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Pharmacokinetic assessment of transdermal patch loaded with solid dispersions of tenoxicam

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Abstract

Tenoxicam (TNX), synthetic NSAID indicated for the therapy of rheumatoid arthritis and to relief acute pain. It has poor solubility. Solubility of tenoxicam was enhanced by formulation of solid dispersions. To assess whether solubility is increased or not, the present research work is aimed to estimate the in-vivo plasma concentration of patch with solid dispersions of tenoxicam and patch loaded with pure tenoxicam using RP-HPLC method. Pharmacokinetic parameters like C_{max}, $t_{1/2}$, and AUC_{0-24} of patch made with solid dispersions of tenoxicam were found to be 2.131µg/ml, 7.968hrs and 27.598µg/ml/hr respectively and C_{max}, $t_{1/2}$, and AUC_{0-24} of patch with pure tenoxicam were found be 0.971µg/ml, 8.065hrs and 9.524µg/ml/hr respectively. t_{max} for both formulations was found to be almost 5hrs. IVIVC shows that the patch loaded with solid dispersions of tenoxicam has regression value of 0.969 indicates good correlation.

Keywords: Tenoxicam, transdermal patch, pharmacokinetic assessment, RP-HPLC method, IVIVC.

Introduction

Tenoxicam which is a NSAID has analgesic, anti inflammatory and antipyretic effects is indicated for medication of rheumatoid arthritis. The mechanism of tenoxicam is by inhibiting the cyclooxygenase there by inhibiting prostaglandin synthesis. Pain receptors which are sensitized by prostaglandins, thus inhibiting the prostaglandin synthesis causes anti inflammatory effect. It is a BCS class II with poor solubility with a maximum dose of 20mg per day. Also it possess first pass metabolism. During the treatment of RA with NSAIDs, it causes gastric irritation when it was ingested through oral route. Also to bypass first pass metabolism transdermal drug delivery is preferred and to increase its solubility first tenoxicam was formulated as solid dispersions then it was loaded in to patches. RA effects joints, upon topical application tenoxicam diffuses easily through the skin and reaches throughout the body. The plasma concentration of drug after specified period time intervals can be estimated by RP-HPLC method. Hence, present research work is focused on the estimation of the pharmacokinetic parameters of patch containing solid dispersions of tenoxicam and patch containing pure tenoxicam upon application at the joints of bovine type II collagen induced RA rats[1,2].

Methodology

A gift sample of tenoxicam was obtained by Reddy's laboratory, 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. HPLC analytical grade acetonitrile, water, methanol was purchased from Hi media, INDIA. Sodium hydroxide and potassium di hydrogen phosphate was bought from Hi media, INDIA. Incomplete Freund's adjuvant and Collagen (bovine type II) was purchased from Chondrex, U.S.A.

Experimental work: Present work was carried in 4 steps:
Step-1: Formulation of solid dispersions of tenoxicam: Dispersions of TNX were formulated using solvent evaporation technique. Tenoxicam and PEG 25000 was taken in 1:9 ratio. It was dissolved in 1:1 ratio of acetone and chloroform. Dissolved solution was freezed at -20^{0}C then using lyophillizer solvent was removed. Then resultant dispersions obtained were transferred in sample holders and kept in dessicator. The prepared solid dispersions were used for the preparation of transdermal patch to avoid first pass metabolism of tenoxicam[3].

Step-2: Preparation of transdermal patch loaded with solid dispersions of tenoxicam: TNX transdermal patches were formulated by solvent casting method using solid dispersion and pure TNX. For the preparation of transdermal patch HPMC K4M, Eudragit RL PO was used as carriers, dichloromethane and carbinol in 1:1 ratio was used as solvent. DiButyl Pthalate having plasticizer property, DMSO having penetration enhancing property was also added. By using this mixture two different transdermal patches were prepared using solid dispersions and pure TNX. Then the solution was stirred in magnetic stirrer for half an hour. Then the obtained mixture was poured in to mould. Inverted funnel is placed on the mould to allow controlled rate of evaporation for uniform drying of patches. The formulated patches were characterized for ex-vivo drug release and pharmacokinetic parameters[4-7].

