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Development and Evaluation of Push Pull Based Osmotic Delivery System for Ketorlac Tromtamine

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ABSTRACT

To develop and evaluate Push Pull Osmotic tablets of ketorolac Tromethamine (KT). Core tablets of KT were formulated by wet granulation method using polymers (HPMC K4M, K15M) , coated with semipermeable membrane (cellulose acetate), plasticizer (PEG 400) , pore former (D-sorbitol) and osmogen (sodium chloride). Compatibility studies were carried out using Differential Scanning Calorimetry(DSC), no incompatibility between the drug and polymers observed. The Physical properties of tablets were evaluated for thickness, hardness, friability, drug content, effect of osmotic agent, percentage of pore former, pH, agitational intensity, weight gain, osmotic pressure and *in vitro* drug release for 12 hours. Release studies best fitted to zero order pattern, indicating drug release was non-Fickian, independent of pH and agitational intensity. The system is simple, cost effective and alternative to conventional osmotic pump since sophisticated laser drilling technique is not required.

Keywords: Core tablets, Osmogen, DSC, Physical properties, zero order drug release

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INTRODUCTION

Oral route of administration is one of the oldest and most extensively used route for the administration of drug providing convenient method of effectively achieving both local and systemic effect. Conventional drug delivery systems have little or no control over the drug release and effective concentration at the target site. So, it is difficult to achieve and maintain the concentration of the administered drug within the therapeutic range, leading to fluctuations in plasma drug levels. Several novel controlled drug delivery systems with many advantages have been developed recent years. Among these system, the Oral Controlled drug delivery system has received greater attention since it is the most popular route of dug administration, as the pharmaceutical agents can be delivered in a controlled pattern over a long period. Among which the Osmotic drug delivery system (ODDS) are gaining more importance resulting in improved patient compliance and therapeutic efficacy. These systems work on the principle of osmotic pressure for controlling the delivery of the drug. The release of the drug is independent of physiological factors of the GIT to a large extent. Oral Osmotically controlled release (OSCR) delivery system provide a uniform concentration/amount of drug at the site of absorption and thus after absorption, allow maintenance of plasma concentration within therapeutic range, which minimizes side effects and also reduces the frequency of administration. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system (Zentneret al.,1985).

Different systems have been developed based on principle of osmotic pressure, including one chamber and multiple chamber systems (Patel and Mehta, 2013). Currently two osmotically controlled delivery mechanisms that are widely used by the pharmaceutical industry are Elementary Osmotic Pump (EOP) and Push Pull Osmotic Pump (PPOP)[1]. The EOP is a system that is not suitable for delivering those drugs having high aqueous solubility. The bilayer PPOP tablets were introduced in an attempt to overcome the limitations. PPOP consists of a bilayer tablet core surrounded by a laser drilled semipermeable membrane. Upon contact with the aqueous fluids, the second layer swells and thereby supplying the driving force against the drug layer. Subsequently, the drug suspension generated in the first layer is delivered via the orifice.

Ketorolac Tromethamine(KT), a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days in adults), management of moderately severe acute pain that requires analgesia at the opoid level. The objective of the study was to develop osmotically controlled

release tablets of KT. The tablets were coated with cellulose acetate as the semipermeable membrane containing plasticizer like polyethylene glycol and pore former. Prepared tablets were also evaluated for thickness, hardness, friability, drug content, *in-vitro* drug release, effect of osmotic agent, percentage of pore former, pH, agitational intensity, weight gain and osmotic pressure.

MATERIALS AND METHOD

Chemicals

KT was obtained as a gift sample from Perkin laboratories,Hyderabad. Sodium chloride was obtained from S.D. Fine Chemicals, Mumbai. Microcrystalline cellulose was obtained from Himedia Laboratories Ltd, Mumbai. Hydroxypropyl methyl cellulose K4M & K15M were obtained from Himedia Laboratories Ltd, Mumbai. Cellulose Acetate with a 39.8 % acetyl content was purchased from Sigma Chemicals (Bangalore, India). Polyethyleneglycol 400 (PEG 400), dibutylphthalate, D-Sorbitol, magnesium stearate, talc, potassium dihydrogen orthophosphate and sodium hydroxide were procured from S.D.Fine-Chem.Ltd. . All the solvents used were of analytical grade.

