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Research Article

Interactive Mixture of Piroxicam and Polymers for Development of Mucoadhesive Fast Disintegrating Sublingual Tablet : In Vitro-In Vivo Evaluation

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Abstract

Oromucosal drug delivery promotes rapid absorption and high bioavailability, with subsequent immediate onset of pharmacological effect. However, many oromucosal delivery systems are compromised by the possibility of the patients swallowing the active substance before it has been released and absorbed into the systemic circulation. The purpose of this study was to develop a mucoadhesive fast disintegrating tablet of poorly soluble piroxicam by direct compression. The tablet is based on interactive mixture of components, consisting of carrier particles covered by fine particles of piroxicam. Increasing the retention of the drug at the site of absorption in the oral cavity though incorporation mucoadhesive component is a significant step. The tablets containing 20 mg of piroxicam were tested both in vitro and in vivo. Box-Behnken statistical design was selected to statistically optimize the formulation parameters and evaluate the main, interaction and quadratic effects of the formulation ingredients on properties of tablet. The tablets were evaluated for hardness, friability, DT, wetting time and in-vitro drug release. FT-IR, DSC and physical compatibility study were conducted for drug excipient interactions. The in-vivo study was performed to evaluate effect of the mucoadhesive, retention and absorption at oromucosal site. It has revealed that there is no interaction amongst the physical interactive mixture of piroxicam. The significant mucoadhesive strength was observed thoughout all formulations. Tablets were subjected to pharmacokinetic evaluation and it showed that AUC 22.87 μg/ml/h, AUMC 466.71 μg/ml/h, Cmax 0.79 μg/ml, tmax 6 hs. The pharmacokinetic indicate that rapid absorption and higher bioavailability of piroxicam when administered as mucoadhesive fast disintegrating tablet.

Keywords: Piroxicam, Mucoadhesive, Box Behnken Design, Interactive mixture, Single dose pharmacokinetics

Introduction

Recent developments in the technology have prompted scientists to develop orally disintegrating tablets with improved patient compliance and convenience. ODTs are solid unit dosage forms disintegrate or dissolve rapidly in the mouth without chewing and water. It provides an advantage particularly for paediatric and geriatric populations, bed-ridden, psychotics, developmentally disabled and the patients with persistent nausea during travelling. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Moreover, drug candidates that undergo pre-gastric absorption when formulated as ODTs may show increased oral bioavailability. It provides good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients [1-2].

Box Behnken experimental design is one of the best tools for studying the effect of different variables on the quality determinant parameters of any formulation. Multiple regression analysis of results gives an equation that adequately describes the influence of the independent formulation variables on the selected responses [3]. Piroxicam (PIRO) is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam family that has been recognized for its value as a chemopreventative, anti-tumor agent, acute and chonic musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthitis, rheumatoid arthitis, dysmenorrhoea and sometimes for pain associated with it [3]. Oxicams derive their anti inflammatory effect from inhibition of cyclooxygenase (COX) activity and subsequent repression of prostaglandin synthesis [4].

The studies described in this work were designed to evaluate a new sublingual tablet system using low doses of piroxicam. In this system, water-soluble carrier particles are covered with piroxicam and a bioadhesive material during dry mixing. In principle, the tablet quickly disintegrates into the ordered units consisting of carrier, piroxicam and bioadhesive component. These units initially adhere to the mucosa, the water-soluble carrier particles gradually dissolve and along with them piroxicam also dissolves. With this approach, optimal exposure of active substance to the dissolving fluids is combined with bioadhesive retention of the drug in the oral cavity [5]. For poorly soluble, highly permeable (class II) drugs (like piroxicam), the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal (GI) tract [5-6]. Therefore, together with permeability, solubility and dissolution behaviour of a drug are key determinants of its oral bioavailability. This undesired property, may also increase the amount of GI damage, due to long contact of drug with the mucous of GI. The results of pharmacokinetic studies indicated rapid and higher oral absorption of piroxicam when administered as MFD tablet. Single dose pharmacokinetics was studied after administration of mucoadhesive fast disintegrating piroxicam tablet and marketed formulation in rabbit and the improved systemic exposure of the parent drug, especially regarding absorption rate was observed.

Material and Methods

Materials

All the Analytical grade materials were used. Piroxicam reference standard was collected from Asoj Soft Caps. Pvt. Ltd., India. Mucoadhesive fast disintegrating tablets were formulated using mannitol, sodium croscramellose (SCC), microcrystalline cellulose (MCC), dicalcium phosphate (DCP), magnesium stearate and mango flavour as an excipients. Acetonitrile (HPLC grade), Distilled water (HPLC grade) were used as analytical grade solvent for analysis purpose [7-8]. The reagents 0.1 N Sodium Hydroxide, Phosphate buffer solution pH 7.2, simulated salivary fluid (pH 6.8) was prepared according to compendial procedure [9].

Formulation of piroxicam fast disintegrating mucoadhesive tablet

Preparation of mixtures/powder blend

Coarse mannitol particles were covered with piroxicam by dry mixing. This material was mixed in a teflonized metal jar of All Purpose Mixer

(Shakti corp., Mumbai) at 90 rpm for 24h. SCC and MCC were added to the interactive mixture and mixed at 30 rpm for an additional 48 hs. The DCP and mango flavour was added in interactive mixture and mixed for 1 h at 30 rpm [10-11].

Determination of mixture homogeneity

The content of piroxicam was used to express the quality (i.e. heterogeneity) of the mixtures. Samples of each mixture weighing 120 mg were withdrawn with the aid of sample thieves/Spatula [11]. The amount of piroxicam in the samples was measured spectrophotometrically (Shimedazu corp. Japan) at a wavelength of 354 nm.

Compaction of tablets

All tablet masses were mixed with magnesium stearate in the tumbling mixer at 30 rpm for 2 min. Tablets were made by direct compression method [12] in 8 stations Rota press (Karnavati, Ahmadabad) using 5mm flat edged punches. A total number of fifteen formulations (F1 to F15) of piroxicam tablets were prepared and before tablet preparation, the mixture blend of the formulations were subjected to precompression study parameters like Angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio [12-16].

Drug - excipient compatibility study

Fourier transform infrared (FTIR) spectroscopic analysis

Compatibility between drug and excipients was determined using FT-IR (Cary-60 ATR), spectra were recorded on a Cary-60 ATR FTIR spectrometer in the range of 4000- 400cm-1, study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients [17].

Differential scanning calorimetry (DSC) analysis

DSC curves of the powdered samples were obtained in a DSC-METTLER with TDA trend line software, using aluminum crucibles with about 2mg of samples, under dynamic N2 atmosphere and at a heating rate of 10°C/min in the temperature range 25-400°C [17].

Optimization of mucoadhesive fast disintegrating tablet by Box-Behnken Design

The objective functions for the present study was selected as maximizing the hardness while controlling the disintegration time. Hence, a Box-Behnken statistical design with 3 factors, 3 levels, and 15 runs was selected to statistically optimize the formulation parameters and evaluate the main, interaction and quadratic effects of the formulation ingredients on the hardness, disintegration time, % friability and wetting time of tablet.3-factor, 3-level design was used to explore the quadratic response surfaces and for constructing polynomial models thus helping in optimizing a process using a small number of experimental runs. The experimental design consists of a set of points lying at the midpoint of each edge and the replicated centre point of the multidimensional cube (Table 1).

