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Research Article

DEVELOPMENT AND CHARACTERIZATION OF KETOROLAC TROMETHAMINE (KT) OROBUCCAL FILMS

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ABSTRACT

Ketorolac Tromethamine **(**KT) is a potent non steroidal anti-inflammatory analgesic drug is characterized by gastrointestinal (GI) side effects. KT orobuccal films (OBFs) were developed to either chew (oro) or to be localized delivery of medicinal agent to a specific site in the buccal cavity (buccal), thus reduce GI side effects and improve the drug bioavailability. Twenty seven KTOBFs were prepared by solvent casting technique using hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), Ethyl cellulose (EC), Eudragit RL100, Lutrol F127, and Carbopol 934 in combinations of these polymers (9:1 to 5:5) using HPMC as a basic polymer. Drug polymer interactions were investigated using Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). KTOBFs were evaluated for film appearance, thickness, weight, drug content, surface pH, tensile strength, percent elongation, moisture absorption capacity, mucoadhesion force, in vitro drug release and stability study. FTIR and DSC patterns showed no interaction between drug and polymers which were used. KTOBFs showed acceptable film thickness, weight, surface pH, moisture absorption capacity, elasticity, mucoadhesion and drug content. HPMC appeared to improve the properties of the films, affecting the bioadhesiveness and increasing elasticity. SCMC, Eudragit RL 100, and Lutrol F127 as co-polymers with HPMC improved the properties of KTOBFs rather than EC and Carbopol 934 in terms of elasticity, mucoadhesion, and in vitro drug release. Stability study for KTOBFs showed no change in properties during 10 months storage at room temperature. This study is a promising issue for developing KTOBFs. KTOBFs have rapid onset of action and improve patient compliance due to their small size and reduced thickness compared to lozenges and tablets.

Keywords: Ketorolac, Orobuccal film, Rapid dissolving, Mucoadhesion

INTRODUCTION

Films as dosage forms have gained relevance in the pharmaceutical area as novel, patient friendly, convenient products. More recently orally disintegrated films (or strips) have come to light, thanks to their improved medicinal properties[1,2]. This translates into a less friable dosage form compared to most commercialized orally disintegrating tablets, which usually require special packaging [2,3]. Mucoadhesive buccal films share some of these advantages and more. Due to their small size and thickness, they have improved patient compliance, compared to tablets [3-5]. Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs, films can be formulated to exhibit a systemic or local action [6]. Due to the versatility of the manufacturing processes, the release can be oriented either towards the buccal mucosa or towards the oral cavity. Alternatively, films can be formulated to release the drug towards the buccal mucosa. Films releasing drug towards the buccal mucosa exhibit the advantage of avoiding the first pass effect by directing absorption through the venous system that drains from the cheek[7]. Fast- dissolving drug delivery systems are rapidly gaining interest in the pharmaceutical industry. These systems either dissolve or disintegrate without need for water or chewing [8]. The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patients [9,10]. Some elderly patients may not be able to swallow a daily dose anti-inflammatory and analgesic. Fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as tongue, within few seconds, meaning the consumer can take the product without the need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance [11]. A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration and should release the drug in a unidirectional way toward the mucosa, in a controlled and predictable manner, to elicit the required therapeutic response [12].

Hydroxy propyl methyl cellulose (HPMC) is known for its good film forming properties and has excellent acceptability [13]. Either fast dissolving films or mucoadhesive films may be constituted of hydroxy propyl methyl cellulose. Formulation of these systems is usually simple by solvent casting where the polymer and drug are dissolved in a solvent and a film is cast by solvent evaporation or hot melt extrusion [1,14-16].

Ketorolac Tromethamine (KT) is one of the most potent non steroidal anti-inflammatory drugs that is known to have potent analgesic. Clinical studies have shown that a single dose of Ketorolac is more effective than that of morphine, pethidine and pentazocine in severe to moderate postoperative pain [17, 18]. It has been found effective in the treatment of trauma-related pain as well as pain associated with cancer [19]. Unlike narcotic analgesics, it has the advantage that it does not depress the respiratory and the central nervous system. It has no addiction potential associated with narcotic analgesics and hence it exhibits a more favourable safety profile [20-23].

The aim of this work is to design and evaluate ketorolac tromethamine orobuccal films. The films were developed to either chew (oro) or to be a localized delivery of drug to a specific site in the buccal cavity (buccal).

