**IJPSR (2014), Vol. 5, Issue 6** **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 October, 2013; received in revised form, 15 February, 2014; accepted, 03 May, 2014; published 01 June, 2014

# DEVELOPMENT AND CHARACTERIZATION OF BILAYERD TRANSDERMAL FILM OF DICLOFENAC DIETHYLAMINE

Potlapally Laxmi*, Azeez Mohammad and G. Shirisha

Department of Pharmaceutics, Venkateshwara Institute of Pharmaceutical Sciences, Cherlapally, Nalgonda-508001, Andhra Pradesh, India

**Keywords:**

Diclofenac diethyl amine, Bilayer film, slow- release, wound healing, wound dressing

**Correspondence to Author:**

**Potlapally Laxmi**

Department of Pharmaceutics, Venkateshwara Institute of Pharmaceutical Sciences, Cherlapally, Nalgonda-508001, Andhra Pradesh, India

**E-mail:**
potlapally.laxmi34@gmail.com

**ABSTRACT:** The aim of this research work was to develop and characterise bilayer film and to investigate its potential as slow-release wound healing vehicle. The bilayer is composed of an upper layer impregnated with Diclofenac diethyl amine and a drug-free lower layer, which acted as a rate-controlling membrane. Solvent casting technique was employed to prepare transdermal films. Pre formulation studies are performed to determine solubility, melting point, compatibility and partition coefficient. Alginate based bilayer film for wound healing was successfully developed. The in vitro drug release study implied that by using the bilayer films which retain the drug for a longer period of time thus minimise the dressing changing frequency. The method adopted in this research work is genuine can be used as routine analysis of the drug.

**INTRODUCTION:** Transdermal drug delivery system should duplicate continuous intravenous infusion, which not only by passes hepatic 'first pass' elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug in to systemic circulation. Following skin permeation, the drugs first reach the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action [1, 2, 3].

QUICK RESPONSE CODE

**DOI:**
10.13040/IJPSR.0975-8232.5(6).2508-14

**Article can be accessed online on:**
www.ijpsr.com

**DOI link:** http://dx.doi.org/10.13040/IJPSR.0975-8232.5(6).2508-14

Diclofenac diethyl amine is2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetic acid and having molecular formula $C_{14}H_{11}C_{l2}NO_2$. $C_4H_{11}N$. Diclofenac diethyl amine is non-steroidal anti-inflammatory drugs (NSAIDs). It blocks the cox enzyme and reduces prostaglandins there by ongoing inflammation pain and fever is reduced.

Prostaglandins are produced within the body's cells by the enzyme cyclo oxygenase (Cox). There actually are two Cox enzymes, Cox-1 and Cox-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever. However, only Cox-1 produces prostaglandins that support platelets and protect the stomach.

Wound care is "the provision of the appropriate environment for healing by both direct and indirect methods together with the prevention of skin breakdown [4, 5]. Depending on the severity of the wound the desirable wound dressing may therefore

serve among the purposes of to provide moisture and occlusion protection form infection and contamination, debridement and is application and removal dressing related trauma [6, 7, 8].

**MATERIALS AND METHODS:** Diclofenac diethyl amine was obtained as a gift sample from Sarvootham pvt, ltd, Hyderabad. Sodium alginate, Gelatine (Type-B), Glycerol, Propylene Glycol, Potassium dihydrogen phosphate, Sodium bicarbonate, and Sodium hydroxide was purchased from Himedia laboratories Pvt ltd, Mumbai. Methanol 99% is obtained from SD Fine chemical Ltd, Mumbai. Other ingredients and excipients used were of analytical grade.

**Preparation of films [9, 10]:**

**A. Preparation of Single Layer Film:** Preparation of single layer film was prepared by solvent casting technique. [(6gm Sodium alginate F1) (6gm sodium alginate and 4 gm gelatine F2)]was dissolved in 74 ml distilled water and heated at 40°C until a uniform solution was obtained and allowed to cool.5gm of Diclofenac diethyl amine was dissolved in 20 ml of propylene glycol and methanol co-solvent the ratio of 15:5. The drug solution was then added to polymer gel and stirred homogenously. Then 6ml of glycerol was added in to the polymer gel while stirring. The prepared gel (12.5gm) was poured in 9.6 cm diameter Petri dishes and allows drying in oven for 24hrs at 400C. For evaporating solvent, the rate of evaporation was controlled by inverting the cut funnel over the Petri dishes.

