Research Article ISSN: 2349-2678

Contents lists available at www.ijpba.in

International Journal of Pharmaceutical and Biological Science Archive

NLM (National Library of Medicine ID: 101738825)

Index Copernicus Value 2019: 71.05

Volume 10 Issue 5; September-Octobet; 2022; Page No. 17-27

Development and Evaluation of Targeted Drug Delivery Systems of Tenoxicam TDDS Prepared With Solid Dispersions

K. Muni Raja Lakshmi

Department of Pharmaceutics, S.V.U.College of Pharmaceutical Sciences, S.V.University, Tirupati, A.P, India-517501

Conflicts of Interest: Nil

Corresponding author: K. Muni Raja Lakshmi

ABSTRACT

RA occurs as erosive synovitis, symmetric, lead to joint and cartilage damage, significant disability, and reduction in quality of life. Tenoxicam (4-hydroxy-2-methyl-*N*-(pyridine-2-yl)-2*H*thieno- 1,2-thiazine-3-carboxamide-1,1-dioxide) (*1*) is a NonSteroidal Anti-Inflammatory Drug (NSAID), with analgesic and antipyretic properties.. It is indicated for treatment of rheumatoid arthritis and to control acute pain. It is a BCS class II drug. To improve its solubility it was prepared as solid dispersions by solvent evaporation method using PEG 25000, PVP K-30, and Sodium Starch Glycolate as polymers. Then they were evaluated and the promising formulation was prepared as transdermal patch. The the patch was evaluated and the promising formulation which had highest amount of in-vitro drug release was evaluated for pharmacodynamics activity. At the end of the treatment the inflammation on both hind paws of treated rats were reduced compared to untreated rats. Transdermal patches of tenoxicam made with solid dispersions of tenoxicam were used to treat the rheumatoid arthritis in rats

Key Words: Rheumatoid arthritis, Tenoxicam, Solid dispersions, Transdermal patch.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease of unknown etiology that affects 1.0% of the general population. The incidence of arthritis is more common among women and there are high rates of disease onset associated with pregnancy. Nearly 66% of people with arthritis are younger than 65 years of age. Arthritis affects adults and children of all races and global prevalence is expected to soar in the coming decades. RA is an autoimmune disease of the joints, which leads to changes in the innate and adaptive immune system at cellular level which produces a chronic synovial joint inflammatory response that may affect other peripheral organs. RA is characterized by symmetric, erosive synovitis, which, if uncontrolled, can lead to joint and cartilage damage, multiple co-morbidities, significant disability, and reduction in quality of life. RA has been treated with a combination of anti-inflammatory drugs and immune suppressant drugs to reduce inflammation and even immune system function. Unfortunately, these approaches can create problems due to side effects that include stomach damage, susceptibility to infections, and increased cancer and cardiovascular risk because all of the drugs in use have severe, potentially life threatening consequences due to non-specific targeting, often in combination with impaired immune function (1). Development of new drug molecule is expensive and time consuming. Delivering drug at controlled rate, slow delivery, targeted delivery are methods to decrease adverse effects. So, in order to decrease Nonsteroidal anti-inflammatory drugs -related adverse effects, site-specific delivery and targeted drug delivery system has been developed. The use of targeted drug delivery is expected to increase specificity of drugs and

thus reduce side effects by decreasing the dose of administered drugs (2).

Tenoxicam (4-hydroxy-2-methyl-*N*-(pyridine-2-yl)-2*H*thieno- 1,2-thiazine-3-carboxamide-1,1-dioxide) (*1*) is a NonSteroidal Anti-Inflammatory Drug (NSAID), with analgesic and antipyretic properties.. It is indicated for treatmentof rheumatoid arthritis and to control acute pain. The anti-inflammatory effects of tenoxicam may result from the inhibition of the enzyme cyclooxygenase and the subsequent peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, their inhibition accounts for the peripheral analgesic effects of tenoxicam.

It is poorly soluble BCS class II drug with maximum dose of 20 mg per day, possess first pass metabolism. Hence the aim of the present work is to develop targeted drug delivery system to prevent hepatic metabolism as transdermal patch. The work involves the preparation of solid dispersions to increase water solubility and further development as transdermal patches including evaluation at in-vitro level and invivo level. As arthritis affects joints, up on local application drug can easily diffuses from the site of application into the joints and shows its action on the inflammed area.

