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Original Research Article

Preparation and in vitro evaluation of cyclodextrin based piroxicam transdermal gel (release and permeation study)

Qasim Allawi Bader
College of Pharmacy, University of Karbala, Department of pharmaceutics; Iraq

***Corresponding author**
Qasim Allawi Bader
Email: qasim_bdr@yahoo.com

Abstract: Piroxicam; a widely used non-steroidal anti-inflammatory drug(NSAID) , was prepared as a transdermal gel by mixing with a cyclodextrin in equal amounts and sodium carboxymethyl cellulose (NaCMC) as a matrix polymer in 3 and 6% concentrations. Piroxicam was examined for its melting point and characterized by its fourier transform infrared (FTIR) spectra and differential scanning calorimetry (DSC). The prepared formulas were tested in terms of their release and diffusion behavior and compared with a marketed piroxicam gel. The results of the release and diffusion studies were subjected into different mathematical models to elucidate the pattern and mechanism of their release and diffusion. It was concluded that (F1) which contain 0.15 g of piroxicam and cyclodextrin in a matrix consist of 3% NaCMC represent the best one in terms of release and diffusion during the study period where 95% of piroxicam released during 3 hours and 78% of the drug was diffused through cellophane membrane during 4 hours.
Keywords: non-steroidal anti-inflammatory drug, sodium carboxymethyl cellulose, differential scanning calorimetry.

INTRODUCTION

The skin represent the outer defense system of human body and has different actions in addition to its action as mechanical barrier, it regulates the temperature of our bodies according to the environmental temperature [1, 2]. Traditionally; the topical rout was used for the skin therapy .Recently; the transdermal rout take a consideration to be a candidate alternative site for systemic drug delivery. As the drug that applied transdermally delivered in a sustain manner; its effect can be terminated as required by removing the device; also the active pharmaceutical ingredient (API) that suffer extensive first pass metabolism can be bypassed by this rout of administration.

Hydrogel is three dimensions polymeric network consist of homo copolymers which are not soluble due to the presence of physical or chemical cross links [3], creating a network that is able to absorb large amounts of biological fluids [4]. These networks tend to swell in aqueous media because of their thermodynamic compatibility with water [5]. The hydrogels are characterized for their morphology, elasticity which affects the mechanical strength of the network and swelling properties that determine the mechanism of drug release from the swollen polymeric mass. Non-steroidal anti-inflammatory drugs (NSAIDS) are well known since salicin discovery by Maciagan in 1874 to treat the inflammation of rheumatic fever which was followed by the development of many other NSAIDS. Their mechanism of action can be explained by their action on inflammation, fever and pain [1].

Sodium carboxymethyl cellulose (NaCMC), the polymer used in this study; is an ester derived from cellulose with sodium hydroxide which produce a highly hygroscopic, viscous and most important commercial water soluble polymer [6]. Piroxicam ,NSAID ; is a snowy or slightly creamy crystal-like triturate , essentially unsolvable by water and solvable in methyl chloride, somewhat solvable by ethyl alcohol and the powder exhibit polymorphism [7]. Cyclodextrins (CDs) involve a numerous cyclic oligosaccharides; many of them were used in pharmaceutical, chemical and food industry applications. These are crystalline, soluble in water, cyclic and homogenous non-reducing oligosaccharide. Three most commonly subtypes used are α, β and γ-cyclodextrins. β-cyclodextrin consist of seven unit and were used for their complexation phenomenon [8].

MATERIALS:

All materials that used in this study were from the laboratory grade. (NaCMC) was purchased from local agent for Himedia/ India .NaOH from Carlo Erba (Spain). Marketed piroxicam gel was purchased for comparism.β cyclodextrin from (Himedia lab. PVT.

LTD) in Mumbai India. Pure piroxicam powder was generously gifted from Sammarra Drug Industries (SDI) / Iraq. KH_2PO_4 from Thomas Beaker Chemicals (Mumbai –India).Marketed piroxicam gel (as a reference)

METHODS

Piroxicam characterization

Melting point determination

The test was done by the aid of Biocot instrument (Japan) using dipping method to ensure the purity of drug and increasing the temperature gradually until the drug was completely melt.

FTIR study

Piroxicam powder was mixed with potassium bromide after grinding and pressed in the form of tablets 13 mm in diameter and analysed by Shimadzu FTIR 8000 spectroscopy from (4000-400 cm^{-1})

Differential Scanning Calorimeter (DSC)

This study was performed on DSC shimadzu differential scanning colorimeter with thermal analyzer.

