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# "FORMULATION DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCH OF DICLOFENAC–TIZANIDINE"

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## ABSTRACT

The aim of present research work was to prepare and evaluate transdermal drug delivery of Diclofenac and Tizanidine in combination which necessitates its frequent dosing by oral route. In certain instances skeletal muscle relaxants can also be administered topically. Transdermal drug delivery system of was prepared using combinations of Polyvinyl Pyrrolidone K 30 and Poly vinyl alcohol in different ratios by solvent evaporation technique. Different penetration enhancers were also used like Tween-20, Span-20 and Oleic acid. Plasticizers are a very important excipient in transdermal formulation and in this formulation. Polyethylene glycol 200 is used as a plasticizer. The prepared polymeric Films were characterized for various physiochemical parameters like film thickness, folding endurance, Moisture content, Tensile strength, Moisture vapor transmission, Percentage elongation, Drug content uniformity drug content, In vitro skin permeation, Permeability Coefficient and Flux (J) It was observed in result that Tizanidine -Diclofenac transdermal patch had Polyvinylalcohol, Polyvinylpyrrolidone, plastisizer Polyethylene glycol-200, and solvent system methanol: water formulation code F1, F2 and F3 revealed good *in-vitro* properties. Hence the transdermal patch would prove to be a promising formulation.

**KEYWORDS:** Tizanidine, Diclofenac, Plasticizer, transdermal drug delivery, Penetration enhancers.

## INTRODUCTION

A transdermal patch is used to deliver dose of medication through the skin into bloodstream. These sort of formulations were first approved in 1981 by FDA. Transdermal drug delivery systems provide controlled release, constant administration of the drug, and allow continuous

input of those drugs who has short biological half-life. And eliminates absorption based variations in circulation. Transdermal drug delivery system offers different advantages over conventional drug delivery systems.[1] Transdermal Drug Delivery System adheres to the body surface and delivers the drug, across the skin at controlled rate in to the blood stream. Transdermal drug delivery system is self-contained, discrete dosage form.[2]

Transdermal drug delivery system is also known as a transdermal patch or skin patch which deliver a specific dose of medication to the systemic circulation.[3]

Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation and plasticizers are also used to provide strength and flexibility to transdermal patches.[4-5]

Judicious choice of drug is critical in the successful development of a transdermal product. The important drug properties that affect its diffusion from device as well as across the skin include molecular weight, solubility, physical properties and melting point. Majority of drugs will not penetrate the skin at the rates sufficiently high for therapeutic efficacy. The permeation can be improved by the addition of permeation enhancers like dimethyl sulfoxide, dimethyl formamide, propylene glycol etc into the system.[6-7]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly used drugs to reduce pain and inflammation. Diclofenac an NSAID, have been recommended for the treatment of rheumatoid arthritis and osteoarthritis. It also has anti-inflammatory, antipyretic and analgesic activities. The short biological half-life (about 1-2 hour) and higher dosing frequency make Diclofenac a suitable candidate for transdermal drug delivery system. Tizanidine Clonidine congener and it is a central α2-adrenergic agonist- inhibits release of excitatory amino acids in spinal interneurons It may facilitate the inhibitory transmitter glycine as well. It inhibits polysynaptic reflexes; reduces muscle tone and frequency of muscle spasms without reducing muscle strength.

Using the transdermal route eliminates these side effects, increases patient compliance, avoid first pass metabolism, maintains the plasma compliance, avoids first- pass metabolism, maintains the plasma drug level for longer period of time. Therefore, an improved Diclofenac -Tizanidine formulation with a high degree of permeation could be useful in treatment of locally inflamed skin, inflammatory and painful states of supporting structures of the body.

The aim of present study to develop promising controlled release polymeric transdermal patch for the Diclofenac-Tizanidine to improve the therapeutic effect of drug by retaining the transdermal drug delivery patch on the skin surface and to enhance the penetration power of the drug from patch with the use of different penetration enhancers.

**2. MATERIAL AND METHOD–** The drug Diclofenac and Tizanidine were obtained from Surekha Pharma, Indore and Sun Pharmaceuticals Industries Ltd Gujarat. Glycerol Polyvinyl alcohol Polyvinylpyrrolidone, Methanol Ethylcellulose, Dimethylsulfoxide Tween 80 and Span 80 from Central drug house Delhi. Dibutylphtalate from Qualigens Fine Chemicals.

