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FORMULATION AND EVALUATION OF TRANSDERMAL CELECOXIB MATRIX PATCHES

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ABSTRACT

Background: Celecoxib is a non-steroidal anti-inflammatory drug that has been used extensively to treat patients with arthritis. Its administration is limited due to its numerous disadvantages including gastric irritation and hepatic first pass metabolism. **Objectives**: The aim of the study was to prepare celecoxib containing transdermal patches to overcome all the mentioned disadvantages and to study the effect of polymers and plasticizer on transdermal release of the drug from patch formulations. **Materials and Methods**: Preparation of Celecoxib transdermal patches was carried out using various polymeric substances such as hydroxypropylmethyl cellulose (HPMC) and hydroxyethyl cellulose (HEC) and different plasticizers such as dibutylphthalate (DBP), glycerin (GLY) and propylene glycol (PG). The formulations were characterized using various physiochemical evaluation tests including moisture loss, content uniformity, weight variation, stability, drug release and tensile strength. **Results and Discussion**: According to the findings, transdermal patches containing celecoxib may produce acceptable systemic concentration which will achieve therapeutic effects of the drug and also shows fewer side effects.

KEYWORDS: celecoxib, transdermal patches, polymer.

1. INTRODUCTION

During the last decade, the concept of controlled release formulations received increasing attention and its technology has been progressed a lot. Due to some problems of conventional

methods of drug delivery systems like toxicity and ineffectiveness and also invasiveness of some routs of administration, these methods gain more attentions.[1] As defined, a controlled release drug delivery is a system which can provide predictable and reproducible drug release kinetics.[2] For providing systemic absorption and easy access for drugs, transdermal use of drugs has been proposed as an alternative route of administration. Transdermal Drug Delivery (DDS) systems are topical self-contained discrete dosage forms, which provide a controlled rate drug delivery to systemic circulation when applied to intact skin.[3]

TDD systems are non-invasive, convenient, painless method which avoids gastrointestinal toxicity and the hepatic first pass metabolism. This delivery method is designed in such a way that the therapeutic blood concentration of the drug can be maintained.[4]

Non-steroidal anti-inflammatory drugs (NSAIDs) drugs are a class of drugs, which are mainly used for the control of pain and inflammation in diseases such as rheumatoid arthritis.[5, 8] NSAIDs are structurally diverse group of compounds known to inhibit cyclo-oxygenase (Cox) enzyme. As a result, arachidonic acid would not be converted to prostanoids. Two subsets of cyclo-oxygenase enzymes are: Cox-1 which is responsible for producing prostaglandins and thromboxane in most tissues, and Cox-2 which is found in specific tissues like brain and blood vessels. It also increases during inflammation or fever.[8] Celecoxib acts on cyclooxygenase-2 (COX-2) and is used orally in the treatment of arthritis and osteoarthritis. Its half-life is about 10 hours and 97% of the drug is bound to plasma protein. Serious gastrointestinal discomforts are major side effects of its long term oral administration. As a result of these considerations, an improved celecoxib transdermal delivery system with a high skin permeability could be useful in the treatment of inflammation of skin and other organs as local and systemic treatment, respectively.[9, 27]

2. OBJECTIVES

The objective of this investigation was to design a transdermal therapeutic system of celecoxib to avoid its hepatic first pass metabolism and obtain greater therapeutic efficacy. Also, this type of drug delivery provides better patient compliance by reducing the frequency of administration.[10, 27]

3. MATERIALS AND METHODS

Materials: The materials which were used in this study included: celecoxib that was purchased from Exir company (Iran), Hydroxypropylmethyl cellulose (HPMC), hydroxyethyl

cellulose (HEC), dibutylphthalate (DBP), glycerin (GLY), propylen glycol (PG), ethanol and triacetin which all the materials were purchased from Merck, Germany.

