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Physico-chemical characterization of acrylate pseudolatex films and *in-vitro* release profile of ketorolac tromethamine from the films

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ABSTRACT

The present study was undertaken to develop acrylic transdermal film of ketorolac tromethamine from aqueous pseudolatex by using polymeric combination of Eudragit L-100 and Eudragit S-100 by solvent evaporation method. Physicochemical characterization of the prepared pseudolatex films is done for the drug content, thickness of the film, weight variation, moisture content, moisture uptake, and water vapor transmission, folding endurance and scanning electron microscopic study. The in-vitro release of drug from the pseudolatex films was carried out by using 6 stage dissolution test apparatus rotating paddle type (USP-II) and the effect of two polymers in different ratio in the pseudolatex film on the release of the drug has been studied. The drug-polymers compatibility study was done by Fourier Transform Infrared Spectroscopy (FTIR) and the surface morphology, the distribution of drug in the films was studied by Scanning Electron Microscope (SEM). The polymers used in the films were found compatible by FTIR study and the drug is found uniformly distributed (SEM study) to give dosage uniformity per unit area of the films. The results of physicochemical properties revealed that the pseudolatex films of ketorolac trometamine using Eudragit L-100 and Eudragit S-100 will be sufficiently stable and suitable for transdermal application. The results of in-vitro release profile ascertained that the release rate can be retarded to get controlled release characteristics of the formulation by incorporating higher proportion of EL-100 polymer in the films.

Keywords: Pseudolatex films, Ketorolac Tromethamine, Eudragit L-100, Eudragit -100

INTRODUCTION

Pseudolatex is actually colloidal polymer particles dispersed in water, a two compartment system; one is being a hydrophilic polymer that form a three dimensional network and another compartment being water. Their high compatibility in a number of applications make them promising candidate for preventing the side effects. This is widely studied biomaterial for preparation of controlled release dosage form. It provides more reliable and steady release of drugs. This latex has also been used extensively to formulate oral controlled released drug delivery system in the form of coated small particles, beads or tablets. Drug containing latex particles for topical, ophthalmic or parenteral preparation prepared by dissolving the drug in the polymer solution before emulsification and pseudolatex formation have been reported [1]. Ketorolac is frequently used in the post operative, dental and acute muscutoskeletal pain: 15-30 mg i.m. or i.v. every 4-6 hours (maximum 90 mg/ day). It may also be used for the renal colic, migraine and pain due to bony metastasis. Orally it is used in a dose of 10-20 mg 6 hourly for short term management of moderate pain. It has been rated superior to aspirin (650 mg) and paracetamol (600 mg) and equivalent to ibuprofen [2]. The sustained release formulation of the drug is required to improve the patient

compliance and to reduce the frequency of administration. Its low molecular weight (376.40); low melting point (162°C) ; low dose (maximum daily dose is 90mg) and short half life (5-7 hrs) make it suitable to formulate in transdermal delivery system to get the advantage of reduced side effects, reduction in frequency of administration and improving patient compliance [3]. The objective of the present study was to develop transdermal pseudolatex films of Ketorolac tromethamine for sustained effect of the drug with the polymeric combination of Eudragit L-100 and Eudragit S-100 and to study the physic-chemical properties and release profile of the drug from the films.

MATERIALS AND METHODS

Materials: Ketorolac tromethamine was obtained as a gift samples from Cipla (India) Pvt. Ltd. Eudragit L-100 and Eudragit S-100 were obtained as a gift samples from Evonik Industries Limited. Glycerol and sodium hydroxide purchased from Merck Specialities Private Limited, Mumbai. Acetone and Potassium dihydrogen orthophosphate were procured from Central Drug House Private Limited, New Delhi.

