PREPARATION AND EVALUATION OF CELECOXIB TRANSDERMAL PATCHES

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ABSTRACT

Celecoxib Transdermal patches were prepared by using different polymers such as hydroxyl-propylmethylcellulose (HPMC), methylcellulose (MC), Polyvinylpyrolidone (PVP).The *in-vitro* release of the drug from the formulations were studied using commercial semi permeable membrane. The prepared formulation were subjected to various physicochemical evaluation test, *in-vitro* dissolution studies, kinetics studies shows diffusion might be one of the prominent mechanism influencing the drug release. To confirm the fact Peppa's plot was drawn, which confirmed that the diffusion mechanism involved in the drug release was of non fickian diffusion type. *ex-vivo* diffusion studies by using rat skin, guinea pig skin & pig ear skin and finally *in-vivo* evaluation studies (the patch F4 HPMC 0.75%, PVP 0.25%) were carried out by using rabbits.

Keywords: Transdermal patches, celecoxib, polymer.

INTRODUCTION

During the last decade, controlled release concept and technology have received increasing attention in the face of growing toxicity and ineffectiveness of drugs when administered or applied by conventional methods (Harvinder Popli *et al.,* 1990). A controlled release drug delivery may be defined as a system that implies a predictability and reproducibility in the drug release kinetics (Chien, Yie, 1992).

The findings accumulated over the years have practically revolutionized the old concept of impermeable skin barrier and motivated a number of Pharmaceutical Scientists to develop patch-type drug delivery system for transdermal rate controlled administration of drugs for systemic medications. Transdermal drug delivery system can be defined as the delivery of drugs through intact skin to reach systemic circulation in sufficient quantity to administer a therapeutic dose.

Celecoxib is a non steroidal anti inflammatory drug (Martindale 1995; Harper, Mary Lea 2001) that exhibits anti inflammatory analgesic and anti pyretic activities, especially in arthritis (Khanolkar Mahesh *et al.,* 2000).

Celecoxib has gastro intestinal side effects including abdominal pain, dyspepsia, and diarrhea. Short-term studies show fewer gastro intestinal ulcers in patients treated with Cox-2 inhibitors. The absorption of Celecoxib given in a capsule was delayed by food, although systemic exposure increased by 3-5 fold (Paul Son *et al.,* 2001). Celecoxib exhibits poor flow properties and compressibility (Pawar *et al*., 2002). Drawbacks such as hepatic first pass metabolism, multiple and increased dose may be required over time and patient compliance. For these conditions transdermal therapeutic system is preferred over conventional dosage forms to achieve prolonged blood level.

In this work it is designed to develop 24 hours transdermal therapeutic system of Celecoxib with the following objectives to overcome gastrointestinal incompatibility and cardiac adverse effects, to avoid hepatic first pass metabolism (Clemett *et al.,* 2000) to reduce the frequency of administration, to obtain greater therapeutic efficacy to improve patient compliance (Basak *et al.,* 1997).

MATERIALS AND METHODS

Celecoxib obtained from Brown & Burk Pharmaceuticals, Pvt.Ltd, Banglore, Hydroxy propyl methyl cellulose (HPMC 15 cps), Methylcellulose (15 cps) gift samples from Strides Arco labs Banglore. PVP (15 cps) received as gift samples from BPRL, Banglore Backing membrane Aluminum foil Foam tape 9773(3M USA).

Fabrication of transdermal patches

Accurately weighed quantities of polymer were dissolved in suitable solvents. HPMC was dissolved in 50:50 mixture of Ethanol: dichloromethane. For Methylcellulose a 50:50 mixture of ethanol and chloroform was used. PVP was dissolved in ethanol. Drug was dissolved in suitable solvent system and weighed quantities of polymers were added. Both were mixed thoroughly. To this plasticizers Dibutyl phthalate 30% w/w was added and mixed thoroughly. This was poured into a glass ring of 2.8ml capacity on mercury surface. It was dried in hot air if necessary after 24 hours of controlled evaporation at room

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temperature. The dried films were taken out and packed in an aluminum foil covering. The backing membrane used was aluminum foil.

In vitro drug release studies

Commercial semi permeable membrane was employed in this study. The freshly treated cellophane membranes used were transparent, regenerated cellulose membranes which were permeable to low molecular weight substances.

