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Formulation and Evaluation of Sustained Release Matrix Type Transdermal Film of Ibuprofen

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Abstract

The present study was undertaken to investigate the effect of different polymers on the release profile of Ibuprofen from the matrix type transdermal film. Transdermal films of Ibuprofen using Eudragit L 100, Kollidon SR and their combination were separately prepared by solvent casting method. Drug release was evaluated for eight hours and the release mechanisms were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The release rate, extent and mechanisms were found to be independent of the polymer concentration in case of Eudragit L 100. But those were found to be directed by polymer concentration for formulations containing Kollidon SR and the combination of Eudragit L 100 and Kollidon SR. Higher polymer content in the matrix decreased the rate and extent of the drug release because of increased matrix strength and gel formation around the matrix particularly for these formulations containing Kollidon SR. On the other hand, a burst drug release was obtained from films containing Eudragit L 100, while the combination of Eudragit L 100 and Kollidon SR gave an intermediate release profile of Ibuprofen from the transdermal films. Proper adjustment of these polymers in the transdermal film of ibuprofen can offer desirable release characteristics.

Key words: Transdermal film, solvent casting, release kinetic, flatness and rate retardant.

Introduction

Being the largest organ of our body, skin plays an important role by offering selective entrance of molecules and preventing access of noxious matters through it though having nano level of span. Therefore, the administration of drug particles topically has attracted researchers for developing an effective and suitable drug delivery system. Transdermal drug delivery system possesses several advantages over conventional schemes. Common limitations of oral drug delivery like first-pass metabolism, gastric irritation and variable rates of absorption can be easily avoided by this system. Rather transdermal drug delivery is often comparable to continuous intravenous infusion for some cases of systemic medications.

Ibuprofen has been rated as the safest conventional NSAID by "spontaneous adverse drug reaction reporting systems" in the UK (Rabia and Nousheen, 2010) and it is the drug of choice in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body, for which a constant and uniform supply of drug is desired (Sudhamani *et al.,* 2010). After oral administration, Ibuprofen is extensively metabolized in the liver and because of its short biological half-life, the drug has to be administered frequently. Whereas the topical application allows a higher local concentration of the drug at the site of the pain and lower or negligible systemic drug levels producing fewer or no adverse drug effects (Reddy *et al.,* 2011). Transdermal delivery certainly appears to be an attractive route of administration to maintain the blood levels of ibuprofen preferably for an extended period of time.

NSAIDs had been in first line of choice for transdermal drug delivery system for a long time due to their improved local effects and possibility to avoid the gastro-irritating effects. Previously different researches were done on naproxen sodium by Masuda *et al.,* (2004), ketoprofen by Barhate *et al.,* (2009), ketorolac tromethamine by Fetih *et al.,* (2011) etc. In case of Ibuprofen, various researches have been carried out. Reddy *et al.,* 2011 has investigated the *in vitro* release of ibuprofen from different topical vehicles. Sudhamani *et al.,* (2010) reported on ibuprofen loaded maltodextrin based proniosomes and Ghosh *et al.,* (2010) studied on

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transdermal delivery of ibuprofen and its prodrugs by passive diffusion and iontophoresis. Along with these, transdermal gel and patches of ibuprofen were also formed by Bazigha *et al.,* (2010) and Thushara *et al.,* (2011), respectively. But works on transdermal film of ibuprofen characterized by rate controlling property are not still adequate though it would be highly effective in pathologic conditions to which ibuprofen is indicated. The present study involves formulation of topical transdermal film of ibuprofen and evaluation of the rate retarding ability of different polymers on the film.

Materials and Methods

Materials: Ibuprofen and Eudragit L 100 were collected from ACI Pharmaceuticals Ltd. Kollidon SR, PEG 6000 and Methanol were found from Renata Ltd, Bangladesh as kind gift. All other ingredients were of analytical grade and collected from local market.

Preparation of the films: The matrix type transdermal film containing ibuprofen was prepared with different amount of Eudragit L 100, Kollidon SR and their combination by solvent casting technique. (Rita and Mohammad, 2011). Accurate amount of drug, polymer and other ingredients (as per Table 1) were mixed in a 50 ml volumetric flask containing 20 ml of methanol. After vortexing the homogenous mixture was poured into a petridish (90 mm diameter lubricated previously using minute amount of magnesium stearate and glycerin for the easy removal of the films. The petridish was then kept in a clean room for solvent evaporation and after 48 hours, the films were withdrawn from the petridish and were stored in a desiccator until further use.

Table 1. Composition of different formulation for transdermal films of ibuprofen (in gm).

