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## Multi-compartmental transdermal patch for simultaneous delivery of multiple drugs: formulation and evaluation of newly developed novel dosage form

Vijayan Venugopal\*, Jayaraja Kumar, Selvadurai Muralidharan, P. Vasanth Raj

Unit of Pharmaceutical Technology, Faculty of Pharmacy, AIMST University, Bedong-08100, Malaysia

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### ABSTRACT

**Objective:** To evaluate the formulation of multi-compartmental transdermal patches for simultaneous delivery of multiple drugs: aceclofenac and serratiopeptidase.

**Methods:** The patch was prepared by simple solvent casting method using hydroxy propyl methyl cellulose K100M as matrix forming agent and dimethyl sulphoxide as permeation enhancer. The prepared transdermal patch was evaluated by physicochemical parameters and *in-vitro* diffusion studies.

**Results:** The multi-compartmental transdermal patch showed sustained drug release over the period of 12 h.

**Conclusions:** Multicompartmental transdermal patches shows better bioavailability, therapeutic efficacy and very economic as compared with other dosage forms.

## 1. Introduction

Optimum therapeutic outcomes require not only proper drug selection but also effective potent drug delivery system. The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action[1]. The human skin surface is one of the most readily accessible organs of the human body. The potential of using the intact skin as the port of drug delivery to the human body has been recognized for several decades ago[2]. Transdermal patches are a popular route for drug delivery because of the sustained drug levels, low side effects, reduced hepatitis first-pass effect and ease of use, including self-administration. Transdermal patches are used to deliver the drugs across the skin and into systemic circulation are comfort from topical drug penetration, which targets local areas[3].

Drug delivery devices initially having two adhesive layers containing at least one active agent in each layer are kept separate from each other prior to administration of the active agent[4]. At the

time of administration, the separated layers are combined to form a dual layer adhesive transdermal drug delivery device which results in the administration of the at least one active compound after topical application of the device. Sometimes two active ingredients are incorporated into two different compartments in the same patch and both the drugs show their pharmacological action after entering onto the systemic circulation[5].

Aceclofenac is a non-steroidal anti-inflammatory drug (phenylacetic acid derivative) with preferential COX-2 inhibition. It is metabolized to 4'-hydroxyaceclofenac and diclofenac inside inflammatory cells. It inhibits cytokines like interleukin-1, tumor necrosis factor, and prostaglandin E2 production. In the early 1950s it was discovered that intravenous trypsin could unexpectedly relieve the symptoms of many different inflammatory conditions, including rheumatoid arthritis, ulcerative colitis and atypical viral pneumonia[6]. Proteolytic enzymes have a role in the reduction of swelling and edema but the extent of effectiveness is unknown. Serratiopeptidase, a proteolytic enzyme derived from non-pathogenic enterobacteria *Serratia* sp. E-15 has anti-inflammatory and anti-edemic activity in a number of tissues. Anti-inflammatory mechanism involves degradation of inflammatory mediators, suppression of oedema, activation of fibrinolysis, reduction of immune complexes and proteolytic modification of cell-surface adhesion molecules which guide inflammatory cells to their targets[7]. Analgesic effect is believed to be due to cleavage of

\*Corresponding author: Vijayan Venugopal, Unit of Pharmaceutical Technology, Faculty of Pharmacy, AIMST University, Bedong-08100, Malaysia.  
Tel: +60103708790  
E-mail: vijayanv2@gmail.com

bradykinin, a messenger molecule involved in pain signaling[8].

Aceclofenac and serratiopeptidase are available in the form of tablets in various dosage strengths, but they bring about various problems like nausea, abdominal pain and less bio-availability due to first pass metabolism *etc.* Problems associated with oral dosage form can be overcome by formulating multi-compartmental transdermal patches. Up-to-date multiple drug therapy through transdermal patch is ineffective. To improve the efficacy of multiple drug therapy and avoid incompatibility of drugs, multi-compartmental transdermal patches are designed. This type of patches can accommodate number drugs and delivery compatibly to human body without side effect. The aim of the present research work is to increase the penetration of drugs aceclofenac and serratiopeptidase by formulating multi-compartmental patches.

## 2. Materials and methods

### 2.1. Preparation of aceclofenac drug solution

A total of 100 mg of aceclofenac drug was accurately weighed and dissolved in 2 mL of ethanol. To this added 10 mL of 2.5% hydroxy propyl methyl cellulose (HPMC) K100M solution, 3 mL of 30% polyethylene glycol (PEG)-400 and 1% dimethyl sulphoxide (DMSO). All the ingredients were mixed thoroughly and kept aside for 2 h to remove air bubbles.

