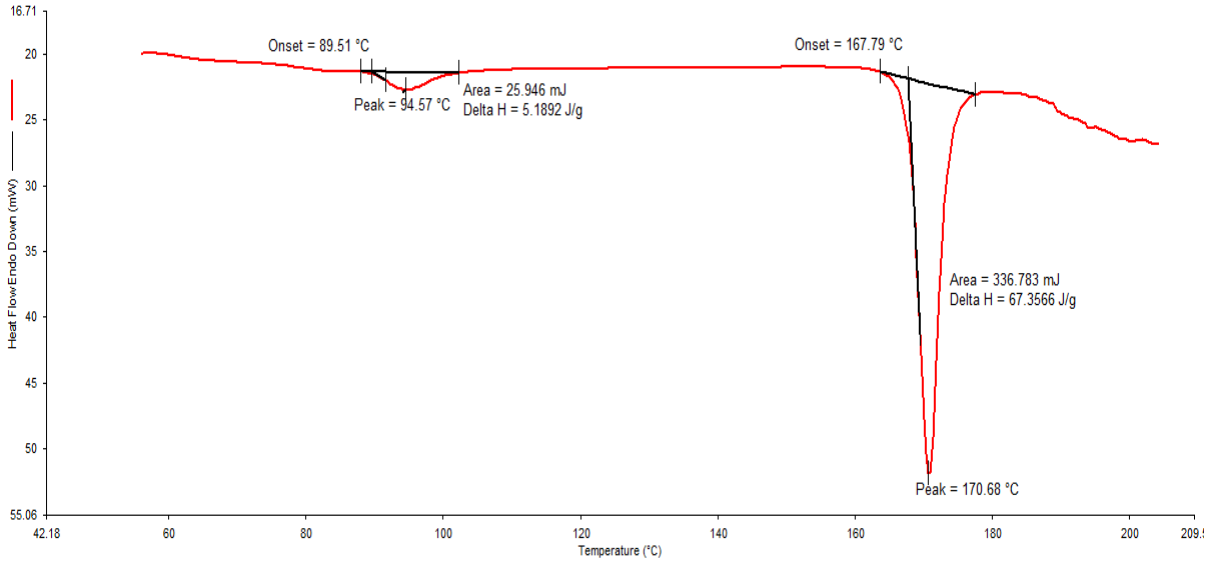

Figure No. 2: DSC thermogram of drug+excipients

Table No. 1: Various formulations development for optimization of core tablets

Ing	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
PULL LAYER						
Drug	**35**	**35**	**35**	**35**	**35**	**35**
Sodium chloride	12	12	12	12	12	12
HPMC	24	24	24	24	24	24
PVP K30	3.6	3.6	3.6	3.6	3.6	3.6
MCC	12.84	12.84	12.84	12.84	12.84	12.84
Dicalcium phosphate	31.36	31.36	31.36	31.36	31.36	31.36
Talc	0.6	0.6	0.6	0.6	0.6	0.6
Mag. Stearate	0.6	0.6	0.6	0.6	0.6	0.6
TOTAL	120	120	120	120	120	120
PUSH LAYER						
HPMC K4M/K15M	**16**	**24**	**32**	**16**	**24**	**32**
Sodium	8	8	8	8	8	8

chloride						
MCC	10.56	8.96	7.36	10.56	8.96	7.36
Dicalcium phosphate	42.44	35.84	29.44	42.44	35.84	29.44
PVP K30	2.4	2.4	2.4	2.4	2.4	2.4
Mag stearate	0.4	0.4	0.4	0.4	0.4	0.4
Talc	0.4	0.4	0.4	0.4	0.4	0.4
TOTAL	200	200	200	200	200	200

Evaluation of process parameters of core tablets:

All six formulations were tested for physical parameters like hardness, thickness, weight variation, friability, and found to be within the pharmacopoeial limits. The results of the tests were tabulated in table 2.

Table No. 2: Process parameters of various formulations

Formulation	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity
F1	201.3±1.52	3.5±0.05	8.06±0.115	0.139	98.28
F2	200.6±1.15	3.5±0.08	8±0.2	0.14	99.52
F3	198.3±0.57	3.5±0.05	7.9±0.305	0.138	99.04
F4	204±1.17	3.5±0.08	8.1±0.230	0.160	98.56
F5	199.6±1.52	3.5±0.05	8.2±0.115	0.125	99.41
F6	201±1.73	3.5±0.05	7.9±0.23	0.14	98.28

Table No. 3: Physical parameters of coated tablets

Formulation	Weight gain
F1	8.02±0.064
F2	8.15±0.04
F3	8.15±0.05
F4	8.16±0.05
F5	8.08±0.076
F6	8.15±0.05

The results of the physical tests of the formulations were within the limits and comply with the standards. The weights of the tablets ranged from 118mg to 200mg; the weights being ±5% of the average weight. The thickness was found to be 3.5mm. The hardness of the tablets was in the range of 7 to 8kg/cm^2 and friability was in the range 0.12-0.16%, indicating that the tablets are hard enough to withstand the tumbling action in the coating pan. The drug content on an average was found to be 99%. All these parameters were within acceptable limits (table.3).