**3. Optimization Study**

**An optimization studies was done in two phases**

**I$^{st}$ phase (Table 1)**

Firstly optimization of polymers, plasticizer, solvent system is done to obtain a polymeric film which can fulfill the criteria of suitability required for the transdermal formulation.

1. Film optimization - polymeric film was firstly prepared using EC: PVP and PVA: PVP in combination with different ratio of solvent system.
2. Solvent ratio optimization - methanol: distilled water was taken in different ratio as solvent system.
3. Plasticizer optimization - Different plasticizer ratio was optimized by taking polyethylene glycol, dibutyl phthalate, Glycerol in different concentrations.
4. Drying temperature was optimized

**II$^{nd}$ phase (Table 2)**

The result outcomes after first phase study have been used to optimize enhancer with the polymeric composition. Enhancer's ratio was optimized using different ratios of oleic acid, DMSO, span-80 and Tween-80 in different concentrations.

**4. Preparation of Transdermal patches**

By the results out comes of complete optimization study by using various combinations of Polymeric ratio of polyvinyl pyrrolidone K 30 and poly vinyl alcohol along with different penetration enhancers Tween-20, Span-20 and Oleic acid (Table-1and Table-2) final transdermal patch for the drug is prepared. Polyethylene glycol 200 is used as a plasticizer. Transdermal patches containing Diclofenac -Tizanidine were prepared by the solvent casting technique in glass molds. The polymer solution occupying the surface area of 38.5 cm$^2$ and

0.2 mm thickness was found satisfactory by hit and trial methods the volume of the solution is found to be in between 10-15 ml with accordance to the velocity and flow ability of content of formulation. Then screening was done with various plasticizers to ascertain the desired flexibility and elastic properties of the patch. The pH of the solution after completing the optimization study is found to be in between 5.5 to 6. The adhesive properties of the patch cannot be obtained without plasticizers.

**Table 1: Optimization Studies for the transdermal patch.**

| Form. | Polymeric ratio | Solvent ratio | Plasticizer | Enhancer ratio | | | |
|---|---|---|---|---|---|---|---|
| Code | PVA:PVP | MeOH: Water | Ratio | | | | |
| | | | | DMSO | Tween-20 | Span-20 | Oleic acid |
| TDPI | 700:300 | 20:30 | 0.50% | 0.10% | - | - | - |
| TDPII | 700:300 | 20:30 | 0.50% | 0.20% | - | - | - |
| TDPIII | 700:300 | 20:30 | 0.50% | 0.50% | - | - | - |
| TDP IV | 700:300 | 20:30 | 0.50% | - | 0.10% | - | - |
| TDPV | 700:300 | 20:30 | 0.50% | - | 0.05% | - | - |
| TDPVI | 700:300 | 20:30 | 0.50% | - | 0.50% | - | - |
| TDPVII | 700:300 | 20:30 | 0.50% | - | - | 0.50% | - |
| TDPVIII | 700:300 | 20:30 | 0.50% | - | - | 0.10% | - |
| TDPIX | 700:300 | 20:30 | 0.50% | - | - | 0.05% | - |
| TDPX | 700:300 | 20:30 | 0.50% | - | - | 0.01% | - |
| TDPXI | 700:300 | 20:30 | 0.50% | - | - | - | 0.50% |
| TDPXII | 700:300 | 20:30 | 0.50% | - | - | - | 0.20% |
| TDPXIII | 700:300 | 20:30 | 0.50% | - | - | - | 0.10% |
| TDPXIV | 700:300 | 20:30 | 0.50% | - | - | - | 0.05% |

**Table 2: Evaluation for Optimized formulations of transdermal patch.**

| Formulation Code | Thickness (mm) | Folding endurance test | Moisture Content | Physical appearance of the polymeric film obtained. |
|---|---|---|---|---|
| TDPI | 0.2±0.1000 | + + | 1.05 | Flexible, smooth, tough |
| TDPII | 0.2±0.05774 | + + | 1.06 | Flexible, smooth, tough |
| TDPIII | 0.2666±0.2082 | + + | 1.09 | Flexible, smooth, tough |
| TDPIV | 0.17±0.05774 | + + | 1.45 | Flexible, smooth tough |
| TDPV | 0.23±0.05774 | + + | 1.41 | Flexible, smooth, tough |
| TDPVI | 0.27±0.05774 | + + | 1.37 | Flexible, smooth, tough |
| TDPVII | 0.4±0.1000 | _ _ | 1.79 | Very sticky, glossy, wet film was observed. |
| TDPVIII | 0.33±0.1528 | + + | 1.75 | Less sticky, glossy, wet film was observed. |
| TDPIX | 0.3±0.1000 | + + | 1.67 | Flexible smooth less sticky film observed. This |