Materials:

Tenoxicam was obtained as gift sample from Dr.Reddy's laboratory, Hyderabad, INDIA. PEG 25000, PVP K-30, Sodium Starch Glycolate, Dichloromethane and acetone was purchased from Hi media Laboratories . Eudragit RL PO, HPMC, Dibutyl phthalate, DMSO, Carbinol was purchased from S.D.fine Pvt Ltd. Bovine type II Collagen and Incomplete Freund's adjuvant was purchased from Chondrex, U.S.A.

Methods

Preparation of solid dispersion of tenoxicam:

Solvent evaporation method:

Tenoxicam and carrier(PEG 25000, PVP K-30,Sodium Starch Glycolate) was taken in the ratio of 1:3,1:6,1:9 as shown in **Table 1**. It was dissolved in chloroform and acetone (1:1). Solvent was evaporated using lyophillizer (Lyodel freeze dryer). Dry mass obtained after lyophilisation was passed through sieve no 44 followed by sieve no 66. The resultant solid dispersions were weighed and transferred in sample holders and kept in dessicator.

Table: 1 Composition of solid dispersions of tenoxicam:

S.No	Composition	Drug : Carrier
1	TNX: PEG 25000	1:3
2	TNX: PEG 25000	1:6
3	TNX: PEG 25000	1:9
4	TNX: PVP K-30	1:3
5	TNX: PVP K-30	1:6
6	TNX: PVP K-30	1:9
7	TNX: SSG	1:3
8	TNX: SSG	1:6

Characterization of solid dispersions:

All the prepared solid dispersions were evaluated by Soubility analysis, FTIR analysis, DSC, *invitro* drug release

Solubility analysis:

Each solid dispersion of 20 mg was weighed accurately and transferred to 100ml volumetric flask and dissolved in phosphate buffer pH 5.5(since the transdermal patches are fina preparations the pH 5.5 phosphate buffer is taken as medium to asses solubility) . Volume was made up with phosphate buffer pH 5.5 up to the mark. After suitable dilution, the absorbance of the above solution was measured at 261nm by UV spectrophotometer (Shimadzu).

***In-vitro* drug release profile:**

Solid dispersions equivalent to contain 20 mg of TNX was calculated and weighed accurately the same quantity. Dissolution was performed in USP II apparatus using pH 5.5 phosphate buffer as medium maintained at 50 rpm and temperature of 37 ± 0.5^{0}C. At suitable time intervals aliquots of samples were withdrawn by replacing the volume with fresh solvent. The drug content of samples was estimated at 261nm by UV spectrophotometer (Shimadzu).

Fourier Transform Infrared (FTIR) Spectroscopy studies

To study the interaction between drug and polymers used in the formulation FT IR spectroscopy was carried out for the test samples. FT IR spectrum of pure tenoxicam , the promising solid dispersion of tenoxicam containing TNX:PEG 25000 were recorded.

Differntial scanning calorimetry

Thermal behavior of tenoxicam and promising formulation TNX:PEG 25000(1:9) tenoxicam were analyzed using differential scanning calorimeter (Metler tolbedo, Switzerland). Approximately 10mg of samples was placed in aluminum crimp cells and subjected to DSC under constant purging nitrogen at 20 mL/min. Thermograms were recorded by heating samples from 30°C to 400°C at a heating rate of 10°C/min with empty aluminium pan as the reference.

Formulation of patch:

Preparation of transdermal patch of tenoxicam solid dispersions:

6 formulations of transdermal patches were prepared by solvent casting method using promising solid dispersion TNX:PEG 25000(1:9) and TNX . The composition is given in **Table :2** HPMC K4M, Eudragit RL PO and the solid dispersion were dissolved in dichloromethane and carbinol (1:1). DiButyl Pthalate (plasticizer), DMSO (penetration enhancer) were added. The solution was stirred for half an hour in magnetic stirrer. Then the homogenous mixture was poured in to mould. The solvent was allowed to evaporate at controlled rate by placing an inverted funnel over the mould. The control of evaporation is necessary for uniform drying of patches. The drying was carried out at room temperature for duration of 24 hrs. After 24 hrs the dry patches were removed from moulds and stored in desiccators until used.

