Research Article

Study the Effect of Variables on Piroxicam Microsponge Formulated as Topical Gel for Transdermal Drug Delivery System

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ABSTRACT

The aim of present study was to develop gel formulation of micro sponges of poorly soluble drug piroxicam to enhance the release and dissolution of piroxicam which is the limitation for the preparation in topical forms. Quasi-emulsion solvent diffusion method was used for the preparation of fourteen piroxicam micro sponge formulas. The effects of drug to polymer ratio, Eudragit polymer type, type of organic solvent in internal phase and stirring time on the physical characteristics of micro sponges were investigated and characterized. Production yield, loading efficiency, particle size, surface morphology, and in vitro drug release from micro sponges were calculated. The selected micro sponge formula was incorporated into gel. The prepared micro sponge gel was evaluated for visual inspection, pH, spread ability, viscosity and in vitro drug release. The results showed that the micro sponge formula with Eudragit S100 polymer had the optimum physical properties and enhanced the dissolution and release of piroxicam when compared with other formulas and pure drug. Piroxicam micro sponge carbopol 934 gel produced a significant ($p<0.05$) improvement of the in vitro release than pure piroxicam gel. So quasi emulsion solvent diffusion method was a good method to produce piroxicam micro sponges with markedly enhanced dissolution rate and reduce side effects.

Keywords: Piroxicam; Micro sponges; Eudragit polymer; Gel.

INTRODUCTION

Solubility is one of the important parameters to achieve the desired concentration of the drug in systemic circulation for pharmacological response to be shown. The drugs which are poorly water soluble will be inherently released at a slow rate owing to their limited solubility within the gastrointestinal contents.[1] The dissolution rate is often the rate determining step in the drug absorption for a slightly soluble drug; therefore, the challenge for these drugs is to enhance the rate of dissolution or solubility. This in turn subsequently improves absorption and bioavailability; therefore, formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced.[2]

Solubility is the major problem in formulating drug for the transdermal delivery system. The micro sponges are a micro particulate system comprising highly cross-linked polymeric porous microspheres having numerous voids in the particle resembles a true sponge. Micro sponge delivery system enhances the rate of dissolution of poorly water soluble drugs by entrapping them in the pores of micro sponge. The dissolution rate of poorly soluble drugs related to their size so reducing particle size will greatly result in an increase in dissolution rate of these drugs.[3]Piroxicam is an anti-inflammatory, analgesic, antipyretic agent therapeutically used in the treatment of rheumatoid arthritis osteoarthritis. The aim of present study was to design piroxicam micro sponges and incorporate them in a gel in order to enhance the dissolution and release of piroxicam and reduce its side effects.

MATERIALS AND METHODS

Materials

Piroxicam powder was supplied by Hyper Chem-China, Eudragit polymers(RS, RL and S 100)powder were supplied from Evonik Germany , poly vinyl alcohol obtained from JP & SB Converting Services International S.L. Spain and carbopol 934 from HIMEDIA, India .All other materials used in this study were of analytical grade.

Methods

Preparation of Piroxicam Micro sponges

Piroxicam micro sponges were prepared by quasi-emulsion solvent diffusion method. The organic internal phase consisted of Eudragit RS, Eudragit RL or Eudragit S 100 and glycerol (1ml) dissolved in dichloromethane. Glycerol was used as a plasticizer. Then, piroxicam added to the solution and dissolved under ultrasonication at 35°C for 15 minutes. The resulting solution was then poured into 0.05 g of PVA solution in water (external phase of 200 ml volume). The mixture was stirred at 500 rpm for 1hr, 2hr or 3hr at room temperature to remove ethanol from the reaction flask. The formed micro sponges were filtered and dried at 400C for 12 hr and stored for further investigations [(4)]. The composition of various micro sponge formulations is given in table (1).