| | | | | |
|---|---|---|---|---|
| | | | | concentration was further used for formulation. |
| TDPX | 0.37±0.05774 | + + | 1.12 | Glossy, little wet film was observed. |
| TDPXI | 0.23±0.1155 | _ _ | 2.22 | Sticky, glossy, wet film was observed |
| TDPXII | 0.37±0.1155 | _ _ | 2.33 | Sticky, glossy, wet film was observed |
| TDPXIII | 0.33±0.1155 | _ _ | 2.38 | Sticky, glossy, wet film was observed. |
| TDPIV | 0.27±0.1155 | _ _ | 2.27 | Sticky, glossy, wet film was observed. |

+ + Film have not broken after many repeated folding.

_ _ Film have broken into pieces after many repeated folding.

**Table 3: Formulations of transdermal patch with optimized ratio of polymer and plasticizer.**

| Formulation Code | Polymeric ratio | Solvent ratio | Plasticizer Ratio | Enhancer ratio | |
|---|---|---|---|---|---|
| | PVA: PVP | MeOH: Water | | Tween-20 | DMSO |
| F1 | 700:300 | 20:30 | 0.50% | | |
| F2 | 700:300 | 20:30 | 0.50% | 0.50% | |
| F3 | 700:300 | 20:30 | 0.50% | | 0.50% |

## 4. Characterization of transdermal Patches[6]

### 4.1 Physical appearance

All the transdermal patches were visually inspected for color, clarity, flexibility, and smoothness.

### 4.2 Thickness of the films

The thickness of the drug-loaded transdermal Patches were measured at three different places using a Vernier caliper and mean values were calculated.

### 4.3 Tensile strength

Ratio of the maximum load a material can support without fracture when being stretched to the original area of a cross section of the material. When stresses less than the tensile strength are removed, a material completely or partially returns to its original size and shape. As the stress approaches that of the tensile strength, a material that has begun to flow forms a narrow, constricted region that is easily fractured. Tensile strengths are measured in units of force per unit area.

**4.4 Folding endurance**

This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

**4.5 Percentage moisture uptake**

The weighed films were kept in a desiccator at room temperature for 24 hours and then exposed to 84% relative humidity using a saturated solution of potassium chloride. Finally, the films were weighed and the percent moisture uptake was calculated using the formula:

Percentage moisture uptake = [Final weight - Initial weight/Initial weight] × 100.

**4.6 Moisture content.**

The prepared films were weighed individually and kept in a dessicator containing silica at room temperature for 24 hours. The films were weighed again and again until they showed a constant weight. The percent moisture content was calculated using the following formula:
Percent moisture content = [Initial weight - Final weight/Final weight] x100.

**4.7 Moisture vapor transmission (MVT)**

MVT is defined as the quantity of moisture transmitted through unit area of film in unit time .Glass cells were filled with 2 g of anhydrous calcium chloride and a film of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH) at 27 ± 2 °C for 24 h.

**4.8 Drug content uniformity**

Transdermal system of specified area (2 $cm^2$) was cut into small pieces and taken into a 100 ml volumetric flask and 100 ml of phosphate buffer pH 7.4 was added, and kept for 24 hours with occasional shaking. Then, the suitable dilution was made with phosphate buffer of pH 7.4. Similarly, a blank was carried out using a drug-free patch. The solutions were filtered and the absorbance was measured at 271 nm for Diclofenac and 226 nm for Tizanidine.

**Table 4: Characterization of Transdermal patches.**

| S. No. | Parameter | F1 | F2 | F3 |
|---|---|---|---|---|
| 1 | Thickness (mm) | 0.2±0.1 | 0.2±0.06 | 0.27±0.21 |
| 2 | Folding endurance test | + + | + + | + + |
| 3 | Percent moisture uptake | 4.545 | 3.7037 | 3.5714 |
| 4 | Percent moisture Content | 1.05 | 0.75 | 0.1354 |
| 5 | Water vapor transmission study ($gm/cm^2$/hours) | $5.87x10^{-3}$ | $4.7x10^{-3}$ | $13.7\ x10^{-3}$ |
| 6 | Tensile strength ($N/mm^2$) | 4.69±0.2339, | 3.66±1.180, | 5.13±0.1350 |
| 7 | Percentage elongation | 238± 0.002 | 271± 0.100 | 191± 0.003 |