***In-vitro* drug release profile of core tablets:**

The cumulative percentage of drug release profiles from various core tablet formulations are presented. From the *in vitro* drug release studies formulation F6A has shown approximately 98.8% drug release in 12hr. The release kinetics showed that F6A is 0.9938 which follows a perfect zero-order drug release. Hence F6A was considered optimal and used in further experimentation (Fig 3-8).

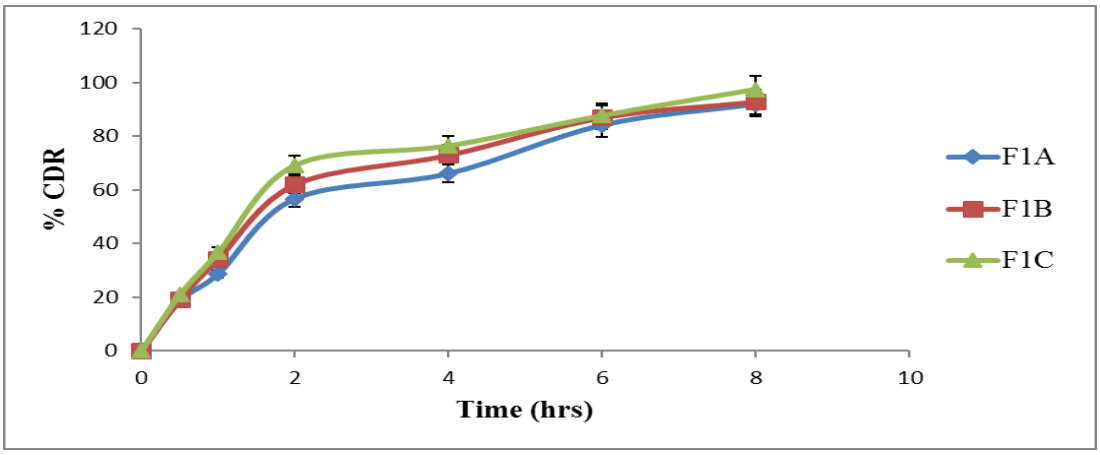

Figure No. 3: *In-vitro* drug release profile of various core tablet formulations