Table 1: The composition of various micro sponge formulas

Formulas		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Internal phase	**Drug: Polymer ratio**	2:1	4:1	6:1	8:1	6:1	8:1	6:1	8:1	6:1	8:1	6:1	8:1
	Drug(mg)	0.4	0.8	1.2	1.6	1.2	1.6	1.2	1.6	1.2	1.6	1.2	1.6
	Polymer(mg)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Type of polymer	Eudragit(RS)	Eudragit(RS)	Eudragit(RS)	Eudragit(RS)	Eudragit(RL)	Eudragit(RL)	Eudragit(S100)	Eudragit(S100)	Eudragit(RS)	Eudragit(RS)	Eudragit(RS)	Eudragit(RS)
	Type of solvent	Ethanol	Ethanol	Ethanol	Ethanol	Ethanol	Ethanol	Ethanol	Ethanol	Ethanol	Ethanol	Ethanol	Ethanol
	Quantity of solvent (ml)	5	5	5	5	5	5	5	5	10	10	5	5
External phase	**PVA (g)**	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
	Water(ml)	200	200	200	200	200	200	200	200	200	200	200	200
	Stirring rate(rpm)	500	500	500	500	500	500	500	500	500	500	500	500
	Stirring time(hr)	1	1	1	1	1	1	1	1	1	1	2	3

Characterization of Micro sponge Formulation

Determination of Loading Efficiency

A sample of piroxicam micro sponges (10 mg) was dissolved in 100 ml of phosphate buffer, freshly prepared (pH 7.4). The solutions were subsequently diluted suitably with the phosphate buffer pH 7.4 and spectrophotometric absorbance was taken at the maximum wavelength of piroxicam. The drug content was calculated from the calibration curve and expressed as the loading efficiency. [5]

$$Drug\ Loading = \frac{\text{Mass of drug present in microsponges}}{\text{Theoretical mass of piroxicam}} \times 100 \quad \text{.....eq} \quad (1)$$

Determination of Production Yield

The production yield of the microsponge was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges obtained.[5]

$$Production\ yield = \frac{\text{practical mass of microsponge}}{\text{Theoretical mass (polymer+drug)}} \times 100$$

.....eq (2)

Particle Size Measurement

Determination of the average particle size of MLX loaded micro sponges was determined with an optical microscope using a calibrated ocular and stage micrometer under a regular polarized light. A minute quantity of micro sponges was spread on a clean glass slide and the average particle size was calculated by measuring 100 particles of each batch. [6]

$d_{av} = \sum nd/\sum n$ .....eq (3)

Where: d av is the average diameter of particles (µm), n is a number of particles per group, and d is the middle value (µm).

Scanning Electron Microscope (SEM) Study

For morphology and surface topography, the prepared micro sponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the micro sponges can be studied by scanning electron microscope (VEGA3 Tescan Czech republic). [7]

Fourier Transform Infrared (FTIR) Analysis

FTIR spectra of the pure piroxicam, a physical mixture of piroxicam and polymer at a ratio (1:1), and selected microsponge formula were recorded in potassium bromide disc using a Shimadzu Model 8300 FTIR spectrometer to ascertain compatibility. [8]

Differential Scanning Calorimetric (DSC) Analysis

DSC can be used to determine the compatibility between the drug and excipients and can also use to evaluate the crystalline state of a drug. Thermal analysis using DSC was carried out on the same samples used in FTIR by using (Shimadzu DSC-60 Thermal Analyzer). Accurately weighed samples (5mg) were loaded into

aluminum pans and sealed. All samples were run at a heating rate of 100 C/min. over a temperature range 0-350 0C in the atmosphere of nitrogen. [9]

Powder X-Ray Diffraction Analysis (PXRD)

X-rays diffraction patterns (diffractograms) can be used to confirm the crystalline nature of a sample. The study was confirmed by powder X-ray diffractometer at continuous scan range of 2θ = 5 - 500; the operating voltage and current were 40 (kV) and 30 (mA) respectively [(10)]. Samples studied by using XRD are the same used in FTIR study.

In-Vitro Drug Release Studies of Micro sponge Formulation

In vitro dissolution study was performed using USP dissolution test apparatus-II (paddle assembly) (Copley dissolution 8000, Copley scientific, UK). The dissolution was performed in 900 ml of phosphate buffer solution (pH 7.4) as a dissolution medium and maintained at 32 ± 0.5°C and 100 rpm for optimum piroxicam micro sponge formulas. A sample of micro sponges equivalent to 20 mg of piroxicam was used in each test. Samples of dissolution fluid (10 ml) were withdrawn at different time intervals and immediately replaced with 10 ml of the fresh dissolution medium to maintain a sink condition. The samples were filtered through a filter (0.45 µm, Millipore), suitably diluted and analyzed at λ max of piroxicam using a UV-visible spectrophotometer (Cary 100, Varian, Australia) [11.] In addition, the dissolution study was performed for the above-mentioned micro sponge formulas in comparison with pure piroxicam powder

Kinetic Modeling of Drug Release

To analyze the mechanism of piroxicam release from the formulas, the in- vitro release data were fitted into various release kinetic models. The models used are zero order, first order, Higuchi model, Hixon- Crowell model and Korsmeyer – Peppas.[12]The model with the highest correlation coefficient was considered to be the best fitted model.