MATERIALS AND METHODS

Ketorolac Tromethamine (Hetero Drugs Limited, Erragadda,Hyderabad - AP. India)., Ethyl cellulose (EC), BDH Chemicals Ltd., Poole, England, Methanol (S D Fine-Chem limited, Mumbai, India), Carbopol 934 (CP) (B.F., Goodrich Chemical Company, Ohio, USA), Hydroxypropyl methylcellulose (HPMC E15) ; Colorcon Limited, Kent, England, Methylene chloride; pure analytical grades, Triethanolamine, (E. Merk, Germany), Sodium Carboxymethylcellulose (SCMC) (C.B.H. Lab Chemicals, Nottingham, U.K.), Eudragit RL-100 (Central Drug House, Mumbai, India), Propylene glycol (E. Merck Ltd, Mumbai, India), lutrol F 127 (Sigma-Aldrich), Potassium sulfate, VEB Laborchemie, Apolda, West Germany.

Methods

Compatibility studies of KT with the formulated additives

To investigate any possible interactions between the drug and the polymers, differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). Physical mixtures of KT and

the polymers; HPMC, EC, Eudragit RL, SCMC and CP; in ratio of 1:1were prepared. Also, KT with polymers combination; HPMC / EC, HPMC/Eudragit, HPMC/CP, and HPMC/Lutrol in ratio 1:0.5:0.5 were subjected to DSC and FTIR.

DSC measurements were performed using a Shimadzu DSC-60 (Kyoto, Japan). Samples weighing approximately 5mg of the above mixture were sealed in aluminum pans and analyzed in an atmosphere of nitrogen at flow rate of 25ml/min. A temperature range of 0ºC to 200 ºC was used, and the heating rate was 10ºC/min.

DSC of plain drug and polymers was also performed.

FTIR spectra were carried out using, (Bruker 22, UK). The samples were prepared as KBr disks compressed under a pressure of 6 tones/cm^2. The wave-number selected ranged between 500 and 4000 cm-1.

Preparation of Ketorolac orobuccal films using different solvent system

Five film forming polymers were used, namely, HPMC, EC, Eudragit RL, SCMC and CP and combination of them with HPMC were used with 10% w/w propylene glycol (PG) as a plasticizer. The films were prepared by solvent casting method [10,21,24]. Two different solvent systems were used. Drug concentration was kept at 3.32 mg/cm^2 of each film. The first casting solvent was methanol/methylene chloride (1:1) mixture. This solvent system was used to prepare orobuccal films (F1-F11) prepared from HPMC alone or in combination with EC, or Eudragit RL. The composition of KT orobuccal films (F1-F11) was mentioned in Table 1.

KT was dissolved in the solvent system. HPMC and EC or Eudragit in different ratios (9:1, 8:2, 7:1, 6:4, and 5:5) were added to the solvent system containing propylene glycol. When a homogeneous solution was affected, it was left for 30 minutes to remove any entrapped air bubbles. Twenty five ml of the solution was poured into a dust free Petri dish previously cleaned and dried. The Petri dish was covered with an inverted glass funnel of stem orifice 0.6 cm diameter. The funnel is an aid to control the rate of evaporation of the solvent and reducing the blistering of the surface of the depositing film. The solvent was allowed to evaporate for 24 hour; the film then was removed from the Petri dish to desiccator containing anhydrous calcium chloride, where it was stored for further 24 hours before use. Square parts of films (2x2) were cut with a sharp razor blade.

Table 1: Composition of Ketorolac orobuccal films formulae in methanol/methylene chloride solvent system

Formula	HPMC	Polymer (mg)	
		EC	Eudragit
F1	1000	-	-
F2	900	100	-
F3	800	200	-
F4	700	300	-
F5	600	400	-
F6	500	500	-
F7	900	-	100
F8	800	-	200
F9	700	-	300
F10	600	-	400
F11	500	-	500

Table 2: Composition of Ketorolac orobuccal films formulae in distilled water solvent system

Formula	HPMC	Polymer (mg)		
		Carbopol	SCMC	Lutrol
F12	1000	-	-	-
F13	900	100	-	-
F14	800	200	-	-
F15	700	300	-	-
F16	600	400	-	-
F17	500	500	-	-
F18	900	-	100	-
F19	800	-	200	-
F20	700	-	300	-
F21	600	-	400	-
F22	500	-	500	-
F23	900	-	-	100
F24	800	-	-	200
F25	700	-	-	300
F26	600	-	-	400
F27	500	-	-	500

The second casting solvent was distilled water. KT orobuccal films (F12-F27) were prepared by using HPMC alone and in combination with Carbopol 934, Na CMC, and Lutrol F127. The composition of KT orobuccal films (F12-F27) is mentioned in Table 2. The rest of method was adopted as above.