Methods

3.1. Preparation of gels

HPMC 2% gels were formulated by dispersing 2 grams of powdered HPMC in 30 ml preheated (90 ^{o}C) deionized water utilizing an electric mixer and then was brought to volume (100 ml) with deionized water while mixing. HEC 5% gels were also provided by the same methods. The samples were refrigerated for 24 hours to achieve full hydration.[11, 23]

3.2. Fabrication of patches

At the first HPMC or HEC as polymers were separately mixed with different amounts of PG, GLY and DBP as plasticizers and triacetin enhancer (table 1, 2). The solutions of drug in solvent (0.8% w/w of total weight) were added and the resultant mixture was poured in a glass dish and stored at 40-42℃ for 24 hours. After solvent evaporation the patches were put on a layer of omnifilm as a protective impermeable layer, while a layer of aluminum foil was used as a disposable layer.[22] Too dry patches were excluded from the study and the remained samples were inspected for their integrity and surface uniformity. Factors including film formation, clarity and turbidity, homogeneity, ease of separation and plasticity were considered for comparison purposes. The accepted samples were analyzed for their ability of drug release, tensile strength and hygroscopicity.[17]

Table1. Amount of ingredients used in selected patch formulations containing 0.8% celecoxib with HPMC 2%

Formulation No.	Polymer	Plasticizer			Release accelerator	Solvent
	HPMC	PG	GLY	DBP	Triacetin	Ethanol
F1	25	25	-	-	-	50
F2	25	-	25	-	-	50
F3	25	12	13	-	-	50
F4	25	5	-	20	-	50
F5	25	16	-	-	9	50
F6	25	-	16	-	9	50
F7	25	7.5	8.5	-	9	50
F8	25	18	7	-	-	50
F9	25	12	4	-	9	50
F10	25	4	-	12	9	50

Table2. Amount of ingredients used in selected patch formulations containing 0.8% celecoxib with HEC 5%.

Formulation No.	Polymer	Plasticizer			Release accelerator	Solvent
	HEC	PG	GLY	DBP	Triacetin	Ethanol
E1	25	25	-	-	-	50
E2	25	-	25	-	-	50
E3	25	12	13	-	-	50
E4	25	5	-	-	-	50
E5	25	16	-	20	9	50
E6	25	-	16	-	9	50
E7	25	7.5	8.5	-	9	50

3.3. Physicochemical evaluation

3.3.1. Loss of Moisture

A dessicator containing anhydrous calcium chloride was used for storage of the accurately weighed patches for three days. Then the films were removed from the container and weighed again. Using formula 1, in which W_i and W_f are the initial and final weights, respectively, the quantity of moisture loss was determined.[11]

$$\text{Loss of Moisture Percent} = \frac{W_i - W_f}{W_i} \; x \; 100$$

3.3.2. Weight variation

10 samples of each formulation were stored at 60 ^oC for 4 hours and then weighed. Weight average and standard error were calculated.[11]

3.3.3. Stability test

After storage of the films at 40 ^oC and 75% humidity for 3 months, their release pattern, tensile strength, release pattern and active content were compared with the initial data.[17]

3.3.4. Tensile strength determination

10 samples of each patch formulation were dried at 60 ^oC for 24 hrs. Then they were placed in an isometric tansducer (Fig.1) and the force required for their rapture was measured by an oscillograph.[11,13]

3.4. Release Study

A vertical Franz diffusion cell, in which the diffusion area was 3.46 cm^2 and dialysis semi-permeable membrane were utilized for release experiments. The membranes were placed in deionized water for 24 hr before the experiment and then they were mounted between

chambers. Formulated patches were placed on the semi-permeable layer and 0.1% HCL solution was used as receptor phase at 32 ^{o}C. At specified time intervals, a one ml sample was removed from the receptor phase and an equal volume of fresh media was replaced to maintain sink condition. Then, the concentration of released drug was measured using a UV spectrophotometer at 251 nm.[23]

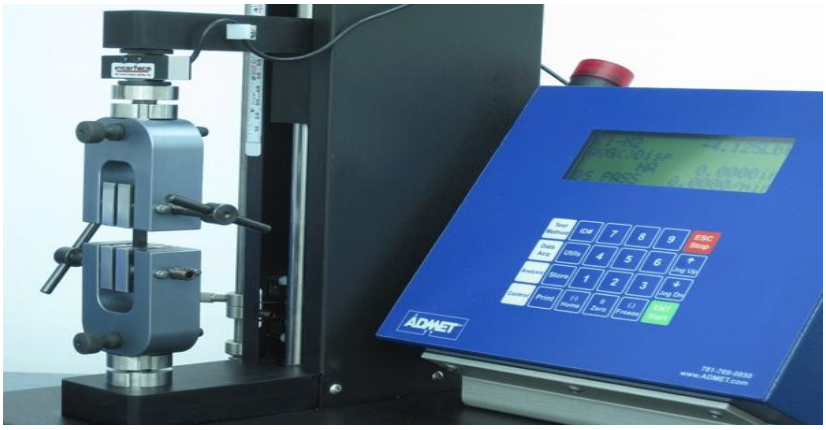

Fig 1. Isometric transducer used for determination of tensile strength

3.5. Drug content determination

Films were put in 20 ml of 0.1% HCL, and then homogenized using a mechanical stirrer. The solution was then filtered and the filtrate was separated and diluted to 50 ml, then analyzed spectrophotometrically at 251 nm.[23]

3.6. Statistical analysis of data: All of the tests were carried out in triplicate and the results were presented as mean ± Standard Error. The results were analyzed using ANOVA and Tukey test, and any difference with $p<0.05$ was considered as significant.