Preparation of Piroxicam Micros ponge Carbopol 934 Gel

Carbopol 934 gel (1%) was prepared. Carbopol was added to water with vigorous stirring after that methyl paraben (as preservative) dissolved in sufficient quantity of water and then added to the carbopol. The dispersion was homogenized using magnetic stirrer for 1 hr then left for 24 hr for complete swelling of the polymer. Triethanol amine was added drop by drop with continuous mixing, the quantity of TEA was adjusted to achieve gel with the desired pH. A weighted amount of piroxicam micro sponge was incorporated so that the final concentration of piroxicam is 0.5% w/w in the final gel formula. [13, 14]

Physical Properties of Carbopol Gel

Visual Examination

The visual examination includes (color, consistency, and homogeneity).

pH Determination

The pH of the prepared gel was measured using pH – meter by putting the tip of the electrode into the gel and after 2 minutes the result was recorded. [15]

Spread ability

A sample of 0.1g of the gel was pressed between 2 slides with 200g weights and left for about 5 min where no more spreading was expected. Diameters of spread circles were measured in cm and were taken as comparative values for spread ability (diameter of the spread circle – initial diameter. [16]

Viscosity

Rheology includes the measurement of viscosity, which indicates the resistance of a fluid to flow. The viscosity of gel was determined by using Myr Rotational (cup and bop) digital .Viscometer with spindle no. R7 with an optimum speeds 2.5, 3, 4, 5, 6, 10, 12, 20, 30, 50, 60, 100, 200 rpm at room temperature.

Determination of Piroxicam Content in Gel Formula

Piroxicam content in the gel was determined by taking required quantity of the prepared gel which is equivalent to 10 mg of piroxicam and transferred to 100 ml volumetric flask containing phosphate buffer (pH 7.4), it allowed to sonicate and filtered. Then, suitably diluted and analyzed at λ max of piroxicam.[17]

In-Vitro Dissolution Test of Piroxicam Micro sponge Gel

The in vitro release of piroxicam from gel formula was performed by using dissolution apparatus-II (paddle type). A weighing quantity of a gel (2 g that contain 20 mg piroxicam) was uniformly spread on a disk 4.5cm in diameter, and this was immersed in dissolution jar filled with 900 ml dissolution media (phosphate buffer pH 7.4) at 32 ± 0.5°C. The paddle was about 2cm above the disk and rotated at speed of 100 rpm, samples of 10 ml were withdrawn at intervals of 30, 60, 90, 120, 150, 180 minutes and were replaced with equal volume of the fresh buffer solution each time to maintain a constant volume. The samples were filtered through a filter (0.45 µm, Millipore), suitably diluted and analyzed at a maximum wavelength of piroxicam. [18]

Kinetic Modeling of Drug Release from Micro sponge Gel

The in vitro release data were fitted into the kinetic model to analyze the mechanism of drug release.

Statistical analysis

The results of the experiments are given as a mean of three samples ± standard deviation and were analyzed

according to the one-way analysis of variance (ANOVA) test using Microsoft Excel Program 2010. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Quasi-emulsion solvent diffusion method was used. In quasi-emulsion solvent diffusion method, the formation of the micro sponges could be by the rapid diffusion of ethanol into the aqueous medium, might reduce the solubility of the polymer in the droplets, since the polymer was insoluble in water. The instant mixing of the ethanol and water at the interface of the droplets induced precipitation of the polymer, thus forming a shell enclosing ethanol and the dissolved drug. The finely dispersed droplets of the polymer solution of the drug were solidified in the aqueous phase via diffusion of the solvent. The production yield (PY) was between 45%–87% for all formulas. The loading efficiency (LE) varied between 48%–93% for all formulas. The mean particle size of the formulas was between 20-51 µm. There was a significant difference between formulas ($p < 0.05$) in the PY, LE, and mean particle size.