Preliminary trials (plain films) were undertaken for designing the orobuccal films where the effect of various concentrations of the different polymers and plasticizers on the characteristics of the films was assessed. The prepared films were evaluated for surface perfection, smoothness, and ease separation from Petri dish without rupturing, folding or cracking (peelability).

II. Evaluation of Ketorolac orobuccal films

Drug content determination

One square (1cm^2) sample was dissolved in distilled water and the solution was filtered through using 0.45µm membrane filter and ketorolac was assayed UV spectrophotometer measured at λ max 323 nm against a blank of distilled water. .

Film weight uniformity determination

Three films of every formulation were taken and weighed individually on a digital balance (Nahita-300-Spain). The average weight was determined.

Film thickness

The thickness of the prepared films was determined by means of micrometer (Mitutoyo corporation, model PK-1012E, Japan) at three different places and the mean value was calculated.

Surface pH of films

Three films of each formulation were allowed to swell for 2 h on the surface of an agar plate. The surface pH was measured by using a pH paper (placed on the surface of the swollen patch [25]. A mean of three readings were recorded.

Determination of moisture absorption uptake

Films were cut into 2x2 cm square strips (4cm2). The moisture uptake by the films (n=3) was determined by exposing them to an environment of 75% relative humidity (saturated solution of potassium sulphate) at room temperature for one day. The uptake of moisture by the films was measured and calculated as percent increase in weight[10].

Mechanical properties

Tensile strength measurement tester (Tinius-OT-Oslen model H5K5, House field test equipment) was used. The tester has two clamps, the upper one is fixed and the lower is movable with a speed of 1mm/s. The film sample (2x2 cm) was clamped between the two clamps. The force at tearing and elongation were determined [10]. The percent elongation (%*E*) was calculated using the following equation

$$\% E = (Ls - Lo/Lo) X 100$$

Where Lo is the original length and Ls is the length of the film after elongation.

Folding endurance determination

For selected KT OBFs, each film was subjected to folding at the same place till it broke or folded up to 300 times [24].

Determination of mucoadhesion performance of the KT orobuccal films

The effect of bioadhesive polymers (SCMC, CP and Lutrol) on the work of adhesion of HPMC film forming material was studied. The experimental technique used for determining the bioadhesive force has been derived from a previously published method [26-28]. The apparatus was designed for measuring the minimum weight required for detachment of two membranes from each other with a film of polymer spread between them. The minimal weight of water required to detach the sample from the rabbit's small intestine was noted as the mucoadhesive force. All detachment tests were carried out at room temperature (n=3). To prepare the biological membrane, the small rabbit intestine was used fresh and washed with saline before use. The mucin was scraped from the intestine leaving a thin membrane that was dried and used as the model membrane.

Detachment stress (dyne/cm^2) = m.g/ A

Where: m: the weight of water, g: acceleration due to gravity taken as 981 cm/sec^2,

A: area of rabbit's small intestine (area of contact)

In vitro Disintegration Time

The test was performed using the method mentioned by Mutasem et al [29] with slight modification. The film size required for dose delivery (2x2 cm) was placed on a watch glass containing 3 mL of distilled water. The time required for the film (n=3) to break was noted as in vitro disintegration time.

In vivo Disintegration Time

The selected orobuccal films were tested in three healthy volunteers aged (32-45 years). After wipping off excessive saliva, each film was applied to either the tongue or buccal mucus membrane by pressing for 30s onto mucosa. The volunteers were asked to record [30].

a- The adhesion time and time of detachment of film.

b- The strength of adhesion (very adhesive, adhesive, slightly adhesive, unadhesive or slippery).

c- Any local signs of irritation (severe, moderate, slight or non irritant).

d-Bitterness due to swallowing (very, moderate, slight or non).

e- The disintegration of the orobuccal film in the buccal cavity (high, moderate, slight or non).