Table 1. Response variables (F1-F15) obtained from various trial formulations of piroxicam tablets

Run Order	Independent Variables			Hardness (Kg/cm2)	Disintegration Time(sec)	Friability %	Wetting time (Sec)
	(A)	(B)	(C)				
1	0	-1	1	3.1	32	0.81	41
2	0	1	-1	2.9	36	0.96	35
3	1	1	0	4.1	28	0.65	48
4	0	-1	-1	4.4	35	0.62	70
5	0	1	1	2.1	46	1.10	30
6	1	0	1	2.9	39	0.85	38
7	-1	1	0	3.6	50	0.71	47
8	-1	0	1	5.2	47	0.58	125
9	0	0	0	5.9	43	0.56	50
10	1	-1	0	3.2	48	0.79	42
11	0	0	0	3.5	54	0.73	46
12	-1	-1	0	5.2	38	0.58	125
13	1	0	-1	2.9	32	0.85	38
14	0	0	0	6.4	56	0.49	140
15	-1	0	-1	6.4	46	0.49	140

Dependent variables (Factors): Y_1= Hardness (Kg/cm2); Y_2= Disintegration time (Sec); Y_3= Friability (%); Y_4= Wetting time (Sec).
Independent variables: A= Amount of Disintegrant (mg) (Croscramellose sodium), B= Amount of Bioadhesive (mg) (Mannitol), C= Amount of Binder (mg) , (Microcrystalline cellulose

The polynomial equation generated though Reliasoft DOE) is as follows: $Yi = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + b_4 X_1 X_2 + b_5 X_1 X_3 + b_6 X_2 X_3 + b_7 X_{12} + b_8 X_{22} + b_9 X_{32}$

Where; Yi is the dependent variable; b_0 is the intercept; b_1 to b_9 are the regression coefficients computed from the observed experimental values of Y from experimental runs; X_1, X_2 and X_3 are the independent variables that were selected from the preliminary experiments.

$X_1 = (A-X_0)/\Delta X$; X_1 = coded value of the variable A; X_0 = value of A at the center point, ΔX = Step change and so on where A, B etc. are the input variables.

The terms AB and AAi (i =1, 2 or 3) represent the interaction and quadratic terms, respectively.

Statistical analysis

Statistical analysis of the Box-Behnken design batches was performed using multiple regression analysis using Microsoft Excel. The contribution of each factor with different levels to the response was evaluated with two-way analysis of variance (ANOVA) using ®Reliasoft office DOE software [3, 18]. The influence of each factor on the response, the response surface plots were demonstrated using graphical method.

Checkpoint analysis

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points, one from each contour plot, and the theoretical values of hardness and disintegration time were calculated by substituting the values in the polynomial equation. Mucoadhesive Fast disintegrating tablets were prepared experimentally at 3 checkpoints and evaluated for the response [3, 18].

Optimization data analysis [3, 18]

The optimized formulation was obtained by applying constraints on dependent (response) and independent variables (factors). The optimized checkpoint formulation factors were evaluated for various response properties. The resultant experimental values of the responses were quantitatively compared with the predicted values to calculate the prediction error.

Characterization of formulations

Physicochemical evaluation of powder blend

All the ingredients were passed though mesh no 60 and required quantity of each ingredient was taken for specified formulation. The powder blend was evaluated for its precompression behaviour flow properties [19-20] viz; angle of repose, bulk density, tapped density, compressibility index Hausner's ratio, porosity and precompression behaviour.

Physical characterization of tablet

General appearance, thickness, diameter and volume, tablet hardness, weight variation, uniformity of content and friability were evaluated [19-22]. The physicochemical evaluation was performed according to European Pharmacopeia (1997) [12].

The tablet thickness is expressed as averages of 5 measurements made at 5 different points between the 2 surfaces of the compact.

Hardness of the tablet of each formulation was determined using Pfizer hardness tester. Thee tablets from each formulation batch were tested randomly and the average reading was noted.

Randomly selected 20 tablets were weighed individually and together in a single pan balance. As per European Pharmacopeia this method is satisfactory to determine the drug content uniformity. The average weight was noted and standard deviation was calculated.

The test for uniformity of drug content is carried out by collecting a sample of 10 tablets from a batch and determining their individual amount of drugs in each tablet. The content of individual tablets should fall within specified limits in terms of the percentage deviation from the mean. The Roche friabiliator was used for determination of friability.

Drug content

The Powder equivalent to 20mg of piroxicam was weighed and dissolved in 10ml of methanol, volume was adjusted to 100ml with pH 6.8 simulated salivary fluids. The solution was filtered, diluted and analyzed at 354 nm using UV–visible spectrophotometer [23].

Disintegration time

Nine hundred millilitres of water maintained at 37°C. DT was determined at the point at which the tablet disintegrated and passed though the screen of the sinker completely (opening of mesh of the sinker: 3–3.5 mm in height and 3.5–4 mm in width) [24].

In vitro dispersion time

In vitro dispersion time i.e. time required to breakdown the tablet into small particles and make dispersion was measured by dropping a tablet in a beaker containing 50 ml of simulated salivary fluid pH 6.8 [25].

Wetting time and water absorption ratio

A piece of tissue paper folded twice was kept in a Petri dish containing 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined [24-25].

Measurement of tablet tensile strength

A diametral compression test was performed according to European Pharmacopoeia (resistance to crushing of tablets) (n = 35). The tablet crushing load, which is the force required to break a flat-faced tablet into halves by compression in the radial direction, was measured using a tablet hardness tester [26]. Tensile strength for crushing (Ts) was calculated using the following equation:

$$Ts = \frac{2F}{\pi.dt} \quad \text{Equation 1}$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

Measurement of tablet porosity

The tablet porosity was calculated from the dimensions and weight of the tablet and the apparent particle density of the mixture [27-28]. The apparent density (ρapp) of the compact, were calculated from the ratio of the tablet mass to the volume of the compact.

$$(\rho app) \text{ of compacts} = \frac{\text{Mass of the tablet}}{\text{Volume of the compact}} = \frac{gm}{r2h} \quad \text{Equation 2}$$

The porosity of the compacts was calculated using the relationship

$$\text{Porosity } (\varepsilon) = 1 - \frac{\rho \text{ app density of compacts}}{\rho \text{ true density of particles}} \quad \text{Equation 3}$$

Where, ε is the porosity of the compacts, ρapp is the apparent density of the compact, and ρ true is the true density of the particles. The ratio of ρapp/ρtrue is a measure of the relative density or the solid fraction of the compact.

In vitro dissolution test

The release rate of piroxicam from mucoadhesive fast disintegrating tablets was determined using USP dissolution testing apparatus II (paddle method, Electrolab, TDT-06T, Mumbai, India). The dissolution test were performed using 900 ml of simulated salivary fluid (pH=6.8), at 37 ± 0.5°C and 50 rpm. A sample (1ml) of the solution was withdrawn from the dissolution vessel periodically and replaced with fresh dissolution medium of same quantity. The samples were filtered though a whatman filter [28-30]. Absorbance of these solutions was measured at 354 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer.

Measurement of bioadhesion strength

Modified physical balance method was used for determining the ex-vivo bioadhesive strength. The fresh goat sublingual mucosa was cut into approximately 2 cm^2 pieces and placed in a stainless steel plate. The powder (using double-sided tape) was attached to the upper probe. The powder was applied by immersing the probe into a powder bed and gently shaking it to remove any excess, so as to achieve a monolayer of particles, which was visually validated. After spreading 30 μl of buffer onto the mucosa with a pipette to standardise hydration, the powder was brought into contact with the mucosa under a approximate force of 0.5 N over 30 seconds [7, 31]. After completion of preload time, preload was removed from the clamp and water was added into the beaker from burette at a constant rate. The weight of water required to detach the powder from mucosa was noted as mucoadhesive strength and experiment was repeated with fresh mucosa in an identical manner. a shorter duration of contact (30 sec) was chosen for these studies, mainly because of the intention to reflect a quickly disintegrating system.

