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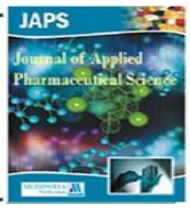

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Evaluation of Kollidon SR based Ketorolac Tromethamine Loaded Transdermal Film

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ABSTRACT

The present study concerns the development of polymeric films of Ketorolac tromethamine by solvent casting method to explore the possibilities of using kollidon SR as a transdermal drug delivery system. Ketorolac tromethamine was used as a model drug & incorporated in low doses. The films were prepared by using various amounts of Kollidon SR to prolong the drug release with localized action. Some films were also prepared containing certain percent of PEG-6000 along with the drug & polymer. The prepared polymeric films were evaluated for various parameters like weight uniformity, flatness, % elongation, surface pH, uniformity of drug content, in-vitro dissolution studies. The drug-polymer ratio was found to influence the drug release. The rate of drug release decreased with increased polymer concentration. About 10% increased in polymer concentration causes 50% decreased drug release. All the formulation followed Higuchian kinetics & the mechanism of release was diffusion mediated. When PEG-6000 was used as a channeling agent in this formulation drug release was increased accordingly but higher concentration of PEG-6000 results in decreasing release rate of drug because of increasing viscosity of the matrix channels.

Keywords: Ketorolac Tromethamine, Transdermal drug delivery system, Transdermal film, Kollidon SR, PEG-6000.

INTRODUCTION

Poor bioavailability due to hepatic metabolism (first pass) & the tendency to produce rapid blood level spikes (both high & low), leading to a need for high &/or frequent dosing, is produced by the most common form of delivery of drugs. To solve this problem emphasis is given to study alternative route of drug delivery. Although continuous intravenous infusion has been racognized as a superior mood of drug delivery because of bypassing the hepatic first pass elimination & maintaining a constant, prolonged, & therapeutically-effective drug level in the body, recently transdermal delivery (TDD) through intact skin is popularized because it pick out the benefits of intravenous drug infusion without its potential hazards (Chien YW;1992). Advances in the field of polymer science have paved the way for transdermal delivery system designs that have considerable flexibility. Kollidon SR is a hydrophobic polymer. It is generally used as a rate-retarding agent in matrix tablet formulations & other dosage forms (that is microcapsules, slow release beads etc). However, there are limited information for the use of Kollidon SR in TDDS, paying the attention on this area we have aimed to study the feasibility of this polymer to formulate TDDS. We also manipulated the drug release from the kollidon SR based film by incorporating various % of PEG-6000 in the formulation in present of kollidon SR. Ketorolac tromethamine (KT) is used here as a model drug. It is a non-steroidal anti-inflammatory

drug with potent analgesic effect. For the selection of this drug there also some reasons. If we considered the oral bioavailability of KT 90% with a very low first-pass metabolism, its short biological half-life (4-6hr) produces many adverse effects, such as upper abdominal pain and gastrointestinal ulceration which restricted oral administration (Reinhart DI, 2000). As a consequence, the concept regarding delivery of KT in the form of transdermal delivery has been suggested. The usual oral dosage regimen of KT is 10-20 mg 6 hourly for short-term management of moderate pain, & 15-30 mg i.m. or i.v. 4-6 hourly (maximum 90 mg/day) (Tripathi KD, 2003). To reduce the frequency of administration and to improve patient compliance & reduce severity of upper GI tract, a sustained release TDDS of KT is required. Although, here we used KT as a model drug but, the pharmaceutical & patient benefit scheme of the prepared TDDS cannot be overruled.

METHODS AND MATERIALS

Materials

Ketorolac tromethamine (KT) was received as a gift sample from Glove Pharmaceuticals Ltd. Bangladesh. Kollidon SR (polyvinyl acetate-polyvinyl pyrrolidone (BASF, Germany), PEG-6000 (BDH chemicals Ltd, Germany), Dichloromethane (Merck, Germany), Methanol (Merck, Germany), Potassium Dihydrogen phosphate (BDH, U.K.), Sodium hydroxide (Merck, Germany). All chemicals, reagents, solvents used were of analytical grade.