Preparation of hydrogel formula by using sodium carboxymethyl cellulose

Hydrogel was prepared in 3 and 6% concentrations by dissolving the quarterly weighed amounts of NaCMC in 100 ml of phosphate buffer (pH6.8)

Preparation of medicated hydrogel

Pre weighed equal amounts from the drug and cyclodextrin in a molar ratio of 1:1 (0.1gm of each one), then they were dissolved in 20 ml of buffer, this mixture was mixed with CMC gel and they were left for 48 hour before evaluation. The components of the formulas under study and the composition of standard marketed piroxicam gel were shown in table 1.

Table 1: composition of the formulas under study

Formula code	Piroxicam (g)	Cyclodextrin (g)	NaCMC (g)	Phosphate buffer pH 6.8 (ml)
F1	0.15	0.15	3	100
F2	0.15	0.15	6	100

Evaluation of hydrogel

All the prepared formulas were evaluated for their release and diffusion characteristics in vitro only to be compared with commercial one.

In vitro release study

In vitro release study was performed by using USP dissolution apparatus (paddle type) with slight modification by placing weighed amounts of the different formulas (F1, F2 and Reference) equivalent to 1 g in a tea bag and soaked in 500 ml phosphate buffer (pH 6.8) and the apparatus was set on 50 rpm and 37° C to mimic the biological conditions. Equal aliqoutes withdrawn in programmed periods 15, 30, 60,120 and 180 minutes and substituted by similar volumes of fresh buffer. The sample inspected by the UV apparatus in the stated ƛ max .The experiment was done in triplicate to validate the results.

In vitro diffusion study:

The diffusion experiment was done at the same apparatus of release study by using cellophane membrane (M. wt. of 13000 Dalton) and the samples were withdrawn in 15, 30, 60, 120, 180, 240 and 300 minutes time intervals which were examined in UV apparatus at the same wave length . The experiment was done in triplicate

Mathematical Modelling of release and diffusion results

Collected quantities of piroxicam that released from films at diverse periods of time were applied to zero, first order, "Higuchi" and Koresmeyer-Peppas classical model to describe the release and diffusion pattern of the drug [9, 10].

Zero order kinetic

Explains the concentration independency release pattern as shown in equation (1):

$$\mathbf{D_t = D_o - K_o t} \text{ …….. (1)}$$

$\mathbf{D_t}$ is the drug quantity that dissolved over time t and $\mathbf{D_o}$ is the original quantity of the drug in solution (usually zero) and K_o is the zero order constant. When this kinetic is applied, a plot of $\mathbf{D_t}$ against t provide conventional graph with K_o as a slop [11].

First order kinetic:

It defines the arrangement that exhibit a concentration dependent manner of drug release as illustrated in equation (2):

$$\boldsymbol{log\ D_t = logD_0 - K/(2.303)t^{-1}} \text{ …… (2)}$$

$\mathbf{D_t}$ represent the released quantity at time **t**. $\mathbf{D_o}$ the formal quantity of drug in solution and *K* is the release constant. A plot of log ($\mathbf{D_t - D_o}$) against **t** will produce a

trend line with a slope k/ (2.303) and intercept at **t** = 0 of log D_o when such kinetic was applied [12].

Higuchi model:

When the fraction of the drug released from a certain matrix is directly proportional to the square root of time, as shown in equation (3).

$$M_t / M_\infty = K_H\sqrt{t} \quad \text{.....} \quad (3)$$

The terms ($\mathbf{M_t}$, $\mathbf{M_\infty}$) were cumulative amounts of drug released at t and infinite time respectively, K_H Higuchi constant which reflects characteristics of the formulation. To know whether tested formulas obey Higuchi release (i.e. Fickian diffusion), $\mathbf{M_t / M_\infty}$ vs. $\mathbf{t^{1/2}}$ was plotted to give a trend line with regression near to 1 and a slope equal to K_H [13].

Korsmeyer-Peppas model (Power law):

The power law describes the drug release from the polymeric system.