Effect of Drug: Polymer Ratio on Piroxicam Micros ponges

The drug-polymer ratio has a considerable effect on the nature of micro sponges. It was indicated that increasing the drug: polymer ratio increased the production yield and loading efficiency ata higher drug: polymer ratios, the available polymer can encapsulate more amount of drug. The highest loading efficiency, greater the amount of drug was encapsulated. As noticed in F1(drug: polymer ratio 2:1) has 61% production yield and 48% loading efficiency while F4(drug: polymer ratio 8:1) has 85% production yield and 79% loading efficiency. As the ratio of drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high drug to polymer ratios, the amount of polymer available per micro sponge was comparatively lower. Probably in high drug-polymer ratios, less polymer amount surrounds the drug and micros ponges with smaller size were obtained.[19]

Effect of Polymer Type on Piroxicam Micro sponges

Polymer types have a significant effect on loading efficiency and particle size of micro sponge this due to the difference in the viscosities of Eudragit types. As observed F8(prepared with Eudragit S100) had higher LE (93%) when compared with F4(prepared with Eudragit RS) which had much lower LE(79%).This may be attributed to the increasing viscosity of the internal phase containing the Eudrgit S100 reducing the drug mobility outside the formed droplets, and hence entrapping larger amount of drug.[20] The larger the difference in viscosities between the dispersed phase (internal phase) and the dispersion medium (external phase), the lower the mean particle sizes resulted and vice versa. This was attributed to the fact that when the dispersed phase with higher viscosity was poured into the dispersion medium of high viscosity itself, the emulsion was hardly broken into small droplets, and the bigger ones were formed.[21]

Effect of Volume of Internal Phase on Piroxicam Micro sponge

An increment in solvent volume (ethanol) from (5 ml to10 ml), the loading efficiency will be increased; this result may be related to the higher solubilization of drug. The high volume of the inner phase solvent resulted in the uniform mixing of drug and solvent which consequently lead to higher loading efficiency.[22]An increment in ethanol volume leads to decrease in the viscosity of the inner phase; thus smaller droplets are formed of the emulsion leading to a decrease in mean particle sizes. As shown in F3 (5ml ethanol) has 74% loading efficiency and about 30.05 mm particle size while F10 has 82% loading efficiency and 20.08 mm particle size. Further enhancement in the volume of the inner phase, failure to form micro sponges this may be related to the deficient elimination of the inner phase solvent with the production globules that could not consolidate as most of the inner phase stay in it. So the inner phase must be used in its optimum volume to ensure the production of quasi-emulsion globules, and consolidation of the remedy and polymer thereafter.[23]

Effect of Stirring Time on Micro sponges

The stirring time had a significant effect on the formation of micro sponges, it was observed that production yield was decreased significantly as the stirring time increased as shown F3(1 hr) has 80% production yield while F12(3hr) has 45% production yield. One hour stirring was appropriate for the preparation and additional stirring time has no significant effect on the formation of micro sponges. In this respect, the optimum stirring time was selected as 1 hr.[24]

Evaluation of the Shape and Surface Morphology by Scanning Electron Microscope (SEM)

SEM pictures of micro sponge formula F8 with Eudragit S100 polymer presented in figure (1).It was detected by SEM analysis that the micro sponges were finely spherical, smooth, and porous. The surface topography reveals that piroxicam micro sponges contained tiny pores. The pores were induced by the diffusion of the volatile solvent (ethanol) from the surface of the micro particles.[25] Drug crystals were observed over the particle surface because the optimum micro sponge formulas prepared with higher drug/polymer ratio (8:1).So at higher drug/polymer ratios, more drugs will reach the surface of the micro sponges being dissolved in the solvents during diffusion. Moreover, as the diffusion of solvents becomes slower with the increase

in drug /polymer ratio, there is more time for the formation of drug crystals.

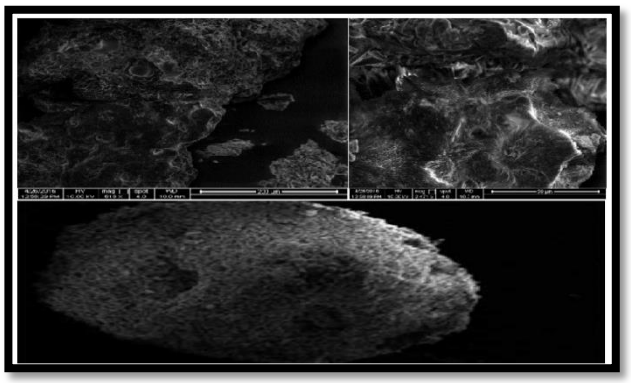

Figure 1: SEM for Selected Formula (F8) of Micro sponge at Piroxicam: Eudragit (1:8)