Ingredients	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12	F 13
Ibuprofen	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Eudragit L 100	1.0	1.1	1.2	1.3	1.4	1.5	-	-	-	-	1.5	1.5	1.5
Kollidon SR	-	-	-	-	-	-	0.8	0.9	1.0	1.1	0.9	1.0	1.2
PEG 6000	1.5	1.5	1.5	1.5	1.5	1.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tween 80	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Determination of thickness of the film: Thickness of the transdermal films was determined by a slide caliperse at three different positions of the film to assess the uniform distribution of the content.

Weight uniformity studies: A specified area of patch (4 cm^2) was cut from different parts of the film and weighed with an electronic balance. The average weight and standard deviation values were calculated from the individual weight.

Flatness test: Three longitudinal strips were cut from each film at different portion like one from centre, other one from left side and another one from right side. The length of each strip was measured, then it was kept for 2 hours and then the variation in length because of non-uniformity in flatness if any was measured by determining percent constriction by using formula given below (Rita and Mohammad, 2011):

Flatness = $(L_2 - L_1) / L_1 \times 100$

where L_1 is the initial length of each strip and L_2 is the final length of each strip.

Assay of transdermal films: Accurately weighted 12.6 mg of pure drug was dissolved in 100 ml of methanol to prepare the standard solution and it was then suitably diluted. Equivalent to 12.6 mg of drug, 4 cm^2 of each film was dissolved, diluted suitably and filtrated. USP-33 suggests the assay of dissolution samples of Ibuprofen Tablets at 221 nm on UV Spectrophotometer. Therefore the standard and sample solutions were then analyzed on UV Spectrophotometer at 221 nm wavelength. The amount of drug loading was then calculated by comparing the absorbances according to the Beer-Lambert's law.

In vitro dissolution studies: In vitro drug release studies of the film was conducted for a period of 8 hours using a six station USP XXII type I apparatus equilibrated at 37 ± 0.5º C and 50 rpm. The dissolution studies were carried out in 900 ml of 7.4 phosphate buffer under sink condition. At every 15 minutes interval on the first hour and then every one hour interval, an aliquot of 10 ml was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After

filtration and appropriate dilution, the sample solution was analyzed at 221 nm by an UV spectrophotometer (Shimadzu, Japan). The amount of drug released at different hour intervals was calculated by comparing with previously prepared standard curve of ibuprofen in 7.4 phosphate buffer medium.

Kinetic modeling of drug release: Different kinetic models (zero-order, first-order, Higuchi's equation and Korsmeyer's equation) were applied to interpret the drug release kinetics from matrix type transdermal film with the help of Equation 1- 4.

$M = M_o - K_o t$ ... ... (I)

$In\ M = In\ M_o - K_1 t$ ... ... (II)

$Q = K_h \sqrt{t}$ ... ... (III)

$M_t / M_\alpha = K_k t^n$ ... ... (IV)

To characterize the drug release rate in different experimental conditions, MDT (mean dissolution time), $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ values were calculated from dissolution data according to the following equations:

$T_{25\%} = (0.25/k)^{1/n}$

$T_{50\%} = (0.5/k)^{1/n}$

$T_{80\%} = (0.8/k)^{1/n}$

Mean Dissolution Time can also be calculated by the following equation (Mockel and Lippold, 1993):

$MDT = (n/n+1).\ K^{-1/n}$

Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A higher value of MDT indicates a higher drug retaining ability of the polymer and *vice-versa*. The MDT value was also found to be a function of polymer loading, polymer nature and physico-chemical properties of the drug molecule.

Results and Discussion

All the formulations were found to be able to produce transparent to colorless flexible films. The thickness and weight of different sites of the film were found to have good results having a limited deviation at each measurement. The calculated drug loading obtained from the drug content test yielded a satisfactory result ranging from 95.87% - 99.84% of the theoretical drug distribution (Table 2).

Table 2: Physicochemical evaluation of transdermal films.