The semi permeable membrane was tied to one end of open ended cylinder which acts as donor compartment. The transdermal film was placed over the semi permeable membrane, then the receptor compartment was fixed, so that the semi permeable membrane was in contact with the medium of 50ml of phosphate buffer (pH 7.4). The contents of the receptor compartment was agitated by a magnetic stirrer at a speed of 45 rpm at room temperature.1ml of the samples was collected at pre-determined time interval from the receptor compartment over a period of 24 hrs, after each sampling, equal volume of fresh media was replaced. The amount of drug release from the patch at different time intervals was determined by measuring the absorbance after suitable dilution by UV spectrophotometer at 251.2nm (Saha *et al.,* 2002; Murthy, *et al.,* 2001).

Physico chemical evaluation of transdermal patches

1. Percentage moisture loss

The films were weighed accurately and kept in the desiccator containing anhydrous calcium chloride. After 3 days the film were taken out and weighed then moisture loss was calculated using the formula

$$\text{Percentage moisture loss} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

2. Percentage moisture absorption

The percentage moisture absorption was studied by placing reweighed films of six numbers in each formulation in a desiccator containing 100ml of saturated solution of aluminum chloride, maintained at 79.5% RH. After 3 days, the films were taken out and weighed (Koteshwar *et al.,* 1992).

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Intital weight}} \text{x}100$$

3. Film thickness

The thickness of the film was measured at three different points using a screw-gauge and average thickness was found out

4. Weight variation

Each film was weighed individually & average weight of three films was found out.

5. Folding endurance

It was determined by repeatedly folding a small strip of film at the same place till it break. The number of time, the film could be fold at the same place without breaking gave the folding endurance value. The average of the three reading was calculated (Sachan *et al.,* 1997).

6. Drug content uniformity

A fabricated film was cut into small pieces and put in a 100ml of phosphate buffer 7.4 pH solution. This is then stirred in a mechanical stirrer to get a homogenous solution and filtered. The filtrate of 1ml was withdrawn and made up to 100ml, again from this 1ml was pipetted out and made up to 10 ml with buffer 7.4 pH. The drug content was analyzed at 251.2nm by UV spectrophotometer [SHIMADZU 1201]

Ex-vivo skin permeation studies

a) Rat skin

Male rats weighing 105-120gm, free from any visible sign of disease were selected. Using a depilatory preparation the hairs of the male albino rat was cutting by scissor. After cleaning the skin with pH 7.4 phosphate buffer, animal was sacrificed by excessive ether inhalation. An incision was made on the flank of the animal and the skin was separated. The prepared skin was washed with pH 7.4 phosphate buffer and used (Jouni Hirvonen *et al.,* 1991).

b) Guinea pig skin

The hairs of the male guinea pig were removed on abdominal area with scissor. After cleaning the skin with pH 7.4 phosphate buffer, animal was sacrificed by spinal traction method, and the skin was separated by incision made on the flank of the animal. The prepared skin was washed with pH 7.4 phosphate buffer and used (Ramesh panchagunla 1997).

c) Pig ear skin

Superficial skin was taken from the back of pig ear and using a depilatory preparation hair was removed. The cleared area was washed with pH 7.4 phosphate buffer.

The collected and prepared skins were tied on the donor compartment with transdermal patch. While placing the patch, the donor compartment contains patch on stratum corneum side of skin and dermis side was facing receptor compartment. Receptor compartment contains 100ml of pH 7.4 phosphate buffer and every one hour 1ml of sample was taken and replaced the same with receptor fluid. After 24 hours sampling absorbance taken at 251.2nm against blank of pH 7.4 phosphate buffer by UV spectrophotometer.

Primary skin irritation test

Primary skin irritation and corrosion are evaluated most often by modification described by Draize and his colleagues in 1994, which is based on scoring method.

Scores as assigned from 0 to 4 based on the severity of erythema or oedema formation. The safety of the patch decreases with increase in scoring. The following table explains the scorings approach for cutaneous toxicity for a transdermal patch.

In vivo drug release study

Selection of animals

Rabbit's crytolagus cuniculus of male sex 10-12 weeks old weighing 2-3 kg were selected. They were kept with husk bedding and were fed with standard rodent pellet diet and water. Light & dark cycles with 12 hours light and 12 hours dark were maintained. The temperature and relative humidity conditions were 28^{o}C ± 2% and 60^{o}C ± 15% respectively.