Formulation development

Drug-Excipient Compatability Studies – (DSC)

DSC was performed to determine the purity of the drug along with the excipients using DSC-4000 (Perkin Elmer). The samples (1-5mg) were placed in aluminium pans and scanned in the temperature range of 50-200^{0}C at a heating rate of 10^{0}C/min the system was cooled down by liquid nitrogen gas. Empty aluminium pan was used as reference (M. Rani et al., 2003). The physical mixtures were prepared by triturating drug with various excipients with 1:1 ratios in a mortar and pestle for about 5 min.

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 pore forming agent.

Pull layer is formulated by accurately weighed quantities of drug (ketorolac tromethamine), polymer (HPMC), osmogen (sodium chloride) and diluent MCC pH 101 were mixed in a mortar. 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^{0}c for 30 minutes. The dried granules were

passed through sieve #22 and mixed with required quantities of lubricant (talc) and glidant (Magnesium stearate).

Push layer was formulated by accurately weighed quantities of polymer(HPMC K4M, HPMC K15M), osmogen (sodium chloride), diluents MCC PH 101 were mixed in mortar. Required quantities of binder (PVP K30 in IPA 5% solution) was added and mixed thoroughly to form wet mass suitable for granulation. The dough mass was passed through sieve #16 to form granulues which were dried in an oven at 50^{o}c for 30 minutes. The dried granules were passed through sieve #22 and mixed with required quantities of lubricant (magnesium stearate) and glidant (talc).

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 Pull layer was 120mg and push layer was 80mg.

Coating of Bilayer tablets

The tablets were coated with cellulose acetate (3% w/v in acetone) along with a suitable pore former D- Sorbitol. PEG 400 was added as plasticizer. The coating process parameters were optimized as follows: - pan diameter, 9 inch; spray gun (pilot scale); baffles, 4; speed of pan, 25 rpm; nozzle diameter, 1mm; spray pressure, 40-50 lb/ sq.in; drying temperature, 55^{o}c. After being coated, the bilayer tablets were dried overnight at 60^{o}c to remove any residual solvent. The coated tablets had smooth, uniform surfaces without any defects.

Table 1: Various formulations for optimization of core tablets

Ingredients	**F1C (mg)**	**F2C (mg)**	**F3C (mg)**	**F4C (mg)**	**F5B (mg)**	**F6C (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 chloride	8	8	8	8	8	8
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
Magnesium 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**

In pull layer, the amount of ingredients is same for all formulations. Only change is seen in push layer.

Table 2: Semipermeable coating formulations

S.NO	Ingredients	A	B	C
1.	Cellulose acetate(gm/ml)	3	3	3
2.	D-sorbitol(gm/ml)	0.075	0.15	0.3
3.	PEG 400(gm)	0.5	0.5	0.5
4.	Acetone (90:10)(ml)	100	100	100

Preparation of coating solution

Coating solutions of cellulose acetate in acetone (5%, 8% &10%w/v) containing D-Sorbitol as pore forming agent were prepared for semipermeable membrane coating. 1%w/w PEG-400 was added as plasticizer.

Coating of core tablets

The coating was carried out by pan coater (V.J.Instruments, Mumbai), having diameter of 50cm, with the rotating speed kept at 23rpm. 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 contains microcrystalline cellulose/dibasic calcium phosphate, magnesium stearate and talc except drug). Heated air was passed through the tablet bed and pan speed was increased to 20-30rpm. Coating solution was sprayed (Table2) with the help of low pressure (10-15psi) air-atomized spray gun at a fixed rate of 6ml/min. Coated tablets are dried at 50^{o}c for 4h.

Characterization of tablets

Weight variation test

Twenty tablets were randomly selected from each batch and weighed individually. The average weight and standard deviation of 20 tablets was calculated (I.P.1996).

Thickness

Thickness of core tablets was measured using a screw gauge. Ten tablets from each batch were randomly selected and was expressed in millimeters.

Hardness and friability

Hardness and friability of randomly selected tablets was measured using Monsanto Hardness tester and on Roche friabilator respectively (Sharma et al., 2012).

%F=1-(loss in weight/initial weight)*100

Content uniformity

Ten tablets were weighed individually and finely powdered; quantities of the powder equivalent to 35mg of ketorolac tromethamine were accurately weighed, transferred to a 100ml volumetric flask containing 50ml of pH 7.4 phosphate buffer and allowed to stand for 5h with intermittent sonication to ensure complete solubility of the drug. 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 324nm. The drug concentration was calculated from the calibration curve.