**+ + :** Results were satisfactory.

**Table 5: Drug content uniformity of the formulation.**

| S. No. | λ max | % drug content |
|---|---|---|
| F1. | 271 | 91.1±0.8 |
| | 226 | 80.2±0.4 |
| F2. | 271 | 91.1± 0.5 |
| | 226 | 85.8±0.2 |
| F3. | 271 | 90.4± 0.6 |
| | 226 | 78.9±0.8 |

**4.9 In vitro skin permeation studies Preparation of the skin barrier:** Fresh full-thickness goat skin was used for the study. The skin was immersed in water at 60$^{o}$C for a period of 5 minutes. The epidermis was peeled from the dermis.

**4.10** The *in vitro* skin permeation studies were carried out using a Keshary-Chien diffusion cell. A 2 $cm^2$ patch is placed in intimate contact with the stratum corneum side of the skin; the topside was covered with the aluminum foil as a backing membrane. Magnetic bead was placed in the receptor compartment filled with 20 ml of phosphate buffer, the whole assembly was kept on the magnetic stirrer, at a speed of 100 rpm and the temperature conditions controlled at 37± 2°C.The cell contents were stirred with a magnetic stirrer. Sample of 1 ml was withdrawn at interval 1,2,3,4,5,6,7,8, 9,10, 11,12,16,20 and 24 hour simultaneously replaced with equal volume of replaced with equal volume of phosphate buffer. The samples were withdrawn and filtered through whatman filter paper and diluted upto 5 ml with phosphate buffer.

**Table 6: *In vitro* drug release.**

| Formulation Code | Tizanidine released from formulation at λmax 226 nm | Diclofenac released from formulation at λ max 276 nm |
|---|---|---|
| F1 | 72.75% | 60.94% |
| F2 | 92.63% | 75.16% |
| F3 | 84.30% | 71.20% |

**Table 7: Permeability coefficient and Flux values of the formulations.**

| S. No. | Permeability Coefficient (P) mg/cm/hr | | Flux (J) mg/cm$^2$/h | |
|---|---|---|---|---|
| | Diclofenac | Tizanidine | Diclofenac | Tizanidine |
| F1. | 0.02 | 0.08 | 1.37 | 0.06 |
| F2. | 0.34 | 0.09 | 23.46 | 0.64 |
| F3. | 0.04 | 0.009 | 2.96 | 0.07 |

### 5.1.6 Differential Scanning Calorimetery

Differential scanning calorimetery (DSC) of drug, Diclofenac Sodium, Tizanidine Hydrochloride, Polyvinly alcohol, Polyvinylpyyrolidone and mixture of all ingredients in Tizanidine Hydrochloride- Diclofenac Sodium transdermal formulation were carried out by heating the sample from 30°C to 400°C heating rate of 10°C/min. in a nitrogen environment. Thermograms obtained are shown in figure 1(a-e). It was observed that no interaction has occurred between drug and the polymer.