Permeability study

The in vitro drug transport though the artificial cellulose acetate membrane (molecular weight cut off 1000 Da) was carried out using a vertically static type Franz diffusion cell. Formulations containing 20 mg of piroxicam in tablet were placed on the cellulose membrane surface facing the donor compartment and (1ml) of the sample solution was withdrawn from the compartment periodically and replaced with fresh medium of same quantity. The drug content in the collected samples was determined using an UV visible spectrophotometer at 354 nm (UV/visible spectrophotometer, Shimadzu-120, Japan).

The permeability coefficient though the membrane (Kp) was determined (Permeability coefficient (Kp) = (Jss. H)/C0), Where as H is the thickness of membrane and, C0 is the initial drug concentration [32]. The steady state flux was calculated (Steady state flux (Jss) = dM/S.dt) Where as dM is the amount of drug that permeates though a unit cross section area, S, per unit time, t [33]. The slope of the steady-state portion of the permeation curve created by plotting the cumulative amount of drug permeated in micrograms versus time in hours is the flux [31].

Single dose pharmacokinetics study

Administration of formulation to Rabbits

Two groups of white rabbits (2.5–3.3 kg), each consisting of thee species were taken from animal house, Tatyasaheb Kore College of Pharmacy, Warananagar, India. The rabbits were allowed to eat commercial food pellets and drink water except during the first 5 h of each test, when they were under anaesthesia. All procedures with animals were reviewed and approved by the Institutional Animal Ethics Committee (1090/PO/AC/07/CPCSEA), of Tatyasaheb Kore college of Pharmacy, Warananagar, India.

Before each test the rabbits were given atropine (0.02mg/kg) to prevent excess salivation, and then anaesthetized with pentobarbitol sodium 25 mg/kg by i.v. directly into a ear marginal vein. Anaesthetized rabbits were positioned on a table with the lower jaw supported in a horizontal position. After collecting the zero hour blood sample (blank), the dose is adjusted as per body weight and tablet was kept sublingually. Blood samples (1 ml) were collected periodically from marginal ear vein after administration. The blood samples were allowed to centrifuged at 3000 rpm and the serum separated was collected into dry tubes. All the samples were stored under refrigerated conditions prior to assay. Serum concentration of piroxicam was determined by the HPLC method using UV detector [33-36].

Piroxicam analysis

Piroxicam concentrations were determined in rabbit plasma by high performance liquid chomatography with UV detection. The mobile phase consisted of 50:50 acetonitrile: Simluated salivary fluid at a flow rate of 1 ml/min with the retention time 4 to 8 min.

The stock solution of piroxicam was subsequently diluted with acetonitrile and to this solution added 1 ml of plasma from undosed subjects. The tubes were then centrifuged at 2500 rpm for 15 min. In the supernatant solution 0.2 ml of 1.47 M aqueous $HClO_4$ was added and peak area of these solutions were measured in HPLC-UV detector at 354 nm against blank prepared [23].

Estimation of piroxicam in serum samples

In a dry centrifuge tube 1 ml of blood, 5ml of acetonitrile was added centrifuged at 2500 rpm for 15 min. From this solution 4 ml of supernatant was collected into a dry test tube and 0.2 ml of 1.47 M aqueous HClO4 solution was added and mixed. The peak area of the resulting solution was measured at 354 nm against a blank prepared in the same manner with blood collected before drug administration [33].

Pharmacokinetic data analysis and bioavailability evaluation

The maximal plasma concentration (Cmax) and the time to reach maximum plasma concentration (Tmax) can be directly obtained from the plasma data. The pharmacokinetic parameters were determined for each individual animal using noncompartmental analysis. Values calculated following the sublingual administration were maximal plasma concentration (Cmax) and the time to reach maximum plasma concentration (Tmax), the area under the plasma concentration-curve (AUC), area under the first moment curve (AUMC), mean residence time (MRT), apparent volume of distribution steady-state (Vd) where, plasma clearance (Clp), elimination rate constant (ke) and terminal half-life (t1/2). The AUC and AUMC were calculated using trapezoidal rule with extrapolation to infinity (∞) [34-36].

Accelerated stability study of optimized batch

The optimized formulation was kept in 5 ml of glass vial and closed. The vials were kept at $40\pm2°C/75\pm5\%$ RH for three months in a stability chamber. After end of stipulated period, tablets were evaluated for mean dissolution efficiency and drug content [37-38].

Result and Discussion

Formulation of tablet

The drug dissolution rate is affected by the particle size of both drug and carrier as well as by the physicochemical properties of the carrier. Highly water soluble carrier materials are less bioadhesive than insoluble carriers, probably because of tensile fracture goes though the partly dissolved carrier particles rather than though the mucosa or between the mucosa and the bioadhesive material. However, it is not always desirable to concentrate only on optimal bioadhesion. The choice of carrier for these types of tablets involved consideration of both a high dissolution rate to optimize absorption of piroxicam over the sublingual mucosa and adequate bioadhesive properties to minimize swallowing of the substance. Since mannitol fulfills both these criteria, it was chosen as the carrier material. SCC also has bioadhesive properties and was therefore expected to prolong the residence time of the ordered units at the sublingual mucosa. It is also very effective disintegrant. MCC is a moderately deformable binder and is unlikely to significantly impair the disintegration process. The homogeneity of mixture was calculated and was found at acceptable level. The content of piroxicam was determined and found to be $99.10\pm1.1\%$.

Precompression characterization

Mannitol and Microcrystalline cellulose were selected as the basic excipients because of proven safety. Due to excellent compactability, it was used in tablet formulations to prevent capping. Furthermore, sodium croscramellose was also used as a superdisintegrant because it swells to a large extent when it comes into contact with water. Since the powder material was free flowing, tablets were obtained of uniform weight variations as per pharmacopoeial specifications. Bulk density was found to be between 0.52 ± 0.01 to 0.72 ± 0.02 gm/cm^3 and tapped density between 0.59 ± 0.44 to 0.83 ± 0.02 gm/cm^3 for all formulations. From density data % compressibility was calculated and was found to be between 5.7 ± 0.007 to 18.0 ± 0.010 %. Angle of repose was found to be in the range of 28.87 ± 0.65 to 33.70 ± 0.53.

A Hausner ratio value of less than 1.20 is indicative of good flowability of the material, whereas a value of 1.5 or higher suggests a poor flow display by the material exceptionally few formulation crosses the limits of hausner ratio. The Carr index is also called "percent compressibility".A value between 5 and 15, 12 and 16, 18 and 21, and 23 and 28 indicates excellent, good, fair, and poor flow properties of the material, respectively.

The Hausner ratio and Carr index are measures of interparticle friction and the potential powder arch or bridge strength and stability,

respectively and widely used to estimate the flow properties of powders. The Hausner ratio and Carr's index values for mannitol and MCC products suggest the good flow properties. All the formulation shows the fair to good flow properties for compression and hence tablets were prepared accordingly (Table 1).

Kawakita plot

'a' is properties of consolidation as close packing and b is packing velocity. The constant 'a' is equal to the minimum porosity of the bed prior to compression while 'b' which is termed as the coefficient of compression, is related to the plasticity of the material. The grater the value of b indicates good compactibility, and if packing velocity is high means yield pressure are breaking strength is less (Figure1). All the formulations indicate the good flowability but at the same time it shows the poor compactibility.