(If there is deviation from Fick's law or not), as stated in the subsequent equations:

$$Q_t / Q_\infty = k_{kp}t^n \quad \text{.....} \quad (4)$$

$$log[Q_t / Q_\infty] = log\ k_{kp} + n\ log\ t \quad \text{.....} \quad (5)$$

Where $[Q_t / Q_\infty]$ the drug released at **t** time, $\mathbf{k_{kp}}$ represent the constant that including geometrical and structural characteristics of a intended (controlled) release (CR) system , (**n**) the diffusional release advocate indicative for drug release mechanism of the dissolution process. To describe the release behavior, the dissolution records (Q_t / Q_∞ **<0.6- 0.7)** were assessed [14]. So a conspiracy of $\mathbf{log}[Q_t / Q_\infty]$ against **log t** was illustrated with a slope data of **n** and the intercept of $\mathbf{log\ k_{kp}}$, **n** value obtained from equation (5) was used to determine the different release mechanism as shown in table (2) [15].

Table 2: Values of release exponent (n) and its interpretation [15]

release exponent (n)	transport mechanism	rate as a function of time
≤ 0.5	Fickian diffusion	$t^{0.5}$
0.5 < n < 1.0	Anomalous transport	t^{n-1}
t^{n-1}	Case-II transport	Zero order release
n > 1.0	Super Case-II	t^{n-1}

RESULTS AND DISCUSSION

Melting point determination

The measured melting point of piroxicam was 201º C. , this result resemble the reported one [16], which point toward the purity of the drug powder

Determination of λ max

A solution containing 30 µg/ml of piroxicam in pH (6.8) phosphate buffer was scanned by "UV-Visible spectrophotometer" at 190-400 nm. The spectrum attained with a wave length of maximum absorption (λ max) 332 nm as illustrated in figure (1).

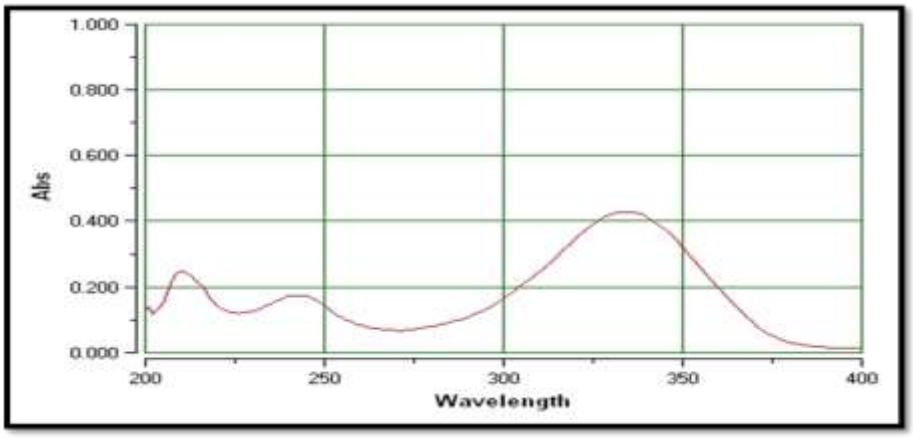

Fig 1: Determination of λ max

Spectrophotometry calibration curve

The calibration curve of piroxicam in pH (6.8) phosphate buffer was represented in figure (2). A trend line (R^2 = 0.999) was obtained by scheming the absorbance versus concentration. This indicates Beer's rule alliance of the calibration curve within the range of concentrations used.