Table 2: Composition of TDDS

INGREDIENTS	**FORMULATION CODE**					
	TT1	TT2	TT3	TT4	TT5	TTNX
HPMC K4M (mg)	50	50	100	100	50	100
Eudragit RL PO (mg)	100	50	50	150	150	50
DBT(ml)	2	2	2	2	2	2
DMSO(ml)	0.5	0.5	0.5	0.5	0.5	0.5
	TNX:PEG 25000(1:9) equivalent 20mg of TNX	TNX:PEG 25000(1:9)equivalent 20mg of TNX	TNX:PEG 25000(1:9)equivalent 20mg of TNX	TNX:PEG 25000(1:9)equivalent 20mg of TNX	TNX:PEG 25000(1:9)equivalent 20mg of TNX	20mg of TNX
Carbinol(ml)	2.5	2.5	2.5	2.5	2.5	
Dichloromethane(ml)	2.5	2.5	2.5	2.5	2.5	

Characterization of transdermal patch:

The patches were produced in case of all 6 trails. These patches TT1 to TT5 and the patch made with pure TNX were tested for physical appearance, pharmacotechnical properties and ex-vivo skin permeation studies.

Physical appearance

All prepared patches were inspected for clarity, color, flexibility, transparency and smoothness.

Thickness of the patch was determined by measuring the thickness at 5 sites on three patches of each formulations using digital vernier calliper and the average was calculated.

Folding endurance was determined by repeatedly folding one patch at the same place till it break. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance. This test is performed to check the suitability of sample to withstand folding and brittleness. Uniformity of weights were determined by weighing five matrices of each formulation. After each patch unit was weighed individually on a digital balance, the average weight of path was taken as the weight of the patch.

Drug content uniformity:

Uniformity of drug content of the transdermal patch was determined based on dry weight of drugs and polymers used by means of a UV spectrophotometer method, different formulations were cut in specified surface area of 2 cm2, and dissolved separately in 2ml of methanol and make up the volume to 10ml with phosphate buffer pH 5.5 and stirred for 30 minutes. The resultant solutions were filtered with Whatmann filter paper and analysed for drug content at 261nm in UV spectrophotometer. The average reading of three patches was taken as the content of drug in one formulation.

Percentage of moisture content:

The patches were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hours. Individual patches were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Water vapour transmission rate (WVTR) :

WVTR is defined as the quantity of moisture transmitted through unit area of patch 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 hours.

Percentage moisture uptake

The patches were kept in a desiccator with silica gel for 24h and weighed (Wi). The patches were then transferred in to another desiccator containing NaCl solution until constant weight was obtained (Wm). Moisture uptake study was calculated according to the formula.

Moisture uptake capacity (%) = (Wm - Wi / Wi) x 100.

pH measurement

pH of the swollen film was measured by using pH meter which was calibrated before use.

Flatness :

Longitudinal strips were cut out from the prepared films and the length of the strip was measured at two different places. Flatness was calculated to find out the constriction of the film after drying.

Constriction (%) = $(L_1\text{-}L_2/L_2)$ x 100

Ex-vivo permeation studies:

Ex-vivo permeation studies were conducted using goat skin. Hair from the abdominal region was removed carefully by using an hand razor. The dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in saline phosphate buffer pH 5.5. The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Patch was placed on to the skin membrane over an area of 1.131cm^2 and placed across the donor compartment The whole assembly was kept on magnetic stirrer, maintained at 37±0.5°C with stirring at 50 rpm.

Samples were withdrawn at regular time intervals of 0, 15, 30, 45, 60,120,180 min from the receptor compartment. The fresh buffer in receptor compartment was replaced after each withdrawal. Samples were analyzed at λ_{max} of 261nm using UV-visible spectrophotometer Shimadzu, INDIA. Cumulative % of drug permeated were calculated and plotted against time.

Pharmacodynamic studies:

Induction of arthritis (8):

Male albino wistar rats were injected subcutaneously with 200 µg of bovine type II collagen emulsified with incomplete Freund's adjuvant at the base of the tail until needle tip reaches 0.5 cm from the base. Needle length should be completely subcutaneous and wiped before each injection to prevent leakage of emulsion. Onset of arthritis in rats is much faster than mice (around 4 weeks) and clinically apparent arthritis with swollen joints appears around 12-14 days after the immunization.