### 2.2. Preparation of serratiopeptidase drug solution

A total of 100 mg serratiopeptidase powder was dissolved in 5 mL of water. As the powder remains undissolved added another 3 to 4 mL of water, and the completed solution was kept for centrifugation for half an hour. The solution was filtered by using Whatman filter paper and collected the filtrate. Take 5 mL of above filtrate in beaker and to that added 10 mL of 2.5% HPMC K100M and mixed the solution. Both the drug solutions were kept aside for some time to remove the air bubbles. Finally added 1% DMSO as permeation enhancer.

### 2.3. Preparation of patch

Initially a glass plate having appropriate size was made ready for the preparation of patch. Glycerol was applied over the glass plate and inverted the position to remove excess glycerol. Then the polymer solutions were poured on the glass plate and the two solutions were kept separated by using a small groom stick. In one compartment of the glass plate contains aceclofenac and other compartment was serratiopeptidase solution and kept aside for 24 h without disturbing. After that the groom stick was removed, covered with the funnel. The dried patches were removed from the glass plate and cut into small pieces of 2 cm × 2 cm dimensions[9].

### 2.4. Determination of proteolytic activity of serratiopeptidase

The proteolytic activity of serratiopeptidase was determined as per Food Chemical Codex 2003 reported method. The quantification was depended on 30 min proteolytic hydrolysis of casein at 37 °C

and pH 7.0. The unhydrolysed casein was completely removed by filtration and the solubilised casein (tyrosine) was estimated by UV spectrophotometric method at 275 nm. In this method enzyme activity (IU/mg) was expressed in terms of one bacterial protease unit (PC) and defined as that quantity of enzyme that produces the equivalent of 1.5 µg/mL of L-tyrosine per minutes under the conditions of assay[10]. Enzyme activity was calculated by using the equation:

$$PC/g = (A_U/A_S) \times (22/30W)$$

Where  $A_S$  is absorbance of 1.5 µg/mL of L-tyrosine,  $A_U$  is absorbance of the sample enzyme, 22 is the final volume of the reaction mixture, W is weight (g) of the original sample taken.

## 2.5. Evaluation parameters

### 2.5.1. Surface and thickness

The surface of patch was observed by using SEM (SGS Sdn. Bhd, Malaysia). The thickness of patch was measured by vernier calipers at 3 different places. As the thickness of single patch was very small and in order to get accurate measurement, four patches were combined and thickness were noted for four patches.

### 2.5.2. Folding endurance

The folding endurance of patches were determined by repeatedly folding one film at the same place till a line of breaking forms, but it should not break. The number of times the film would be folded at the same place without breaking was taken as the value of folding endurance.

### 2.5.3. Weight variation

The patches were subjected to weight variation by individually weighing 6 selected patches randomly. Such variations were carried out for each formulation.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Individual weight}} \times 100$$

### 2.5.4. Moisture uptake studies

The moisture uptake was determined by subjected the patch to desiccator over anhydrous calcium chloride at room temperature for 24 h. The patches were re-weighed for determining the decrease in weight. The percentage moisture uptake was calculated by using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

### 2.5.5. Drug content

The patch aceclofenac portion was dissolved one in 10 mL of ethanol and serratiopeptidase portion in 10 mL of water. Filtered the solutions with Whatman filter paper (0.45 µm, Whatman, Maidstone, UK). The aceclofenac absorbance was measured at 273 nm in a double beam UV-visible spectrophotometer (Shimadzu, Japan) and the absorbance value correlates the aceclofenac quantity in the patch. The zone of gelation technique was performed for water solution in which a patch was dissolved and the diameter of the zone indicates the quantity of serratiopeptidase in a single patch.

### 2.5.6. In-vitro drug release study

Patch of 2 cm<sup>2</sup> was subjected to *in-vitro* diffusion studies by using Franz diffusion cell (Electrolab, India) containing cellophane membrane[11]. The donor compartment and receptor compartment was separated by cellophane membrane attached with patch. The receptor compartment was filled with 100 mL of poly butylenes succinate pH 7.4 as a diffusion medium at (37 ± 2) °C. The amount of drug permeated through membrane was determined by withdrawing 3 mL of sample at predetermined time intervals, *i.e.* (30 min, 1, 2, 4, 8, and 12 h) and replaced with equivalent amount of PBS pH 7.4. The withdrawn samples were analyzed by UV spectrophotometer at 272 nm. Same time the samples were analyzed for proteolytic activity as described earlier.