**B. Preparation of Bilayer film:**

a) **Preparation of Drug Free Layer:** The drug free films were prepared by solvent casting technique. The polymers (6gm sodium alginate F3) (6gm sodium alginate & 4gm gelatin F4) were dissolved in 94ml distilled water. 20ml of co solvent mixture propylene glycol and methanol (15:5) was added to sodium alginate and gelatin gel, 6ml of glycerol was added in to the polymer gel while stirring then this polymeric solution (45gm) was poured within 9.6 cm diameter a Petri dish and allow to dry in oven for 72hrs at 40$^0$C. For evaporating solvent, the rate of evaporation was controlled by inverting the cut funnel over the Petri dish.

b) **Preparation of drug loaded layers:** The drug loaded films were prepared by solvent casting technique. The polymers (6gm sodium alginate F3) (6gm sodium alginate&4gm gelatin F4) were dissolved in 74ml distilled water. 5gm of Diclofenac diethyl amine was dissolved in 20ml of co solvent mixture (propylene glycol and methanol 15:5) 6ml of glycerol was added in to the polymer gel while stirring then the drug solution was added to sodium alginate and sodium alginate & gelatin gel, then this solution (12.5gm in each) was poured on dried drug free layers and allow to dry in oven for 24hrs at 40°C. For evaporating solvent, the rate of evaporation was controlled by inverting the cut funnel over the Petri dish.

**Physicochemical characterization of transdermal films** [9, 10, 11]:

1. **Physical appearance:** The prepared patches were physically examined for colour, clarity and surface texture.

2. **Thickness uniformity:** The average thickness of the films was determined by using digital calliper.
   Thickness measurements were performed in triplicate

3. **Folding endurance:** The folding endurance was measured manually for the prepared films. A strip of film (2 x 2 cm2) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

4. **Solvent loss:** The solvent loss was calculated by difference between the weights of each layer before and after drying.

$$\text{solvent loss(g)} = \text{wt of hydrogel before drying} - \text{wt of dried film after drying}$$

5. **Drug content uniformity:** The drug content uniformity test was performed to ensure the uniform distribution of the drug throughout the films. This test was only carried out for the drug-loaded formulations. Samples with a 1 cm × 1 cm area were trimmed from three random sites in each film using scissors and dissolved separately in beakers containing 100 ml PBS (pH 7.4) that was heated at 40 ◦C for 25 min. Then, the DDEA concentration in the films was determined by measuring the absorbance of the film relative to the blank PBS sample. The test was repeated at least three times for each film and the average values were calculated.

6. **Moisture vapour transmission rate:** The films were cut using a 30 mm diameter circular template. The cut films were fixed over the brim of a 6 ml glass vial (30 mm diameter), containing 3 g of fused calcium chloride as desiccant. The vial was weighed and kept in desiccators at RH of 84% controlled with saturated solution of potassium chloride at $25^0$C. The vial was removed from desiccators and weighed at every 1 h interval for a period of 48 h. The experiment was run in triplicate and the average values were calculated.

$$MVTR = WT/S$$

Where W is g of water, T is number of hours of experiment, S is exposed surface area of the film.

7. **Expansion study:** The procedure for the expansion study was adapted from previous studies the expansion ratio was performed on a gelatine medium to imitate wound surfaces. To prepare the gelatine medium, 4 g of gelatine powder was dissolved in 100 ml of distilled water at $90^o$C and stirred until the clear solution was formed. Then, 25 g of clear gelatine solution was poured into the glass Petri dishes and allowed to cool to room temperature ($25^o$C) overnight. Then, 3 cm diameter of films were trimmed and placed on the gelatine surface. The change in diameter at time intervals of every 1 h ($D_t$) for a period of 48 h was measured.

$$\text{Expansion} = \frac{\text{diameter of sample at time t}(D_t)}{\text{diameter of sample at time 0}(D_o)}$$