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR as shown in figure (2) was performed to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic stretching vibration of the Piroxicam. The main characteristic peak of Piroxicam FTIR was the secondary amine N-H stretching appeared at 3384 cm^{-1}.[26] Piroxicam has two inter convertible crystalline forms, namely the needle and cubic forms. The IR absorption peaks at 1633$cm^{-1}$and 1629 cm^{-1} are assigned to the stretching of the amide carbonyl groups of the needle and cubic form of piroxicam respectively. In this study, the peak at 1633 cm^{-1} was found in the IR spectrum of piroxicam, suggesting that the needle form of piroxicam was used in the present study. The piroxicam spectra also exhibited other characteristic peaks like=N stretching vibration of pyridyl nitrogen assigned at 1568.49cm^{-1} C=C stretching of pyridine ring at 1527.2 cm^{-1}, C=C stretching of aromatic ring at 1433cm^{-1}, C-N stretching at 1349.79 cm^{-1},C-O stretching at 1221.9 cm^{-1}, S(=O)2 stretching at 1146.37cm^{-1} , -SO2- N stretching at 1032cm^{-1} ,aromatic CH bending at 829 cm^{-1},ortho-disubstituted phenyl at 771 cm^{-1} and C-S stretching at 663 cm^{-1}. Eudragit RS100 showed an ester C=O stretching peak at 1736cm^{-1} (142) the band 3336.88 cm^{-1} which indicate that the piroxicam was remained in the cubic polymorphic form and no interaction with excipients occurred.

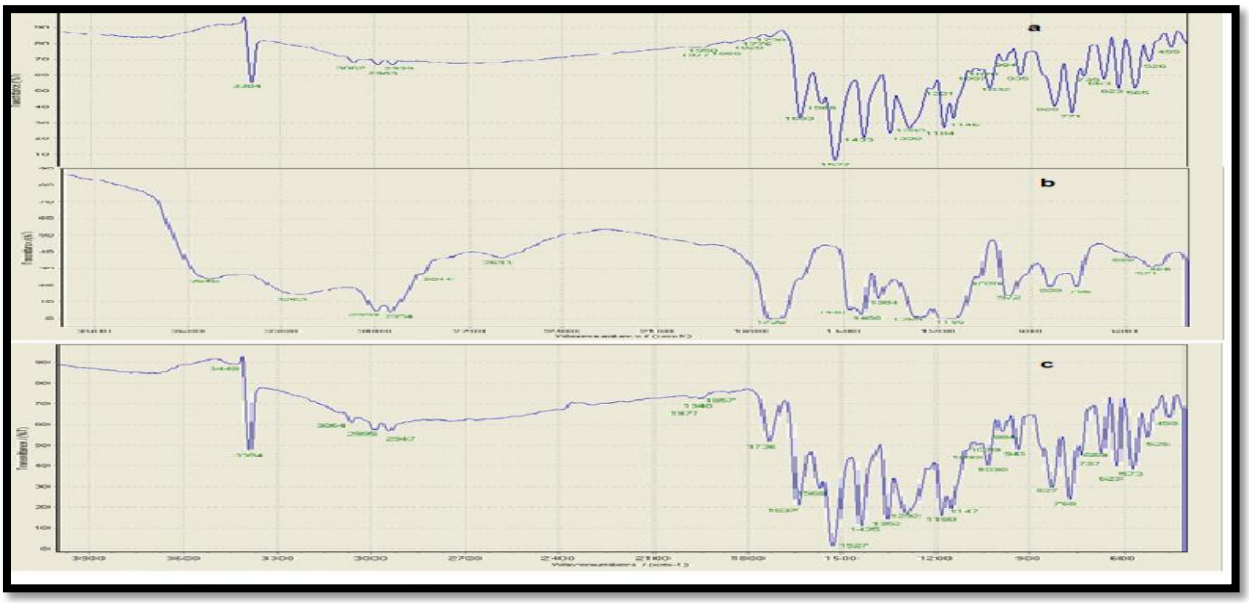

Figure 2: FTIR Spectrum of a) Pure Piroxicam, b) Eudragit S 100, c) Selected piroxicam Micro sponge Formula F8