Formulation	Thickness (mm)	Weight (g) (Pieces of 4 cm^2)	Theoretical drug loading in 4 cm^2	Calculated drug loading in 4 cm^2	Flatness (%)
F 1	0.65 ± 0.05	0.19 ± 0.05	12.60	12.30	100.0
F 2	0.65 ± 0.05	0.23 ± 0.03	12.60	12.21	100.0
F 3	0.63 ± 0.05	0.26 ± 0.02	12.60	12.11	99.8
F 4	0.65 ± 0.05	0.26 ± 0.02	12.60	12.48	100.0
F 5	0.62 ± 0.05	0.29 ± 0.03	12.60	12.08	100.0
F 6	0.65 ± 0.05	0.36 ± 0.05	12.60	12.49	100.2
F 7	0.33 ± 0.03	0.11 ± 0.02	12.60	12.53	100.0
F 8	0.32 ± 0.03	0.12 ± 0.02	12.60	12.12	100.1
F 9	0.35 ± 0.03	0.11 ± 0.02	12.60	12.35	100.3
F 10	0.33 ± 0.03	0.13 ± 0.03	12.60	12.31	100.0
F 11	0.73 ± 0.05	0.39 ± 0.03	12.60	12.46	100.0
F 12	0.75 ± 0.05	0.36 ± 0.02	12.60	12.58	100.0
F 13	0.75 ± 0.05	0.38 ± 0.03	12.60	12.31	99.9

In vitro drug release profile obtained for formulations containing Eudragit L 100 showed rapid drug releasing characteristics of each formulation. In all these cases, a burst release of ibuprofen occurred (Table 3). No significant change in cumulative percent release was found when the polymer concentration was increased in the films. So it can be stated that Eudragit L 100 does not have any rate retarding effect on Ibuprofen in transdermal films. Similar findings were observed by Vijaya *et al.* (2011) who found more than 90% release within 40 minutes from a transdermal film of amitriptyline hydrochloride prepared with Eudragit L 100. This may be due to the fact that the polymer has got high solubility at higher pH value. Eudragit L 100 is comprised of copolymers of methacrylic acid and ethyl acrylate that form salts with alkalis at higher pH. Thus, films prepared by the copolymers disappear above pH 5.5 and open a gateway for the drug to be dissolved.

In case of formulations containing Kollidon SR, *in vitro* dissolution studies of the prepared transdermal films showed that the polymer was capable to sustain drug release from the film particularly for the formulations F 7, F 8, F 9 and F 10. The release rate decreased upon increase of the polymer concentration in the film. At 30

minutes time point, formulations F 7, F 8, F 9 and F 10 showed a cumulative percent release of 54.50%, 35.57%, 33.75% and 33.37%, respectively at an increasing order of only 0.1 g of polymer in the film. The differences became more unambiguous as the time progresses. At three hour time point, the cumulative percentage of release was found to be 90.58%, 67.41%, 55.96% and 48.97% for those formulations respectively. So the rate of release of drug decreased as a function of increasing the polymer content. All the determinant ($T_{25\%}$, $T_{50\%}$, $T_{80\%}$ and mean dissolution time represented the same (Table 4). Similar findings were observed by Rita and Mohammad(2011) who observed the gradual rate retarding effect of ketorolac tromethamine from transdermal film prepared with Kollidon SR at increasing order.

Table 3. Cumulative percent release of formulations containing Eudragit L 100.

Time (Min)	Cumulative Percent Release					
	F 1	F 2	F 3	F 4	F 5	F 6
0	0.00	0.00	0.00	0.00	0.00	0.00
15	73.26	80.07	75.53	80.23	78.79	78.07
30	75.68	82.89	78.19	82.95	80.94	80.88
45	78.61	84.69	80.49	85.14	83.82	83.04
60	81.02	86.88	82.58	87.23	86.95	86.1
120	83.66	88.71	85.03	89.05	89.49	88.64
180	86.49	91.31	87.82	91.33	91.72	90.69
240	88.90	93.50	90.46	93.40	93.80	92.75
300	91.55	95.13	93.12	95.26	95.56	95.38
360	94.71	96.84	95.42	96.91	97.21	97.04
420	96.74	98.33	97.89	98.51	98.64	98.64
480	99.27	99.77	99.94	99.9	99.92	99.97

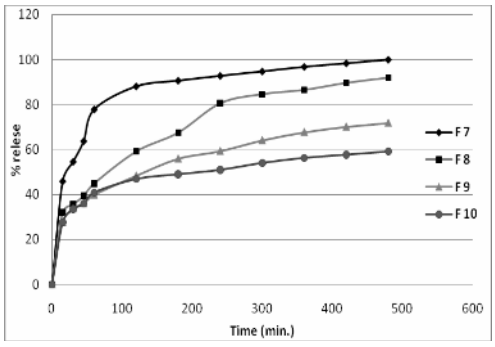

Figure 1. *In vitro* release profile (zero order plot) of ibuprofen from transdermal films with different proportions of Kollidon SR.