Table 3: Evaluation of Ketorolac Tromethamine orobuccal films

Formula	Film weight (mg)	Film Thickness (+0.02mm)	Surface pH	Moisture absorption capacity (%)	Tensile strength (Kgf)	Percent elongation (%)	Mucoadhesion Force (dyne/cm^2)	Drug content (%)
F1	728	0.19	7	23.98	0.132	16.65	12140	102
F2	720	0.18	7	20.8	0.122	14.16	7970	111
F3	715	0.17	7	18.04	0.137	7.5	8338	113
F4	711	0.16	7	17.16	0.164	6.66	5640	111
F5	709	0.15	7	15.27	0.063	6.25	9564	120
F7	710	0.17	7	11.8	0.222	16.67	11036	98
F8	711	0.16	7	9.12	0.13	13.33	9810	92
F9	722	0.18	7	9.18	0.108	6.66	7848	97
F10	732	0.3	7	6.5	0.02	5.8	8583	111
F11	696	0.13	7	5.3	0.095	5.5	10545	100
F12	725	0.19	7	25.67	0.232	50.42	11236	106
F13	718	0.14	9	12.9	0.031	27.5	6744	99
F14	723	0.19	9	11.4	0.003	19.2	6224	112
F18	712	0.17	7	32.43	0.009	20.3	12262	85
F19	690	0.10	8	33.57	0.066	22.92	16554	118
F20	695	0.13	7	36.12	0.013	29.99	11235	93
F21	689	0.1	8	37.3	0.107	33.41	23298	116
F22	693	0.1	6	39	0.071	37.9	12262	115
F23	712	0.13	7	41.2	0.020	25.8	12315	120
F24	719	0.16	7	44.7	0.012	13.3	12848	117
F25	729	0.18	7	47.65	0.138	12.6	13998	115
F26	718	0.14	7	48.4	0.083	11.6	14715	112
F27	717	0.13	7	51.7	0.053	13.8	14960	110

In-vitro release studies of Ketorolac orobuccal films

The in-vitro release test was performed using USP XXX dissolution apparatus II. The release studies were carried out at 37 ± 0.5 °C with stirring speed of 50 rpm. The film size required for dose delivery (2x2 cm) was attached to glass plates (5x4.5cm) using Amir adhesive. The edges of the film were covered with Amir adhesive to avoid direct drug release from edges. The glass plate assembly was immersed in 300 ml of freshly distilled water [10,31,32]. Aliquots of 3ml of release media were collected at predetermined time intervals of 5, 10, 15, 20, 30, 45, and 60 min and replaced with equal volumes of distilled water. The collected samples were filtered through 0.45 um membrane filter and the concentration of the dissolved drug was determined spectrophotometerically at **λ** max 323 nm. The results were the average of three determinations.

For selected KT orobuccal films, in-vitro dissolution test was performed using USP XXX dissolution apparatus I. The film size required for dose delivery (2x2 cm) was added in the basket of dissolution tester. The rest of procedure was adopted as above.

Effect of casting solvent on the release of drug from HPMC polymeric films

The effect of casting solvents used for preparing KT OBFs from HPMC polymer (F1 and F12) was studied. The films were prepared as mentioned above and then the release study was performed. The surface morphologies of the drug, F1 and F12 films were examined by scanning electron microscope. Each film was mounted on aluminum stubs using a double sticky cellophane tape, gold-coated in a vacuum evaporator and observed under Jeol (Jem 100S, Japan) scanning electron microscope (SEM).

Stability study

The promising KT OBFs were stored at room temperature for ten months. Each film was wrapped in a butter paper followed by aluminium foil and placed in an aluminium pouch. The films were evaluated for appearance, drug content, taste, and in vitro drug release.

RESULTS AND DISCUSSION

HPMC a polymer with excellent film forming ability was used as a primary film former in films [13, 33, 34]. Film modifiers, EC, Eudragit RL or mucoadhesive polymer CP, SCMC and Lutrol F127 were used. Propylene glycol was used as the plasticizer.

DSC patterns (figure 1) revealed that no change in the place of characteristic peak of the drug. The IR spectra (figure 2) revealed that no interaction between the drug and the used polymers occurred as there was no shift in the IR peaks of the drug.