In-vitro drug release studies

In-vitro evaluation was carried out by USP rotating paddle method. The test was carried over a period of 12 hours using 900ml of different buffers. The stirring speed of the paddle was 100 rpm and the temperature maintained was 37±0.5°C. 5 ml of aliquots were withdrawn at predetermined time intervals and was replenished by 5 ml of fresh dissolution medium each time and analyzed using UV-Visible spectrophotometer (Elico, India) at 324 nm.

Characterization of Optimized formulation

Effect of pH

Release studies of the optimized formulation were conducted according to pH change method to study the effect of pH on drug release. The release media was simulated gastric fluid (pH 1.2), Phosphate buffer (pH 6.8) and Phosphate buffer (pH 7.4) (Rani etal., 2003).

Effect of agitational intensity

In order to verify effect of agitational intensity release studies of optimized formulation, the release studies was carried out in USP-II dissolution apparatus at varying rotational speeds (25,50 and 100rpm)(Shah et.al.,2012).

Effect of osmotic pressure

Ketorolac tromethamine tablets loaded with osmotic agent i.e., sodium chloride of various concentrations (0%, 2.5% & 5% w/v) and their release profiles are observed (Wakode et.al., 2008).

Effect of weight gain

Core tablets of ketorolac tromethamine were coated with coating solutions and increase in weight of the tablets was observed .

SEM studies of core tablet before and after dissolution

To investigate the changes in the membrane structure of optimized formulation(F6A)were examined during dissolution process (both before and after dissolution studies) using SEM. Membranes were dried at 45^{o}c for 12 hrs and stored between sheets of wax paper in a dessicator until examination(Shahi et,al.,2012).

Release Kinetics

In order to describe kinetics of drug release from control release formulation, various mathematical models (zero-order, first-order, Higuchi and Korsmeyer-Peppas) were applied to the dissolution data of the optimized formulations. The selection criteria of best model was based on Goodness-of-fit test (R^2) (Sharma et.al., 2012).

RESULTS AND DISCUSSION

Drug-excipient compatabiity studies

Figure 1 indicates that the melting of drug is at 171.26°C. No change in the endotherm of the drug was observed in the mixture of both, which indicates the absence of any interaction between the drug and excipients (Figure 1).

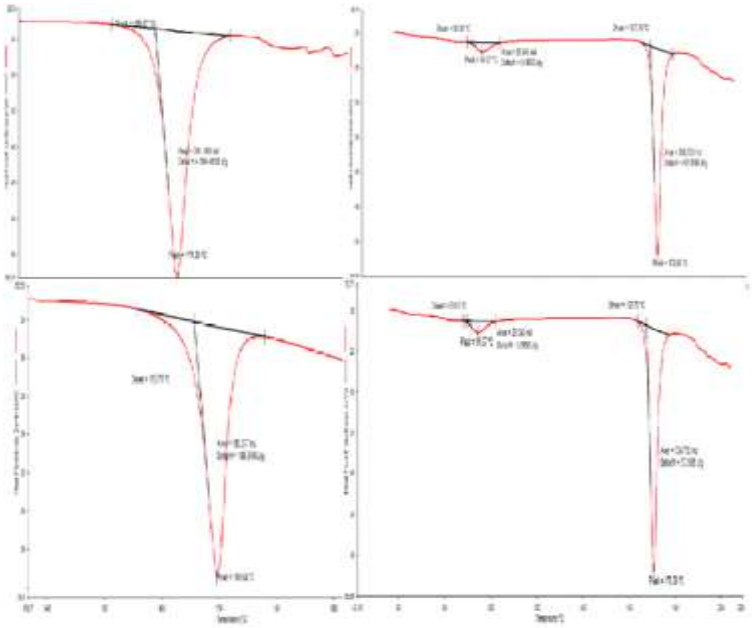


Figure 1: DSC Thermograms

A- DSC thermogram of pure drug

B- DSC thermogram of drug and HPMC K15M

C- DSC thermogram of drug and HPMC K4M

D- DSC thermogram of physical mixtures

Characterization of tablets

Weight variation test`

Weight variation of prepared tablets indicated no significant difference in the weight of individual tablet from average value (Table 3).

Thickness

Thickness was found to be in the range of 3.5±0.5mm (Table 3).

Hardness and friability

Hardness of the prepared tablets was observed in the range 7.9 to 8.1 kg/cm^2. Friability of all tablets was found to be below 1% (Table 3).

Content uniformity

The drug content in all the batches of KT tablets was in the range of 98.28 to 99.04%. This assured the uniformity of drug content in the tablets (Table 3).