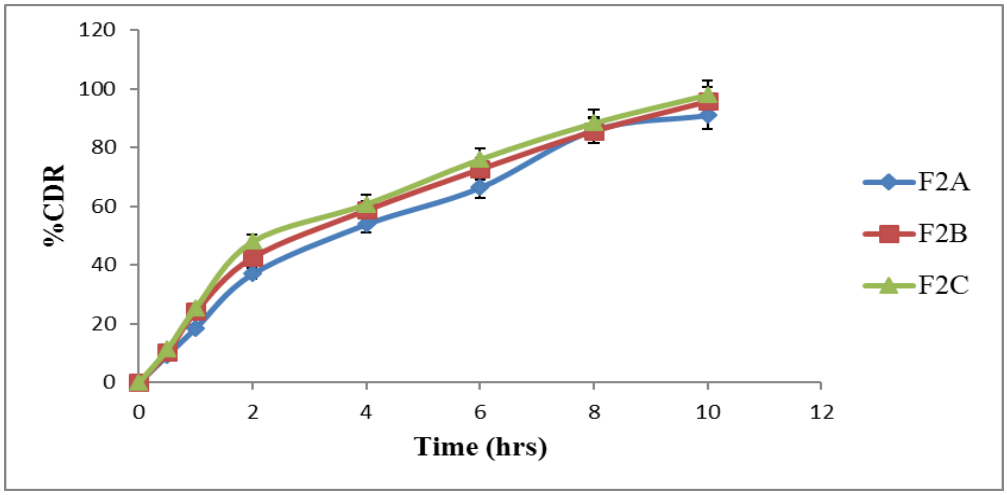

Figure No. 4: *In-vitro* drug release profile of various core tablet formulation

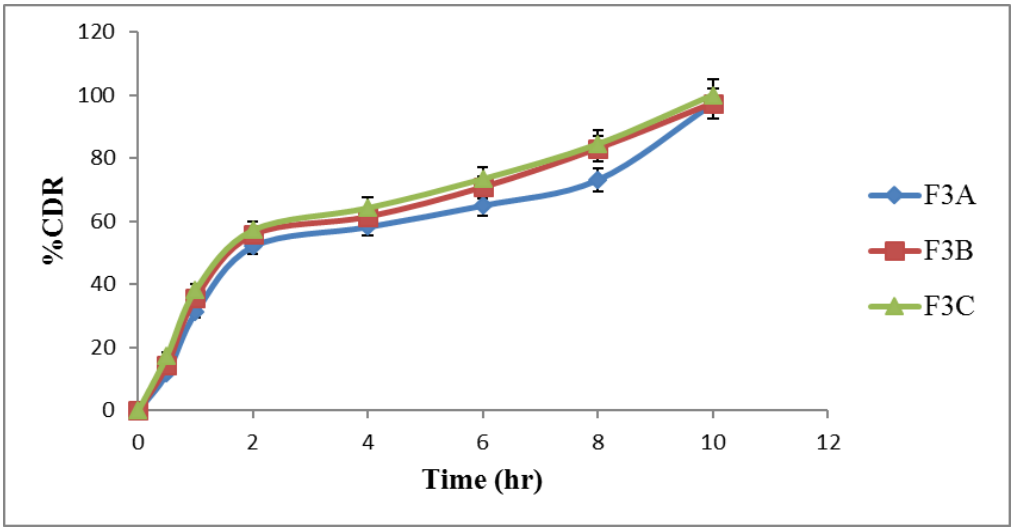

Figure No. 5: *In-vitro* drug release profile of various core tablet formulation

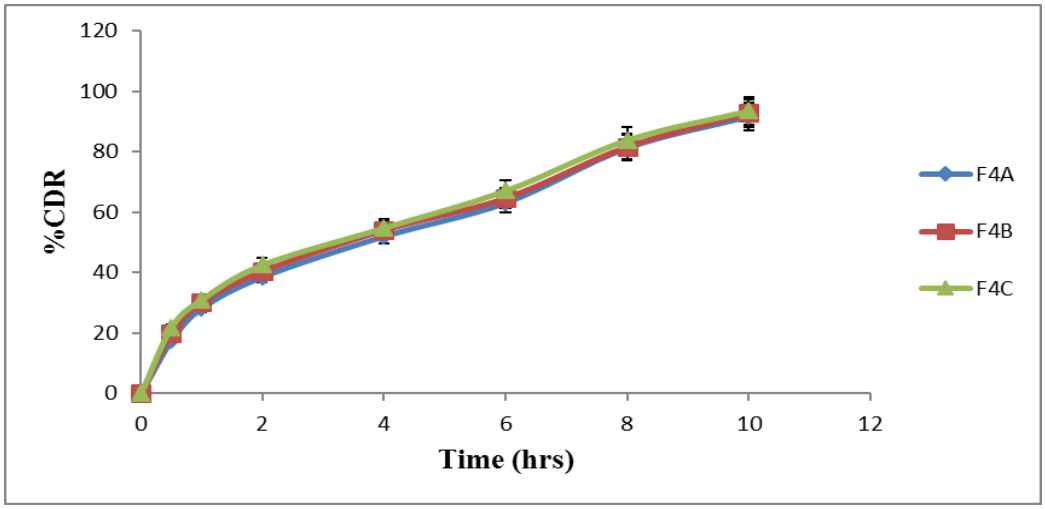

Figure No. 6: *In-vitro* drug release profile of various core tablet formulation

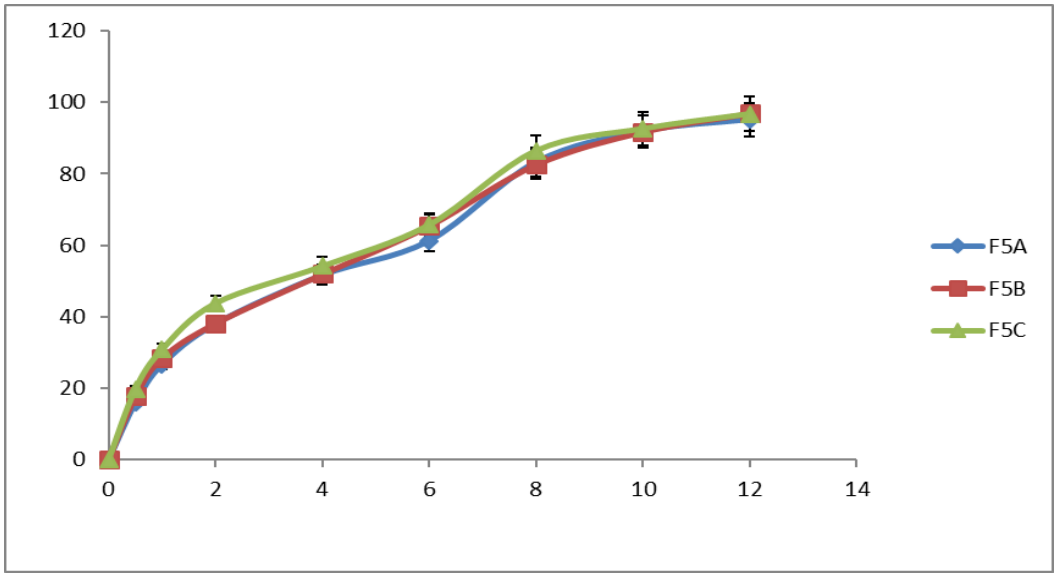

Figure No. 7: *In-vitro* drug release profile of various core tablet formulation

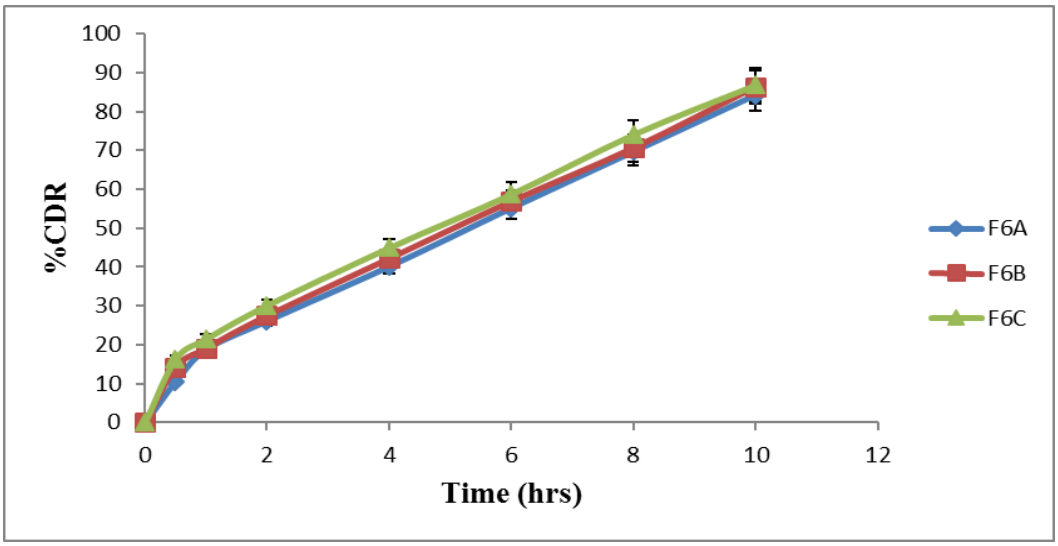

Figure No. 8: *In-vitro* drug release profile of various core tablet formulation

Dissolution profile modeling: Dissolution data of the optimized formulations were fitted to various mathematical models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas) to describe the kinetics of drug release. An ideal osmotic system should be able to release a high percentage of drug content with a constant release rate (zero-order kinetics) during dissolution. Goodness-of-fit test (R^2) was taken as a criterion for selecting the most appropriate model (table.4).