Patch exhibiting highest diffusion was studied for antiarthtic effect by using male albino wistar rats as animal model. (Ethical committee Reg.no:1677/PO/A/12//1AEC may 2016) Rats were divided in to four groups. Each group contains 6 rats.

Group I: normal (will receive vehicle used to reconstitute the drug)

Group II: Disease control (arthritis induction but no drug given)

Group III: Arthritis induction then given standard drug (betamethasone 0.5mg/ml/kg)

Group IV: Arthritis induction then applied patch topically.

Treatment (9):

After 14 days of induction, group I and group II rats are given with vehicle(olive oil). Group III rats are treated with betamethasone orally which is suspended in olive oil. Group IV are treated with SD of TNX Patch which is applied topically. (9).

Arthritis score assessment (8)

The incidence and severity of arthritis were evaluated using a system of arthritic scoring every 2 days beginning on the day after collagen emulsion injection. Lesions of both hind paws of each rat were graded from 0 to 4 according to its clinical arthritic signs described by Brand et al. (2007). The total arthritis scores were calculated from the sum of both hind paws, with a maximum possible score of 8 for each rat.

Table 3: Qualitative scoring system used to assess severity of paw inflammation.

Score	Condition
0	Normal
1	Mild, but definite redness and swelling of the ankle or wrist, or apparent redness and swelling limited to individual digits, regardless of the number of affected digits
2	Moderate redness and swelling of ankle of wrist
3	Severe redness and swelling of the entire paw including digits
4	Maximally inflamed limb with involvement of multiple joints

Radiology score assessment (8)

At the end of the experiment (day 42), rats were anaesthetised intramuscularly with 0.1 ml of Ketamine and 0.15 ml of xylazin per 100 g of body weight of rat. Anaesthetised rats were placed on a radiographic box at a distance of 107 cm from the X-ray source. Radiographic analysis of normal and arthritic hind paws was performed by using X-ray machine, with a 48 kVp exposure for 0.5 mAs.

Results and discussion:

Table: 4 Solubility analyses of solid dispersions prepared with different polymers

S. No	Formulation	% Solubility of TNX
1	TNX	18.85 ± 0.02
2	PEG1	49.08 ± 0.01
3	PEG2	70.67± 0.02
4	PEG3	92.27± 0.01
5	SSG1	41.23± 0.01
6	SSG2	66.75± 0.02
7	SSG3	84.41± 0.01
8	PVP1	53.03± 0.02
9	PVP2	74.59± 0.04
10	PVP3	80.59 ± 0.03

Percent Drug solubility values ranging from 18.85 ± 0.02 to 92.27± 0.01indicated reasonable enhancement in solubility of tenoxicam when they are prepared as solid dispersions.

In-vitro dissolution profile:

In-vitro drug release profile of pure tenoxicam and solid dispersion of tenoxicam