Determination of partition coefficient

25 ml phosphate buffer (pH 7.4) and n-octanol was taken in a 100 ml conical flask with 5 mg of drug. The mixture was shaken for 6 hours on a mechanical shaker. Then both phases were separated by centrifugation and the absorbances of both phases were determined spectrophotometrically at 324.5 nm against blank solution. After calculating the concentration of drug in both phase value of partition coefficient (P) was determined by the help of following equation:

$$P = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in buffer}}$$

Drug Polymer compatibility study by FTIR [3]

To study the possible interaction between the drug (ketorolac tromethamine) and polymers (eudragit L-100 and S-100) in the patches, IR study was carried out on pure substances and their physical mixtures. The spectra were recorded by using IR spectrophotometer (Perkin Elmer FT-IR) by KBr pellet method.

Fabrication of pseudolatex transdermal films [1]

Acrylic films of ketorolac tromethamine from aqueous latex were prepared by solvent evaporation. Weighed amount of polymers [Eudragit L-100(EL-100)/Eudragit S-100(ES-100)] were dissolved in organic solvent (acetone) with slow and continuous magnetic stirring. Composition of different formulations given in Table1. Drug was dissolved in phosphate buffer (pH 7.4). Clear drug solution was then dispersed into polymer solution with magnetic stirring, plasticizer (glycerol) was then added slowly, 40% of the polymer. Drug containing latex was then poured on the petridishes (9.5 cm dia.). The organic solvent was evaporated subsequently to leave the pseudolatex films.

Table 1. Composition of pseudolatex films containing Ketorolac Tromethamine

Formulation code	EL-100:ES-100	Plasticizer (Glycerol in % w/w)	Solvent (acetone)/ batch in ml	Buffer (phosphate buffer pH 7.4)/ batch in ml
FLS-1	1:1	40	10	0.5
FLS-2	2:1	40	10	0.5
FLS-3	1:2	40	10	0.5
FLS-4	3:2	40	10	0.5
FLS-5	2:3	40	10	0.5

Thickness measurement: The thickness of the prepared films were measured using slide calipers (DIAL CALIPER, Aerospace) by taking measurement at 5 different places of each formulation and average thickness was recorded. **[4]**

Weight variation: Studied by taking individual weight of 5 randomly selected films for each formulation prepared in different batches. This was done in Mettler Toledo balance. **[5]**

Drug content: Individual films of specific areas were cut into thin slices and kept in a 100 ml of phosphate buffer (pH 7.4) and shaken continuously in a mechanical shaker for 24 hrs. Next day it was sonicated for 15 minutes and

after filtration the drug content was assayed spectrophotometrically at 324.5 nm against the blank solution prepared by same method using the patch of the same formulation having no drug. **[6]**

Moisture content determination: 3 patches of each formulation were weighed individually and kept in dessicators containing activated silica gel at room temperature. The weights were taken periodically until two successive weights remain constant. The percentage moisture content was calculated as a difference between initial and final weight with respect to final weight. **[7]**

$$\text{\% Moisture content} = \frac{\text{Final weight}}{\text{Initial weight} - \text{Final weight}} \times 100$$

Moisture Uptake Capacity: Moisture uptake capacities of each formulation were determined by exposing the formulations in high relative humidity (84%) at room temperature; using supersaturated solution of potassium chloride in a dessicator. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. **[8]**

$$\text{\% Moisture uptake} = \frac{\text{Final weight- Initial weight}}{\text{Initial weight}} \times 100$$

Water vapor transmission rate: Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was placed in each vial and the prepared films of each formulation were fixed over the brim with the help of adhesive. The cells were accurately weighed and kept in closed desiccators containing saturated solution of potassium chloride to maintain a high relative humidity (84 %). The cells were taken out and weighed after 6, 24, 48 and 72 hrs of storage. Water vapor transmission rate is usually expressed as the number of grams of moisture gained/h/cm2. **[9]**

Flatness

The longitudinal strips were cut from the centre and both sides of the films. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured as % constriction, and a) percent constriction was considered to be equivalent to 100% flatness [3]