Methods

Preparation of the films

The matrix type transdermal patch containing Ketorolac tromethamine (KT) was prepared using different amount of Kollidon SR. A solvent casting technique was used for the preparation of the films. Accurate amount of drug & polymer were mixed & triturated well in a mortar-pestle. And then 5ml dichloromethane were poured into this mixture in a 25ml volumetric flask. After vortexing, the homogeneous mixture was poured into a petridish of 75mm diameter (Shah et al.;1992). The petridish was lubricating using paraffin wax for the easy removal of the films. The petridish was then kept in a clean room for solvent evaporation. After 24 hrs, the films were withdrawn from the petridish & were stored in a desiccator until further use. Films F1, F2, F3 were prepared using different amount of Kollidon SR only. Some other films F4, F5, F6 were also made where certain percent of PEG-6000 (i.e. 5.56, 11.11 & 16.67%) were used along with the drug & polymer (Table 1).

Table 1: Polymeric composition used in the formulation of transdermal films.

Formulation	F1	F2	F3	F4	F5	F6
KT	20	20	20	20	20	20
Kollidon SR	75	125	150	150	140	130
PEG-6000	-	-	-	10	20	30

Note: All the amounts are in mg unit.

Weight uniformity studies (Rhaghuram et al.; 2000)

The prepared patches were dried before testing. A specified area of patch (4 cm^2) was cut in different parts of the patch & weighed in the electronic balance. The average weight & standard deviation values were calculated from the individual weight.

The patch to patch weight uniformity was also measured in this work. This was carried out by individually weighing three randomly selected patches. Such determination was carried out for each formulation.

Flatness test

In this test three longitudinal strips were cut from each film at different portion like one from centre, other one from left side, & another one from right side. The length of each strip was measured, then it was kept for 2 hrs & then the variation in length because of non-uniformity in flatness was measured by determining percent constriction. It was determined from the below mentioned formula (Wade et al.; 1994).

$$\text{Flatness} = \frac{L_2 - L_1}{L_1} \times 100$$

Where

L_1 is the initial length of each strip and

L_2 is the final length of each strip

Percentage elongation test

In this test three longitudinal strips were also cut from each film at different portion like one from centre, other one from left side, & another one from right side. The length of each strip was measured, then it was pull from its two sides & then the percentage elongation break was determined by noting the length just before the break point. It was determined from the below mentioned formula (Lec et al.;1991).

$$\text{Elongation percentage} = \frac{L_2 - L_1}{L_1} \times 100$$

Where

$L_1$is the initial length of each strip and

L_2 is the final length of each strip

Surface pH studies

Surface pH studies were carried out for each formulation of films. For this purpose the film was cut into 4 cm^2 pieces from different places of the test film. This piece of film was then immersed in the buffer pH 7.4. After a few minutes it was put up from the medium & then P^H value of the wet film was measured by pH meter (Electrode Hanna instruments pH 210) (Bottenberg et al.; 1991).

Drug content studies

Drug content studies were conducted for all prepared batches of films. For this purpose the film was cut into 4cm^2 pieces from different places & was weighed accurately. The 4cm^2 films was then cut into small pieces & were taken in a 10ml volumetric flask. And then 5ml methanol was added. The films were dissolved completely by vigorous shaking. Required amount water was added to adjust the volume upto 10ml. After shaking, the mixture was filtered. Then 1ml of the filtrate was diluted 10 times by distilled water. A blank was prepared using a drug free patch treated similarly. Finally absorbance of the samples was measured by a Shimadzu UV spectrophotometer at 322nm (Costa et al.; 1997).