4. RESULTS

The results of visual inspection showed that F_4, F_8 and F_9 were proper regarding their film formation, clarity, ease of separation and flexibility. So the other samples were excluded and hygroscopicity, content uniformity, release and tensile strength of the suitable formulations were evaluated. The moisture absorption capacity of F_4, F_8 and F_9 were 8.21±0.20, 8.51±0.31 and 8.69±0.16, respectively (table 3).

Table 3. Result of humidity of celecoxib patches

	F_4	**F_8**	**F_9**
Median	8.21	8.51	8.69
Probability	0.254948		0.255944

Figure 2 shows drug release from F_4, F_8 and F_9 formulations during the evaluation time. For all of the selected formulations, due to the presence of drug on the surface of patches, a burst release was occurred. The phenomenon that has been reported for many transdermal preparations is necessary to begin their pharmacological effect in a relatively short time period. Moreover, the amount of released drug from F_9 was more than the other formulations in the same time period. Tukey test showed that celecoxib permeation from the patches after 3 month of storage did not significantly altered (*P* value of 0.136, 0.295 and 0.309 for F_4, F_8 and F_9, respectively). The results of tensile strength measurement were 0.60, 1.49 and 1.52 $g.cm^2$ for formulations of F_4, F_8 and F_9 respectively. Statistical comparison indicated that the flexibility of F_9 was significantly more than F_4 and F_8 (P<0.031). The results of tensile strength measurement are show in the table 2. The results of content uniformity of the formulations did not show any significant difference (p>0.05); and also after three months of storage, their strength, hygroscopicity and quantity of active content did not changed significantly (p>0.05).

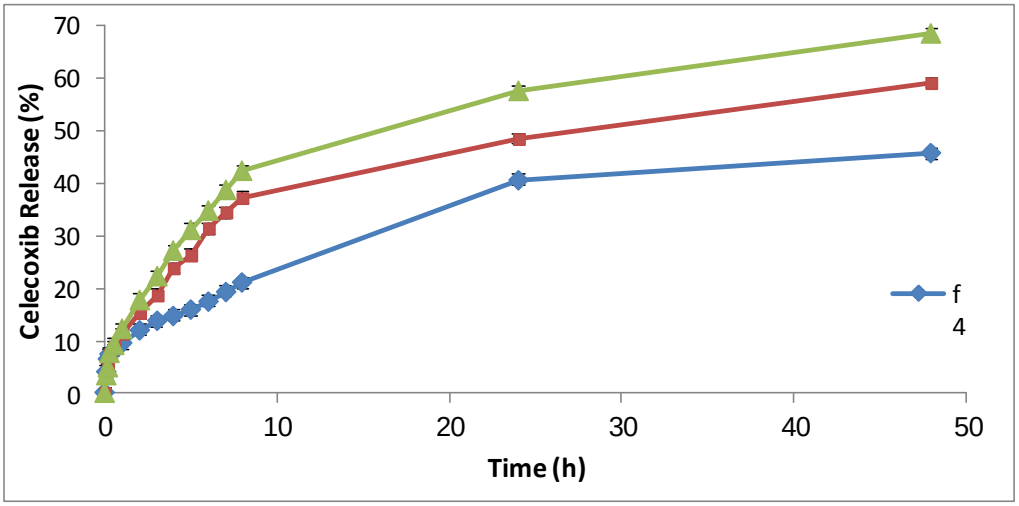

Fig.2. Release profile of celecoxib from patch formulations F_4, F_8 and F_9

Table 2. The results of tensile strength Determination of the selected microemulsion formulations

No. fourmulation	Load at break (N)	Stress at break (Mpa)	Elongation at break(mm)	Elongation (%)	Strain at break
F_4	0.60±0.07	1.92±.21	14.57±0.56	46.33%	0.46
F_8	1.49±0.34	4.82±0.8	13.90±0.65	48.57%	0.48
F_9	1.52±0.44	4.61±1.36	15.04±0.55	50.13%	0.50