## 3. Results

In the present experiment, multi-compartmental transdermal patches of aceclofenac and serratiopeptidase were formulated by using HPMC K-100M, plasticizer PEG-400 and DMSO as permeation enhancer. The formulated patches were characterized for physico chemical properties, *in-vitro* diffusion studies using synthetic membrane. The Fourier transform infrared spectroscopy (FTIR)

spectrum of aceclofenac showed the following functional groups at their frequencies, which showed in Figures 1, 2 and 3, 3069.10 cm<sup>-1</sup> (N-H stretching), 3027.82 cm<sup>-1</sup> (COOH), 1912.19 cm<sup>-1</sup> (RCOOR). The characteristic absorption peaks of serratiopeptidase were obtained at 2925 cm<sup>-1</sup> (N-H stretching), 2354 cm<sup>-1</sup> (-C<sub>6</sub>H<sub>4</sub>-), 3068 cm<sup>-1</sup> (halides) and 1738 cm<sup>-1</sup> (C = O stretching). All the characteristic peaks of aceclofenac and serratiopeptidase were presented in spectra at respective wavelength as compare with standard drug spectra.

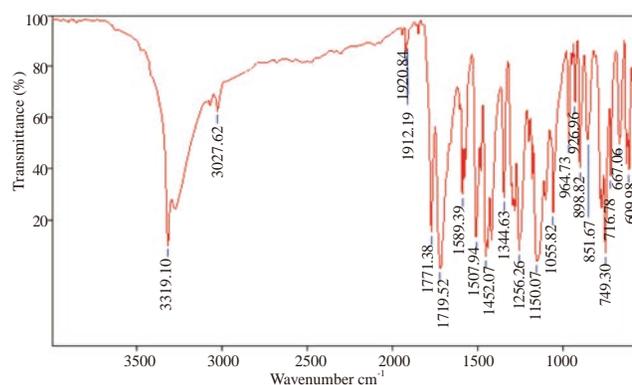


Figure 1. FTIR spectrum of aceclofenac.

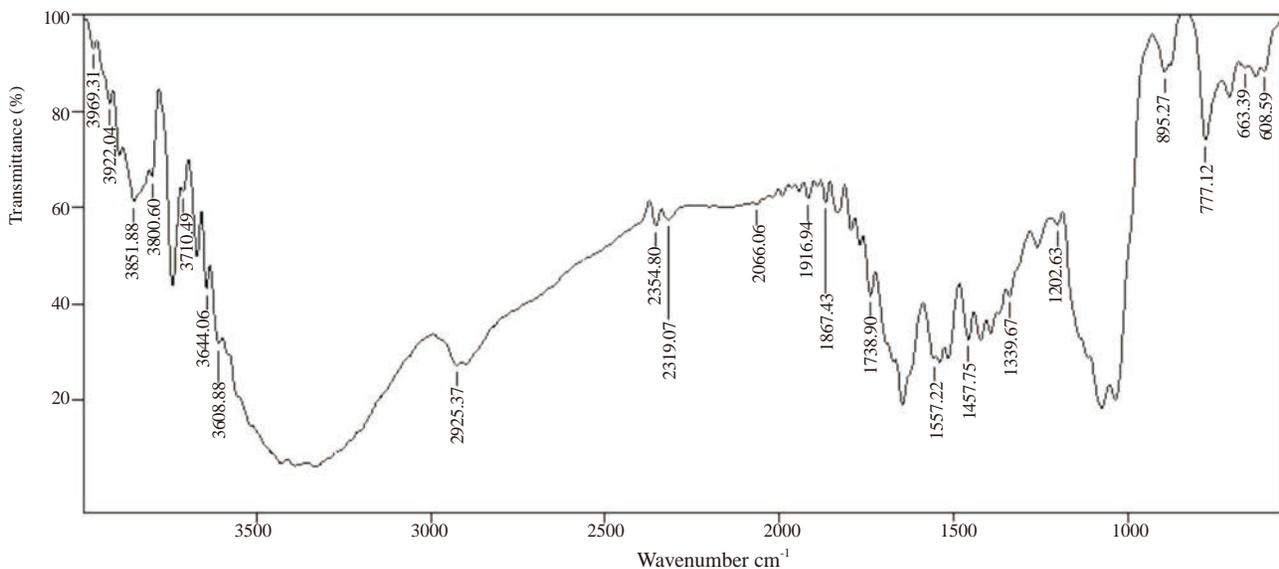


Figure 2. FTIR spectrum of serratiopeptidase.