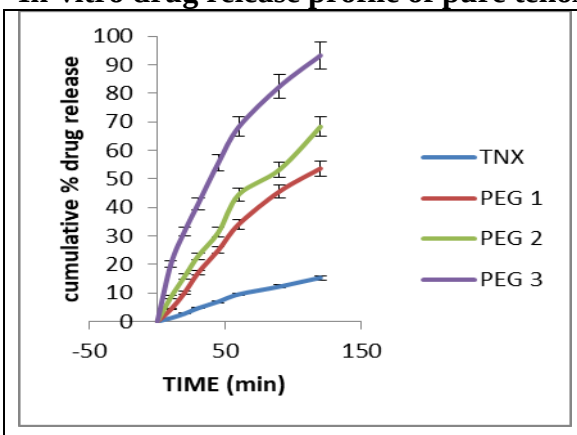


Figure 1: Invitro drug release of TNX and SD's prepared with PEG

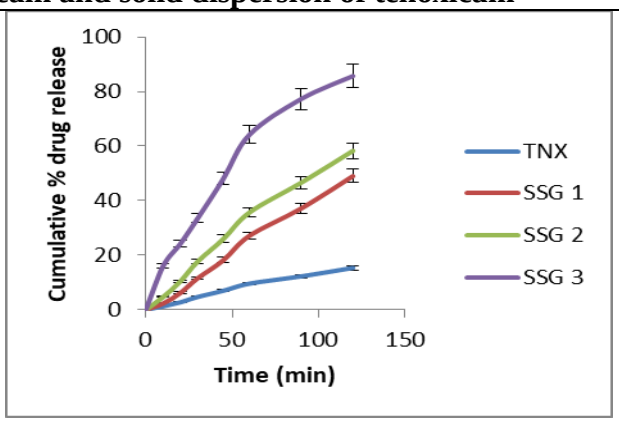


Figure 2: Invitro drug release of TNX and SD's prepared with SSG

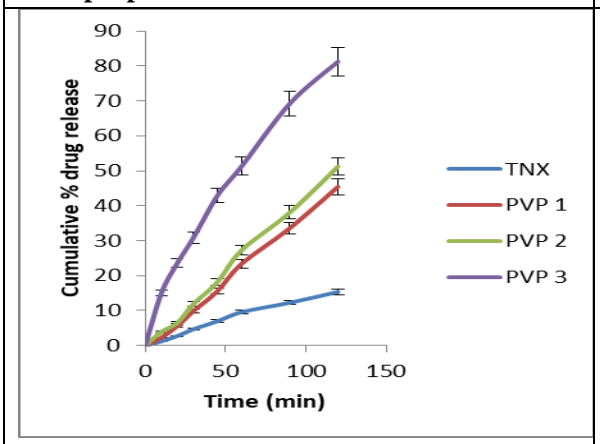


Figure 3: Invitro drug release of TNX and SD's prepared with PVP

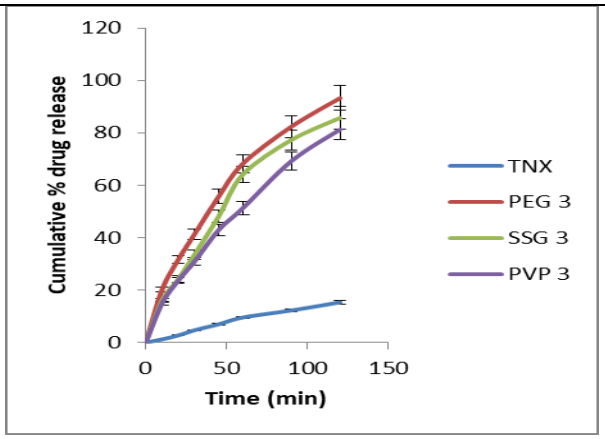


Figure 4: Comparision of invitro drug release of TNX and SD's prepared with different polymers

Figure 1: shows in- vitro drug release profile of TNX and SD's of tenoxicam with PEG25000 in the ratios of 1:3,1:6,1:9 **, Fig.2.** shows in-vitro drug release profile of TNX and SD's of tenoxicam with PVP K 30 in the ratios of 1:3,1:6,1:9, **Fig.3** shows in- vitro drug release profile of TNX and SD's of tenoxicam with SSG in the ratios of 1:3,1:6,1:9 and **Fig.4** shows comparative in-vitro drug release profile of TNX and SD's of tenoxicam which shows highest drug release with polymers PEG 25000, PVP K 30, SSG.

FTIR:

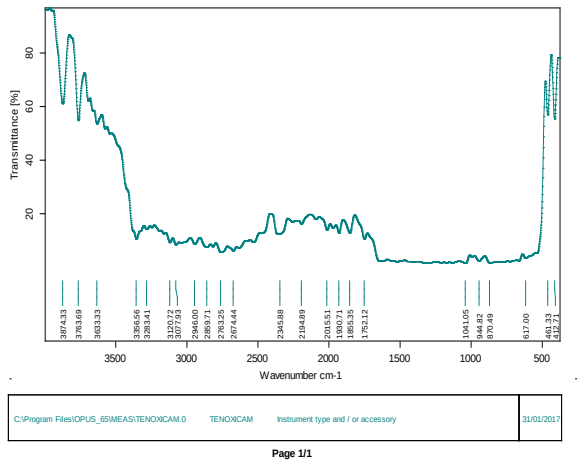


Figure 5: FTIR spectra of tenoxicam

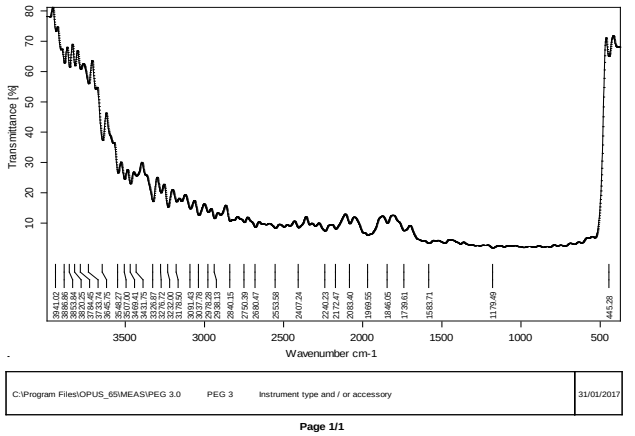


Figure 6: FTIR spectra of solid dispersion of tenoxicam with PEG

IR spectrum of pure TNX in **Fig.5** revealed O-H Stretching at 3336.56 cm-1 .All these peaks are present in the promising formulation TNX: PEG 25000(1:9) in **Fig.6** with slight shift. This indicated absence of drug excipient interaction between TNX upon combining with PEG 25000.

DSC:

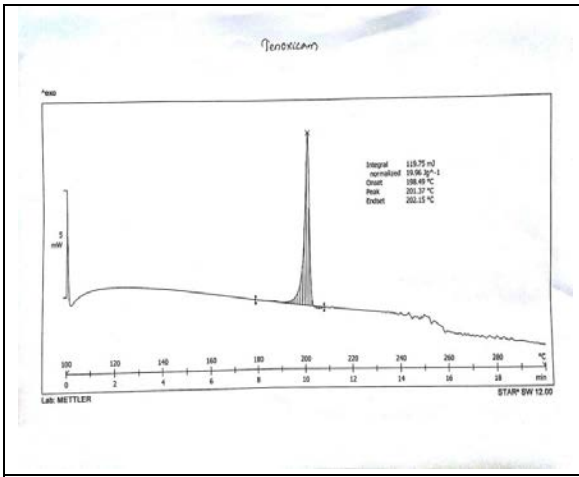


Figure 7: DSC thermogram of tenoxicam

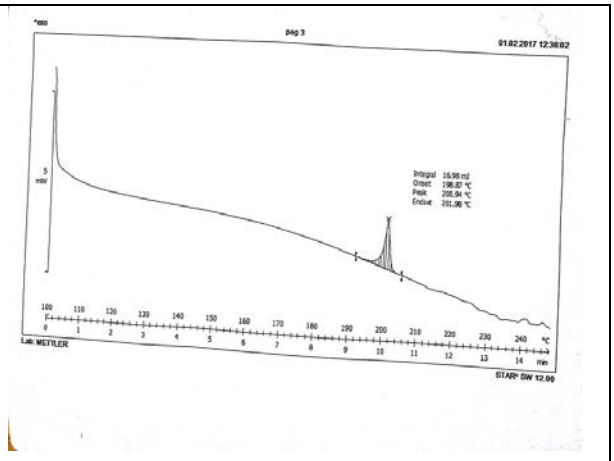


Figure 8: DSC thermogram of tenoxicam prepared with PEG

DSC thermogram of TNX in **Fig. 7** revealed the melting peak at 201.37 and the promising formulation in **Fig.8** revealed at 200.94. This indicates there is no interaction between TNX and PEG 25000.

Of all the formulations, Solid dispersions having 1:9 ratio of drug and PEG shows high cumulative drug release. Also from FTIR and DSC studies, it shows that there is no interaction between polymer and drug So, solid dispersions prepared with PEG was formulated as tdds to achieve targeted delivery

Characterization of Transdermal patch:

Drug content:

Table.5 Drug content

S.No	Formulation	% drug content ±S.D
1	TT1	98.6±0.46
2	TT2	98.9±0.51
3	TT3	99.7±0.40
4	TT4	98.8±0.52
5	TT5	98.8±0.47
6	TTNX	96.8±0.38