5. DISCUSSION

In the present study, we tried to prepare celecoxib transdermal patches. For this purpose, solvent evaporation technique has been applied. Different hydrophilic polymers such as HPMC and HEC have been used for the preparation of the patches. The impact of vehicle on physicochemical properties, stability and drug release from skin preparations has been well documented.[8] Among several polymers, HPMC and HEC are more in common use due to their ability to embed and release drugs in a proper manner. Skin route of administration is non-invasive and can provide acceptable systemic circulation concentration level through skin layers which is a non invasive route. Physical properties of HEC based patches were not acceptable. Undesirable flexibility and some incompatibilities between polymer and the other ingredient such as the solvent in most cases have been previously reported.[27] In our study, the maximum acceptability was seen for HEC, trieacetin, PG and ethanol containing formula. Although rigidity and phase separation occurred in some HPMC containing patches, they were generally more acceptable than HEC based formulations. Also, there was a good cooperation between PG and triacetin to plasticize HPMC containing formulas. Besides glycerin did not act properly as a plasticizer and caused softening of patches. In addition, because of its hydrophobicity, dibutylphthalate caused phase separation. The ability to absorb moisture is commonly considered as a good characteristic for patches.[4, 6] Based on our study, F_4, F_8 and F_9 formulations showed no phase separation and rigidity and similarly absorbed humidity had similar hygroscopicity nearly 10 % of their original weight that was clearly more than the results of the other studies. Also, regarding their resistance against tension, they were comparable to previous HPMC containing fabricated patches. It has been previously demonstrated that HPMC based patches should have a tensile strength around 1.52 g/cm and also, the flexibility of dermal preparations is directly affected by their tensile strength.[27] According to the results of release experiments, by increasing the percentage of HPMC in formulations, the cumulative released of celecoxib was decreased. The suggested mechanism is probably related to enhancement of the drug-polymer interaction by raising of the polymer molecules. Several factors affect skin permeation including, nature of membrane, formulation factors and dosage form components. The current study was conducted to evaluate behavior of different types and concentration of polymer, type of solvents and also plasticizers. After incorporation of the drug into the patches, their physical properties and total qualities of the fabricated patches were evaluated. In conclusion, from the results of present work, it can be deduced that HPMC is a good candidate polymer for formulation of

celecoxib patches and effective transdermal absorption may be expected due to their acceptable release profile.

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7. AUTHORS' CONTRIBUTION

The work was supervised by Moghimipour E. All of the experiments, data collection, and also preparation of primary draft of the manuscript were conducted by Baniahmad B.

8. FINANCIAL DISCLOSURE

The authors have no conflict of interest.

9. REFERENCES

1. Langer R, Peppas N. Chemical and physical structure of polymers as carrier for controlled release of bioactive agents: a review. J MacromolSci Rev MacromolChem phys., 1983; 23(4): 61-126.
2. Pandey S, Praveen SH, Udupa N Formulation and evaluation of nimesulide transdermal drug delivery systems. Indian Journal of Pharmaceutical Sciences., 2000; 62(5): 376-379.
3. Chienyw. Concept and system design for the rate controlled drug delivery system. New York: Marcel dekker., 1992; 52(16): 321-337. PMID: 18483865.
4. Cheinyw. Transdermal Controlled Systemic Medications. Marcel Dekker: New York, 1987; 23(43): 179. PMID: 22396901.
5. Rainsford KD: Anti-inflammatory drugs in the 21st century. Sub-Cellular Biochemistry. 2007; 42(15): 3-27. PMID: 24369317.
6. Harris Raymond C and Breyer Mathew D: Update on cyclooxygenase-2 inhibitors. Clinical Journal of the American Society of Nephrology., 2006; 1(7): 236-245. PMID: 24373107.
7. Saha, RN., Sajeev, C., Girish, B., Studies on design and evaluation of controlled release polymeric discs for ocular delivery of Flubiprofen and celecoxib. Indian Jof Pharmaceutical Sciences, 2002; 64(3): 352-326.
8. Davies NM, McLachan AJ, Day RO, William KM, Clinical Pharmacokinetics and Pharmacodynamics of Celecoxib: A selective Cyclo -oxygenase 2 inhibitors. Clin Pharmacokinetic., 2000; 38(6): 225-242. PMID: 14965322.