Different homogenous Ketorolac Tromethamine orobuccal films were prepared; the films are translucent, colorless, thin and soft, and with no spot found on the films. The prepared films were evaluated in terms of physic-mechanical properties and the results were given in Table (3). Assay of drug content at different places in each film showed that the drug was uniformly distributed throughout the films; and were also within the required compendia specifications (92-120%). The average thickness of the films ranged from 0.1-0.3 mm. The surface pH was ranged from 6-9. No significant difference was found within surface pH of different films except for films F13 and F14 composed from HPMC and Carbopol 934, since their pH were shifted towards alkaline pH. The average film weight ranged from 690-732 mg. Presence of moisture in films helps from becoming dry and brittle due to the plasticizing effect of water; all KT OBFs lose water in dry conditions and pick moisture over 75% RH for 24 hours. The moisture absorption capacity was done for one day as the patient put the film in mouth and uses it for fast action. The moisture absorption capacity was ranged from 5.3-51.7%. This was explained on the basis that, the addition of more hydrophobic polymer; EC or Eudragit; to hydrophilic polymer HPMC will decrease the moisture absorption properties of the mixture polymer (F11, F10, F9 and F8). This results were in a good agreement with El-nabarawi [24], where the author studied tenoxicam release from films containing different ratios of HPMC and EC.

Considering mucoadhesion performance of the KT orobuccal films, hydration of mucoadhesive polymer is an important factor affecting adhesion. Adhesion occurs shortly after the beginning of swelling but the bond formed is not strong. Uptake of water results in relaxation of the originally stretched, entangled or twisted polymer chains. This result in exposure of all polymer bioadhesive sites for bonding to occur. The faster the swelling of the polymer, the faster the initiation of diffusion and formation of adhesive bonds resulting in faster initiation of bioadhesion [35-37]. The prepared polymeric films swelled in the following order namely Lutrol F127-HPMC films > SCMC-HPMC films > EC- HPMC films > Eudragit RL100-HPMC films > Carbopol -HPMC films indicating that the percentage swelling of HPMC-E15 films was reduced by the addition of Carbopol 934P, EC and Eudragit-RL 100, and increased by the addition of SCMC, and Lutrol F127. The bioadhesive properties of the prepared ketorolac films are shown in Table 3. Carbopol had the least bioadhesive properties whereas EC and Eudragit had moderate bioadhesive properties. SCMC and Lutrol had the highest mucoadhesive force respectively. Increasing the concentration of SCMC, and Lutrol increased the mucoadhesive force. This could be attributed to the hydrogen bond formation and Van der Wall forces [38].

KT OBFs should possess moderate tensile strength and high % elongation. The results revealed that, the range of 0.003-0.23 kg and the percent elongation ranged from 1.6-50.42%. All films showed folding endurance up to 300 folding except for films F5, F6, F10 and F11.

In vitro disintegration time was within 3 minutes for all prepared films. For in vivo disintegration time for selected films; F2,F3,F7,F8,F13,F14,F18,F19,F23 and F24; were disintegrated and dissolved within 60s on the tongue. The response answer of the adhesion time equal to 15 min with good adhesion strength, non irritant, no bitterness and moderate disintegration of the selected films applied in vivo to three healthy volunteers. Addition and increasing the amount of SCMC to HPMC increased the adhesion time as follows: F27> F26>F25>F24>F23.

In-vitro release studies of Ketorolac orobuccal films

The twenty three ketorolac orobuccal films investigated showing complete drug release within one hour figure (3). It was noticed that the films containing higher amount of HPMC got hydrated rapidly; and began to dissolute the drug. This may be due to the water solubility of the drug and the polymer. The drug release from most of the films was ~80% after 20 minutes except for F4, F12, F20 and F23. However, after about 5 min, marked differences in the drug release were seen between F8 and all other formulations. The difference in release may be attributed to the differences in the composition of film forming materials. In case of KT OBFs composed from HPMC and EC or Eudragit or Carbopol or Carbopol or Lutrol. Increasing the proportion of polymer modifier in HPMC matrix more than 1-2 parts does not significantly increase the amount of drug release but definitely increases the duration of drug release. These results were in a good agreement of Narasimharao et al [39].