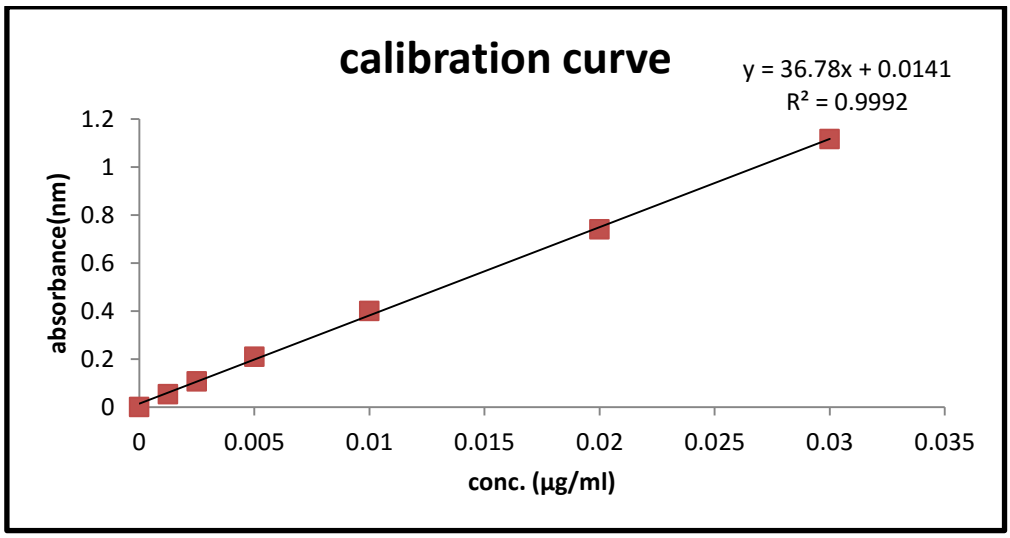

Fig 2: The calibration curve of piroxicam in phosphate buffer (pH 6.8).

FTIR spectroscopy of piroxicam

FT-IR spectra of pure piroxicam powder were shown in figure (3) and its interpretation was listed in table (3).

Table 3: Interpretations of FT-IR spectra of piroxicam powder [17].

3338.78 cm^{-1}	the cubic polymorphic form of the drug
1629.85 cm^{-1}	amide carbonyl stretching data
1529 cm^{-1}	second amide band
1435 cm^{-1}	asymmetric methyl group stretching
1352 cm^{-1}	asymmetric methyl group bending
1149 cm-1	–SO2-N- group band
775 cm^{-1}	ortho-disubstituted phenyl stretching

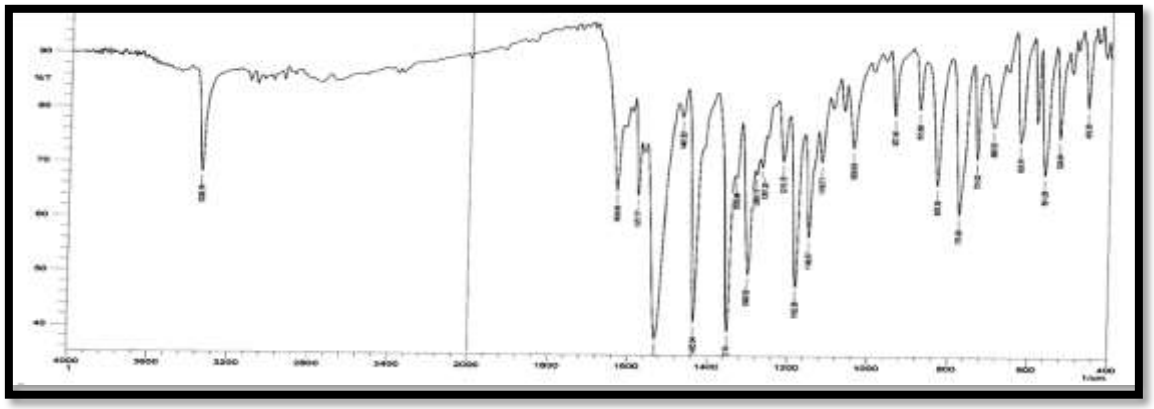

Fig 3: FTIR spectroscopy of pure piroxicam powder.

DSC study of pure piroxicam

DSC was achieved in order to evaluate the thermo tropic properties and thermal performance of the drug (Piroxicam). DSC thermogram in figure (4) representing a clear distinctive peak around its conveyed melting point. These indicate that Piroxicam was used in its crystalline state.