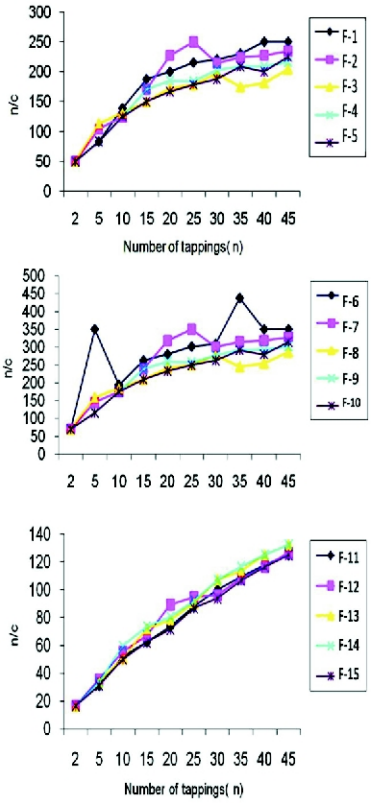

Figure 1. Kawakita plots explaining the flowability of powder

Drug excipient compatibility study

It is well known that interactions between the active substance and excipients can influence the pharmacological properties and behavior of drugs in biological systems. The mixtures of excipients and piroxicam were mixed together and analyzed by FTIR and DSC.

FTIR Spectral Analysis

FTIR study reveals that NH2 stretching, O-H stretching, CH stretching of methyl, C=O aromatic stretching, C=N stretching, C-O stretching of tertiary alcohol and –NH- out of plane bending of pure piroxicam and the piroxicam formulations containing higher proportion of the above excipients were almost in the same region of wave number ranging from 3443cm^{-1} to 621.10 cm^{-1}. It showed that IR spectrum of pure piroxicam and piroxicam formulations containing higher proportion of superdisintegrant were similar fundamental peaks and patterns (Figure 2). The results proved that there were no significant interactions between the drug and all excipients.

Figure 2 . FTIR Spectra of pure piroxicam and its physical mixture

Differential scanning calorimetry

DSC curves of pure piroxicam and physical mixture of piroxicam and excipients were obtained (Figure 3-4). Pure piroxicam showed a sharp melting endotherm at (201.4°C). This is attributed to the melting of the active substance. DSC thermograms of physical mixture of drug and excipients showed the melting peak of the drug at (167.74°C). Physical mixture of all above ingredients showed their identical peaks at defined temperature range. The shifting of melting endotherm was may be due to higher concentration of excipient in samples. Presence of all peaks indicates that all ingredients are compatible with drug means there is no incompatibility between selected ingredients [28-29].

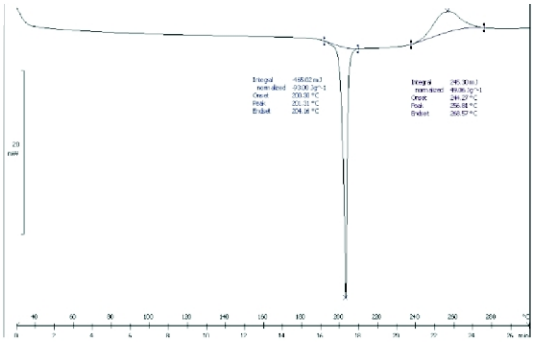

Figure 3. Differential scanning calorimetry thermogram of pure piroxicam

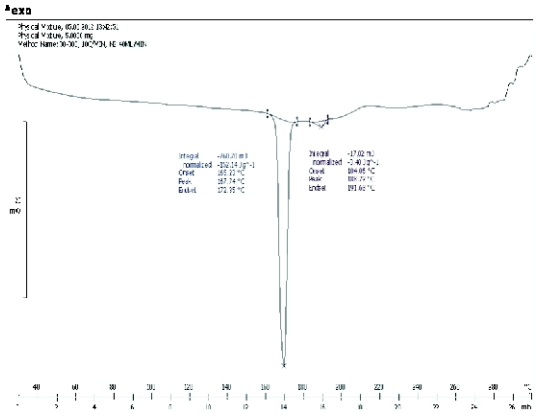

Figure 4. Differential scanning calorimetry thermogram of piroxicam and its physical mixture

Box-Behnken experimental design

Systematic optimization procedures are carried out by selecting an objective function, finding the most important or contributing factors and investigating the relationship between responses and factors. A Box Behnken experimental design has the advantages of requiring fewer experiments (15 batches). The all selected dependent variables obtained at various levels of the 3 independent variables (X_1, X_2 and X_3) were subjected to multiple regression to yield a second order polynomial equation.

$Y_1 = 4.9667 - 0.9125\ X1 - 0.400X_2 - 0.4125\ X_3 + 0.625\ X_1X_2 + 0.30\ X_1 X_3 + 0.125X_2X_3 + 0.1417\ X_{11} - 1.083\ X_{22} - 0.7533X_{33}$

$Y_2 = 57.66 - 4.25\ X_1 + 0.875\ X_2 + 1.875\ X_3 - 8.00X1X_2 + 1.5\ X1\ X_3 + 3.25\ X_2X_3 - 6.4583\ X_{11} - 10.2083X_{22} - 10.2083X_{33}$

$Y_3 = 0.5933 + 0.0975\ X_1 + 0.775X_2 + 0.0525\ X_3 - 0.0675X_1X_2 - 0.0225\ X_1\ X_3 - 0.0125\ X_2X_3 - 0.0454\ X_{11} + 1.3463X_{22} + 1.446X_{33}$

$Y_4 = 98.667 - 33.87\ X_1 - 14.750X_2 - 6.125\ X_3 + 21X_1X_2 + 3.750\ X_1\ X_3 + 6\ X_2X_3 - 4.0417\ X_{11} - 37.20X_{22} - 17.45X_{33}$

Physical characterization of tablets

General appearance, thickness, diameter and volume of tablet

Drug uniformity results were found to be good amongst different batches of tablets, and the percentage of drug content was more than 98%. The results also showed acceptable and homogenous distribution of drug in tablets. The weight and thickness of the formulations ranged from 117 to 121 mg and from 2.78 to 3.08 mm, respectively. All tablets prepared in this study meet the USP requirements for weight variation of all formulae was less than 2% (USP 31). In all the formulations, the hardness test indicated good mechanical strength. Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the compendial limits (USP 31) and had a good mechanical resistance (Table 2).

Table 2. Polynomial equation values in terms of actual values (coefficients)

Sr. no.	Term	Hardness	Disintegration time	% Friability	Wetting time
1	* Intercept	4.97	57.67	0.59	98.67
2	A:Superdisintegrant (r^2)	-0.91	-4.25	0.10	-33.88
3	* B:Binder(r2)	-0.40	0.88	0.08	-14.75
4	* C:Bioadhesive (r^2)	-0.41	1.88	0.05	-6.13
5	* AB	0.63	-8.00	-0.07	21.00
6	* AC	0.30	1.50	-0.02	3.75
7	* BC	0.13	3.25	-0.01	6.00
8	* AA	0.14	-6.46	-0.05	4.04
9	* BB	-1.08	-10.21	0.13	-37.21
10	* CC	-0.76	-10.21	0.14	-17.46

In vitro disintegration study

In principle, the tablets should disintegrate rapidly, to instantly generate many ordered units consisting of mannitol, piroxicam and SSC. The disintegration time of the all batches of tablets containing piroxicam was 28-63 sec. The higher value was probably caused by adhesion of the tablets to the discs (because of the addition of bioadhesive), which fudged the endpoint. It seems reasonable from these results that the tablet will adhere to the mucosa in the mouth. The in vitro data obtained with discs probably better reflects the disintegration time in vivo into ordered units. However, the movements that occur in the mouth may contribute to the disintegration of the tablets.