Differential Scanning Calorimetric (DSC) Analysis

The DSC technique gives an idea about the physical features of the specimen as crystalline or amorphous nature and explains a possible interaction between drug and other compounds in micro sponges. According to the thermograms, piroxicam shows a sharp characteristic endothermic peak at 201◦C corresponding to the melting point of piroxicam in the crystalline form, which are the same as reported by another study.[27] Eudragit S100 showed the broad endothermic peak .The DSC thermogram curve of F8 showed only the typical signals for drug crystals . The disappearance of polymer peaks mainly due to the lower amount of polymer used in the preparation of piroxicam micro sponge in comparison to the amount of drug [the drug to polymer ratio used in F8 is (8:1)]. [(28)] In addition to the amorphous nature of the polymer. Such results showed no interaction between piroxicam and polymers, indicating that micro sponge production process used for the preparation of piroxicam micro sponges did not change the nature of the drug in micro sponges. The DSC of piroxicam, Eudragit S100 and selected formula of micro sponge are shown in figure (2)

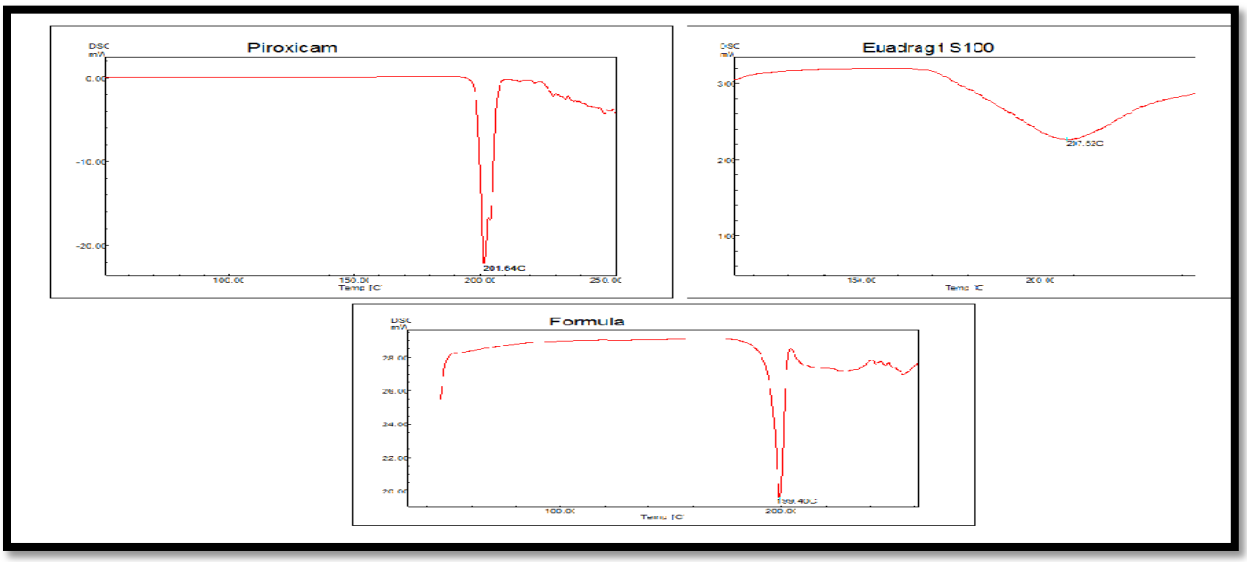

Figure 3: DSC of pure piroxicam, eudragit S 100, selected piroxicam micro sponge formula F8

Powder X-Ray Diffraction Analysis

Powder x-ray diffraction (PXRD) was performed for further confirm the physical state of piroxicam. The PXRD patterns of piroxicam as a pure drug showed sharp and numerous distinctive diffraction peaks indicating the crystalline nature of the drug and this result agreed with the result of DSC.[29] Reflection on the charts showed that there is a decrease in the intensity of the peaks while most of them remain with no appearance of new diffraction peaks which rules out any possible chemical interaction between the components, suggesting that the overall structure of the compound has not changed which was identical to what was obtained from the DSC and FTIR.. Eudragit S100 is amorphous in nature characterized by low intense peak. A PXRD analysis of F8 still showed clearly the typical signals but with lower intensity for drug crystals only because the systems prepared using lower amounts of polymer and these results agreed with the results of DSC study. No appearance of new diffraction peaks which rules out any chemical interaction between the components. A decrease in the intensity of the strongest peak which indicates the reduction in crystallinity and these results are consistent with those from DSC and FTIR. The diffraction patterns of polymer, drug, and selected formula F8 are shown in figure (4)