Table No. 4: Correlation coefficient (R^2) of different kinetic models for various formulations

Formulation	%drug release	Time (hrs)	R^2 value				n value
			Zero-order	First-order	Higuchi	Kores Meyer-Peppas	
F1A	91.82	8	0.887	0.9862	0.9795	0.9651	0.576
F1B	92.84	8	0.8463	0.9868	0.9686	0.9461	0.5562
F1C	97.39	8	0.8202	0.9598	0.9543	0.9285	0.5343
F2A	90.95	10	0.925	0.9864	0.988	0.973	0.6637
F2B	95.8	10	0.9666	0.9387	0.9821	0.9849	0.7553
F2C	97.96	10	0.9192	0.9149	0.9844	0.9462	0.6952
F3A	97.3	10	0.8746	0.7970	0.9531	0.898	0.5898
F3B	97.31	10	0.869	0.8825	0.967	0.9056	0.5489
F3C	100.02	10	0.8638	0.7517	0.9692	0.922	0.505
F4A	95.75	12	0.9423	0.9637	0.9939	0.9939	0.5226
F4B	96.44	12	0.935	0.9584	0.9948	0.9946	0.4907
F4C	96.94	12	0.9266	0.9617	0.9948	0.9617	0.4686
F5A	95.13	12	0.9432	0.9672	0.9893	0.9912	0.5519
F5B	96.94	12	0.9445	0.9572	0.9949	0.9572	0.5271
F5C	96.74	12	0.9222	0.9663	0.9908	0.9895	0.4904
F6A	98.8	12	0.9938	0.7983	0.9687	0.9906	0.6769
F6B	99.81	12	0.9884	0.7414	0.9718	0.9878	0.6172
F6C	99.89	12	0.9813	0.7481	0.9809	0.9881	0.5753