The most important parameter that needs to be optimized in the development of sublingual tablets is the disintegration time of tablets. In the present study, all the tablets disintegrated in the range varied from 28 ± 3.61 to 63 ± 1.53 Sec. In the USP, the disintegration apparatus for oral tablets is used without the covering plastic discs, and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for sublingual tablets (USP 31). All the formulations met the requirement for disintegration specification. The rapid and desired disintegration of tablets is due to the presence and good proportion of Mannitol, MCC and SCC and can be explained with following reasons.

MCC has good wicking and absorbing capacities and tablets of MCC disintegrated rapidly due to the rapid passage of water into the tablets resulting in the instantaneous rupture of the hydrogen bonds. The ratio of MCC in tablet formulations changes between 10% to 20% and verifies the findings, that the optimum concentration of MCC may be less than 15%. MCC accelerates water penetration into tablets can cause easily swelling of SCC, and this reveals readily superdisintegrant property of SCC. But, there is another important point that must be taken into consideration that the ratio of SCC in sublingual tablet formulation is very important because it was reported that disintegration time increased with increase in the level of SCC in the tablets. It was shown that the increase in the level of SCC had a negative effect on the disintegration of the tablets. At higher levels, formation of a viscous gel layer by SCC might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. Thus, tablet disintegration is retarded to some extent with tablets containing SCC. So it can be concluded that the use of SCC in sublingual tablet formulations in 10 mg gives the tablet desired disintegration time. On the other hand, mannitol has a highly water soluble property and this may leave pores in the tablet matrix after rapid dissolution of it. These pores can accelerate capillary action that may be responsible for penetration of surrounding fluid in the tablet matrix and there after rapid disintegration.

Water absorption, porosity and wetting time

Water uptake is increased with increased mannitol content and caused a great deal of swelling. During the manufacture of MCC, accessible amorphous regions of cellulose molecules are hydrolyzed away, so that MCC shows relatively high crystallinity. It can absorb only small amounts of water, and reaches equilibrium rapidly (Table 2).

Wetting is closely related to the inner structure of tablets and to the hydrophilicity of excipients. According to Washburn's equation, the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of powders which is expressed by contact angle and surface tension. It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. Since the hydrophilicity of MCC is lower than Mannitol, wetting time generally decreases with an increased MCC content. When the MCC content exceeded 90%, however, the wetting time showed a reverse tendency. This suggested that the inner structure of these tablets underwent some change at a high MCC concentration. Since MCC particles are of a concave convex shape and their pores are fairly collapsed by compression.

Tablet tensile strength

It was generally recognized that tensile strength was influenced by the number of contact points between the powder particles and the interparticle binding force, such as the surface molecular interaction and mechanical interlocking. The number of contact points was altered by the porosity of the tablet and by the shape and diameter of constituent particles. MCC was easily compressed, when compressed under the same pressure, tablets containing more MCC showed lower porosity.

Both tablet strength and disintegration times were effected by tablet porosity. The porosity of the tablet may affect the action of the disintegrant. A relatively low porosity was most effective action for the action of a disintegrant. However, no general relationship between porosity and disintegration time was seen and it was concluded that the material properties of the tablet components, such as solubility and bounding ability, would also affect disintegration time. The tablet porosity was approximately 25% for all thee batches, which appears adequate considering the results for tablet strength.

In vitro dissolution studies

In formulated tablets, roughly 50% of the substance was dissolved from the tablet within 1 min, and more than 90% drug within 10 min. The dissolution profiles for all the batches are comparable with those obtained for ordered mixtures i.e. compaction of the ordered units did not negatively influence the dissolution rate. After initial rapid disintegration, ordered units are quickly exposed to the solvent and drug dissolution starts more or less instantly. In these studies a large amount of dissolution medium (900 ml, pH 6.8) was used. However the volume of fluid used in in vivo was much smaller.

According to the compendial requirement, the amount of drug dissolved from sublingual tablets must exceed 80% in 15 min. Therefore, the resulted dissolution profile met the above mentioned requirement.

Fast dissolution of the drug from the formulations can be explained with the few comments like; manufacturing method can be one of the most important parameters for the dissolution. As it is known, the tablets prepared by direct compression disintegrate into piroxicam particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. It is well known that the addition of mannitol can improve the flow and bond properties of other excipients during direct compression. In particular, mannitol with higher solubility might also facilitate the dissolution of solid dosage forms. When evaluate all formulations, mannitol ratios can give us the chance of preparing sublingual tablets without changing their basic tablet characteristics especially disintegration and dissolution profiles.

Bioadhesion

The bioadhesive strength was influenced by the ratios of bioadhesive polymers. In all the formulation batches, as the mannitol concentration increased, the mucoadhesive strength of powder increased. The higher bioadhesive strength may be due to the formation of secondary bonds with mucin and entanglement and interpretation of polymeric chain with mucin. The magnitudes o the adhesion force of tablets was observed (0.22 ± 0.02 and 0.80 ± 0.03). The unexpectedly high bioadhesive values for DCP and mannitol tablets were probably attributable to some kind of attraction between the smooth surface of tablet and mucosa.

Statistical analysis

Effect of formulation variables

The results clearly indicate that the hardness value is strongly affected by the variables selected for the study. This was also affected by the wide range of values for coefficients of the terms of polynomial equation for Y_1. The main effects of X_1, X_2 and X_3 represent the average result of changing one variable from its low level to its high level. The interaction terms (X_1X_2, X_1X_3, X_2X_3, X_{12}, X_{22} and X_{32}) shows how the hardness changes when remained variables are simultaneously changed. The negative coefficients for all 3 independent variables indicate an unfavourable effect on the hardness, while the positive coefficients for the interactions between 2 variables indicate a favourable effect on the hardness (Table 3).

Table 3. Regression analysis of Y_1, Y_2, Y_3 and Y_4 for fitting to quadratic model

Quadratic model	(%) R^2	(%) Adjusted R^2
Response Y_1	71.47	20.10
Response Y_2	91.29	75.62
Response Y_3	72.92	24.16
Response Y_4	75.79	32.22

Among the thee independent variables, the lowest coefficients value is for X_2, indicating that this variable is insignificant in prediction of hardness (Figure 5).

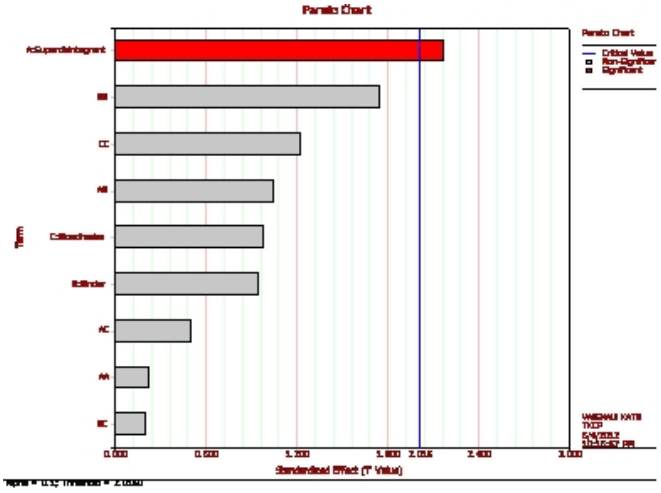

Figure 5 . Pareto chart showing the standardized effect of independent variables and their interaction on hardness

Y_1, Y_2, Y_3 and Y_4 values measured for the different batches showed wide variation (values ranged from 2.1 to 6.4 Kg/cm2 for Y1; 28 to 63 second for Y_2; 0.51 to 2.90% for Y_3 and 32 to 141 second for Y_4) which clearly indicate that the Y_1, Y_2, Y_3 and Y_4 values is strongly affected by the variables selected for the study (Table 2).