As the films got hydrated they began to disintegrate and release the drug. Films prepared using mixture of polymers (except F1 and F12) showed different release rate. This could be explained by the fact that, the transport would be expected to occur through channels formed due to dispersed HPMC within the other polymer and presence of KT (water soluble). By reducing HPMC percentage in films makes the network smaller and less able to contain the swelled polymers and the film starts significant erosion. So it could be concluded that the percentage of HPMC has to be more than 60%. This was in a good agreement with Najafie et al [40]. It could be seen that addition of bioadhesive polymers predominately decreased the release rates from the different mucoadhesive films. These polymers exhibit high swelling resulting in an increase in diffusional path length of drug and consequent reduction of drug release [25]. This depends of course on the type, concentration of polymer and film thickness. In case of dissolution study, selected KT orobuccal films; F2, F7, F18 and F23; were dissolved within 10 minutes.

Effect of casting solvent on the release of drug from HPMC polymeric films

The effect of casting solvents used for preparing KT OBFs from HPMC polymer (F1 and F12) was studied. F1 was prepared by methanol/methylene chloride (1:1) and F12 was prepared using distilled water. The amount of drug release was higher for F1 than F12. This could be explained on the basis of the observed differences in distribution would appear to be due to differences in the rate of precipitation of the drug and polymer as drying proceeds. Since organic solvents are usually employed in film coating, it seems likely that the precipitation of the hydrophilic component (drug) of the film would be affected to a greater extent. In general, a shift to a more polar solvent might result in more rapid precipitation of the hydrophilic agent. Shifts in solvent polarity would also influence such factors as solvation of polymers and viscosity of resulting solution. This results was in a good agreement of Shah and Sheth [41] who studied the effect of solvent on timed release films composed of HPMC and EC. To investigate this effect, scanning electron microscope was used to examine the surface morphology of the drug in F1 and F12 and plain drug. Figure (4a) showed the morphology of KT and appears as needle crystals. Figure (4b) showed the morphology of F1 surface. F1 showed that, the film surface was tough surface and the drug was not embedded inside the polymer matrix. This could be explained by appearance of the needle crystals on the surface of F1 which casted from organic solvent. The drug and polymer have unequal solubility in the organic media which leads to unequal precipitation between drug and polymer. Figure (4c) showed the surface morphology of F12. The film surface was homogenous surface and the drug was completely embedded inside the polymer matrix. This could be explained on F12 was casted from aqueous solvent. The drug and polymer have equal solubility in the aqueous media which leads to equal precipitation. This result was also confirmed by the release of drug from F1 and F12, where F1 gave higher drug release from F12. This could be explained on the fact that the drug was embedded inside HPMC (F12) and take time to be soluble and then diffuse through the polymer to the external release medium.

The selected films; F2, F7, F18 and F23; did not show any significant change in appearance, weight loss, drug content and release study during 10 months storage at room conditions.

CONCLUSION

A novel orobuccal ketorolac tromethamine films were developed using hydroxy propyl methylcellulose as a basic polymer by solvent casting method. The physico- chemical properties of the prepared formulations were achieved by the use of one part of either ethyl cellulose, Eudragit RL, SCMC and Lutrol with HPMC. The selected four formulations showed no change in their physicomechanical properties during 10 months storage, satisfactory drug release during 15 minutes and non irritant to mouth.

This novel dosage form could be of particular benefit to patients treated with ketorolac where fast pain relief is required without gastrointestinal disorders.