8. **Tensile strength:** Tensile strength and percentage elongation at break were evaluated using a Universal Testing Machine. The films under investigation were cut using dumbbell shape template. The tensile properties of the films were examined by stretching the dumbbell shaped specimens (30 mm in length and 5 mm in width) to break at a crosshead speed of 5 mm/min. TS (Mpa) was calculated by dividing the required maximum load (N) for breaking film by transverse sectional area of the film (thickness × width). Percentage elongation at break (E %) was calculated by dividing the initial gage length of the sample (30 mm) by difference in the length at the moment of rupture and multiplying by 100. At least 5 repeats were carried out for each film formulation and the average values were calculated

9. **Morphology cross-section studies using scanning electron microscopy:** Morphology cross-section study of films was per-formed on a SEM at 12kV. Film samples were examined for cross-section characteristics, which were affixed to aluminium stubs with double-sided cellophane adhesive tape and sputter-coated with a layer of gold prior to imaging at magnifications: 100× to1000×.

10. ***In vitro* permeation studies** [12]: Drug permeation studies of Diclofenac diethyl amine liberated from dried single layer and bilayer films were investigated using Franz diffusion cell a clean, dried receptor cell was filled with phosphate buffer solution (PBS) pH 7.4 and allowed to equilibrate at 37.C. The cellulose acetate (pore size 0.45 m) membrane was mounted between receptor and donor compartment. Then, film was placed above the cellulose acetate membrane and sandwiched between receptor and donor compartments. The temperature of the receptor compartment was maintained at $37^o$C with circulating water jackets throughout the entire experiment.

All openings including donor top and receptor arm were occluded with par films to prevent evaporation. Using a glass syringe, the volume of 0.5 ml samples were withdrawn from the receptor medium at regular time intervals for 48 h and receptor volume was kept constant by replacing equal volume of fresh PBS solution of 37$^{o}$C. The samples were measured by using UV spectrophotometer at 285nm. The cumulative amount of Diclofenac diethyl amine drug diffusion was plotted against time. The Diclofenac diethyl amine drug flux was obtained from the steady state slope of each plot. The average values were calculated from Franz cell experiments.