Table 3: Process parameters of Optimized formulation in each batch

Formulation	Weight variation (%)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity(%)
F1C	201.3±1.52	3.5±0.05	8.06±0.115	0.139	98.28
F2C	200.6±1.15	3.5±0.08	8±0.2	0.14	99.52
F3C	198.3±0.57	3.5±0.05	7.9±0.305	0.138	99.04
F4C	204±1.17	3.5±0.08	8.1±0.230	0.160	98.56
F5B	199.6±1.52	3.5±0.05	8.2±0.115	0.125	99.41
F6c	201±1.73	3.5±0.05	7.9±0.23	0.14	98.28

In vitro Drug release

In vitro drug release study was carried out to study the effect of polymer in push layer on %CDR. Different percentage of pore former in the semi permeable coating was also studied. F1C formulation showed maximum release at 8hr, where as F2C and F3C formulations showed maximum release at 10hr and F4C, F5B & F6C formulations showed maximum release at 12hr (Table 4) (Figure 3).

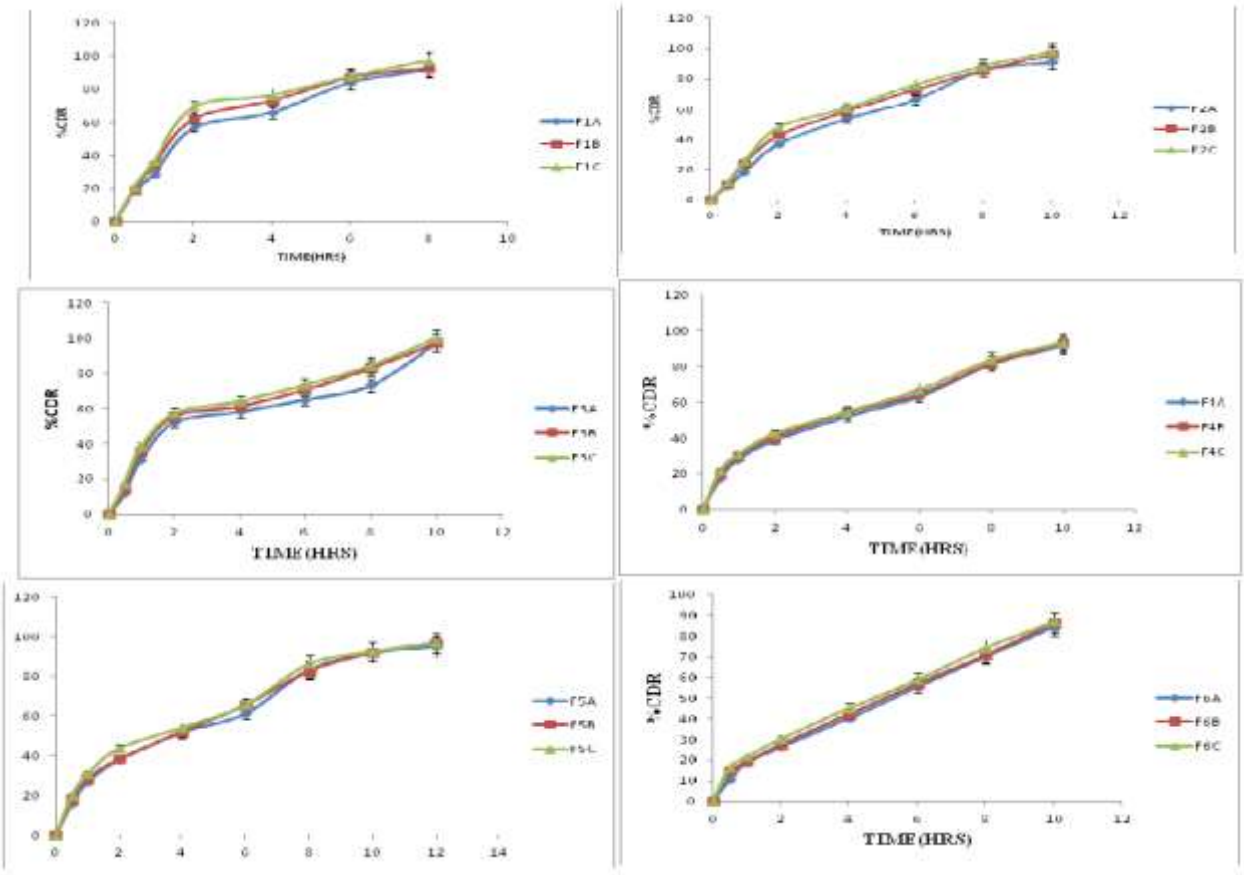


Figure 3: *in vitro* drug release profiles of various formulations

Table 4: *in vitro* Drug release profile of various core tablet of optimized formulation in each batch