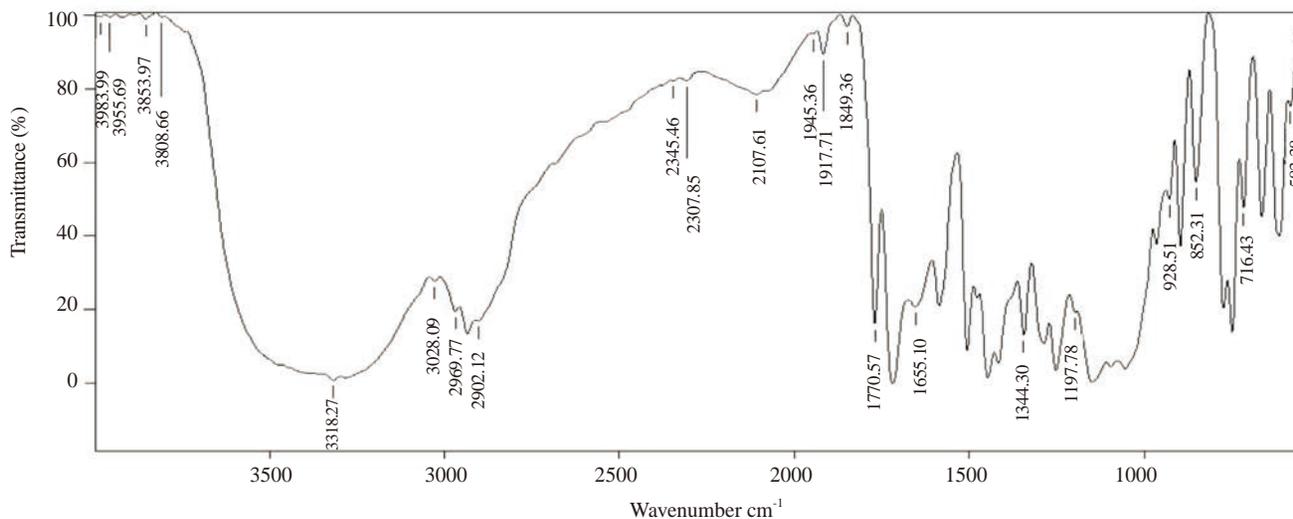


Figure 3. FTIR spectrum of aceclofenac, serratiopeptidase and polymers.

The patch surface was observed by SEM and the compartment was clearly visible (Figure 4). The thickness of patch was measured by vernier calipers at 3 different places. As the thickness of single patch was very small and in order to get accurate measurement, four patches were combined and thickness were noted for four patches. The measured value was divided by 4 to get the thickness of single patch. The thickness of the patch varies from 291 to 305 μm (Table 1). The folding endurance measures the ability of patch to withstand the rupture, the folding endurance was in the range between 6 to 275 (n = 3). The weight of the prepared patches was uniform in all six formulations and varies in the range to 11.10 to 37.04 mg/patch. The percent moisture uptake studies were performed by keeping a patch of specified dimensions i.e. 2 cm × 2 cm in a decimator for 24 h at room temperature. The formulated patches showed the least moisture uptake in the range of 25.21 mg/cm<sup>2</sup>/h to 68.67 mg/cm<sup>2</sup>/h (Table 1).



Figure 4. SEM image of patch.

The multi-compartmental patches of specified area was dissolved one in 10 mL of ethanol and the other in 10 mL of water in separate beakers. The drug content for aceclofenac was found to be in the range of 18.63 to 29.88 μg/patch and for serratiopeptidase the drug content ranges from 17.60 to 22.60

μg/patch. *In-vitro* diffusion studies of all the formulations of transdermal patches of aceclofenac and serratiopeptidase were carried out in pH 7.4 phosphate buffers. The study was performed for 12 h, and cumulative percentage drug release was calculated at different time intervals. The plot of time versus cumulative percentage drug release for formulations (Figures 5 and 6) was showed the *in-vitro* drug release data.