Folding Endurance: Folding endurance was determined by repeatedly folding the films at the same place until it broke. The number of time, the patch could be folded at the same place without breaking is considered as the folding endurance value. The average of the three readings was calculated. **[7]**

Scanning electron microscope: distribution of drug and polymer in the film were studied using scanning electron microscope (JSM, 6100, JEOL, Tokyo, Jpan). For this study, the sections of each sample (blank and drug containing patch) are cut and then mounted onto the stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope [3]

In vitro release study: The release of the drug, ketorolac from the pseudolatex films was studied by using 6 stage dissolution test apparatus USP-II (rotating paddle type) apparatus. Films were fixed on a glass disc and the disc was placed at the bottom of the vessel. Phosphate buffer (pH 7.4) was used as dissolution medium (900 ml) and the temperature was maintained at 37°C ± 0.5°C. Samples were taken at specified time intervals and analyzed by using a UV spectrophotometer (Shimadzu-1700) at 324.5 nm. **[8]**

RESULTS AND DISCUSSION

Partition coefficient determination:

To assess the partitioning of drug between skin and in vitro study fluid (phosphate buffer 7.4), the partition coefficient was determined. The calculated logarithmic value of partition coefficient (log P) of ketorolac tromethamine in n-octanol and phosphate buffer pH7.4 is 1.042. The value shows that the drug has sufficient

lipophilicity, which is necessary to formulate a transdermal patch. It also shows that the drug is biphasic in nature which ensures easy permeation of the drug through the skin.

FT-IR study: The IR spectrum of pure drug (ketorolac tromethamine), and physical mixture of drug and polymers are shown in the figures 1 and 2 respectively. In the spectrum of ketorolac tromethamine (pure drug), major peaks (3,348 cm^{-1} [NH stretch]; 1,727 cm^{-1}C =O stretch (acid); 1,173 cm^{-1} C = O stretch (diaryl ketone); were seen in subsequent spectra i.e. in the physical mixture also. This indicated no major interaction between the drug and the polymer.