In-vitro release studies

For the preparation of Phosphate buffer pH 7.4, potassium Dihydrogen phosphate 0.68gm was diluted to 1000ml with distilled water. Sodium hydroxide was used to adjust pH. The USP apparatus II (paddle method) was used for the assessment of the release of drug from the patch. The dry films was cut in $4cm^2$ size, weighed, & fixed over a glass plate. As a result drug was released only on one direction. The glass plate was then placed in a 500ml of the dissolution medium i.e. phosphate buffer p^H 7.4 & the apparatus was equilibrated to 32 ± 0.5^0C. The paddle was then set at a distance of 2.5 cm from the glass plate & operated at a speed of 50 rpm. 5ml of sample was withdrawn at appropriate time interval upto 7 hrs by means of a syringe & replaced by same quantity of fresh phosphate buffer. Then amount of Ketorolac released was determined spectroscopically at 322nm.

The results of in-vitro release profile obtained for all the KT formulations were analyzed with different kinetic model for the assessment of actual drug release mechanism. These are first order kinetic model, zero order kinetic model, Higuchi model (Higuchi T, 1963), korsmeyer-peppas model (Peppas, 1985).

Statistical analysis

Values are presented as mean ± SEM. Student's t-test was applied to describe the statistical significance and $p < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Physicochemical parameter

Whole weight of the film was analyzed. It was seen that the uniform weight was maintained in each formulation which was confirmed from the SEM value of each formulation. The petridish with 75 mm diameter was used for the preparation of the film. Five pieces of $4cm^2$ was cut from different site of each film & was analyzed for weight uniformity & result showed that good uniformity of weight among the formulation was performed. The average weight & SEM value are summarized in the Table 2.

Table 2. Physicochemical evaluation of transdermal patch.

Code	Whole weight(mg) ±SEM	Weight(mg) ±SEM($4cm^2$ film)	Drug content(mg/ml) /$4cm^2$ film ±SEM	Flatness (%)	Elongation(%)±SEM	Surface pH±SEM
F1	96.44±0.78	9.152±0.41	1.19±0.173	100	32.25±7.38	6.79±0.069
F2	151.62±2.16	15.43±0.82	1.37±0.051	100	30.24±10.29	6.77±0.064
F3	165.27±1.28	16.572±0.83	1.341±0.061	100	28.62±3.405	6.837±0.003
F4	175.18±0.03	16.52±0.55	1.456±0.087	100	19.97±2.99	7.087±0.023
F5	184.59±2.69	16.56±0.38	1.48±0.046	100	8.76±1.468	6.79±0.006
F6	176.92±0.57	16.408±0.75	1.31±0.173	100	7.2±1.89	6.98±0.003

The drug content of three pieces of film ($4cm^2$) of each formulation was analyzed. The formulated patches were smooth, uniform and flexible. The drug is uniformly distributed throughout the patch. Flatness of each longitudinal strip was calculated & the result was 0% constriction i.e. 100% flatness. It means there is no possibility of variation of length due to non-uniformity of flatness. The results are given in Table 2.

The percentage elongation of three longitudinal strips of each formulation was measured & it was observed that with the increase of polymer amount there was negligible increase of % elongation. The percentage elongation for PEG-6000 loaded formulation was found to be very insignificant. Value of percentage elongation was decreased after addition of plastic material. Surface pH of three pieces from each formulation was measured & it was observed that all formulation was almost close to neutral pH i.e these will be safe & non-irritating. The results are summarized in Table 2.

In-vitro dissolution studies

In-vitro dissolution studies of the prepared transdermal films shows that the polymer imparts sustaining action on drug release from the film. With the increase of amount of polymer in formulation F1, F2, F3, the release rate of drug was retarded. The drug release from formulation F1 was 94.46% in 5 hrs when it was 44.60% for F3 in 7hrs. In formulation F1 & F2, initial rapid release were observed, gradually approaching constant values for the rest of the time, thus confirming to the controlled released behavior of the formulation. The water soluble part of Kollidon (povidone) is leached out to form pores through which the active ingredient slowly diffuses outwards (BSAF SE, 2008). Brust effect might be due to the initial migration of the drug towards the surface of the matrix (Pratibha, Anikurma, Atul, 2010).