## RESULTS:

### Analytical methods used in the determination of Diclofenac diethyl amine: (Figure 1 - 3)

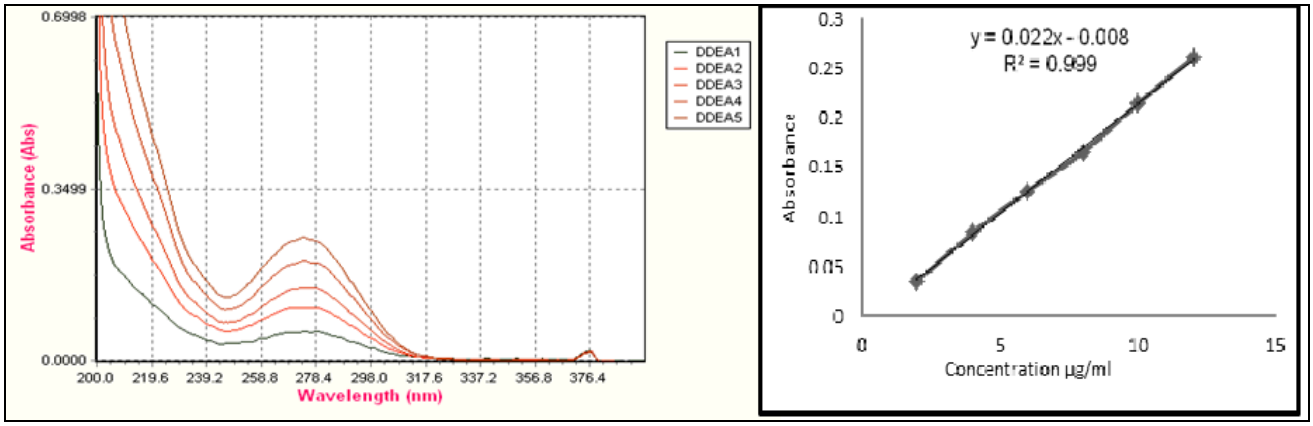



**FIGURE 1: UV SPECTRUM OF DRUG, CALIBRATION CURVE OF DRUG IN pH 7.4 PHOSPHATE BUFFER**

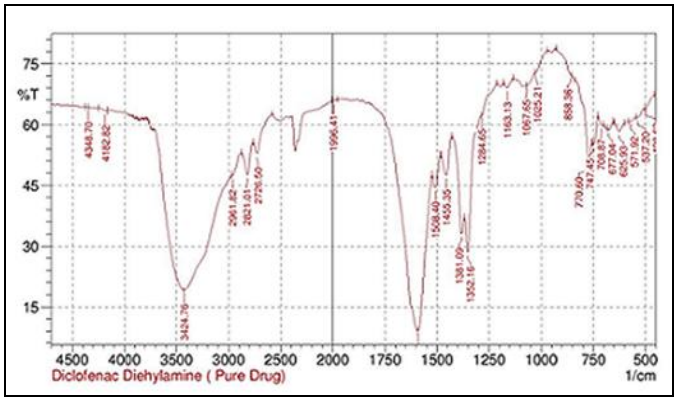
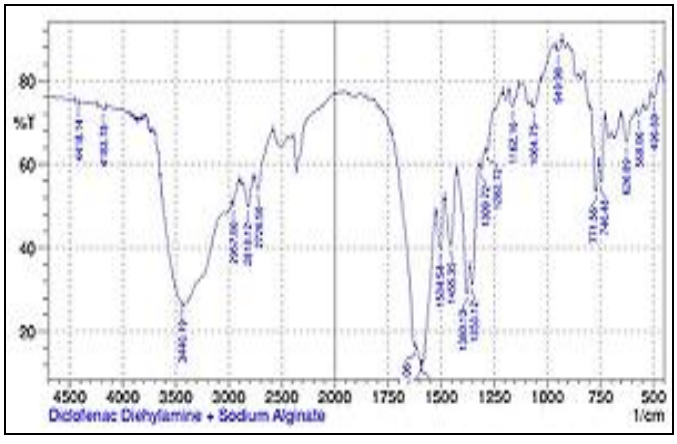



**FIGURE 2: FT-IR SPECTRUM OF DICLOFENAC DIETHYL AMINE**



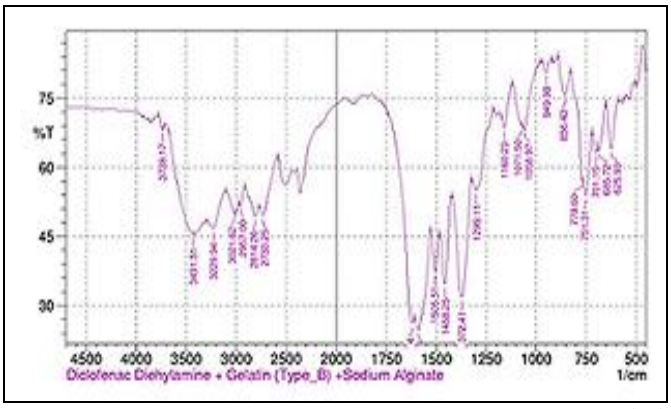




**FIGURE 3: FT-IR OF SINGLE LAYER FILM ($F_1$) FORMULATION & BILAYER FILM ($F_2$) FORMULATION**

**Evaluation of Transdermal Films:** The Drug, polymers and the fabricated transdermal films with combination of Sodium alginate and gelatin were subjected to various evaluation parameters like compatibility studies using FTIR absorption spectra, Preparation of calibration curve, physical properties, thickness of the patch, folding endurance, solvent loss, Drug content uniformity, Moisture vapour transmission rate, Expansion study, Tensile strength, Morphology cross-section studies, *In vitro* permeation studies. $F_1$ and $F_4$ films are selected for further evaluation studies as they are good in their physical appearance.