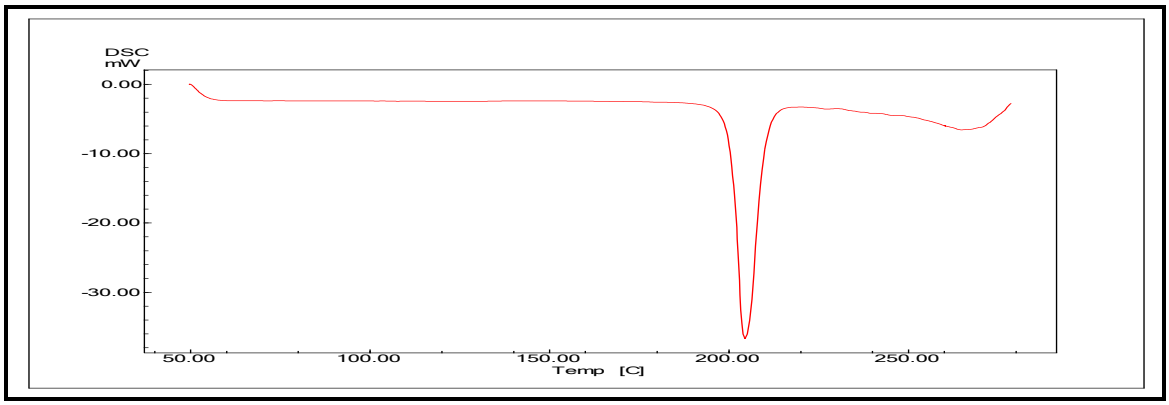

Fig 4: DSC thermograph of Piroxicam.

Evaluation of prepared hydrogel

In vitro release study

The release behavior of piroxicam from the gel in all the three formulations was compared for approximately three hours across an artificial barrier (tea bag) and they are shown in figure (5) and release data values were shown in table (4) which reveal that the percent of piroxicam released was ranked from 90, 92 and 95% at the end of three hours for F2, reference and F1 respectively. It is commonly settled that in vitro drug release records for transdermal formulations cannot be utilized to precisely predict permeation via the skin, because the barrier properties of the stratum corneum which can be rehabilitated by the composition of vehicle or the including of the permeation enhancers in the formulation [18]. The peak release of piroxicam from (F1) may be attributed to enhanced solubility of drug within the gel matrix due to the presence of cyclodextrin that consequently facilitate the drug to be released from the hydrogel into the test media . The total percent of piroxicam released at the end of 3 hours was below the optimum for all formulations under the study which may be attributed to the slow erosion of the polymeric matrix under the test circumstances that resulted in slow diffusion of entrapped drug [19]. From the obtained records, it was detected that there was an inverse relationship between the polymer concentration and the percent of piroxicam released as shown in table (4) which can attributed to the augmented viscosity of the formulations upon improved intertwined nature of the polymeric network which is related to the rise in polymer concentration [20].

Release differences of piroxicam from NaCMC can be attributed to chemical factors like molecular mass, type of polymer and tendency of the vehicle to fix the drug [21]. It's mostly documented that if the vehicle capture the drug firmly, the release will be slow as it mainly happened through the spaces or channels within the hydrogel network [22], it was expected that the drug will be trapped in the polymer network at higher polymer concentrations [23]. In addition, increasing polymeric concentration could magnify the density of chain structure, thereby limiting the movement area of piroxicam **[**24].

The release data was analyzed by different mathematical models to find best fitting of the release data as shown in table (5). The data obtained from (F1) fitted better to the Higuchi model than to the zero order model, an clue that the former more suitable to describe the piroxicam release kinetics from the test formulation and the release was matrix-diffusion controlled. Matrix increase of CMC marks considerably the release process. Release profiles of piroxicam matrices exhibit release rates declining with an increasing CMC content (table 4 and figure 5). Mechanisms of liberation of piroxicam from NaCMC matrices presented in figure (5) are best fitted to zero order due to increased interaction of polymer molecules leading to more viscous polymeric matrix as the CMC percentage increased.