9. Saha RN, Sajeev C, Girish B, Punnarao Studies on design and evaluation of controlled release polymeric discs for ocular delivery of flurbiprofen and celecoxib. Indian J Pharm Sci., 2002; 26(7): 325-326.
10. Baboota S, Shakeel F, Ahuja A, Ali J and Shafiq S: Design, development and evaluation of novel nanoemulsion formulations of transdermal potential of celecoxib. ActaPharmaceutica., 2007; 57(3): 315-32. PMID: 17878111.
11. Aquil M., Sultana Y., Ali A. Matrix type transdermal drug delivery system of Metoprolol tartrate: In vitro characterization. Acta.Pharm., 2003; 53(6): 119-125. PMID: 14764246.
12. Barry B. Transdermal drug delivery. In: Aulton M E.Pharmaceutics the science of dosage form design. 2nd ed. Spain Churchil Livingstone; Spain., 2002; 15(7): 499-533. PMID: 25466399.
13. Dmochowski R.R., Starkman J.S. Davila GW. Transdermal drug delivery treatment for overactive bladder. Int. Braz J Urol., 2006; 32(5): 513-520. PMID: 23891744.
14. Godib B., Touitou E. Transdermal skin delivery: Predictions for humans from in vivo, exvivo and animal models. Advanced Drug Delivery Reviews., 2007; 59: 1152-1161. PMID: 17889400.
15. Khafagy E.S., Morishita M., Onuki Y., Takayama K. Current challenges in non-invasive insulin delivery systems: A comparative review. Advanced Drug Delivery Reviews., 2007; 59: 1521-1546. PMID: 17881081.
16. Margetts L., Sawyer R. Transdermal drug delivery: principles and opioid therapy. ContinEducAnaesthCrit Care Pain., 2007; 7 (5): 171-176. PMID: 20490571.
17. Nafee N.A., Ismail F.A., Boraie N.A., Mortada L.M. Mucoadhesivebuccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing. International Journal of Pharmaceutics., 2003; 264(1-2): 1-14. PMID: 12972331.
18. Qvist M.H., Hoeck U., Kreilgaard B., Madsen F., Frokjaer S. Release of chemical permeation enhancers from drug-in-adhesive transdermal patches. International Journal of Pharmaceutics., 2002; 231(2): 253-263. PMID: 11755277.
19. Salaamat-Miller N., Chittchung M., Johnston T.P. The use of mucoadhesive polymers in buccal drug delivery.Advanced Drug Delivery Reviews., 2005; 57(11): 1666-1691. PMID: 16183164.
20. Staskin D.R. Transdermal systems for overactive bladder: principles and practice. Rev Urol., 2003; 5(SUPP.8): 26-30. PMID: 19709479.

21. Thien Hai N., Kim J., Park E.S., Chi S.C. Formulation and biopharmaceutical evaluation of transdermal patch containing benztropine. International Journal of Pharmaceutics., 2008; 357: 55-60. PMID: 18417307.
22. Uhrich K.E., Cannizzaro S.M., Langer R.S., Shakeshef K.M. Polymeric Systems for Controlled Drug Release. Chem. Rev., 1999; 99: 3181-3198.PMID: 25476787.
23. Moghimipour E, Rezaee S, Omidi A. The effect of formulation factors on the release of oxybutinin hydrochloride from transdermal polymeric patches. Journal of Applied Pharmaceutical Science., 2011; 1(10): 73-76. ISSN: 2231-3354.
24. Arora, P., Mukherjee, B., Design Development Physicochemical and invitro and in vivo evaluation of transdermal patches containing diclofenacdiethylammonium salt. J Pharm Sci., 2002; 16(22): 91-105. PMID: 12210054.
25. Gupta, R., Mukherjee, B., Development and In vitro Evaluation of Diltiazem Hydrochloride Transdermal patches based on Povidone- ethylcellulose Matrices. Drug DevInd Pharm., 2003; 29(12): 1-7. PMID: 12602487.
26. Tripathi KD: Essentials of medical pharmacology. JaypeeBrothrs Medical publisher (p) Ltd., 2008; 6(3): 180-196. PMID: 19856581.
27. Murthy TK, Reddy MN, Sankar DG, UV spectrophhotometric methods for the determination of celecoxib and tizanidine hydrochloride. Indian J Pharm Sci., 2001; 22(12): 521-523.