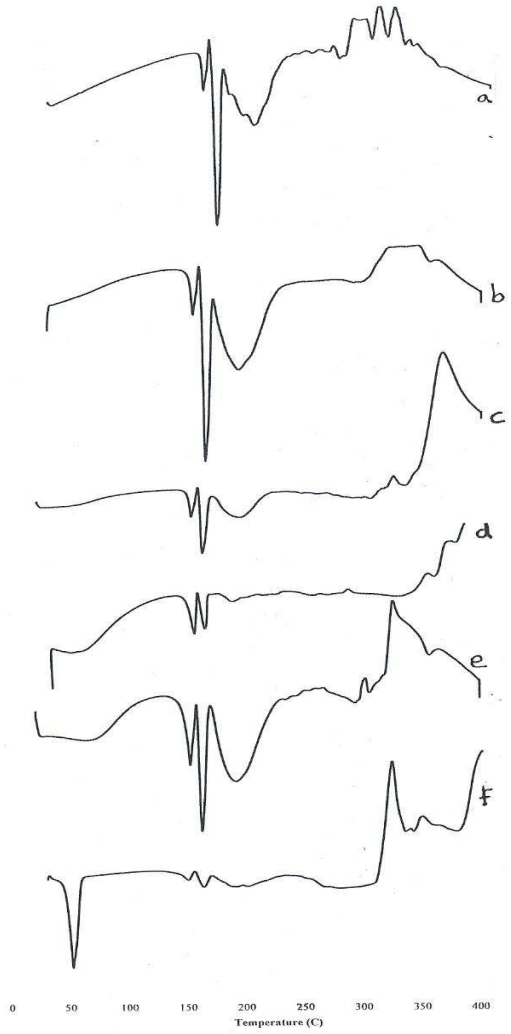


Fig. 1: DSC patterns of KT (a), KT/HPMC (b), Kt/HPMC/EC (c), KT/HPMC/Ed (d), KT/HPMC/SCMC (e) and KT/HPMC/ Lutrol (f).

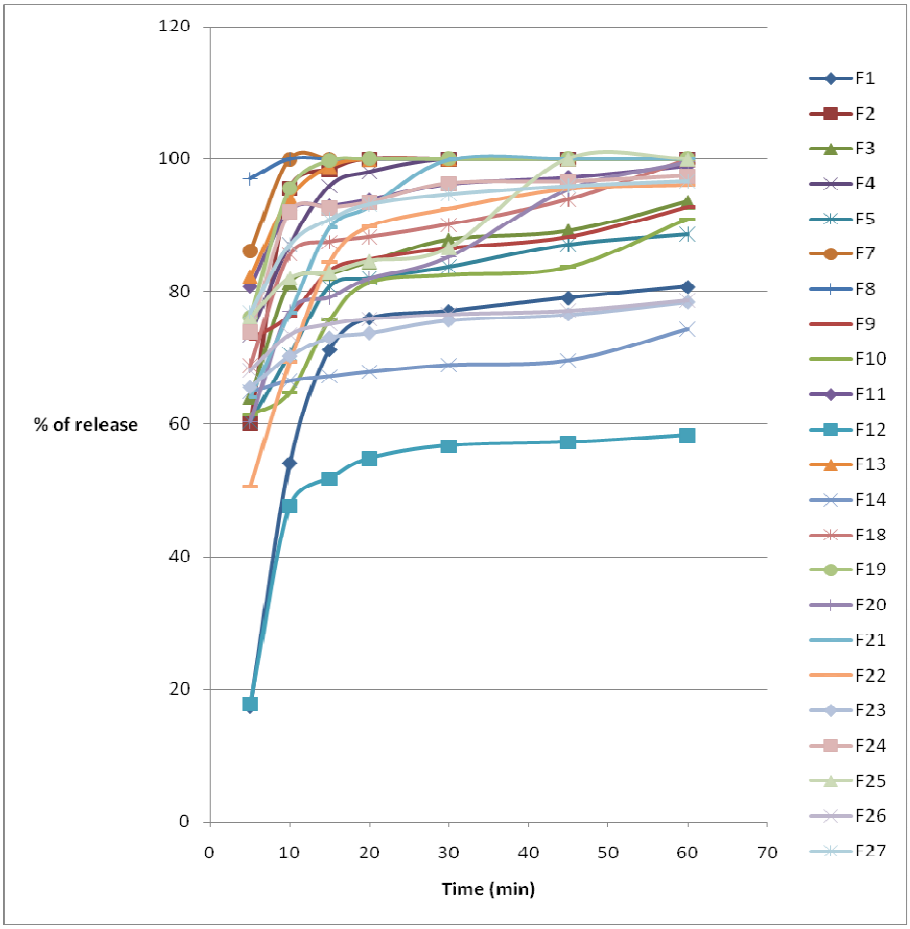
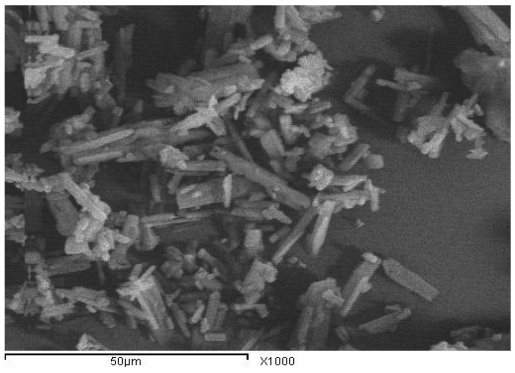