TIME(hrs)	F1C (%)	F2C (%)	F3C(%)	F4C(%)	F5B (%)	F6C(%)
0.5	20.89	11.36	17.44	21.92	17.64	16.34
1	36.72	25.44	38.3	31.05	28.44	21.53
2	69.14	48.06	57.21	42.61	38.17	30.15
4	76.37	60.77	64.22	54.79	51.93	44.99
6	87.67	76.02	73.42	67.06	65.44	58.79
8	97.39	88.34	84.47	83.82	82.59	74.13
10	-	97.96	100.02	93.47	91.77	86.85
12	-	-	-	96.94	96.94	99.89

Characterization of Optimized formulation

Effect of pH

The Optimized formulation was subjected to dissolution studies separately in the release media simulated gastric fluid (pH 1.2), Phosphate buffer (pH 6.8) and Phosphate buffer (pH 7.4). The system was independent of the pH since there was no difference in drug release (Figure 2a).

Effect of agitational intensity

The effect of agitational intensity on formulation F6A was studied at 25, 50 &100 rpm. The release profile of KT was fairly independent of the agitational intensity (Figure 2c).

Effect of weight gain

Drug release has been decreased with an increase in weight gain of the coating membrane of varying thickness (5%, 8% &10%) (Figure 2b).

Effect of Osmotic pressure

Ketorolac tromethamine release from the optimised formulation decreased with varying concentrations of osmogen increased; hence the delivery system is dependent on osmotic pressure (Figure 2d).

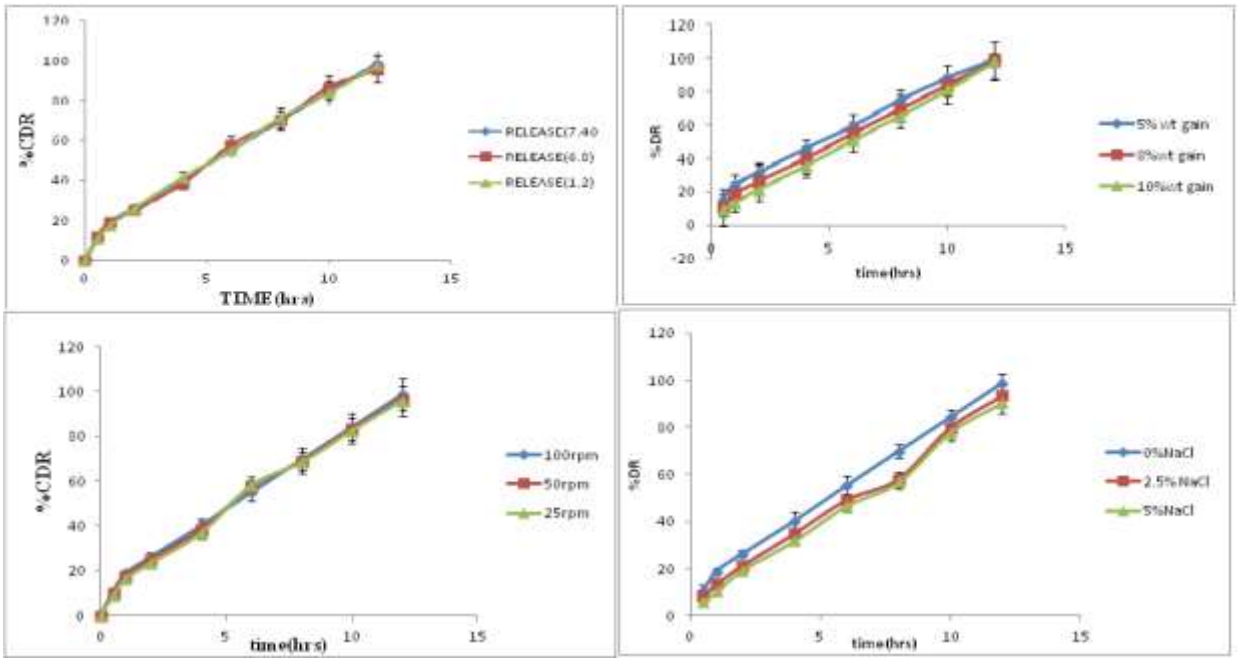


Figure 2: Effect of pH, weight gain, agitational intensity, osmotic pressure of optimized formulation