Step-3: Study of ex-vivo permeation drug diffusion of patch formulated with pure tenoxicam and solid dispersions of tenoxicam: Study of ex-vivo diffusion permeated through goat skin was carried out. In franz diffusion apparatus, lower compartment i.e., receptor was fulled with phosphate buffer pH 5.5. Donor compartment transdermal patch was placed. Between two compartments goat skin was placed. Franz diffusion cell was maintained at 100 RPM and at temperature 37^{o}C. At predetermined time intervals sample was withdrawn from receptor compartment and analysed by UV-Visible spectrophotometer at 261 nm[8-10].

Step-4: RP-HPLC method for pharmacokinetic assessment of patch loaded with pure tenoxicam and patch loaded with solid dispersions of tenoxicam: Pharmacokinetic study was carried out by albino wistar male rats weighing 200gm to 220gm. The studies were approved by Animal ethical committee, SPMVV. (Reg.no:1677/PO/A/12/1AEC,May 2016). Rats were categorised into two batches containing 6 rats in each batch. Pharmacokinetic assessment were carried out for patch loaded with tenoxicam dispersions and patch containing pure tenoxicam. Patch containing 8 mg/kg of rat weight of tenoxicam was supplied at the joints of RA induced rats.

At predetermined time intervals blood from retro orbital plexus of rats was collected into ependorrf tubes containing 20% sodium citrate solution. Methanol was added to trigger the denaturing of proteins present in plasma. The blood samples were then placed in a centrifuge and the rpm was maintained at 15000, which is continued for 15 mins for coagulation. The floated plasma was decanted using filter paper with a pore size of 0.45µm Millipore. To this filtrate aceclofenac (IS) in the concentration of 0.15µg/ml was added. Acetonitrile and water in 61:39v/v of mobile phase was uilised to fill the remaining volume of 1ml. The sample of 25micro litre was instilled using hamilton syringe in column of Hibar C 18. To detect the tenoxicam, wave length of 375nm was kept in HPLC instrument. In HPLC mobile phase was flowed at 1 ml/min[11-14].

Step-5: In-Vitro and In-Vivo Correlation: IVIVC was also carried by comparing plasma concentration obtained from estimation of pharmacokinetic parameters with ***ex-vivo*** drug release profile which is obtained from cumulative percent diffusion of drug from patch in franz diffusion cell to study the accumulation of tenoxicam after applying patch loaded with solid dispersions of tenoxicam[15-17].

Results and discussion

Ex-vivo permeation data for transdermal patch containing pure tenoxicam and patch containing solid dispersions of tenoxicam was given in Table-1. Plasma concentrations of tenoxicam after topical application of patches estimated by RP-HPLC method are shown in Table-2. Relevant HPLC chromatograms of tenoxicam for patch containing solid dispersions of tenoxicam and patch containing pure tenoxicam are shown in Figure-1 and 2.

Table-1: Cumulative percent drug diffusion of tenoxicam patches.

Time (Min)	Cumulative percent drug diffusion of	
	Transdermal patch with pure tenoxicam ± SD	Transdermal patch with solid dispersions of tenoxicam ± SD
0	0	0
10	10.26±0.12	56.36±0.15
20	12.58±0.21	64.81±0.14
30	15.29±0.14	75.23±0.18
45	17.92±0.15	81.69±0.19
60	21.27±0.18	90.25±0.25
90	26.49±0.26	93.09±0.21
120	30.62±0.18	97.26±0.42

Table-2: Mean plasma concentration vs. time data after topical application of patch containing pure tenoxicam and patch containing solid dispersions of tenoxicam.

Time (hrs)	Mean plasma conc of patch containing pure tenoxicam (µg/ml)	Mean plasma conc of patch containing solid dispersions of tenoxicam (µg/ml)
0	0	0
0.166	0.061	0.163
0.33	0.154	0.198
0.5	0.162	0.254
0.75	0.216	0.539
1	0.264	0.863
1.5	0.298	1.056
2	0.426	1.624
4	0.971	2.131
8	0.778	1.267
24	0.125	0.624