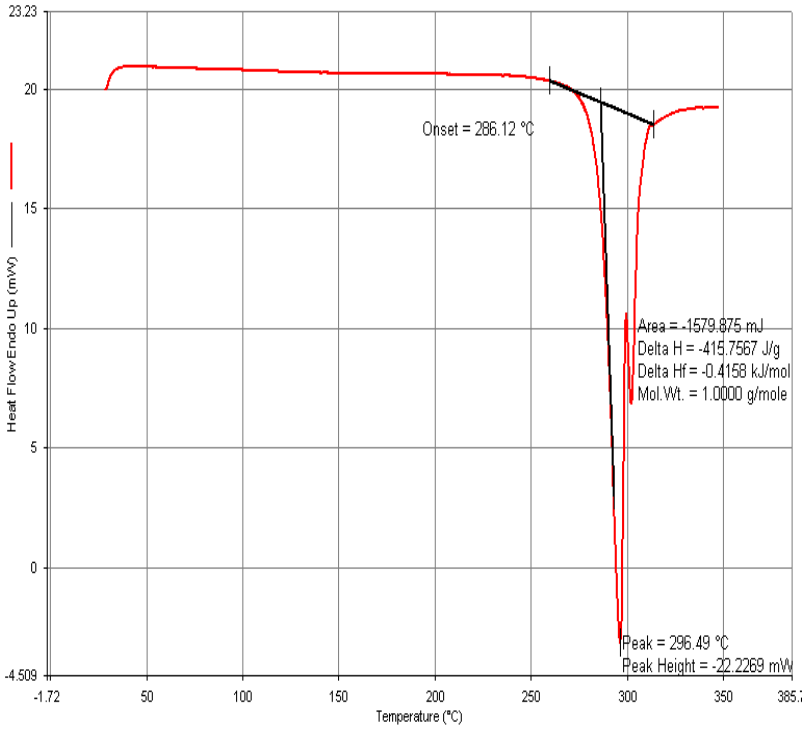
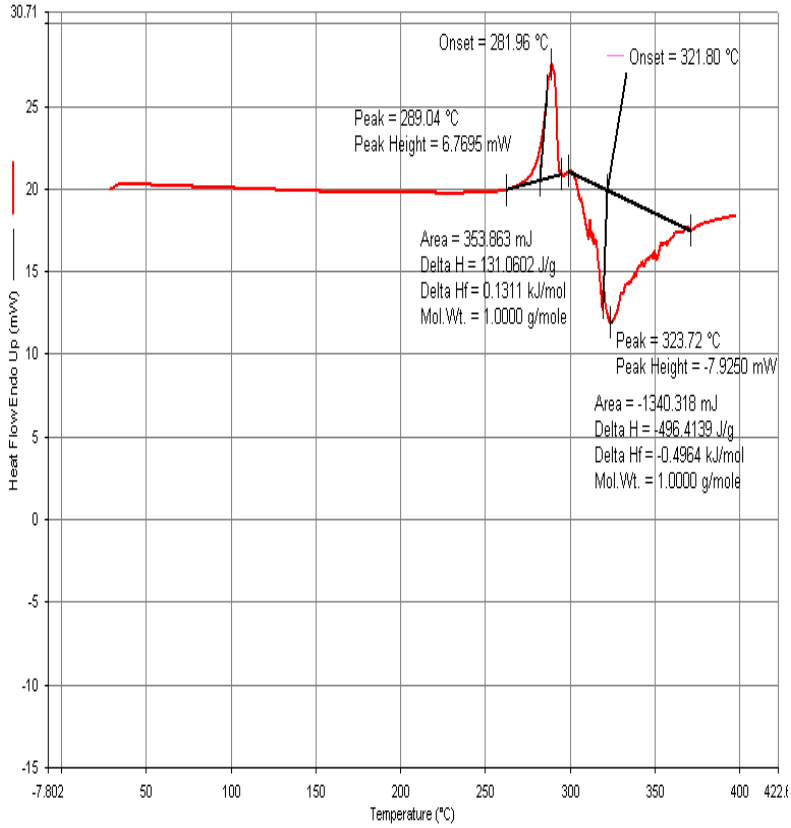
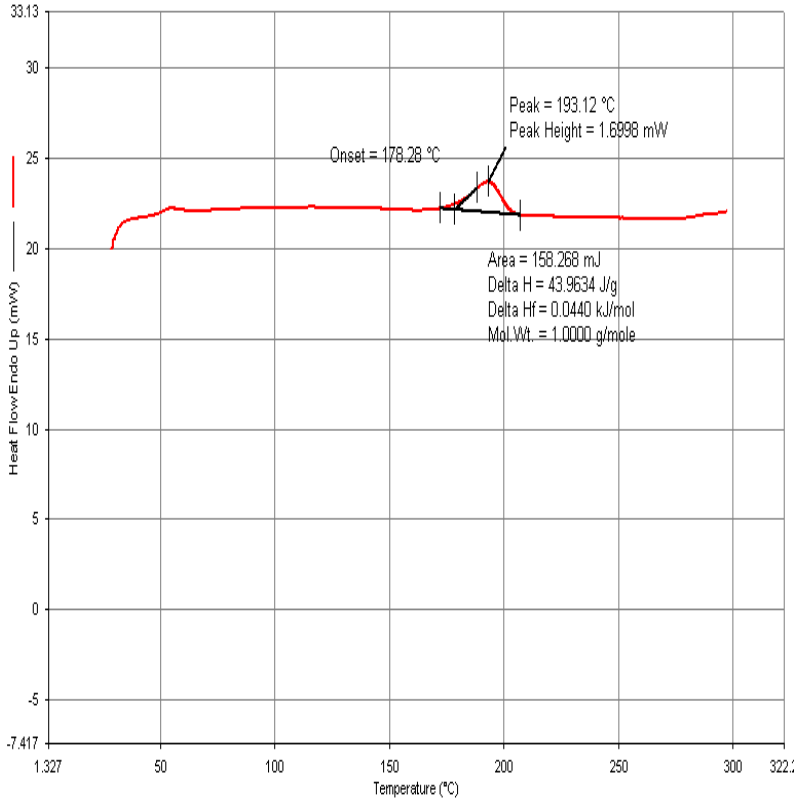