Table 6: Physicochemical properties

Formulation	Weight variation(mg) ±S.D	Thickness (mm) ±S.D	Folding endurance± S.D	Moisture content (%)	Water vapour transmission rate ±S.D	Percentage moisture uptake ±S.D	pH±S.D	Flatness (%)
TT1	37.6± 1.35	1.147±0.03	70±6.39	1.49 ±0.03	0.23 ± 0.029	2.93±0.21	6.97±0.36	100
TT2	39.5±1.78	1.216±0.02	132 ± 6.3	1.48±0.01	0.35 ±0.063	2.96±0.46	6.98±0.62	100
TT3	32.6±2.68	1.236±0.03	194±4.5	1.45±0.05	0.12 ± 0.036	2.45±0.41	6.99±0.21	100
TT4	38.5±2.06	1.333±0.15	91±6.9	1.56±0.02	0.39 ±0.034	3.01±0.55	7.01±0.15	99.9
TT5	35.6±1.87	1.465±0.21	86±6.72	1.61±0.04	0.28±0.042	3.08±0.56	6.99±0.61	100
TTNX	32.5±2.06	1.238±0.26	189±5.3	1.46±0.02	0.15±0.04	2.51±0.21	7.02±0.15	100

The drug content of all the prepared transdermal patches was found to be in the range of 96.8% to 99.7%. All the formulations were evaluated for pharmacotechnical properties and results are shown in **Table 6.** It was found that weight variation of the prepared patches was in the range of 32.5±2.06 mg to 39.5±1.78 mg which shows that negligible variation in weight of the patches. The thickness of patches was found between 1.147±0.03 mm to 1.465±0.21 mm. The folding endurance of patches TT1,TT4 and TT5 are 70±6.39,91±6.9 and 86±6.72 respectively which indicates that their inability to withstand rupture whereas the folding endurance of patches TT2,TT3, and TTNX was found to be 132± 6.3,194±4.5 and 189±5.3 respectively and it shows that these formulations have ability to withstand rupture. This is due to presence of less amount of Eudragit RL PO than HPMC K400. Percentage moisture content and water vapour transmission rate of the prepared patches was in the range of 1.45±0.05 to 1.61±0.04 and 0.12 ± 0.036 to 0.35 ±0.063. This shows that the increase in Eudragit RL PO increase the moisture content and water vapour transmission rate due to its hydrophilic nature. pH of all patches was in the range of 6.97±0.36 to 7.02±0.15 indicating no skin irritation property of patches as the skin pH value is 5-7. Almost all formulations of patches have the flatness of about 100 indicating the prepared patches are uniform in size.

***Ex-vivo* permeation studies:**

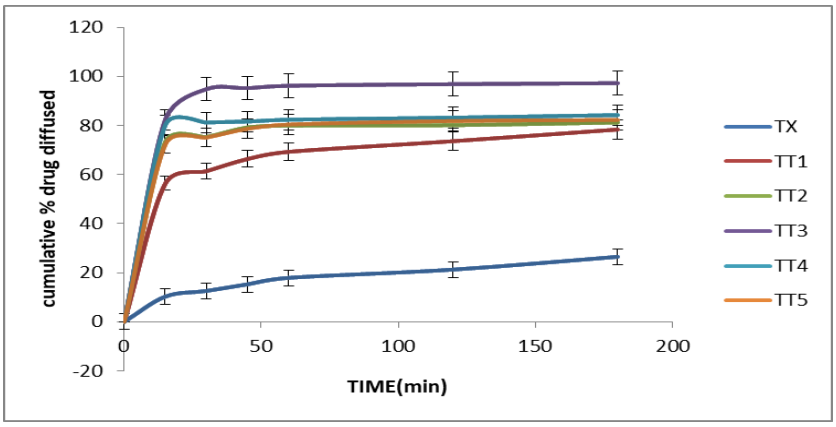


Figure 9: *ex-vivo* permeation

From ***ex-vivo*** permeation study, results showed that increasing the amount of Eudragit RLPO, a hydrophilic polymer led to decrease in diffusion. This may be attributed to permeability through the lipohilic barrier (skin). HPMC K4M is insoluble in water due to its less hydrophilicity so, it forms insoluble matrix when combined with Eudragit RLPO. HPMC K4M forms a firm gel layer along with Eudragit RLPO and helps in release of drug as it is incorporated as solid dispersion of Tenoxicam in the patches, it releases the Tenoxicam rapidly in to circulation. Patches with high amount of HPMC K400, because of its tendency to mask the quaternary ammonium groups of Eudragit RLPO to some extent it modifies release rate from the matrix. Patch containing pure tenoxicam has drug permeation of 17.92 in 60 minutes whereas patch TT3 evidenced reasonable enhancement of of 84.29% in 60 minutes. The presence of less amount of Eudragit RLPO in formulation TT3 lead to increased permeation through skin, followed by swelling owing to the presence of HPMC that could modify the drug release.