Method

A set of healthy rabbits were selected. They were checked to ensure that they were free from disease. The dorsal surface of the selected rabbits was cleaned and hair was removed. The dose of Celecoxib was calculated according to the body weight. i.e., 7.33mg (Ghosh, 2005). The patch F4 [HPMC 0.75%, PVP 0.25%) was placed on the dorsal surface (Udupa, 1993).

At specific interval the patch was removed from the rabbit carefully and analyzed for remaining drug content.

Initial drug content was determined before placing the film. The remaining drug content was subtracted from the initial drug content of the film. The value obtained denotes the amount of drug in diffused from the patch into the body (Chakkapan 1994).

Amount of drug released at any time interval =
Initial drug content before placing the film -
Remaining Drug content after removal of the film

***In vitro in vivo* correlation**

In-vitro and *in-vivo* correlation was carried out for the therapeutic efficacy of a pharmaceutical formulation. It is governed by the factors related to both *in-vitro* and *in-vivo* characteristics of the drug.

Percent *in vitro* release on x-axis was plotted against *in-vivo* drug release on y-axis for the same period of time.

RESULTS AND DISCUSSIONS

In the present study, efforts have been made to prepare Celecoxib Transdermal patches using solvent evaporation technique. The films were prepared by using different hydrophilic polymers such as HPMC, PVP and MC.

Physico-chemical evaluation data of table 2 indicates that the formulation F4 (HPMC 0.25%, PVP 0.25%) has shown highest maximum absorption than the other formulation. This may be due to the presence of high hydrophilicity of HPMC and PVP. The Batch F10 (MC 0.33%, HPMC 0.33%, PVP 0.33%) has shown the least percent moisture absorption. This might be due to the presence of the polymers in equal composition hindered the moisture absorption characteristics.

The batch F3 (MC 1%) has shown high percent moisture loss when compared to F8 (MC 0.25%, PVP 0.75%). This could be attributed to the low moisture retaining capacity of the Methyl Cellulose, when compared to the combination of Methylcellulose and PVP.

The thickness of the films varied from 0.20 to 0.29 mm. The minimum Standard deviation values assured that the process used for preparing the delivery system is capable of giving reproducible results. This fact is further confirmed by drug content and weight uniformity studies. In order to evaluate the flexibility, the films were subjected to folding endurance studies. The values in the range of 69 to 84 were observed in all batches. This revealed that the prepared films were having capability to withstand the mechanical pressure along with good flexibility

In vitro dissolution studies

In vitro release study of Formulation F1 (PVP1%) was found to shown the release of loaded drug for 24 hours to the extent of 77.93%. The *in vitro* drug release plot has shown that the drug release followed zero order kinetics which was evidenced from the regression value of the above mentioned plot. The Higuchi's Plot has shown the regression value of 0.9826, which indicated that diffusion might be one of the prominent mechanism influencing the drug release. To confirm the fact Peppa's plot was drawn, which has shown the slope value of the 1.0240, which confirmed that the diffusion mechanism involved in the drug release was of non fickian diffusion type (Haririan *et al.,* 2001).

The batch F2 (HPMC 1%) and F3 (MC 1%) has shown release upto 24 hours to the extent of 75.50% and 67.71%. In both the drug release was diffusion mediated. Batch F2 and F3 have shown non fickian type of diffusion, which was revealed by the slope value of 1.0730 and 0.9903 obtained from the peppa's plot.

The batch F4 (HPMC 0.75%, PVP 0.25%) has shown drug release for 24 hours to the extent of 90.67%. The in-vitro drug release plot has shown that the drug release followed zero order kinetics which was evidenced from the regression value of the above mentioned plot. The rate of release of the loaded drug from the batch increased considerably to the extent of 3.3823 mg/hr in the batch F1 formulated with PVP alone. This substantial increase may be attributed to the slow dissolving nature of HPMC, which might have facilitated more drug release from the

Table 1: Composition of transdermal patches

Formulation code	M.C	H.P.M.C	P.V.P
F1			1%
F2		1%	
F3	1%		
F4		0.75%	0.25%
F5		0.25%	0.75%
F6		0.5%	0.5%
F7	0.75%		0.25%
F8	0.25%		0.75%
F9	0.5%		0.5%
F10	0.33%	0.33%	0.33%

Drug loaded in each film: 30 mg, Plasticizers: Dibutyl phthalate (30% w/w of polymer), Backing membrane: Aluminium foil.