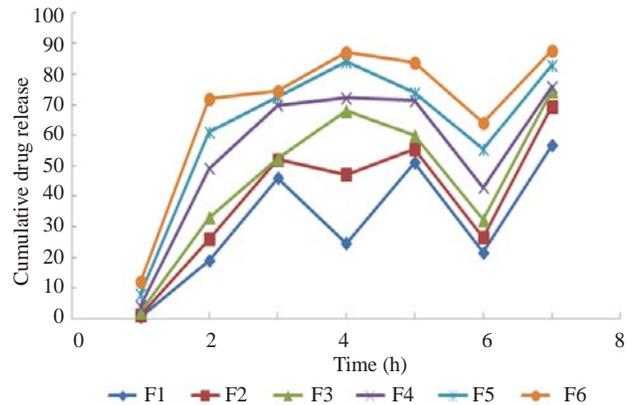


Figure 5. *In-vitro* diffusion studies of aceclofenac.

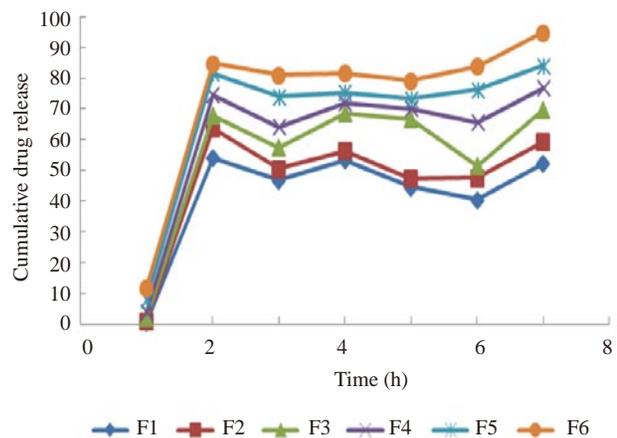


Figure 6. *In-vitro* diffusion studies of serratiopeptidase.

Table 1

Physicochemical properties of formulation.

Parameters	F1	F2	F3	F4	F5	F6
Thickness (μm)	295.00 ± 1.52	300.00 ± 0.08	305.00 ± 2.51	304.00 ± 0.52	291.00 ± 2.51	299.00 ± 0.64
Weight variation (%)	37.04 ± 1.96	15.68 ± 0.76	17.77 ± 1.00	36.65 ± 0.68	11.10 ± 1.03	27.63 ± 0.70
Folding endurance	6.00 ± 0.62	220.00 ± 1.00	275.00 ± 2.08	232.00 ± 0.57	260.00 ± 1.15	215.00 ± 1.15
Moisture uptake (%)	50.40 ± 0.65	66.66 ± 0.66	25.21 ± 0.26	33.33 ± 0.15	40.10 ± 0.54	68.67 ± 0.40
Drug content (μg)	(A)18.63 ± 0.28 (S)19.00 ± 0.28	20.26 ± 0.14 19.00 ± 0.49	21.53 ± 0.94 21.20 ± 0.06	25.19 ± 1.43 22.60 ± 0.37	29.88 ± 1.35 17.60 ± 0.04	15.84 ± 0.91 18.20 ± 0.05

A: Aceclofenac; S: Serratiopeptidase; n = 3.

#### 4. Discussion

Multi-compartmental transdermal patch is a new novel drug delivery system for simultaneous delivery of multiple drugs without any interaction. The single dose patch can provide treatment from a day to week. These patches can also improve bioavailability of

drug by bypassing first-pass metabolism and increase the therapeutic efficacy of drug by deliver into the blood circulation.

The FTIR peaks can be considered as characteristic peaks of aceclofenac and serratiopeptidase and prominently observed in infrared spectra of aceclofenac with polymers and serratiopeptidase with polymers, which indicate that there is no interaction between

drugs (aceclofenac, serratiopeptidase) and polymers.

The multi-compartmental transdermal patch mainly helps for treatment of chronic inflammatory complaints. The multi-compartmental patch preparation is very easy to prepare and to avoid incompatibility between drugs. A single patch can produce efficient anti-inflammatory action throughout the period. During the preparation of the patch HPMC K100M that produce significant fabric matrix layer to control drug release, PEG as a plasticizer it helps in maintaining the elasticity of patch. Enzymes are large molecular weight substance, therefore it is difficult to permeate through membrane. The permeation was improved by addition of DMSO.

All the patches have uniform thickness throughout. Average thickness was found in the range of 291 to 305  $\mu\text{m}$ . Drug loaded patches were tested for uniformity of weight. The patches were found to be uniform. The weights of the patches were found to be in the range of 11.10 to 37.04 mg/patch. Folding endurance was one of the physical stability determining parameter for patches. The folding endurance measured the ability of patch to withstand the rupture, and it was in the range between 6 to 275 times. The moisture uptake studies were analyzed and recorded at room temperature and at constant relative humidity for 24 h. The moisture uptake can be accelerated due to the increasing of hydrophilic polymer ratio. Drug content in all formulations was found to be uniform ranging from (15.84  $\pm$  0.91)% to (29.88  $\pm$  1.35)% for aceclofenac and from (17.60  $\pm$  0.04)% to (22.60  $\pm$  0.37)% for serratiopeptidase drug. It showed the uniformity of drug dispersed throughout the area of patch.

