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Research studies on polymeric effect of indomethacine transdermal films

Subash. S. Pillai*[1], K.L.Senthil Kumar[1], T.Panneerselvam[2], A.R.Shabaraya[2], T.K.Muneer[3]

[1]Department of Pharmaceutics, Prist University, Thanjavur, Tamilnadu, India
[2]Dept. of Pharmacy, Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India
[3]Department of Pharmaceutics, M.S.R. College of pharmacy; Bangalore, Karnataka, India
Corresponding author email- subashpillai79@rediffmail.com

The objective of this study was to design and evaluate transdermal patches of Indomethacine using HPMC, EC and Eudragit RLPO using solvent casting technique. The *in vitro* drug release studies were performed by using the USP (paddle type) dissolution list apparatus in 1000 ml of 0.1N HCl (Medium Employed) at 37° C room temperature for an rpm maintained at 100 within a stipulated time interval of 15 minutes. The withdrawn Samples were analyzed by using UV visible spectrophotometer at 268 mm using regent blank. The prepared transdermal patches had undergone physic chemical evaluator parameters such as PMA, PML, swelling index, water vapour transmission rate, film thickness, weight cheek, and folding Endurance and drug content clearance. *In vitro* dissolution study of drug along with different combination of polymers; i.e. HPMC, EC and Eudragit has been performed; out of which batch B6 shows the best moisture of films and the graph representing the best controlled drug release. As the percentage of ethyl cellulose was reduced the rate of the release of the drug was increased. [Batch B6 > HPMC: EC: Eudragit RLPO - 2:1:2]. Films with batch code B6 shows better stability and suitability. Higuchi's plot revealed that the predominant Mechanism of drug release was diffusion

Key Words: Indomethacine, Eudragit RLPO, Controlled release, Fabrication solvent casting technique.

Sustained release, sustained action, prolonged action, controlled release extended action, timed release, depot and repository dosage forms are certain terms used to identify drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing Medication over our extended period of time after administration of a single dose. The term controlled release has become associated with that system from which therapeutic agents may automatically delivered at pre-defined rates over as long period of time products of this type have been formulated for oral, injectable and topical use, and include insets for placement in body cavities as well.

The terms transdermal drug delivery system includes all topically administered drug formulation intended to deliver the active ingredient into the general circulation (A1Saidan 2004). Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drug via spleen to the systemic circulation. The ideal characteristic of TDDS involves.

- ⇨ NON-irritant
- ⇨ Small and flexible
- ⇨ Absence of problem.
- ⇨ Reliability

- ⇨ Capacity
- ⇨ Targeting
- ⇨ The polymer must not decompose on storage or during shelf life.
- ⇨ The cost of the polymer stoned be weigh
- ⇨ It should adhere quickly to moist tissue and should possess some site specificity.
- ⇨ Agent independent.

The transdermal drug delivery systems are designed to support the passage of drug substances from the spleen to the systemic circulation (Benowitz 1992). The basic components of device include polymers matrix, drug, excipients and adhesives packaging.

Materials and Methods

The Present work was performed to prepare and evaluate Transdermal patches of Indomethacine. It was carried out as follows.

- ⇨ Casting of plain transdermal patches.
- ⇨ Preparation of drug incorporated polymeric films.
- ⇨ Physico-chemical evaluation of transdermal patches which includes Percentage moisture absorption, percentage moisture loss, swelling index, time taken for swelling, water yapour transmission rate, thickness, weight uniformity and folding endurance.*In vitro* diffusion studies of transdermal patches.

Standard curve for indomethacine

Primary stock solution

Indomethacine of 100mg was accurately weighed and dissolved in water to obtain 100ml of solution with a concentration of 1000mcg/ml (**Table 1**).

Table 1. Standard curve data for indomethacine

Concentration [mcg/ml]	Absorbance
1	0.008
2	0.014
3	0.018
4	0.024
5	0.028
6	0.034
7	0.040
8	0.046

Secondary stock solution

1 ml of primary stock solution was diluted to 100ml with water to get a concentration of 10mcg/ml from the secondary stock solution aliquots ranging from 1ml to 8ml were pipette out and dilute to 10ml with water to get the concentration range of 1mcg/ml to 8mcg/ml. The absorbances were measured at 296 nm and the values are determined.