It was also affected by the variables selected and wide range of values for coefficients of the terms in equations. The main effects of X1, X2 and X3 represent the average result of changing one variable at a time from its low level to its high level. The negative sign for the coefficients in polynomial equation indicates a negative effect on responses, while the positive sign indicate a positive effect. The statistical analysis of the full model indicates that the independent variables had a significant effect on the responses.

The standardized effect of the independent variables and their interaction on the dependent variable was investigated though a Pareto chart (Figure 6-9) which depicts the main effect of the independent variables and interactions with their relative significance on the Y1, Y2, Y3 and Y4. The length of each bar in the chart indicates the standardized effect of that factor in the responses. Factors remains inside the reference line indicate that these terms contribute the least in prediction of responses.

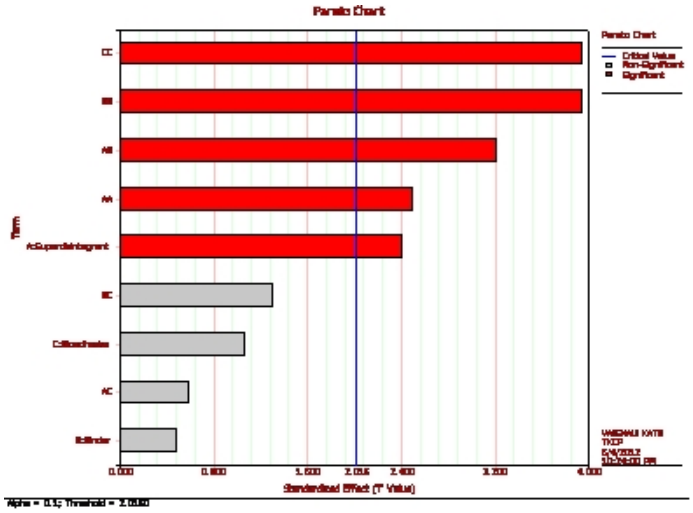

Figure 6. Pareto chart showing the standardized effect of independent variables and their interaction on disintegration time

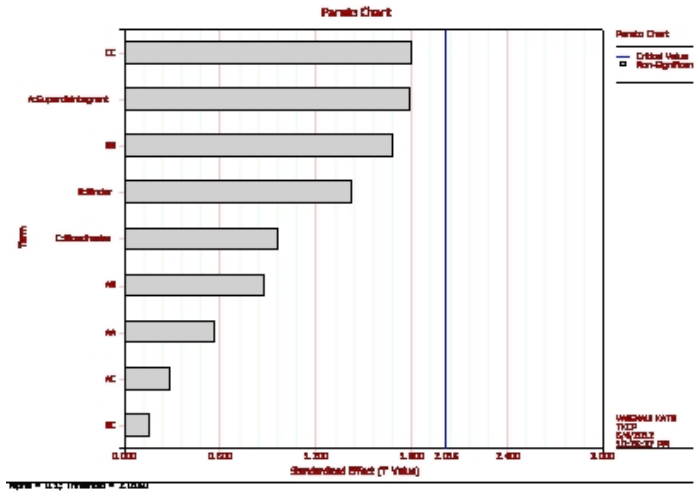

Figure7. Pareto chart showing the standardized effect of independent variables and their interaction on percentage friability

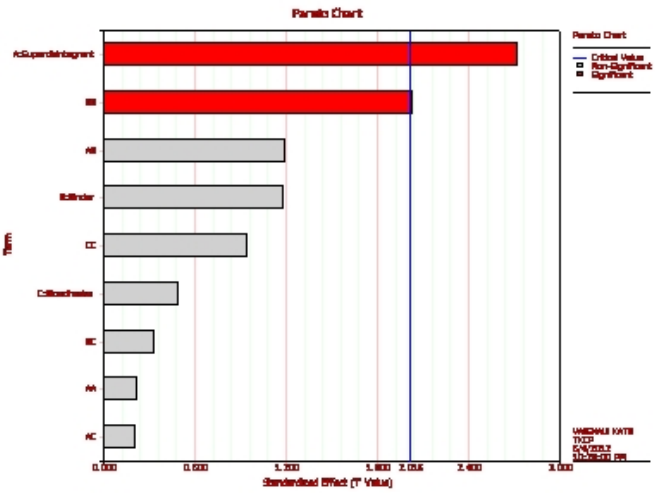

Figure 8. Pareto chart showing the standardized effect of independent variables and their interaction on wetting time

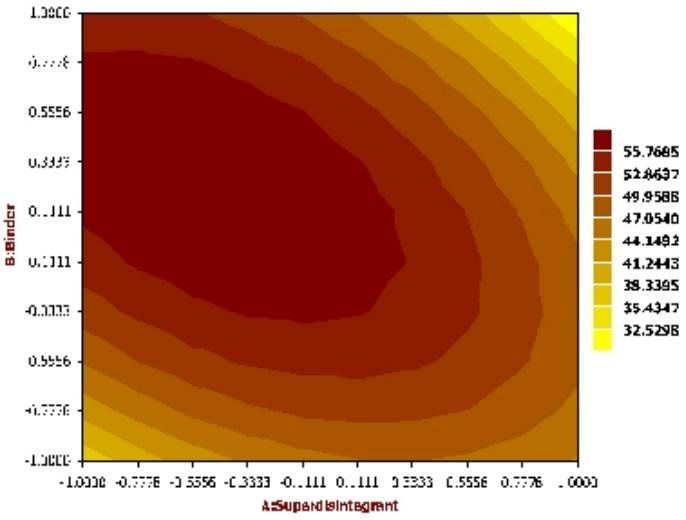

Figure 9. Contour plot showing effect of disintegrant concentration and binder concentration on response Y_3

ANOVA, Pure error and Lack of fit

The result of ANOVA demonstrates that the model was significant for all dependent variables (Table 3). All the independent variables were found to be significant for all response variables. The quadratic model was found to be significant for Y_2 and linear model was found to be significant for Y_3 and Y_4. So above result indicates that both the factors play an important role in the formulation of tablet containing piroxicam. The data of pure error and lack of fit can provide a mean response and an estimate of pure experimental uncertainty. The residuals are the difference between observed and predicted values. The ANOVA for the dependent variables demonstrates that the model was significant for all response variables (Table 4).

Table 4. Checkpoint Analysis formulations of piroxicam tablets

Run Order	Independent variables			Hardness (Kg/cm^2)		Disintegration time (sec)	
	A	B	C	*Measured (n=3)	Predicted	*Measured (n=3)	Predicted
5	0	1	1	2.37±0.40	2.4375	42.33±2.52	43.25
6	1	0	1	2.93±0.21	3.325	39.67±1.53	40.125
7	-1	1	0	3.63±0.15	3.9125	54.33±2.08	54.125

The effects are like, the amount of MCC and SCC were found to be significant, along with its quadratic and interaction terms for all the dependent variables. Hence the above results lead us to believe that concentrations of disintegrant have an important role to play and an optimal concentration in sublingual tablets give rise to rapid disintegration time, good crushing strength values and sufficiently low friability percentages, in order to successfully withstand the mechanical stress, during packing, transportation and handling. The data for pure error and lack of fit provides a mean response and an estimate of pure experimental uncertainty. The residuals values represents the differences between the observed and predicted values, given that computed F values were respectively lower than critical F values, which denotes non-significance with regard to lack of fit.