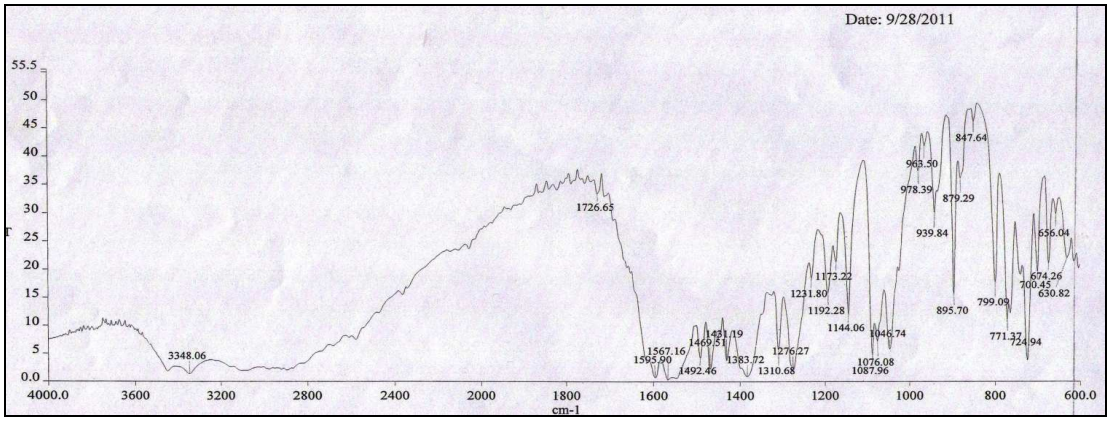


Fig.1 FTIR spectra of pure drug Ketorolac Tromethamine

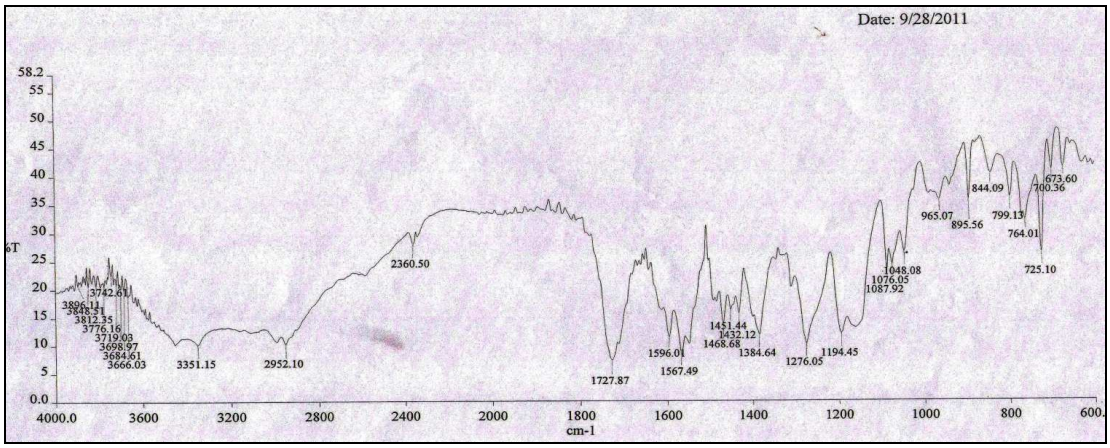


Fig.2 FTIR spectra of physical mixture of Ketorolac Tromethamine, Eudragit L-100 and Eudragit S-100.

Determination of thickness:
The thickness of the pseudolatex transdermal films was determined by dial calipers at different points of the film. The thickness of the films was varied from 0.105 to 0.115 mm (Table2). The value of the film thickness showed that the films are thin.

Determination of weight variation:
The range of variation of weight of the films was 73.60 to 81.12 mg (Table2). The variation in weight of the transdermal films among different batches was found consistent.

Determination of drug content:
Estimation of drug content is essential for the content uniformity of different films from single batch. The % drug content was ranges from 96.56 to 99.12. Uniformity in drug content of the films showed the process employed to prepare films was suitable to give the minimum batch variability.

Table 3. Drug content in films prepared in different batches.

Formulation code	% Drug content
FLS-1	96.56
FLS-2	99.12
FLS-3	97.45
FLS-4	97.37
FLS-5	98.73

Determination of % Moisture content:

The moisture content study showed how much moisture was present in the formulation. % of moisture in the films was varied from 7.23 to 10.16% (Fig.3). Moisture content (2-10%) in the films prevents them from being a completely dried and brittle. **[10]**

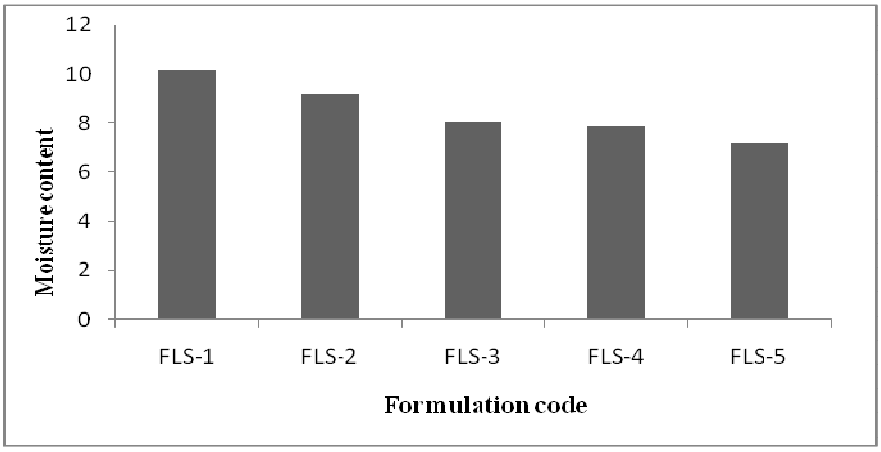


Fig.3. % Moisture content of different pseudolatex films of Ketorolac Tromethamine