Table 2 Composition of formulation

Batch code	Polymers			Solvent	Plasticizer
	HPMC KAM %	EC %	Eudragit RLPO %	Chloroform (ml)	Glycerine % w/w
B1	1	1	1	2.5	30
B2	2	1	1	2.5	30
B3	1	2	1	2.5	30
B4	1	1	2	2.5	30
B5	2	2	1	2.5	30
B6	2	1	2	2.5	30
B7	1	2	2	2.5	30
B8	2	2	2	2.5	30

Concentration of plasticizer = 30% w/w; Amount of drug loaded in each film 10 mg
1% w/v = 50 mg; 2% w/v = 100 mg; 3% w/v = 150 mg

Solvent casting technique

The films were prepared by the method of solvent casting technique (Cevc 2003). Fabrication of drug reservoir films with hydroxy propyl methyl cellulose, ethyl cellulose and Eudragit. Accurately

weighed quantity of hydroxy propyl methyl cellulose, Hydroxy propyl ethyl cellulose and Eudragit of composition of different formulations get mixed with 10mg of Indomethacine. Then add 2.5ml distilled water. Then there solutions were mixed to get a clear solution. Glycerin was added as plasticizer. Then it was poured over the mercury surface in a petridish and allowed to dry at room temperature (**Table 2**).

Table 3 ***In vitro*** **drug release data for batch-6**

Time in minutes	Square root of time	Cumulative drug release [%]
5	2.236	25.93
10	3.612	58.13
15	3.873	72.43
20	4.472	88.08

Physico–chemical evaluation

Percent moisture absorption

The percent moisture absorption tests were carried out to check the physical stability of the transdermal films at high humid condition (Florance 1994). In the Present Study; the Moisture absorption capacities of the film were determined as follows. Three 1.00 cm diameter films were cut out and weighed accurately, and allow the films to keep in a desiccators containing saturated solution of aluminums chloride, keeping the humidity inside the desiccators, at 79.5% the films were removed after 3 days. Weigh it and the percentage moisture was calculated average percentage moisture of three films was found.

Percentage moisture loss

This test was also carried out to check the integrity of films at dry condition. Three 1.00cm diameter films were cut out and weighed accurately and kept in a desiccators containing fused anhydrous calcium chloride (Rim 2005). After 72 h the films were removed and weighed. Average Percentage Moisture Loss of three films was found out.

Percentage Moisture Loss = [(initial weight final weight) / initial weight] x 100.

Swelling index

Three films are taken each batch and it is put in pH 6.6 phosphate buffer and the weight is measured every three minutes; till the weight becomes constant.

Water vapour transmission rate

For water vapour 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 of anhydrous calcium chloride was taken in the cells and the polymer films were fixed over the brim with the help of the solvent (Riciere 2001). The cells were accurately weighed; kept in a closed desiccators containing saturated solution of KCl to maintain humidity of 84% RH. The cells taken weighed after 6, 12, 24,36 ,48, 72 h of storage. The amounts of water vapour transmitted were found using the formula.

Water vapour Transmission Rate= Final weight - initial weight/ time × Area

Water vapour Transmission Rate is usually expressed as the number of grams of moisture grams / h /sq from the data obtained, water vapour Transmission rate was calculated.

Thickness

Thickness of the films were measured at six different points using a screw gauge and average thickness of three films were found out.

Weight of films

Each film was weighed individually and average weights of three films were found out.

Folding endurance

It was determined by repeatedly folding a small strip of film at the same place, till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance (Prausnitz 2004).

Drug content

A film size of 1cm was cut and dissolved in phosphate buffer. After adding suitable reagent and dilution, optical density was found out at 269nm. The average drug content of the three buccal films was determined.

***In vitro* drug release studies for indomethacine**

Here, dissolution test apparatus USP [Paddle type] was employed throughout the study. The medium employed was 0.1N HCl at 37^{o} C room temperature. The dissolution was carried out at an rpm maintained at 100 within a stipulated interval of 15 minutes (Jain 2003).

A film of size diameter was cut and introduced into the cylinder filled with equal quantity of 0.1n HCL as the medium (Vavrova 2005). Samples of 10ml were withdrawn at every 15 minutes duration for continuous 2 h. The volumes of sample withdrawn were replaced by the same volume of dissolution medium (Nicoli 2001). Filter the above sample and then taken 5ml from each sample and made at 50ml with the medium. The withdrawn samples were analyzed by using visible-UV- spectrophotometer at 269nm using reagent blank (**Table 3**).

Results and Discussion

In the present study, the transdermal patches of indomethacine were prepared by using different polymers such as HPMC KAM, EC and Eudragit RLPO by solvent casting technique. *In vitro* dissolution study of drug along with different combination of polymers HPMC, EC and Eudragit RLPO has been performed. The higher rate and percentage of release of drugs in film containing less concentrations of EC in batch B-6 [HPMC: EC: Eudragit]-2:1:2] has been performed. As the percentage of EC was reduced, the rate of release of drug was increased. Hence moreover; the batch B-6 shows the best moisture of films and the graph representing the best sustained drug release. Film with batch code B-6 shows better stability and suitability.

Conclusion

The formulation B-6 containing 2 parts of HPMC, 2 parts of Eudragit and 1part of EC has shown best release in concentration independent manner. Higuchis plot revealed that the predominant mechanism of drug release is diffusion. Hence the formulation B-6 achieved the objectives of present study such as reducing the dose, improving bioavailability by avoiding first pass metabolism and it may have better patient compliance.

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