A modification was made on film F3 (88.24% polymer) with the addition of 5.56% PEG-6000 (F4). Generally, incorporation of a water soluble excipients results in a increase in the drug release rate due to an increment in total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug) (Boza et al.; 1995). It was observed that the release of drug was increased from 44.60% to 85.42% due to incorporation of PEG-6000 which act as a channeling agent. But in formulation F5 contains 11.11% of PEG-6000 & 77.78% of polymer, the drug release was 55.98% after 7hr. For formulation F6 the release rate was 39.48% containing 16.67% PEG-6000 & 72.22% Kollidon SR. The sudden decrease of release of drug is due to progressive dissolution of PEG-6000 which yields an increase in viscosity of the matrix channels acting as a barrier that decrease the drug release rate (Holgado et al.; 1995). One of the disadvantages of Polyethylene glycols are the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol (Raymond, 2006). KT is a water soluble drug & molecular weight of PEG-6000 is 7300-9300 (20), for that in these formulation PEG-6000 is act as release retardant. On the otherhand Kollidon SR is also a release retardant, as a results PEG-6000 synergistically reduces release. The study of drug release kinetics by zero order, first order, Higuchi, Korsmeyer-peppas & Hixson-crowell equation (Table 3) showed that formulations F1 & F2 were governed by Korsmeyer-Peppas model & F3 was followed by Higuchi kinetic model & also formulation F4, F5, F6 followed Korsmeyer-peppas model. To confirm the release pattern release

Table 3. Drug release kinetics for various formulation of transdermal film.

Code	Zero order		1st order		Higuchi		Korsmeyer-peppas		Hixson-crowell	
	R^2	K_0	R^2	K	R^2	K_H	R^2	n	R^2	K_{HC}
F1	0.967	12.32	0.808	0.656	0.957	38.73	0.980	0.360	0.421	-0.350
F2	0.814	7.044	0.657	0.621	0.873	23.45	0.958	0.270	0.323	-0.270
F3	0.901	5.494	0.855	-0.081	0.984	18.51	0.890	0.893	0.606	-0.351
F4	0.282	5.201	0.487	-0.149	0.510	20.20	0.810	0.082	0.169	-0.212
F5	0.543	4.663	0.689	-0.076	0.758	15.91	0.95	0.152	0.249	-0.210
F6	0.601	0.601	0.681	-0.041	0.784	10.48	0.907	0.163	0.267	-0.194

exponent (n) was calculated from Korsmeyer-peppas model & it was observed that F1 & F2 was Fickian diffusion mediated & F3 was Non- Fickian diffusion mediated i.e. increase in the polymer proportion caused increasing of release exponent (n), indicating the shifting of release mechanism. Release mechanism of F4, F5, F6 was Fickian diffusion mediated.

Figure 3(a,b) shows the overall effect of polymer (Kollidon SR) & PEG-6000 on the release rate of drug from the transdermal film. From this figure it can be clearly identified that increasing of polymer decreasing drug release & addition of PEG-6000 increase release rate but in higher concentration decreases release of drug.

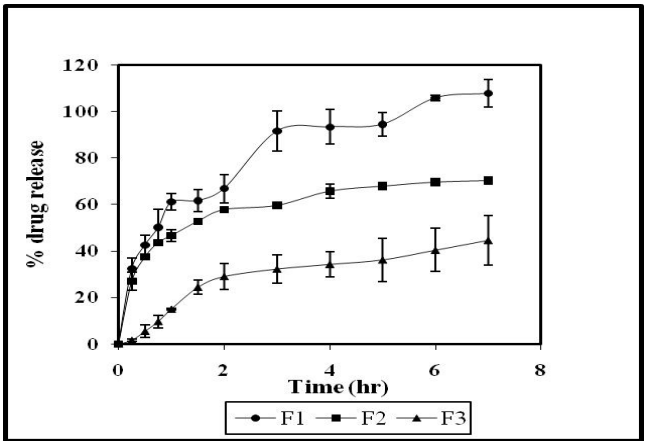


Fig 1. In-vitro release profile (Zero order plot) of KT from transdermal patches with different proportions of kollidon SR