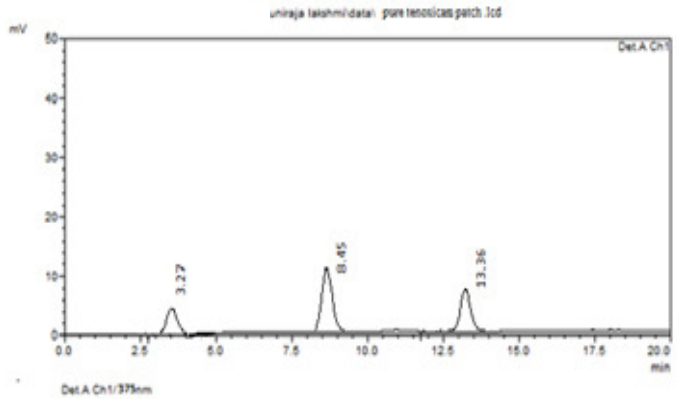

Figure-1: HPLC chromatogram of tenoxicam and aceclofenac in rat plasma after topical administration of patch with pure tenoxicam.

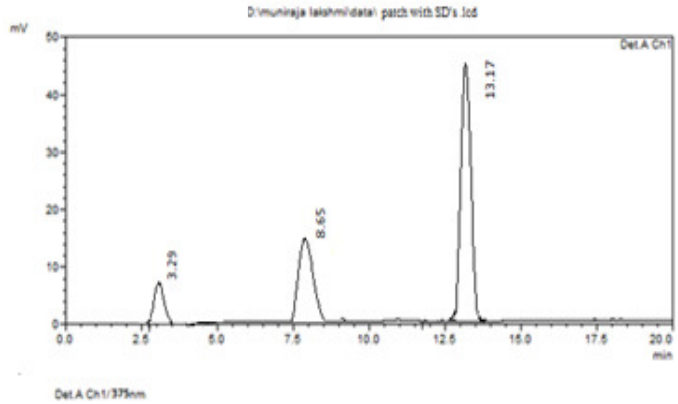

Figure-2: HPLC chromatogram of tenoxicam and aceclofenac in rat plasma after topical administration of promising patch with solid dispersions of tenoxicam

Bioavailability curve is drawn by plotting concentration of plasma on y axis time on x-axis which is shown in Figure-3. In bioavailability curve, the concentration of plasma values are extrapolated to get residual concentrations by using residual exponential method various parameters like C_{max}, t_{max}, K_e, K_a, elimination half life, volume of distribution, half life, AUC_{0-24} were calculated. The calculated values were shown in Table-3. Parameters of maximum concentration (C_{max}), half life ($t_{½}$,) and AUC_{0-24} of patch loaded with solid dispersions of tenoxicam 2.131µg/ml, 7.968hrs, 27.598µg/ml/hr respectively. C_{max}, $t_{½}$, AUC_{0-24} of pure tenoxicam patch was found to be 0.971µg /ml, 8.065hrs, 9.524µg/ml/hr respectively.

From the Table-3 it was evidenced that t_{max} for patch loaded with dispersions of tenoxicam and patch loaded with tenoxicam was 5.201hrs and 5.529hrs respectively indicated less variation. Also it was evidenced that the drug available in plasma is more for patch loaded solid dispersions of tenoxicam i.e., 2.131µg/ml where as for patch loaded with tenoxicam has less concentration i.e., 0.971µg/ml. Hence, from pharmacokinetic data it was revealed that parameters like C_{max} and AUC_{0-24} are more for patch prepared with solid dispersions of tenoxicam.

For IVIVC, *Ex-vivo* permeation data and *In-vivo* plasma concentration data was shown in Table-4 and the curve was given in Figure-4. Patch containing solid dispersions of tenoxicam has percent drug available in plasma is 61.36% whereas percent drug diffused in *ex-vivo* permeation study is 97.26%. IVIVC shows that the patch loaded with solid dispersions of tenoxicam has regression value of 0.969 indicates good correlation between *ex-vivo* diffusion and *in-vivo* plasma drug concentration.