Table 2: Physico-chemical evaluation of transdermal films of celecoxib.

Formulation code	Percent Moisture Absorption (%) ± S.D.	Percent Moisture Loss(%) ± S.D.	Thickness (mm) ± S.D.	Weight Uniformity (gm) ± S.D.	Folding Endurance ± S.D.	Drug content (mg) ± S.D.
F1	17.52±0.57	8.58±0.32	0.21±0.01	0.2414±0.02	79±0.57	91.17±0.52
F2	16.24±0.27	8.21±0.29	0.26±0.05	0.2388±0.02	68±1.14	93.33±0.57
F3	18.20±0.74	14.05±0.66	0.22±0.02	0.1902±0.009	70±0.66	94.37±0.50
F4	26.67±0.70	9.50±0.41	0.21±0.03	0.2109±0.02	81±0.57	92.33±2.15
F5	18.20±0.55	10.80±0.33	0.20±0.06	0.2081±0.01	82±0.57	94.66±0.74
F6	19.26±0.70	10.69±0.87	0.29±0.05	0.2200±0.03	75±0.57	93.33±0.57
F7	20.35±0.36	13.16±0.68	0.21±0.02	0.1854±0.02	74±1.01	84±1.01
F8	21.07±0.79	5.14±0.16	0.23±0.03	0.1941±0.01	69±1.01	84.5±0.72
F9	17.96±0.51	12.58±0.79	0.24±0.03	0.2047±0.03	84±0.56	93.78±0.70
F10	15.78±0.59	9.67±0.10	0.24±0.01	0.2333±0.03	78±0.57	90±0.50

Table 3: Data for *in vitro* and *in vivo* correlation (HPMC 0.75%, PVP 0.25%)

Time in hours	*In vitro* Percentage Release	*In vivo* Percentage Release
2	8.59	3.26
4	13.37	14.64
6	25.78	19.56
8	34.38	27.40
10	38.68	35.60
12	44.41	39.56
14	51.81	44.75
16	61.36	45.80
18	66.14	52.65
20	73.06	66.50
22	81.66	74.82
24	88.91	80.20

matrix. The higuchi's plot was shown the regression value of 0.9864 which indicated that diffusion might be one of the prominent mechanism influencing the drug release. In order to confirm this fact peppa's plot was drawn which has shown slope value of 1.0324, which confirmed that the diffusion mechanism is swelling mediated mechanism involved in the drug release was non fickian diffusion type.

The batch F5 (HPMC 0.25%, PVP 0.75%) and F6 (HPMC 0.5%, PVP 0.5%) and F7 (MC 0.75%, PVP 0.25%) have shown drug release for 24 hours to the extent of 76.71%, 77.89% and 77.92% respectively. The batch F5 and F6, F7 have shown non fickian type of diffusion, which was revealed by the slope value of 1.0348, 0.9977and 1.0216 obtained from the peppa's plot.

The batch F8 (MC 0.25%, PVP 0.75%), F9 (MC 0.5%, PVP 0.5%) and F10 (MC 0.33%, HPMC 0.33%, PVP 0.33%) has shown the release for 24 hours to the extent of 75.44%, 77.59%, and 76.43% respectively. From the slope value of Peppa's it confirms that the drug release was of non fickian diffusion type.

Ex-vivo study was carried out in rat skin, the formulation F4 (HPMC 0.75%, PVP 0.25%) showed drug diffusion for 24 hours upto the extent of 85.39%. The studies, which were carried out in guinea pig and pig ear skin showed drug diffusion of 85.19% and 83.80%. The variation among the used biological membrane could be attributed to the fat content and thickness of the membrane used. As the pig ear has more fat deposition and the thickness, it might have hampered the drug release through the membrane.

As rat skin show good correlation with *in-vitro* release of this formulation F4 was considered for further *in vivo* studies. The *in vivo* drug release shows 82.70% release. To ensure the correlation between the *in vitro* and *in-vivo* release pattern analysis was carried out. They are well correlated, so the release pattern has followed the predicted zero order kinetics in biological system also.

Skin irritation studies revealed that the batch F4 (HPMC 0.75%, PVP 0.25%) has no erythema and oedema.

In conclusion formulation F4 (HPMC 0.75%, PVP 0.25%) has achieved the targets of present study such as extended release, prolonged zero order release, reduced frequency of administration, and thus may improve the patient compliance.

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