***In-vivo* pharmacokinetic activity:**

Arthritis score assessment:

Table 7: Arthritis score analysis

Day	Arthritis score(mean ± S.D)				
	Group I	Group II	Group III	Group IV	Group V
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
14	0.00 ± 0.00	1.60 ±0.02	1.63 ±0.01	1.61 ±0.02	1.69 ±0.03
18	0.00 ± 0.00	1.91 ±0.01	1.39 ±0.01	1.99±0.03	1.53 ±0.02
22	0.00 ± 0.00	2.48 ±0.05	1.34 ±0.03	2.08 ±0.02	1.39 ±0.04
26	0.00 ± 0.00	2.85 ±0.03	1.22 ±0.02	2.26 ±0.06	1.36 ±0.03
32	0.00 ± 0.00	3.35 ±0.02	1.14 ±0.05	2.18 ±0.03	1.24 ±0.02
34	0.00 ± 0.00	3.94 ±0.05	1.09 ±0.02	2.04 ±0.05	1.01 ±0.03
38	0.00 ± 0.00	3.96 ±0.04	0.91 ±0.06	2.03 ±0.02	0.98 ±0.04
42	0.00 ± 0.00	3.97 ±0.06	0.74 ±0.05	2.02 ±0.06	0.84 ±0.05

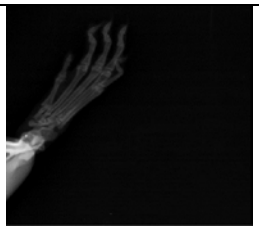
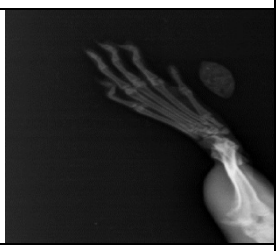
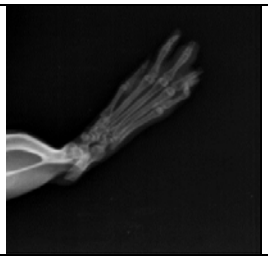
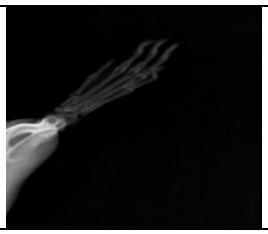
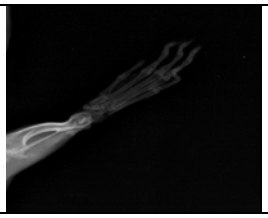
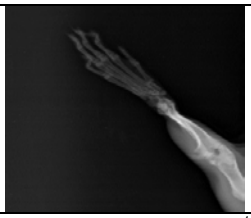
***n=6**

Discussion:

Swelling and inflammation was observed from 14th day of immunisation. Each group contains 6 rats. Arthritis score was measured as mean. From the **Table 7** it is evident that the rats which were untreated show deformities at the end of study. While the rats which were treated with betamethasone and patch contain solid dispersion of tenoxicam shows no deformities and swelling of boths paws are not significant.

Radiographic analysis:

Table 8: Photograph and X-ray images of both hind paws of rat

Group	Photograph of		x-ray image of	
	Right paw	**Left paw**	**Right paw**	**Left paw**
Control:				
I				
Disease control:				
II				
Treated with standard :				
III				
Treated with tenoxicam patch:				
IV				

From the Table **8**, it was observed that both hind paws of rat were swollen and inflammed after 14th day of induction. Treatment was given from fourteenth day to forty two days after induction. At the end of the treatment the inflammation on both hind paws of treated rats were reduced compared to untreated rats. X-ray studies shows that deformities were occur to untreated rats but not to treated rats and inflammation and swelling of paws was reduced in rats treated with standard drug (betamethasone) and TNX patch.

Conclusion:

Transdermal patches containing TNX:PEG 25000(1:9) equivalent 20mg of TNX mg prepared by using (HPMC K 400(100 mg), Eudragit RL PO (50 mg), DBT(2 ml),DMSO(0.5 ml), carbinol (2.5 ml), Dichloromethane(2.5 ml)) were proved as

successful devices for treatment of Bovine type II collagen induced rheumatoid arthritis.

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