All the 6 formulations were subjected to *in-vitro* diffusion studies using locally designed diffusion test apparatus. The samples were withdrawn at time intervals of 30 min up to 12 h and these samples were analyzed in UV-visible spectrophotometer at 272 nm. Cumulative percentage drug release was calculated on the basis of mean amount of aceclofenac present in the respective patch. Formulation F1 to F6 shows the drug release in the range of 72% - 87% at 12 h. The formulation F6 was the best formulation based on their *in-vitro* release.

The cumulative percentage of serratiopeptidase release was showed in the Figure 6. Formulation F1 to F6 showed the drug release in the range of 59% to 88% at 12 h. The formulation F6 was the best based on their *in-vitro* release. All the patches show the immediate release of drug in the range of 19% to 61.78% at 30 min, due to drugs which present in open surfaces of patches following the matrix layer maintains the sustained release of drug over prolong period. Based on the above evaluation studies, multi-compartmental patch showed effective delivery of multiple drugs simultaneously without interacting each other.

The new idea was emerged and implemented into novel drug delivery system. The multi-compartmental transdermal patches loaded aceclofenac and serratiopeptidase was developed by using matrix patch forming polymer *i.e.* HPMC K100M and PEG 600 used as plasticizer. The prepared multi-compartmental patch performed by physiological evaluation studies and those values were significantly satisfied by transdermal patch formulation. The drug release from the

matrix patch was controlled manner over a prolonged period, it was confirmed by diffusion studies and release mechanism was identified as Fickian. From the above studies it was concluded that F6 and F12 formulations were statistically release the drug in slow manner for prolong period of time. In future, successful formulations planned to conduct pharmacokinetic and pharmacodynamics studies in suitable animal models.

### Conflict of interest statement

We declare that we have no conflict of interest.

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### References

- [1] Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. *J Pharm Innov* 2012; **1**: 78-87.
- [2] Arunachalam A, Karthikeyan M, Kumar DV, Prathap M, Sethuraman S, Ashutoshkumar S, et al. Transdermal drug delivery system: a review. *Curr Pharm Res* 2010; **1**: 70-81.
- [3] Latheeshjhal L, Phanitejaswini P, Soujanya Y, Swapna U, Sarika V, Moulika G. Transdermal drug delivery systems: an overview. *Int J Pharm Tech Res* 2011; **3**: 2140-8.
- [4] Patel H, Patel U, Bhimani B, Daslaniya D, Patel C. Transdermal drug delivery system as prominent dosage forms for the highly lipophilic drugs. *Int J Pharm Res Bio Sci* 2012; **1**: 42-65.
- [5] Dhiman S, Singh TG, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. *Int J Pharm Pharm Sci* 2011; **3**(Suppl 5): 26-34.
- [6] Shakeel F, Faisal MS, Shafiq S. Comparative pharmacokinetic profile of aceclofenac from oral and transdermal application. *J Bioequiv Availab* 2009; **1**: 13-8.
- [7] Khan SA, Ahmad M, Kousar R, Murtaza G. Nimesulide-serratiopeptidase sustained release microparticles-combined formulation and *in vitro* characterization. *Adv Clin Exp Med* 2011; **20**: 605-11.
- [8] Vijayan V, Sumanth MH, Suman L, Vinay T, Srinivasrao D, Kumar KJ. Development and physiochemical, *in-vitro* evaluation of antihypertensive transdermal patches. *J Pharm Sci Res* 2010; **2**: 171-7.
- [9] Darwhekar G, Jain DK, Patidar VK. Formulation and evaluation of transdermal drug delivery system of clopidogrel bisulfate. *Asian J Pharm Life Sci* 2011; **1**: 269-78.
- [10] Leuben HL, de Leeuw BJ, Pérard D, Lehr CM, de Boer AG, Verhoef JC, et al. Mucoadhesive polymers in per oral peptide drug delivery. I. Influence of mucoadhesive excipients on the proteolytic activity of intestinal enzymes. *Eur J Pharm Sci* 1996; **4**: 117-28.
- [11] Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system: an overview. *Der Pharma Sin* 2011; **2**: 17-29.