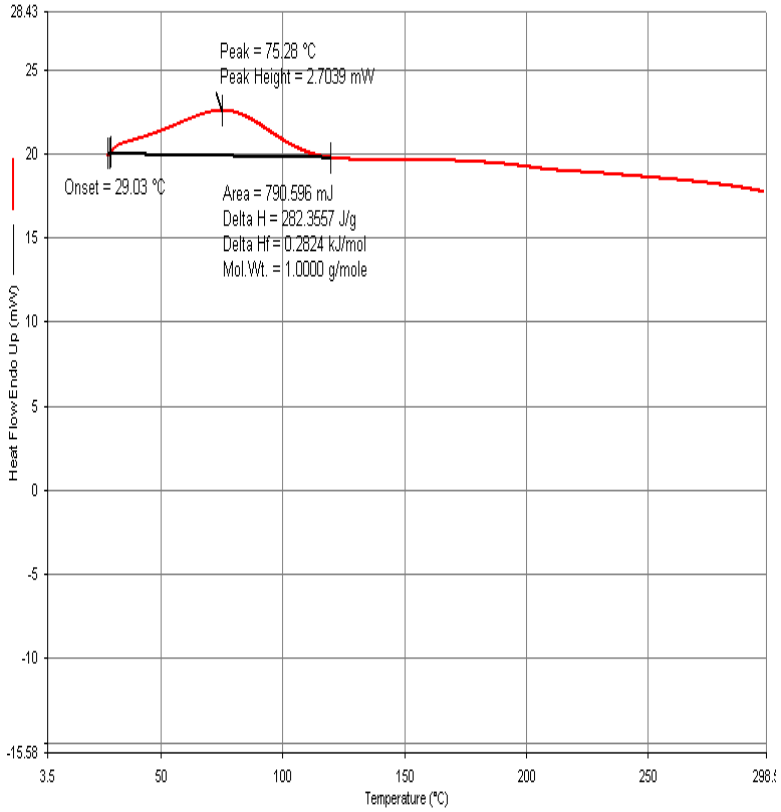

**Fig. 1(a): DSC of Diclofenac Sodium.**



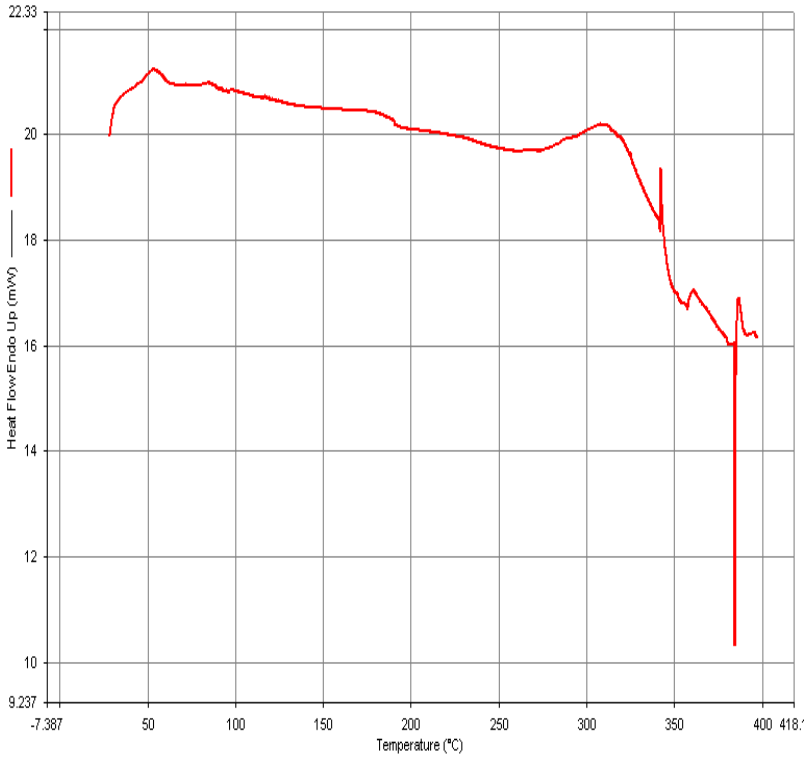

**1(b): DSC of Tizanidine Hydrochloride.**



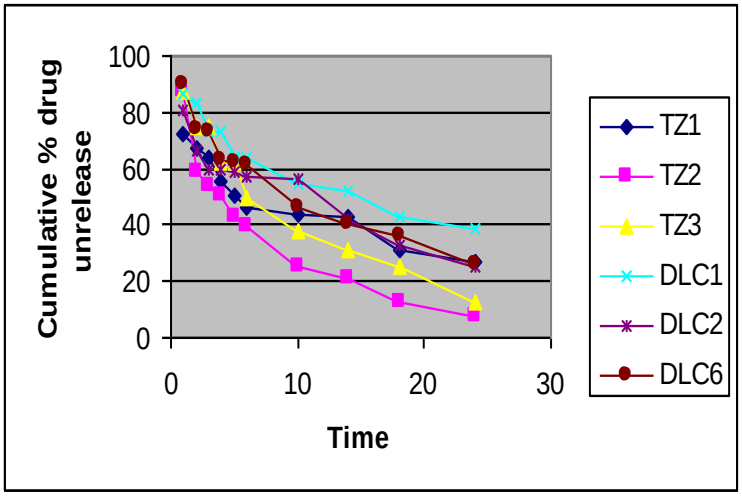

**1(C): DSC of Polyvinly alcohol.**



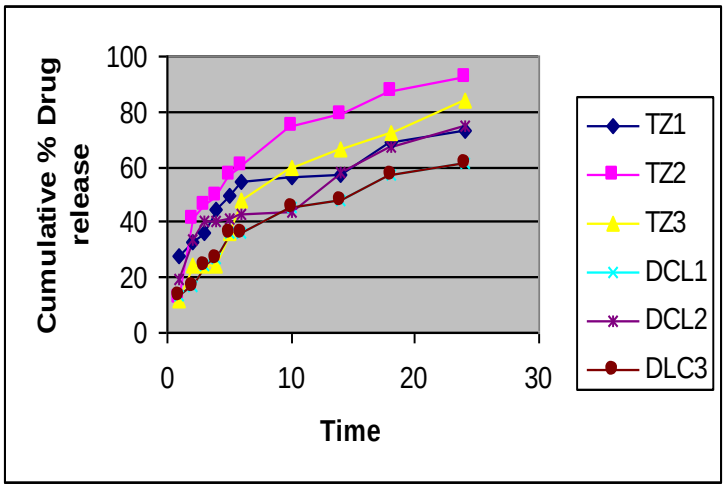

**1(d): DSC of Polyvinylpyrrolidone.**



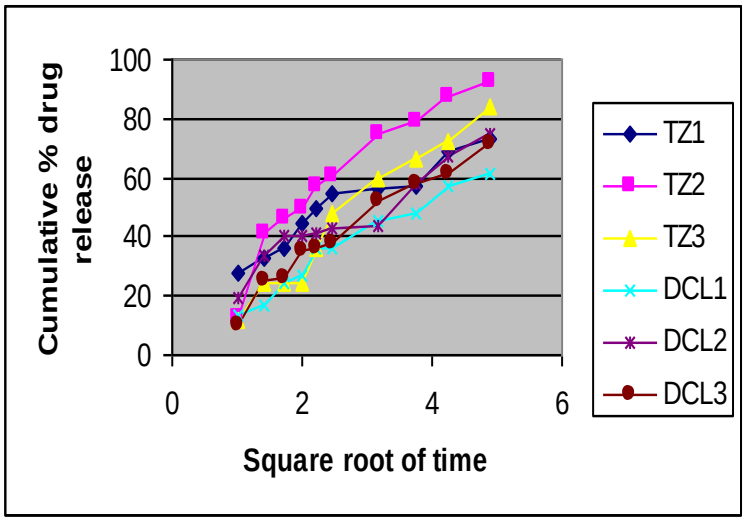

**1(e): DSC of mixture of all ingredients.**



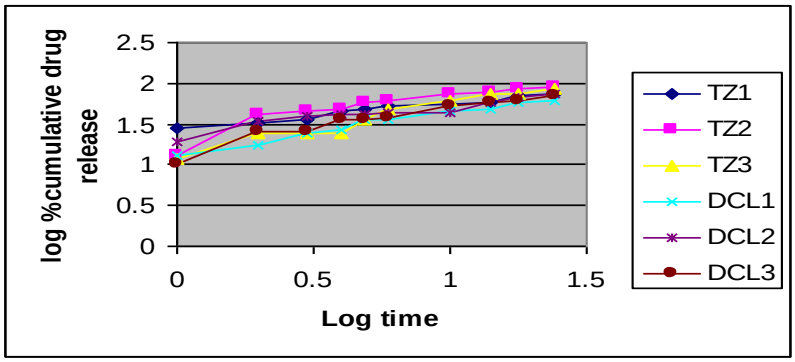

**Zero-order equation (Cumulative % drug release vs. Time).**




**First order equation (Cumulative % drug unreleased vs. Time).**




**Higuchi's diffusion equation (Cumulative % drug release vs. Square root of time).**




**Korsmeyer's equation (log Cumulative % drug release vs. log time).**

## RESULT AND DISCUSSION

Concentration of the drug was estimated using UV spectroscopic. Identification of Tizanidine and Diclofenac at pH 7.4 which was also pH of blood serum was done by UV spectroscopy.

Drug partition coefficient study was performed in n-octanol/water and n-octanol/aqueous buffer.

Further Differential Scanning Calorimetry was performed to show interaction of polymer with the drug, shown in (Fig no.1a to 1d).

Optimization studies were consist of two phases. Phase I consist of optimization studies for the formulation of TDDS using different types of polymers, plasticizers and enhancers. It was observed that PVA:PVP in combination with plasticizer Polyethylene glycol-200 dissolved in solvent system Methanol: Water in 30:20 ratio at 60°C temperature is most suitable, Optimization