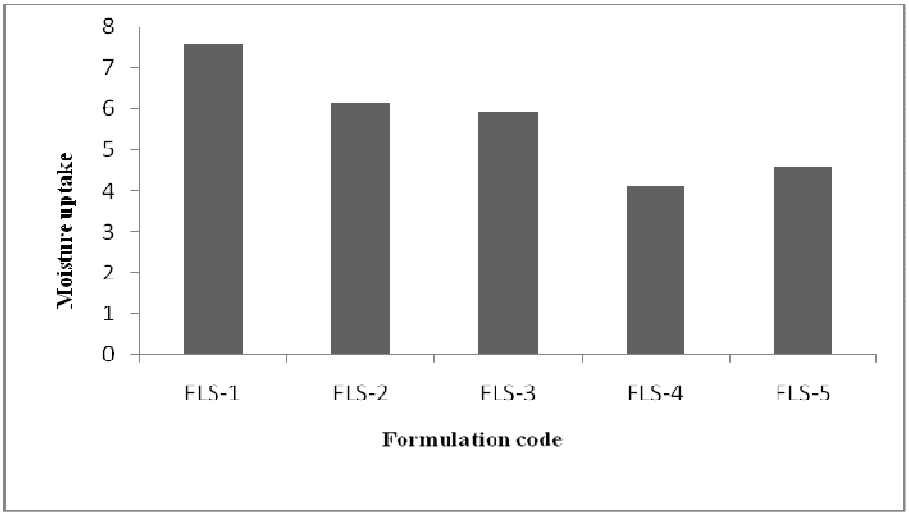


Fig.4. % Moisture uptake of different pseudolatex films of Ketorolac Tromethamine

Determination of Moisture uptake:

Moisture uptake study depicted the capacity of the formulation to hold a maximum content of moisture when the formulation was exposed highly humid climatic condition. Moisture uptake capacities of each formulation were determined by exposing the formulations in high relative humidity (84%) at room temperature; using supersaturated solution of potassium chloride in a desiccators. Uptake of moisture of the prepared films varied from 4.58 to 7.57

(Fig.4). Moisture uptake upto 15%w/w of patches has been claimed not to cause discomfort by enhancing the bulkiness of the films and the presence of such lower level of moisture does not support microbial growth. **[10]**

Determination of water vapour transmission rate:
Water vapour transmission rate was varied from 2.24 to 3.45 gm/cm^2/h (Table2). The value was maximum in case of FLS-5 where the proportion of Eudragit EL100 is minimum and the lowest rate was found in case of the film FLS-2 where the proportion of Eudragit EL100 is maximum.

Determination of folding endurance:
Folding endurance was determined by repeatedly folding the films at the same place until it broke. The number of time, the patch could be folded at the same place without breaking is considered as the folding endurance value. The average of the three readings was calculated. It is varied from 26-39 (Table2).

Table 2. Physicochemical Characterization of acrylate pseudolatex films of Ketorolac Tromethamine

Formulation Code	EL-100 : ES-100	Weight variation (mg)	Thickness (mm)	% Moisture content	% Moisture uptake	Folding Endurance	Water vapor transmission (gm/cm^2/h)×10^{-4}
FLS-1	1:1	73.60±3.25	0.109± 3.6	10.16±0.16	7.57±0.25	26±02	2.35±.0.63
FLS-2	2:1	76.56±5.69	0.105± 4.2	9.19±0.12	6.16±0.36	27±03	2.24±0.59
FLS-3	1:2	75.12±4.92	0.115± 2.9	8.09±0.14	5.91±0.35	35±02	3.03±0.69
FLS-4	3:2	78.65±9.65	0.107± 5.6	7.86±0.24	4.12±0.29	36±03	2.89±1.46
FLS-5	2:3	81.12±5.23	0.113± 4.7	7.23±0.19	4.58±0.15	39±02	3.45±0.98