2a- effect of pH on drug release of optimized formulation

2b- effect of weight gain on drug release of optimized formulation

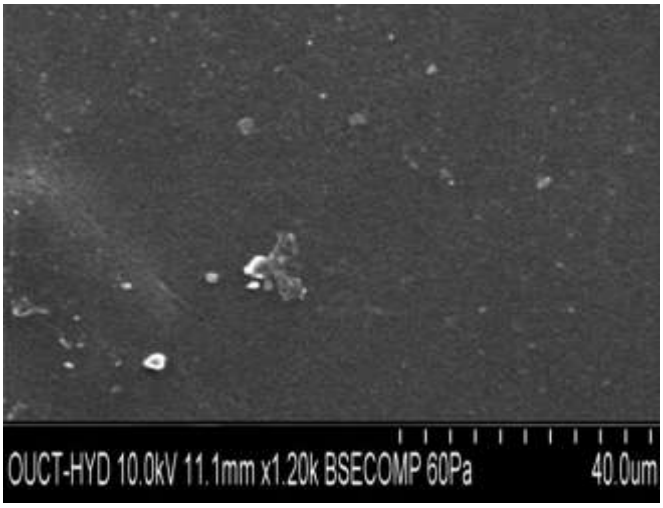
2c- effect of agitational intensity on drug release of optimized formulation

2d- effect of osmotic pressure on drug release of optimized formulation

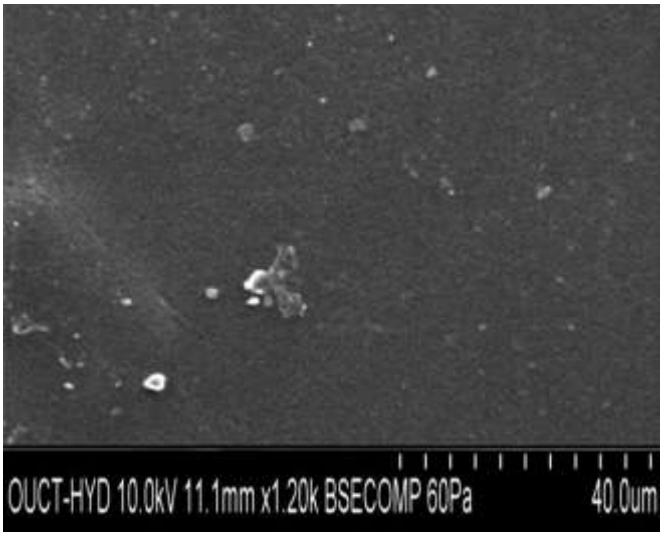
SEM studies of core tablet before and after dissolution

SEM micrographs of membrane surface of optimized formulation containing 2.5% D-sorbitol as a pore former before and after dissolution studies was performed. Figure 4a shows membrane structure before dissolution, initially the surface of coated tablets was smooth before coming in contact with aqueous environment and coats appeared to be free of pores. Figure 4b shows

microporous structure of the membrane after dissolution. This porosity has resulted due to leaching of water-soluble additive., sorbitol during dissolution through which drug release takes place.



4a: membrane structure before dissolution



4b: membrane structure after dissolution

Figure 4a &4b: SEM studies of Optimized formulation

Release kinetics

F6A has showed optimal release kinetics, best fitted to zero order , indicating drug release was non-Fickian, independent of pH and agitational intensity (Table 4).

Table 5: Release kinetics of 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

F6A is the Optimised formulation

CONCLUSION

Push Pull based Osmotic tablets (PPOP) coated with cellulose acetate as semipermeable membrane has been developed for Ketorlac tromethamine (KT). The DSC analysis shown that there is no drug-excipient interactions in the formulations. The physical properties like thickness, hardness, friability and weight variation of the core tablets compiled with the Pharmacopoeial standards. The effect of various formulation variables was studied to optimize release profile. The desired zero order release profile was obtained by optimizing concentration of osmogen, polymer and pore forming agent. The formulation (F6A) delivered KT at zero order rate for a period of 12 hrs. The drug release from the developed formulations was found to be stable, independent of pH and agitational intensity. Thus, this system is simple to prepare and cost effective and thus eliminates the use of sophisticated laser drilling technique.

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