Fig. 3: Percent ketorolac release from OBFs in distilled water



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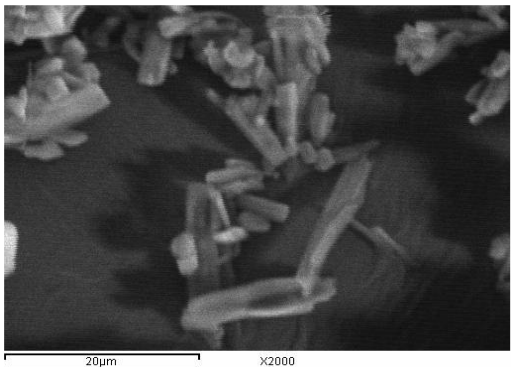

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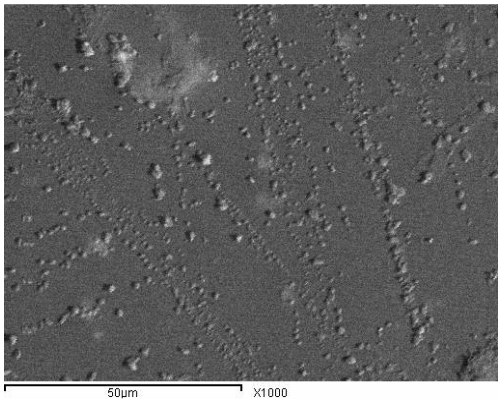

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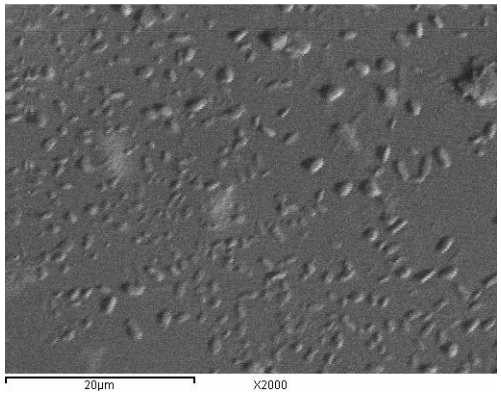
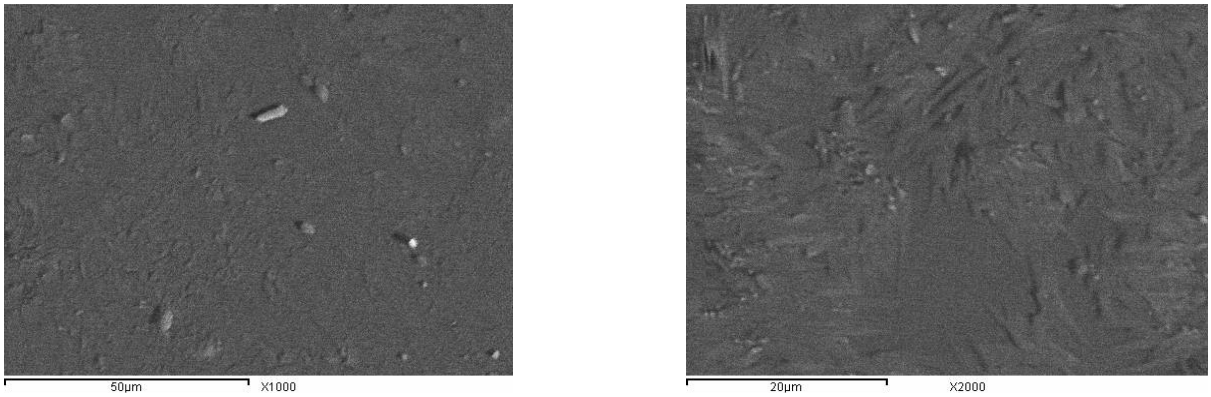


(b=2000X)



(c=1000X) **(c=2000X)**

Fig. 4: SEM micrographs of ketorolac tromethamine (a), F1 (b) and F12 (c)

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