study for phase-II was done with enhancers. The different enhancers selected on the basis of HLB values were Oleic acid, Span 80, Tween 80 and DMSO. DMSO and Span 80 shows best results as they passed folding endurance, thickness, moisture content and physical appearance test, shown in (Table 1-3).

Preparation and evaluation of the transdermal formulation were observed by using three different samples of the formulation F1 i.e formulation without enhancer, F2 i.e formulation with Tween-80 and F-3 i.e formulation with DMSO. All the formulations were considered suitable for characterization of physicochemical properties, shown in (Table 4), drug content uniformity( Table 5) and in-vitro release, shown in (Table 6).Tween 80 formulation shows the release and higher flux value over the other formulations, shown in (Table 7). The in vitro release of formulationis reported in (Table 6).

Analysis of drug release mechanism for F1, F2 and F3 Formulations were subjected to Zero , First, Higuchi and Kohmeyer's model. The Kinetic treatment revealed that drug release from F1,F2 and F3 followed Higuchi model as the correlation coefficient of linear relationship between cumulative percentage drug release and square root of time was found to be 0.9303 and 0.9656 for F1,0.9095 and 0.905 for F2,0.9655 and 0.9687 for F3.The data fitman of drug release profile was done using Kohmeyer's drug model. The mechanism of drug release in these caseswas known to follow anomalous transport mechanism, i.e drug is released by initial swelling and followed by anomalous transport.