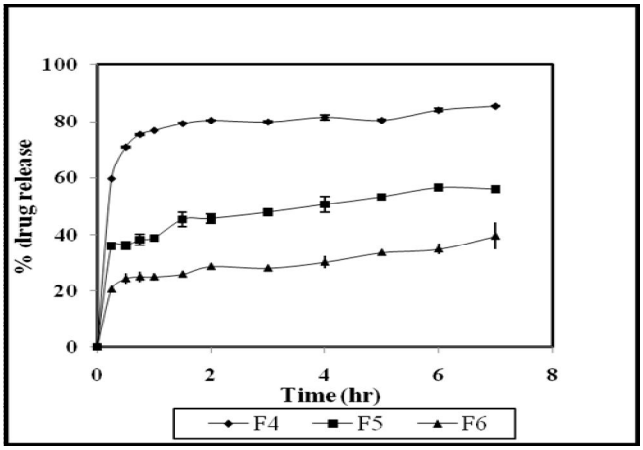
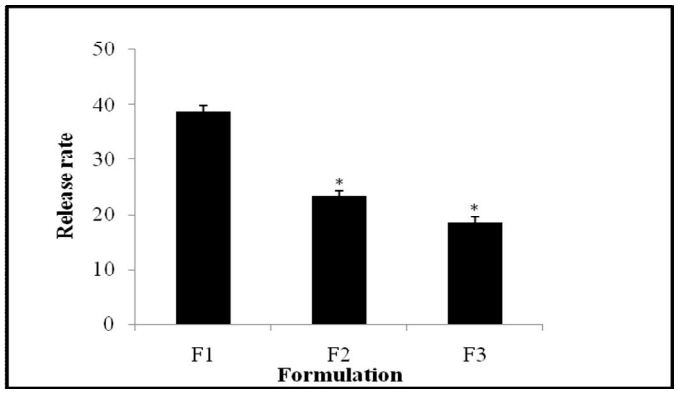


Fig 2. Drug release (Zero order plot) from PEG incorporated Kollidon SR based



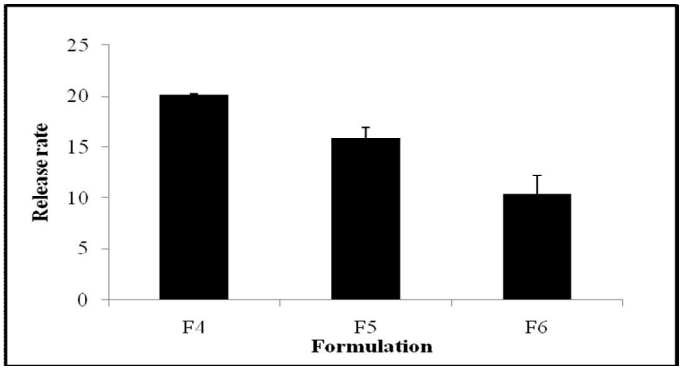


Fig 3. Bar diagram showing effect of polymer content on release rate (Higuchian release) (a) formulation without PEG, (b) formulation with PEG. P<0.05 compared with F1.

CONCLUSION

The present study reveals that the polymeric compositions of transdermal film affect its pharmacotechnical properties & it is possible to design sustain release TDDS with Kollidon SR. Drug release was significantly increased by incorporating PEG-6000 in to the formulation as channeling agent. It was also observed that incorporation of high amount of PEG-6000 decreases drug release. However, further investigation is required to establish in-vivo-in-vitro correlation to confirm the accurate pattern of drug release & permeation in in-vivo environment from these polymeric systems. Thus extensive studies on the prepared films would be required for the development of a transdermal drug delivery patch, using a suitable adhesive layer & backing membrane, for potential therapeutic use.

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