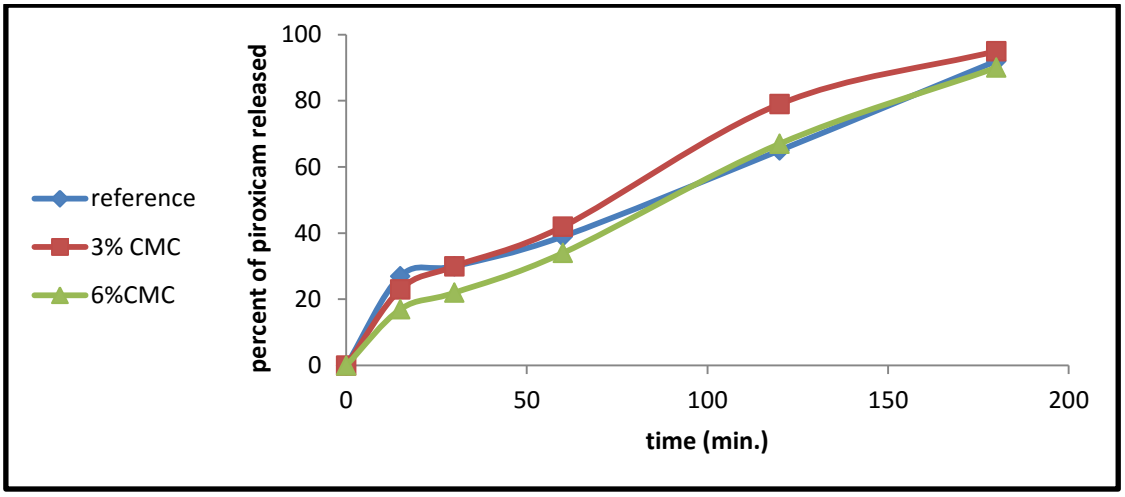

Fig 5: In vitro release profile for all the formulas in phosphate buffer PH (6.8) at 37°C.

Table 4: formulas release data

Time (min.)	Reference %	(F1)3%	(F2)6%
0	0	0	0
15	27	23	17
30	30	30	22
60	39	42	34
120	65	79	67
180	92	95	90

Table 5: The Fitting Results for Different Formulas Of piroxicam Using Different Kinetic Models

Formula No.	Higushi model K_H (min)$^{-1/2}R^2$		First-order K_1(min)$^{-1}R^2$		Zero-order K_0(mg/min)R^2	
Ref.	6.8595	0.9465	0.0055	0.9185	0.4518	**0.9548**
F1 (3%)	7.2591	**0.9751**	0.007	0.9637	0.5039	0.9597
F2 (6%)	6.7691	0.9517	0.0054	0.952	0.4825	**0.9876**

Table 6: The constants of Korsmeyer-Peppas model defining the mechanism of piroxicam release for all formula

formula no.	K_{kp}(min^{-n})	*n*	R^2
Ref.	1.108	0.265	0.9427
F1	0.8457	0.434	0.9954
F2	0.6296	0.0.448	0.978

Korrosmayers-Peppas release exponent (n) for release data as shown in table (6) were ranged from (0.265-0.448) which confirm that Fickian diffusion as the principal pattern of drug release through the system.

In vitro permeation study

To take an approximate view on the events of drug permeation into systemic circulation a permeability testing through cellophane membrane was done. The permeation study was constructed for 4 hrs. and the result that shown in figure (6) reveal that drug diffused from all formulas show that all formulas show a steady state pattern throughout the time of experiment with a significant reduction ($p<0.05$) in the rate of diffusion in F2 and F1 compared with the reference one (54% and 78%) respectively while (99%) for reference gel at the end of the fourth hour and this can be attributed to the thick gel layer that produced after increasing the polymer concentration that has the ability to retard the path of the drug to the dissolution media. *Marcela Ramírez et al.;* reveal a reduction in drug released as the polymer concentration in the evaluation of verapamil transdermal patch using NaCMC as a matrix [25].

For the diffusion a trivial molecule in polymers, cooperative movements of several monomers of the polymer chain was required as the rate of diffusion was governed by polymer flexibility and factors that distressing the chain mobility which guide the diffusion coefficient. As the polymer fragments increased, they begin to interrelate with each other hydrodynamically. The interaction of molecules characterized by the

overlay of the chains and intermolecular entanglement leading to a dynamic network structure of the polymer [25].

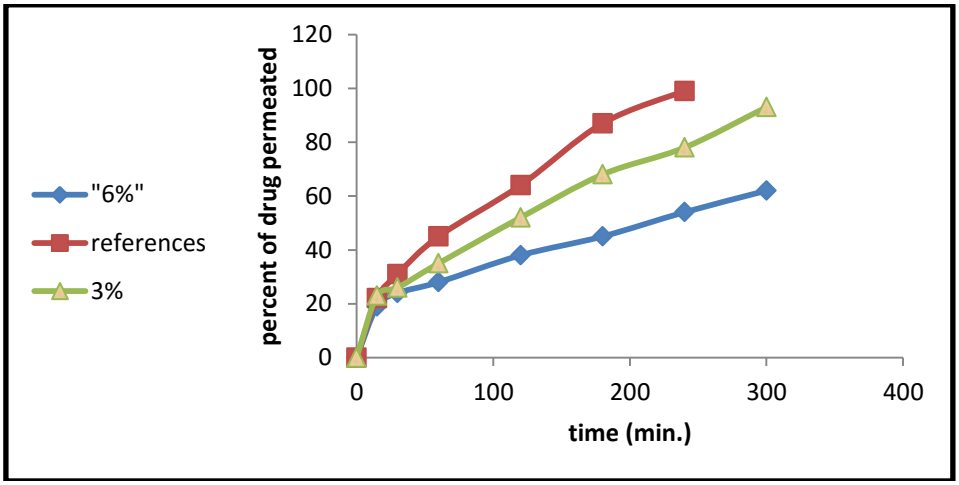

Fig 6: In vitro permeation profile for all the formulas across cellophane membrane in phosphate buffer pH (6.8) at 37°C