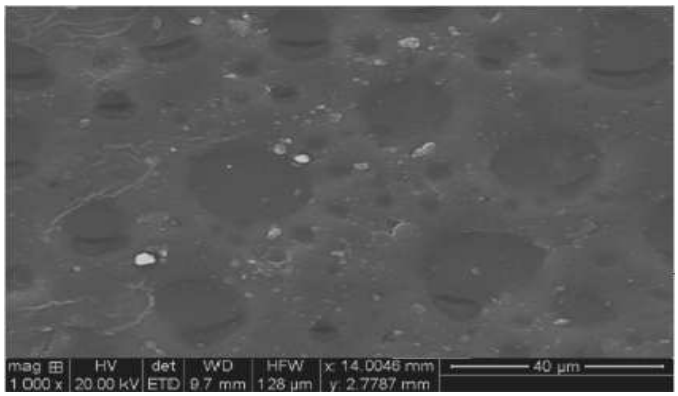


Fig.5 SEM photograph of blank pseudolatex film

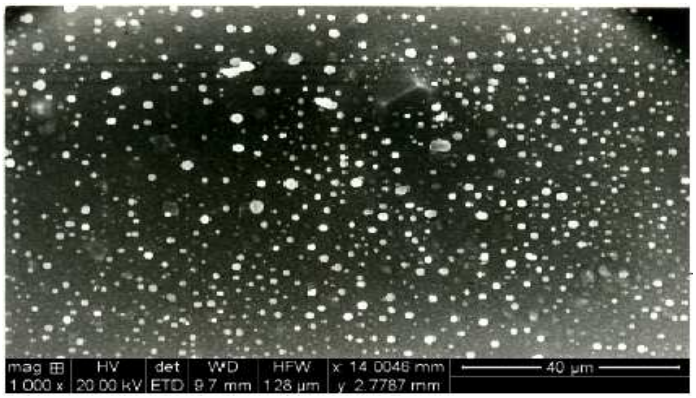


Fig.6. SEM photograph of drug (Ketorolac Tromethamine) loaded pseudolatex film before release study

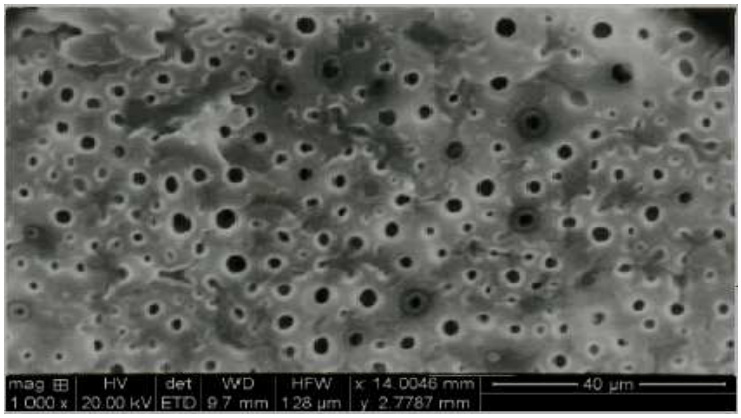


Fig.7. SEM photograph of drug (Ketorolac Tromethamine) loaded pseudolatex film after release study

Scanning electron microscope (SEM):
The surface morphology of the prepared pseodolatex transdermal films without drug, and with drug before and after release study is shown in figures 5, 6 and 7 respectively. Blank photo shows the absence of the drug in the polymer matrix. Drug loaded film indicates the proper uniform distribution of the drug in the film. SEM photograph of the film after release study shows the presence of holes in the films which are formed after removal of the drug from the film.