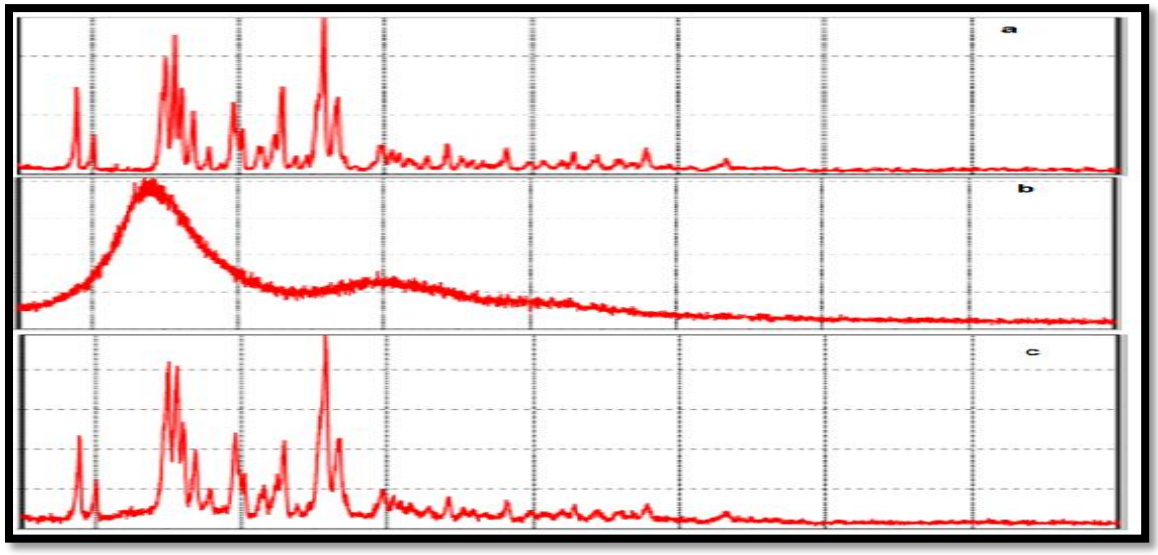

Figure 4: X-Ray Diffraction of a): Pure drug) Eudragit S 100, c): Selected Piroxicam Micro sponge Formula F8

In Vitro Release Studies of Piroxicam Micro sponges

In vitro release profile of piroxicam from different micro sponges formulas which are possessing different polymer types (F4, F6, F8) was carried in comparison with pure piroxicam powder were illustrated in figure (5). It was found that F8 (which contain Eudragit S 100) give significantly higher dissolution rate ($p < 0.05$) as a

result of reduction in particle size and the porous nature of micro sponges, the pores providing channels for drug release.[30]

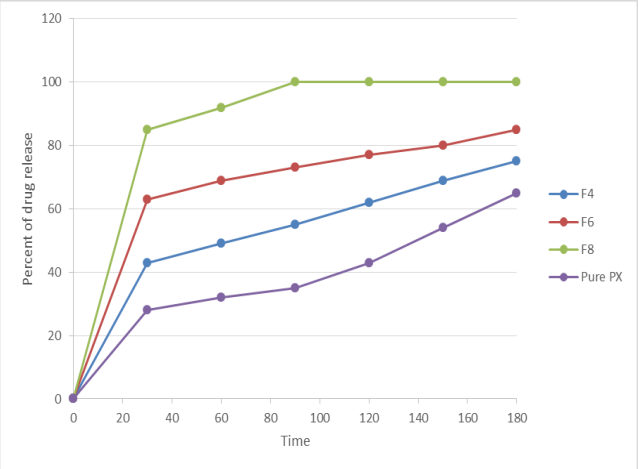

Figure 5: Dissolution Profile of Piroxicam from Micro sponges Formulas (F4, F6, and F8) Along with the Pure Piroxicam powder.

Kinetic Modeling of Drug Release from Micro sponge

The release of piroxicam from micro sponge F8 mainly obeys Hixon- Crowell release kinetic as their (R^2) values gave higher results. The results showed that the release exponent "n" value of F8 micro sponges is >0. 5 and <1 indicating non Fickian (anomalous) transport. Thus, it was proposed that this formula delivered their active ingredient by coupled diffusion and erosion.[31]

Characteristics of Piroxicam Micro sponge Gel

Macroscopic Feature (Organoleptic Properties)

Visual inspection of prepared gel indicated the homogeneity of formulas, no phase separation, non-transparent, with pale-yellow gel

Determination of pH

The result of pH for F8 carbopol 934 gels is 5.70±0.02.