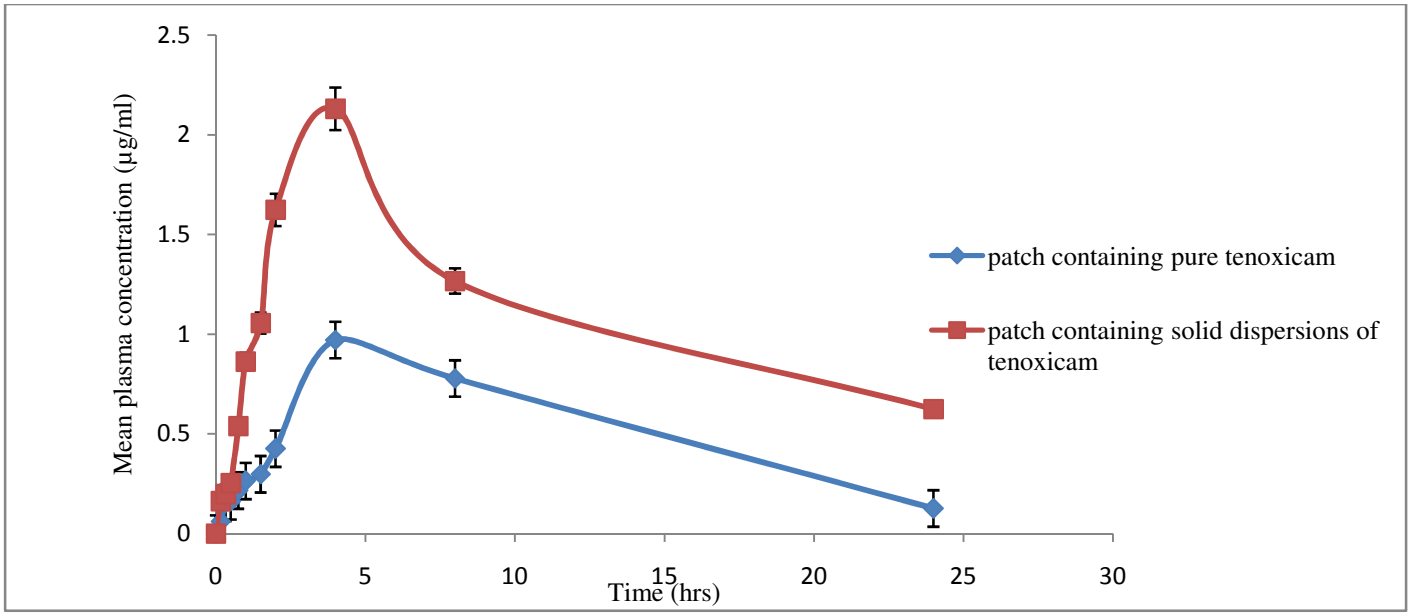

Figure-3: *In-vivo* bioavilability study between mean plasma concentration and time of patch containing pure tenoxicam and patch containing solid dispersions of tenoxicam.

Table-3: *In-vivo* Pharmacokinetic parameters for estimation of tenoxicam in different formulations.

Pharmacokinetic parameter	Pure tenoxicam patch	Patch containing Solid dispersions of tenoxicam
Elimination rate constant (K_e)	$0.0581hr^{-1}$	$0.0675hr^{-1}$
Elimination $t_{1/2}$	13.259hrs	11.564hrs
Absorption rate constant (K_a)	$0.2987hrs^{-1}$	$0.4789hr^{-1}$
$t_{1/2}$	8.065hrs	7.968hrs
Volume of distribution	2.156	3.164
t_{max}	5.529hrs	5.201hrs
C_{max}	0.971µg /ml	2.131µg/ml
AUC_{0-24}	9.524µg/ml/hr	27.598µg/ml/hr

Table-4: IVIVC between e*x-vivo* permeation studies and percent drug plasma concentration of patch containing solid dispersion of tenoxicam.

Time (hrs)	Percentage of drug diffused	Percentage of plasma concentration
0	0	0
0.166	56.36±0.15	28.26±0.03
0.33	64.81±0.14	34.25±0.04
0.5	75.23±0.18	41.32±0.03
0.75	81.69±0.19	48.18±0.02
1	90.25±0.25	55.82±0.01
1.5	93.09±0.21	59.27±0.01
2	97.26±0.42	61.36±0.02