To confirm the omission of non significant terms, F statics was calculated after applying analysis of variance for the full model. The F calculated value 0.80 is less than the tabulated value of 1.39 at 0.05 confidence interval for hardness. Hence it is concluded that the omitted terms do not significantly contribute to predicting the hardness. This implies that the main effect of the amount of binder and the amount of bioadhesive added is significant, as is evident from the high coefficients.

The thee replicated center points in the Box Behnken experimental design made it possible to assess the pure error of the experiments and enabled the model's lack of fit to be checked. In this study, the model was checked for lack of fit for all the responses. For lack of fit P values we obtained 0.75, 0.49, 0.36 and 0.872 for Y1, Y2, Y3 and Y4 respectively and hence the current model provided a satisfactory fit to the data and had no lack off fit. The statistical significance of each effect was tested by comparing the mean square against an estimate of the experimental error. It was noted that X1, X3 and X4 had p-value greater than 0.05, indicating non significance of these variables in prediction of Y_1, Y_2, Y_3 and Y_4.

Contour plots and response surface analysis

Two dimensional contour plots and thee dimensional response surface plots (Figure 10-15), which are useful to study the interaction effects of the factors on the responses.

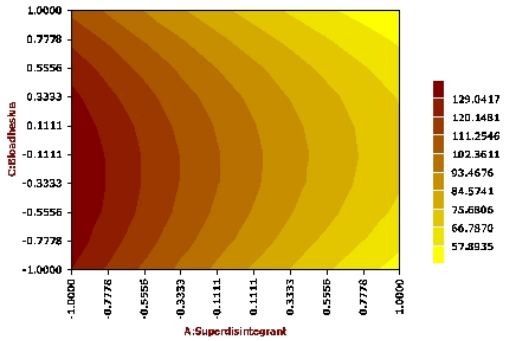

Figure 10. Contour plot showing effect of disintegrant concentration and bioadhesive concentration on response Y3

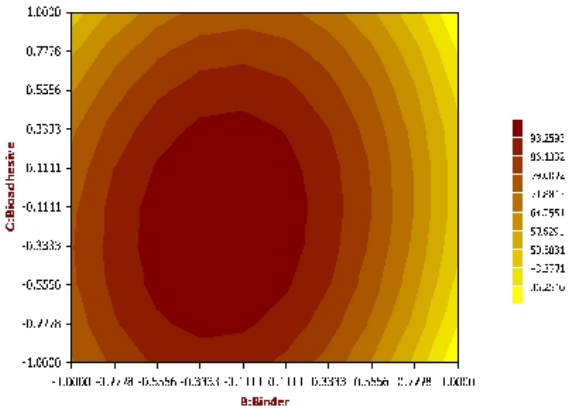

Figure 11. Contour plot showing effect of binder concentration and bioadhesive concentration on response Y3

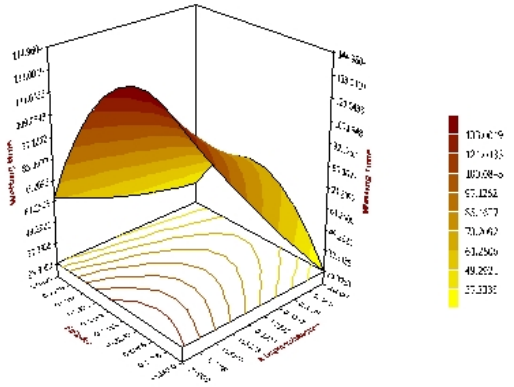

Figure 12. Response surface plot (3D) showing the effect of binder concentration and superdisintegrant concentration on response Y4

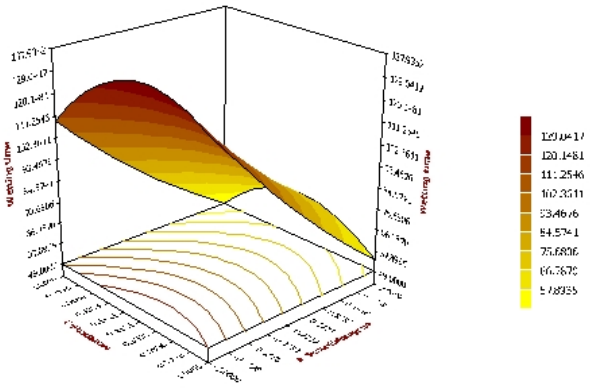

Figure13. Response surface plot (3D) showing the effect of superdisintegrant and bioadhesive concentration on response Y4

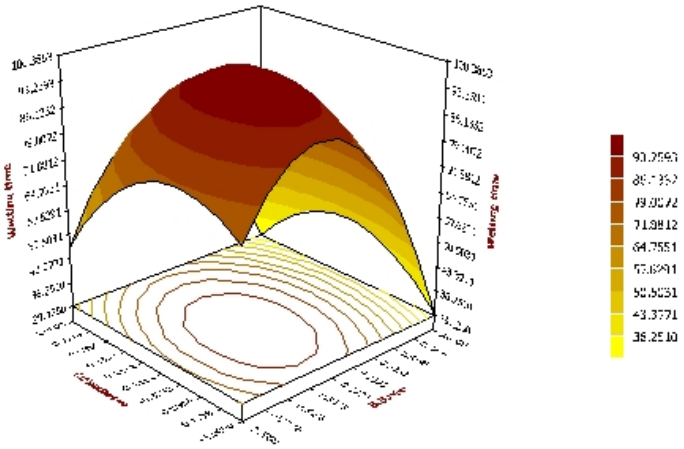

Figure 14. Response surface plot (3D) showing the effect of binder and bioadhesive concentration on response Y4

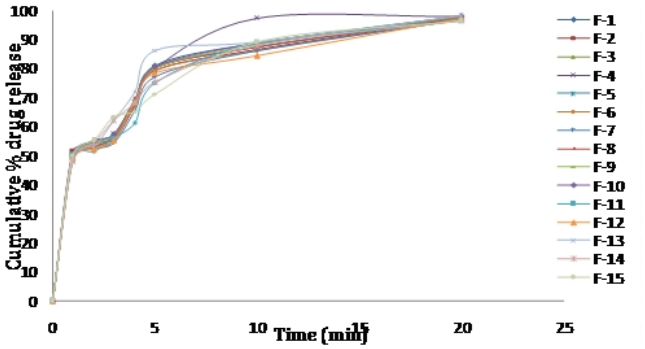

Figure15. Drug release profile of piroxicam formulations (F1-F15)

In all the presented figures, the third factor was kept at a constant level. All the relationships among the thee variables are non linear, the effects of X_1 and X_3 with their interaction on hardness at a fixed level of X_2. The plots were found to be linear up to 66.78% hardness, but above this value, the plots were found to be non linear indicating a non linear relationship between X_1 and X_3. Similarly all values for remained dependent variables.

It was determined from the contour plot that a higher value of hardness could be obtained with and X_1 level range from 5 to 15 and an X_3 level range from 10 to 20. It is evident from the contour plot that the low level of the both X_1 and X_3 favours the hardness of tablet. When the coefficients values of two key variables, X_1 and X_3 were compared, the value for variable X_1 was found to be higher, indicating that it contributes the most to predicting the hardness. The contours of all the hardness values were found to be curvilinear and indicated that a high value of hardness can be obtained for a combination of the two independent variables, the X_1 level in the range of 2.2 to 6.

Checkpoint Analysis

Besides understanding the main and interaction effects on the responses, the experimental design approach is helpful in obtaining the optimized formula in which the levels of X1, X2 and X3 were decided. In this instance, an optimized formula was theoretically obtained to yield hardness 5kg/cm2, disintegration time 63 min, friability 0.58% and wetting time 109 seconds.