**TABLE 1: PHYSICO CHEMICAL CHARACTERIZATION OF SINGLE AND BILAYER FILMS**

| Code | *Physical appearance | *Thickness (mm) | *Folding endurance | *Solvent loss(g) | *content uniformity | *Tensile Strength (Mpa) | *Elongation at break (%) |
|---|---|---|---|---|---|---|---|
| Single layer | + | 0.67±0.02 | No visible crack | 8.48±0.51 | 6.4±2.0 | 20.80±2.29 | 22.78 ± 3.30 |
| Bilayer | + | 3.10±0.0 | No visible crack | 36.29±0.75 | 2.2±0.3 | 26.22± 0.95 | 58.05± 2.54 |

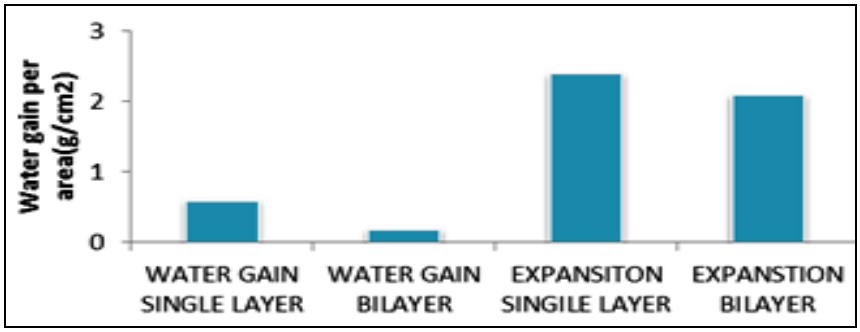



**FIGURE 4: EXPANSION AND MOISTURE VAPOUR TRANSMISSION RATE OF $F_1$AND $F_4$ FILMS**

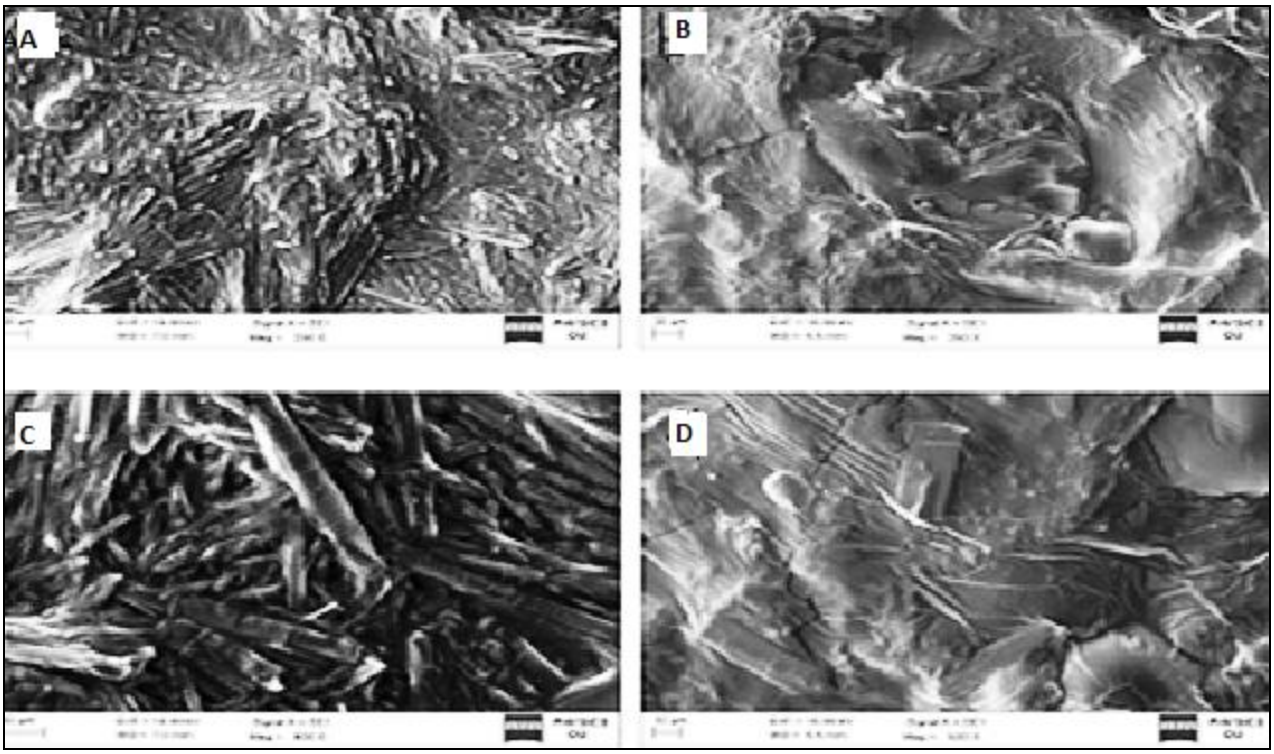



**FIGURE 5: SEM CROSS SECTIONAL MORPHOLOGY OF BILAYER FILMS AT (a) 250x & (c) 800x aND SINGLE LAYER FILMS AT (b) 250x & (d) 500x**

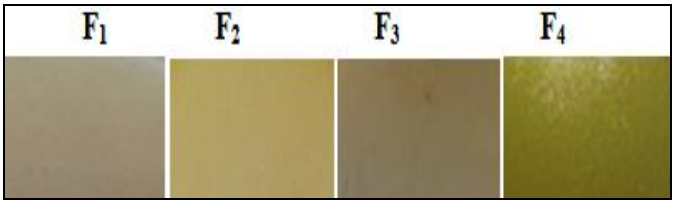



**FIGURE 6: DIFFERENT FORMULATED SINGLE ($F_1$, F2) AND BILAYER FILMS ($F_3$, F4)**

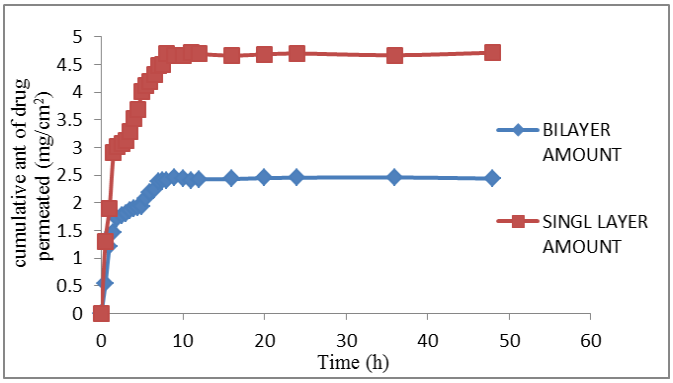



**FIGURE 7: CUMULATIVE AMOUNT OF DRUG RELEASE FROM $F_1$ SINGLE LAYER AND F4 BILAYER FILMS**

**DISCUSSION:** In the present study, bilayer transdermal films of Diclofenac diethyl amine were prepared by Solvent casting method using Sodium alginate and gelatin as polymers. The films $F_1$and $F_4$ were found to be having good film formation and smooth in their appearance. The FT-IR spectral analysis showed that there were no physical and chemical interactions between the drug and polymers and they were found to be compatible with each other.

The drug content Percentage yield was in the range 6.4±2.02, 2±0.3%. A good tensile strength was found in all the films, ranging from 20.80±2.29, 26.22± 0.95MPa. The Moisture vapour transmission rate was found to be low. This helps the formulations to be stable and prevents them from drying and brittle. The percentage of solvent loss was 8.48±0.51, 36.29±0.75g which prevents the films from drying. The cross-sectional micrographs of bilayer and single layer films are shown in Fig. 3.

The Diclofenac diethyl amine would expect to re-dissolve when in contact with solvent.

*In vitro* permeation studies were also performed to compare drug release profiles from single layer and bilayer films. Drug release profile was shown in terms of cumulative amount over 48 h in Fig.5.The flux of Diclofenac diethyl amine was low due to the presence of an extra layer in bilayer film formulations which acted as a controlling membrane. It was proposed that lower layer plays a part in slowed drug release from wound dressings when they come into contact with wound exudates. As the lower layer had fully swollen, the fluid continued to penetrate the upper layer which containing drug.

As a consequence, chain relaxation takes place and the incorporated drug such as Diclofenac diethyl amine begins to diffuse from the swollen upper layer. It had been revealed that slow release of drug from polymeric medicated dressings offer some potential advantages which generally includes prolonging the action of the active drug over longer periods of time by allowing continual release from such dosage form. It had been also cited that the wound care products which release a therapeutic substance to a wound interface in a slow release manner for a prolong period of time could improve the patient compliance by reducing the problem encountered with frequent dressing changes. Thus the present in vitro drug release study implied that by using the bilayer films which retain the drug for a longer period of time thus minimise the dressing changing frequency.