Spread ability Measurement

Spread ability is an important factor in TDD because the efficacy of therapy depends on the patient spreading the drug formulation in an even layer to administer a standard dose. F8 carbopol 934 forms a gel with (4± 0.08 cm) spread ability.

Determination of Piroxicam Content in the Gel Formula

The content of piroxicam in the gel formulas was determined using the ultraviolet technique. The piroxicam contents of the formula are 97.3% ± 0.11 in carbopol 934 gel. The drug content of the formulations showed that the drug was uniformly distributed in the gels.

Viscosity of the Gel

Viscosity holds a major contribution in deciding the drug content and its release from prepared gel formulation.[32] The viscosity study was done to evaluate the effect of the base and concentration on gel viscosity. The viscosity of gels was determined at various shear rates Figure (6). It was found that as the shear rate an increased the viscosity of gel decreased. Also, the increase in polymer concentration caused increase in viscosity of the formed gel. F8 carbopol gel showed approximate viscosity between 4800 CP-152,500 CP.

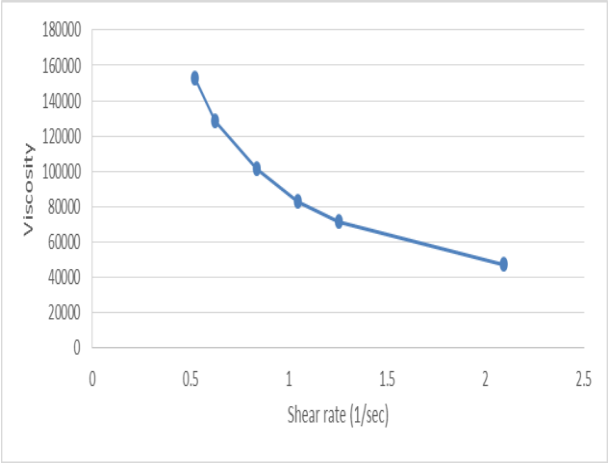

Figure 6: Viscosity versus Shear Rate for Piroxicam Micro sponge Carbopol 934 Gels

In- Vitro Drug Release Studies from Micro sponge Gel

It is showed from the release profile figure (7) that F10 carbopol 934 gel has produced a great improvement in the dissolution rate which is significantly higher ($p<0.05$) than that of pure piroxicam gel . The manufacturer stated that the carbopol 934 gel has the lowest cross–linking density, while that of C 981 is intermediate and that of C 940 is the highest.

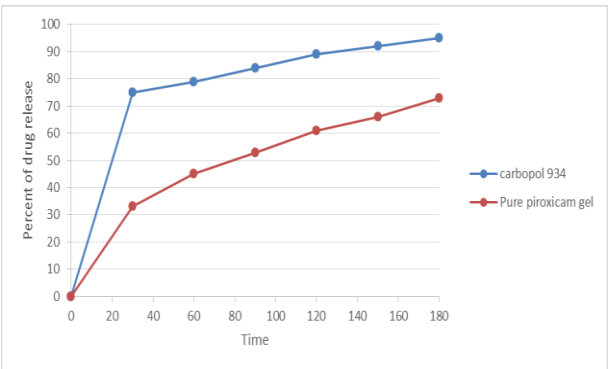

Figure 7: Dissolution Profile of Piroxicam from Micro sponge F8, Carbopol 934 Gel, and Pure Piroxicam Carbopol 934 Gel

Also increasing the polymer concentration in the gel increases viscosity which prolonged drug diffusion through the gel matrix. The same effect was obtained by Attia et al.[33] who studied the diffusion of piroxicam from different polymer gel at different concentrations

of sodium alginate (7%, 10% w/v) hydroxyl propyl methylcellulose (2.5%, 5% w/v) and methyl cellulose (3%, 5% w/v).

Kinetic Modeling of Drug Release from Piroxicam Micro sponge Carbopol Gel

The kinetic data of the in vitro release of piroxicam from gel was found to follow first order release kinetic as their (R^2) values gave higher results. The mechanism of drug release is non ficki and diffusion where release is controlled by a combination of diffusion and polymer relaxation.[34]

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