In the first thermogram Fig 1 (a) sharp endothermic peak were observed between 288 to 290° which represent the glass transition temperature of the drug Diclofenac .Similarly in thermogram 1 (b) at 280 ° a peak was observed which showed glass transition temperature of drug Tizanidine. In the therogram of polymer PVA a peak was observed at 193° which is near to the melting point of PVA that is 200° .In the thermogram of Polyvinylpyrrolidone a peak was observed at 75.2 ° though the glass transition temperature of the polymer is 150° In the DSC thermogram of the mixture no sharp peak were observed of both the drug and both the polymer which shows the sign of interaction between the formulation ingredients and drugs.

## CONCLUSION

The aim of this project was to prepare the transdermal patch of Tizanidine - Diclofenac using compatible polymers and copolymers which may relief patient from muscular spasm giving optimum pH 5.6-6 equal to pH of skin. Systemic circulation of the drug in the patch form is more giving earlier relief with minimum side effects compared to other routes of drug administration.

In this project Tizanidine-Diclofenac transdermal patch were prepared using Polyvinylalcohol, Polyvinylpyrrolidone, plastisizer Polyethylene glycol-200, solvent system methanol: water. Evaluation undergoing various identification and conformation parameters proved that all the preparations F1, F2 and F3 shows good *in-vitro* properties. Hence the transdermal patch would prove to be a landmark in TDDS.

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