CONCLUSION:

Push-Pull based osmotic tablets coated with cellulose acetate as a semi-permeable membrane containing channeling agent sorbitol have been developed for Ketorolac Tromethamine. The desired zero-order release profile was obtained by optimizing the concentration of osmogen, polymer, and pore-forming agent. The drug release was further retarded using proper pore former to achieve the desired zero-order release profile. The developed formulation was found to be stable. And the system delivered ketorolac tromethamine at a zero-order rate for a period of 12 hrs, independent of pH and agitational intensity. This system is simple to prepare and is a cost-effective, alternative to conventional osmotic delivery pump as the sophisticated laser drilling technique is not required.

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REFERENCES:

1. Brahma P Gupta., Osmotically controlled drug delivery system with associated drugs, Journal pharmacy, and pharmaceutical sciences, Volume 13:2010: 571-588.
2. Chiao C. S. L., Robinson J. R.; Sustained and Controlled Release Drug Delivery Systems; 19th edition. Philadelphia: Mark Publishing Company: 1995.
3. David. R. Swanson, Brian L. Barclay, Patrick S.L. Wong, Felix Theeuwes., Nifedipine Gastrointestinal Therapeutic System, American Journal of Medicine, Volume 83: 1987:1-4.
4. Gaylen M. Zentner, Gerald S. Rork, Kenneth. I. Himmelstein, Osmotic flow through Controlled Poroslty films: an approach to delivery of water soluble compounds, Journal of Controlled Release: 2:1985: 217-229.
5. Jain N.K. Advances in Controlled and Novel Drug Delivery, CBS Publishers and Distributors Pvt. Ltd: 2001:18-37.
6. Jerzewski R. L Chein Y. W., Osmotic Drug Delivery. In: Kydonieus A, Editors. Treatise on Controlled Drug Delivery; Fundamentals, Optimization and Applications. New York: Marcel Dekker Inc.; 1992: 265-273.
7. Kewal K. Jain; Drug Delivery Systems- An Overview; 1-50.
8. Kunal N. Patel, Tejal A. Mehta, Design and optimization of Nicardipine hydrochloride push pull osmotic pump tablet using 3^2 full factorial design, *Int J Pharm Biomed Res* 2013: *4*(3):155-163.
9. Li X and Jasti B R; Osmotic controlled drug delivery systems, In: Design of controlled release drug delivery systems; McGraw Hill: 2006: 203-229.
10. Peter Schultz, Peter Kleinebudde, A new multiparticulate delayed release system. Part I: Dissolution properties and release mechanism: Journal of Controlled Release 47: 1997: 181–189.
11. Rajeshri Wakode, Roopali Bhanushali, Amrita Bajaj, Development and Evaluation of Push Pull based Osmotic Delivery System for Pramipexole, PDA Journal of Science and Technology:62:2008: 22-31.
12. Shahla Jamzad, Reza Fassihi, Development of a controlled release low dose class II drug-Glipizide, International Journal of Pharmaceutics: 312: 2006: 24–32.
13. Theeuwes F, Elementary osmotic pump, J. Pharm. Sci. 64:1975: 1987–1991.
14. Prescott. L.F, The need for improved drug delivery in clinical practice, Novel Drug Delivery and its Therapeutic application, John Wiley and Sons, West Susset, U.K: 1-11: 1989.
15. Vincent Malaterre et al., Drug Development and Industrial Pharmacy: 2008:1-7.
16. Vincent Malaterre, Hendrik Metz, Joerg Ogorka, Robert Gurny, Nicoletta Loggia, Karsten Mäder, Benchtop-magnetic resonance imaging(BT-MRI) characterization of push-pull osmotic controlled release systems, Journal of Controlled Release, 133: 2009: 31-36.
17. Vincent Malaterre, Joerg Ogorkaa, Nicoletta Loggia, Robert Gurny, Approach to design Push Pull Osmotic Pumps, International Journal of Pharmaceutics:376: 2009:56-62.
18. Vyas S.P., Roop Khar. Controlled Drug Delivery Concepts and Advances, CBS Publishers and Distributors:2001:477-501.