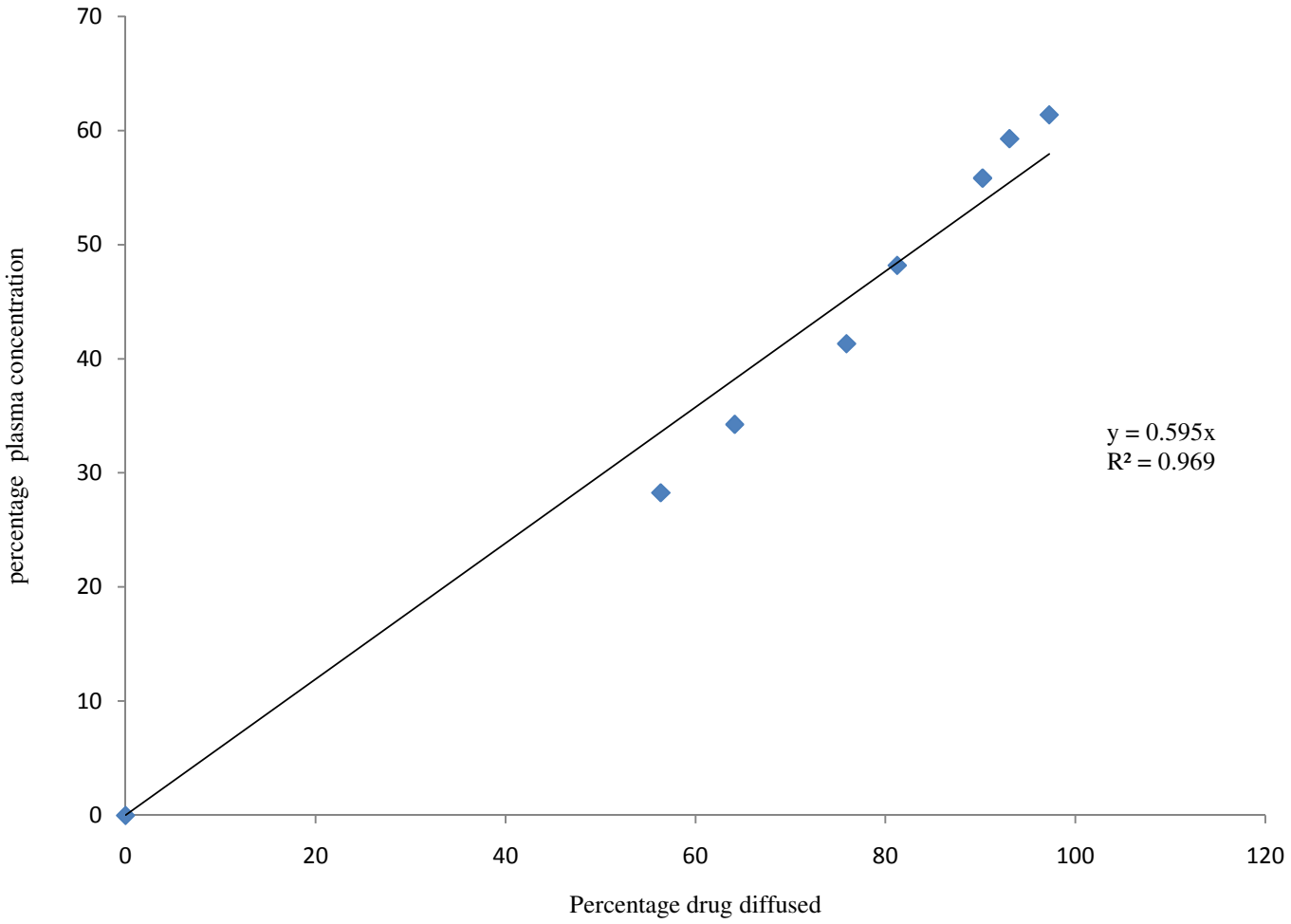

Figure-4: IVIVC for promising patch containing solid dispersions of tenoxicam .

From the data it is expected that reasonable level accumulation of tenoxicam occurs at the site of application which leads to reduction in lesions and swelling on both hind paws for RA induced rats causing the effective recovery.

Conclusion

From pharmacokinetic assessment it was concluded that the patch loaded with solid dispersions of tenoxicam evidenced enhanced plasma concentration and AUC which indicates reasonable plasma availability of drug compared to patch with pure tenoxicam.

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