Table 7: Mathematical modelling of in vitro permeation data

formula no.	Higushi model K_H (min$^{-1/2}$	R^2	first-order K_1(min)$^{-1}$	R^2	zero-order K_0(mg/min)	R^2
reference	6.46	**0.9947**	0.0072	0.8774	0.3816	0.9487
F1 (6%)	3.41	**0.9832**	0.0013	0.9679	0.1778	0.9151
F2 (3%)	5.18	**0.99**	0.0033	0.9348	0.2746	0.9545

The data of permeation study was exposed to goodness of fit by linear regression to confirm the drug diffusion mechanism .Results of the linear regression with regression coefficient are shown in Table(7). 'r' value of zero and first order plots reveal that drug diffusion from all the formulation didn't follow first order kinetics. Figure (7) showed the percent of drug diffused versus square root of time plots. It was observed that 'r' values indicate the release of drug from these formulations was governed by diffusion meticulous process. The Peppas model is widely used to approve whether the diffusion mechanism is Fickian , non-Fickian or zero order as 'n' value could be used to depict diverse diffusion models.

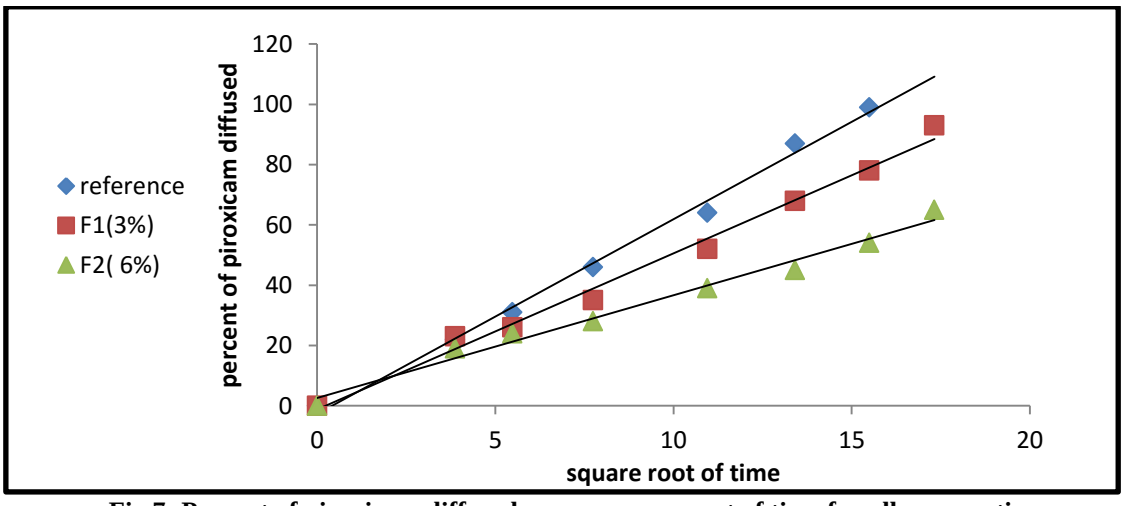

Fig 7: Percent of piroxicam diffused versus square root of time for all preparations.

Korsmeyer equation was fitted to diffusion data and the results shown in table (8), the exponent 'n' was found to be in the range of 0.36 to 0.44 indicating the drug release by Fickian diffusion.

Table 8: Korrosmayers – peppas diffusion analysis data

Formula No.	$K_{kp}(min^{-n})$	N	R^2
Ref.	1.2871	0.44	0.998
F1	1.1695	0.3678	0.9832
F2	1.1353	0.3959	0.9521

CONCLUSION

The piroxicam gel prepared by using carboxymethyl cellulose 3% with cyclodextrin (F1) give a reasonable release profile and best fitted to Higushi model with a release mechanism related to ficks law of diffusion. In spite of low diffused amounts of piroxicam from tested formulas compared with reference one; F1 still represent a promising formula

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