When the Eudragit L 100 was combined with rate retarding Kollidon SR in the formulation, Kollidon SR was found to be capable of retarding the rate of drug release. But the retarding capacity decreased when it was combined with Eudragit L 100. It was observed when the release characteristics of F 6 were compared with that of the formulations F 11, F 12 and F 13. The quantity of Eudragit L 100 was maintained same in the formulations to find the difference in the release pattern caused by Kollidon SR alone. Previously the formulations containing only Eudragit L 100 (F 1 - F 6) showed no rate retarding effect, but in combination with an effective rate retarding polymer, Kollidon SR, Eudragit L 100 diminished the rate controlling ability of Kollidon SR. Equal quantity of Kollidon SR caused 67.41% and 55.96% release after three hours in the formulation F 8 and F 9, respectively when incorporated alone in the transdermal films while 83.22% and 79.38% release at the formulation F 11 and F 12, respectively when used in combination with Eudragit L 100. Further increment of Kollidon SR in F 10 showed a little more retarding effect. Similar findings were found from the comparison of successive dissolution values and MDT of the formulations containing Kollidon SR alone and in combination with Eudragit L 100.

Table 4. Successive fractional dissolution and MDT values (in hour).

Formulation	T 25%	T 50%	T 80%	MDT
F 6	Very small	Very small	0.41	0.64
F 7	0.01	0.25	2.15	1.07
F 8	0.16	1.22	4.86	2.38
F 9	0.18	2.13	11.27	5.47
F 10	0.13	3.39	31.42	15.76
F 11	0.11	0.81	3.22	1.57
F 12	0.12	0.96	3.87	1.89
F 13	0.27	2.13	8.55	4.18

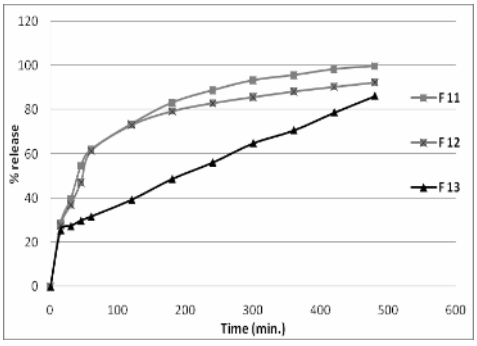

Figure 2. *In vitro* release profile (zero order plot) of Ibuprofen from transdermal films with combination of Kollidon SR and Eudragit L 100.

To know the mechanism of drug release from these formulations, the data were treated in different orders and the correlation coefficient (R^2) values and release

exponents are summarized in the Table 5. All formulations (F 7 - F 13) that showed delayed drug release were found to best fit with Korsmeyer model having R^2 values in the range of 0.945 - 0.997. The lower release exponent (n) values of these formulations obtained from the Korsmeyer plot indicated that Fickian diffusion was the dominating release mechanism. It might be caused due to the viscous gel formation by the polymer around the film and slowed down the rate of drug diffusion through the gel layer. For all the formulations prepared with Kollidon SR alone or in combination with Eudragit L 100, initial rapid release were observed, that gradually approached to constant values for the rest of the time, thus confirming the controlled released behavior of the formulation. The water soluble part of Kollidon (povidone) cought be leached out to form pores through which the active ingredient slowly diffuses outwards. Burst effect might be due to the initial migration of the drug towards the surface of the matrix (Pratibha *et al.* 2010).

Table 5. Drug release kinetics for various formulations of transdermal films.

Formulation	Zero Order		Higuchi		First Order		Korsmeyer	
	Ko	R^2	K_H	R^2	K_1	R^2	n	R^2
F 6	0.091	0.329	2.744	0.528	-0.124	0.967	0.090	0.955
F 7	0.131	0.591	3.648	0.805	-0.008	0.881	0.218	0.945
F 8	0.156	0.831	3.998	0.965	-0.006	0.975	0.340	0.984
F 9	0.111	0.786	2.903	0.941	-0.005	0.983	0.282	0.997
F 10	0.079	0.648	2.166	0.846	-0.002	0.875	0.211	0.987
F 11	0.162	0.741	4.288	0.919	-0.004	0.968	0.340	0.987
F 12	0.147	0.710	3.937	0.898	-0.002	0.971	0.336	0.983
F 13	0.138	0.890	3.437	0.980	-0.001	0.981	0.338	0.992

Conclusion

The matrix type transdermal film of Ibuprofen was prepared successfully by using two different polymers and their combination by solvent casting method. From the *in vitro* drug release data it can be concluded that controlled release of Ibuprofen from the film could be achieved for prolonged period. Further works can be proceeded to predict the *in vivo* performance of these formulations.

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