In vitro dissolution study:
In vitro drug release profile is an important tool that predicts in advance how the drug will behave in vivo. It is essential to conduct a drug release study of the prepared transdermal films to ensure the drug concentration at the surface of the stratum corneum is greater than the drug concentration in the body to achieve a constant rate of permeation through diffusion. Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage form. In vitro release studies showed that EL-100 is less permeable and more retarding the release of drug from the film when present in higher proportion (Fig.8). The film FLS-2 (EL-100:ES- 100:: 2:1) containing higher proportion of EL-100 having highest retarding capacity releasing only 76 % of drug after eight hours of study whereas at the same time the film FLS-3 (EL-100:ES- 100::1:2) containing lowest proportion of EL-100 releases highest percentage of drug (85%).

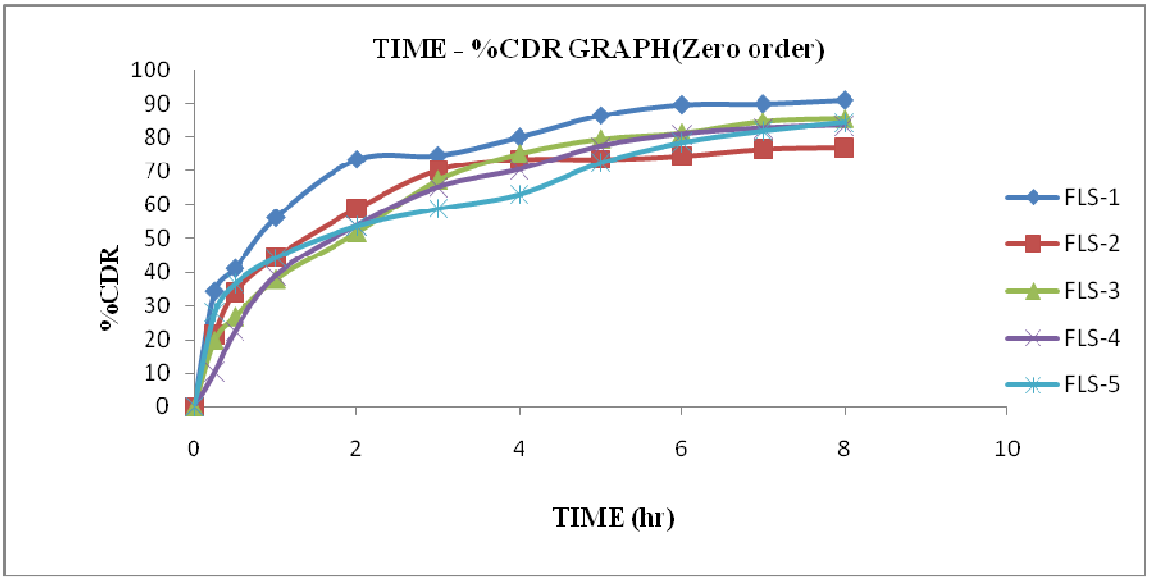
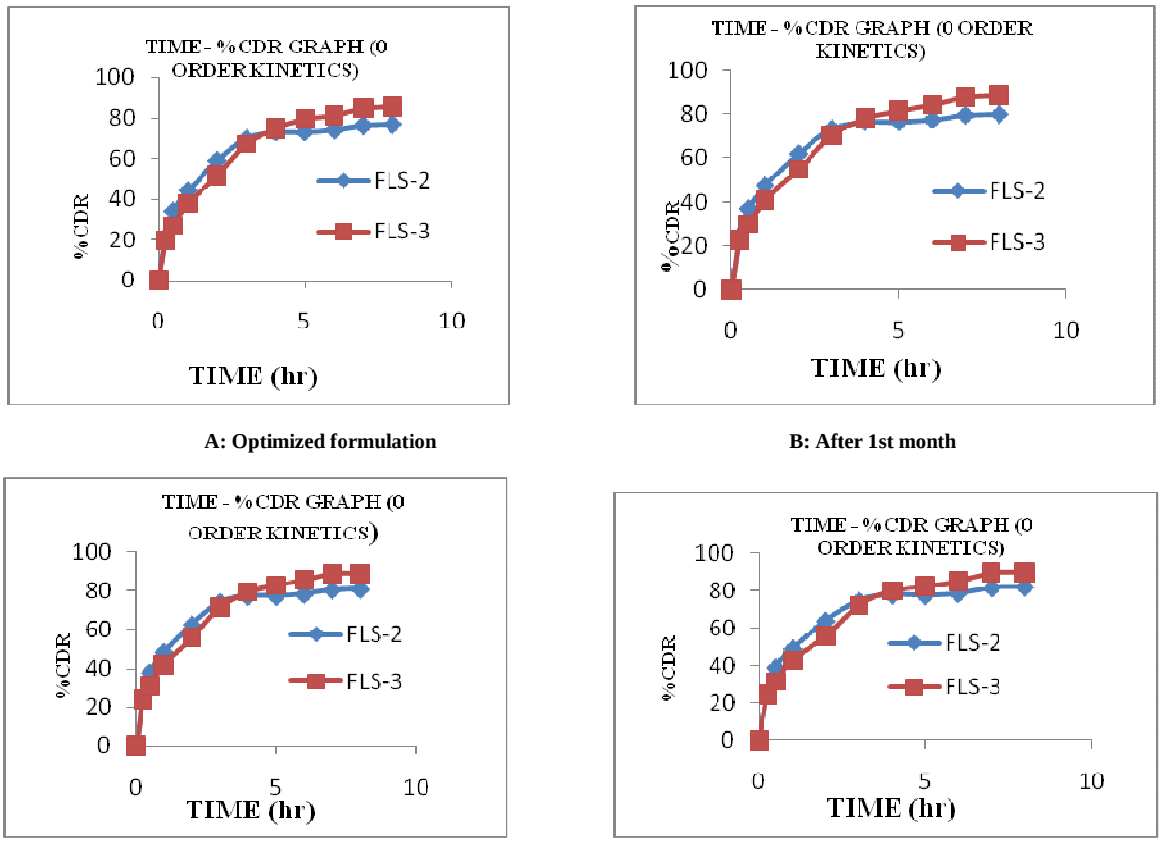