**CONCLUSION:** On the basis of the *in vitro* skin permeation study, the formulations yielded desired drug release by zero-order kinetics. Linear regression analysis of the drug diffusion profile showed that the mechanism of drug release was following diffusion pattern. The bilayer transdermal films we made could provide the delivery of drug at a controlled rate across intact skin and might be used in clinical situations. The formulations definitely improve patient compliance and reduce the wound dressing frequency.The bilayer film with a low Moisture vapour transmission rate may be useful for treating low suppurating wounds.

The mechanically strong bilayer films which hydrate slowly and low drug flux infer that they are potentially better suited for slow release application on wound surfaces.

**ACKNOWLEDGEMENT:** The authors wish to thank the management and staff members of Venkateshwara Institute of Pharmaceutical Sciences, Nalgonda, Andhra Pradesh, for providing support and assistance to conduct this work in the laboratory.

It is my privilege to express my sincere thanks to Dr. K. Venugopal Rao, professor & Mr. V. Harikrishna, Assistant Professor, Head of the Department of Pharmaceutics, Venkateshwara Institute of Pharmaceutical Sciences under whose exemplary guidance, help and encouragement to this work has been successfully completed.

**REFERENCES:**

1. Gros L., Clark W.E: The structure of skin. in “The tissue of the body” 6$^{th}$ed: 29-313.
2. Chien Y.W: Systemic delivery of pharmacologically active molecules across skin in “Targeted drug delivery”, 182-230.

3. Pragya and V. Rastogi: Transdermal patches: A Synergistic approach of drug delivery for NASIDs. IJPSR, 2012; 3(9): 2897-2909.
4. Nauman Rahim Khan, Gul Majid Khan, Abdur Rahim Khan, Abdul Wahab, Muhammad Junaid Asghar and Muhammad Akhlaqand Abid Hussain: Formulation, physical, *in vitro* and *ex vivo* evaluation of Diclofenac diethyl amine matrix patches containing turpentine oil as penetration enhancer , African Journal of Pharmacy and Pharmacology February, 2012; 6(6): 434-439, 15 .
5. Sussman G, Wound Management: How to treat. Australian Doctor 30 November 2001:S1-S8.
6. Atiyeh, B.S Hayek, S.N. Gunn, and S.W: New technologies for burn wound closure and healing—review of the literature. Burns 31: 944–956.
7. Singer A.J, Dagum A.B. Current management of acute cutaneous wounds 2008; 1037–1046.
8. Abdelrahman T, Newton H: Wound dressing's principles and practice 2011; 491–495.
9. Jadhav R.T, Kasture P.V, Gattani S.G and Surana S.J: Formulation and evaluation of transdermal films of Diclofenac sodium. International Journal of Chem Tech Research 2010; 2(1):354-360.
10. Riki V. Darji, Dr. K. R. Patel, Dr. M. R. Patel, and Dr. N. M. Patel: Formulation and evaluation of Tramadol matrix type transdermal patch. International Journal of Universal Pharmacy and Bio Sciences 2013; 2319-8141**.**
11. Hnin-EiThu, Mohd Hanif Zulfakar, Shiow-Fern: Alginate based bilayer hydrocolloid films as potential slow-release modern International Journal of Pharmaceutics 2012; 434: 375– 383.
12. R. Natarajan, N.N. Rajendran, M. RangaPriya, Formulation development and *in vitro* evaluation of cefixime trihydrate loaded chitason – alginate transdermal patches International journal of research and reviews in pharmacy and applied sciences IJRRPAS 2011; 1(4): 240-254.

**How to cite this article**:
Laxmi P, Mohammad A and Shirisha G: Development and characterization of bilayered transdermal film of Diclofenac diethylamine. Int J Pharm Sci Res 2014; 5(6): 2518-24.doi: 10.13040/IJPSR.0975-8232.5(6).2518-24