Fig.8. In vitro drug dissolution profile of Ketorolac Tromethamine from different EL-100/ES-100 pseudolatex films.

Stability study:

Short term stability study of the prepared psedolatex films were conducted as per ICH guidelines. The films were studied under 40 ± 0.5°C and 75 ± 5 % RH. After the study for the period of three months, it was found that the films were stable; there was no microbial growth in the films. The release of the drug from the films was varied a little bit, but it was very close to previous release pattern. The release profile of two optimized batch after the study was shown in the figure 9.



A: Optimized formulation **B: After 1st month**

C: After 2nd month **D: After 3rd month**

Fig. 9. In vitro drug dissolution profile of Ketorolac Tromethamine from two optimized formulation (FLS-2 and FLS-3) pseudolatex films after short term stability study

CONCLUSION

The present study was carried out to develop acrylate pseudolatex transdermal films of ketorolac tromethamine. The characterization of physicochemical properties of the prepared transdermal films had shown that the formulations are physico-chemically stable including the absence of drug polymer interaction, which was ascertained by the FTIR study. SEM study showed that the drug was uniformly distributed in the films.

The release rate of ketorolac tromethamine from the pseudolatex films can be varied by selecting appropriate ratio of polymers EL-100 and ES-100. The release rate can be retarded to get controlled release characteristics of the formulation by incorporating higher proportion of EL-100 polymer.

After short term stability study of the prepared films it was found that the characteristics of the films were remain same as it was earlier. There is no variation in release pattern and no microbial growth on the films was observed.

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