Table 5. Dissolution profile comparison thoughout the accelerated stability

Storage Time	Parameter	Batch F-9		Marketed Formulation
0 M	t% release (10 min) Dissolution Profile	88.78	Similar	95.21
1 M	t% release (10 min) Dissolution Profile	88.54	Similar	95.1
3 M	t% release (10 min) Dissolution Profile	87.21	Similar	93

*Accelerated- 40°C/75% RH

As a confirmation of this process, a new formulation was prepared at the optimum levels of the independent variables and evaluated. The observed value of responses of Y_1, Y_2, Y_3 and Y_4 gave a close agreement with the predicted values (Table 5).

Thee checkpoint batches were prepared and evaluated for hardness and disintegration time. When measured hardness values were compared with predicted hardness values the differences were found to be insignificant. Thus we can conclude that the obtained mathematical equation is valid for predicting the hardness.

Characterization of optimized batch

After studying the effect of the independent variables on the responses, the level of these variables that give the optimum response were determined. The optimum formulation is one that gives high value of hardness and a fast drug release with a low amount of bioadhesive carrier in the resultant tablet. It is evident from the polynomial equation and plots that increasing the amount of superdisintegrant increases in DT and decreases the hardness. It is clear that, medium level was selected as optimum for all the independent variables.

In the numerical optimization techniques, the desirability approach was used to generate the optimum settings for the formulation. For the optimized formulation, % cumulative drug release, dissolution efficiency, permeation, difference factor, similarity factor, dissolution profile, Qt, assay and release kinetics were determined.

Optimized formulation was compared with the reference formulation in terms of DE, f1 and f2, thoughout the stability (Table 6).

Table 6. Dissolution efficiency (DE) and assay values thoughout the stability study

Storage Temperature	Storage Time	Parameter	Formulation Code: Batch F-9	Formulation Code: Marketed Formulation
Accelerated temperature	0 M	Assay	98.70	98.34
		Mean DE	27.58	28.35
	1 M	Assay	98.18	98.10
		Mean DE	28.28	27.54
	3 M	Assay	97.90	97.80
		Mean DE	27.60	27.19
Room temperature	0 M	Assay	99.09	98.34
		Mean DE	27.58	28.35
	1 M	Assay	98.40	98.20
		Mean DE	27.56	28.31
	3 M	Assay	98.10	97.90
		Mean DE	26.94	27.78

*Accelerated- 40°C/75% RH

At time zero, the mean DE values were 27.58 and 28.35, for optimized and marketed formulation respectively (Figure 16).

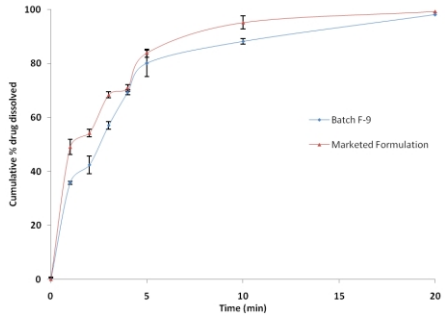

Figure 16. In vitro drug release of optimized formulation (Batch F-9).

Moreover, optimized formulations were considered similar to the reference, by f1 and f2 factor. In this case, dissolution profiles were accepted as similar. At time one month, the mean DE values were 28.28 and 27.54, for optimized and marketed formulation respectively with an acceptable associated variability in terms of SD. At time thee month, the mean DE values were 27.60 and 27.19, for optimized and marketed formulation respectively with an acceptable associated variability in terms of SD (Table 7). Moreover, optimized formulations were considered similar to the reference, though f1 and f2 factor.

Table 7. Pharmacokinetic of Piroxicam mucoadhesive fast disintegrating tablet and marketed formulation after single dose administration

Sr. No.	Parameters	Batch F-9	Marketed formulation
1.	AUC (0-24)	22.87 μg/ml/h	17.82 μg/ml/h
2.	AUC (0-∞)	47.16 μg/ml/h	24.26 μg/ml/h
3.	AUMC (0-24)	466.71 μg/ml/h	309.76 μg/ml/h
4.	AUMC (0-∞)	3390.68 μg/ml/h	873.40 μg/ml/h
5.	MRT= AUMC/AUC	71.89 h	35.99 h
6.	Elimination Rate Constant (KE)	0.014	0.03
7.	Absorption Rate Constant (Ka).	44.17	17.54
8.	Elimination Half life (t1/2)	50.15 h	27.36 h
9.	Absorption Half life (t1/2)	3.91 h	0.04 h
10.	C_{max} (Observed)	0.79 μg/ml	1.08 μg/ml
11.	t_{max} (Observed)	6 hs	7 hs
12.	Systemic clearance	0.02 L/h/Kg	0.04 L/h/Kg
13.	Volume of Distribution (Area)	1.53 Liters/kg	1.63 Liters/kg
14.	Relative Bioavailability % (F)	194	

Permeation study

A drug must be released from its vehicle prior to penetration and partition into the membrane. For certain formulations, drug release from the oral preparation is the rate-limiting step for drug absorption. Therefore, to ascertain that drug release from the vehicle was not the rate-limiting step for absorption, diffusion studies though an artificial synthetic membrane using the Franz diffusion cell. The membrane used must be inert and porous so as to allow drug passage in accordance with molecular weight. When drug molecules have a molecular weight as small as the pores of the synthetic membrane, they are able to pass though it. Drug transfer rates though the cellulose membranes of tablet were compared with the each other.

Low and slow release of drug can be attributed to small volume (2 ml) of donor compartment makes tablets swell. Swollen particles have greater porosity, and drug release occurs by diffusion though the openings created by the porosity of matrix as described by Higuchi square root equation. The observed value of permeability coefficient and Steady state flux was 12.82 ±4.4 cm/h and 256.43 ±89.50 μg/cm2h respectively. In in vivo conditions, pressure applied by tongue to the tablet can prevent swelling and enhances disintegration of tablet and dissolution of drug. On the other hand, SSC and mannitol exhibited more drug release and higher steady state flux and permeability coefficients values. Higher swelling index ratio may cause to extend diffusion pathway of drug in the swollen matrix, and this may decrease the drug release.

In vitro drug release data were fitted to kinetic models such as zero-order, first-order. The regression analysis was performed. No important changes in appearance were recorded thoughout the stability study under both aging conditions. There were no visual signs of capping, lamination etc. after formulation during the stability study.

Single dose pharmacokinetics

After single dose administration, plasma concentrations of piroxicam were obtained within 10 min, with no second peak corresponding to possible gastrointestinal absorption (Figure 17).

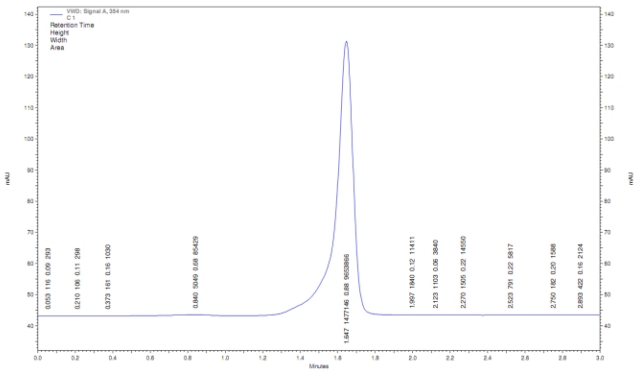

Figure 17. High performance liquid chomatograph of piroxicam in acetonitrile: distilled water (50:50) at 354 nm.

It therefore appears that the bioadhesive component (Mannitol) promoted the retention of the ordered units under the tongue without hindering the release and local absorption of piroxicam. It appears that the fraction of the piroxicam dose that was swallowed was smaller compared to other mucosal delivery systems. This was further supported by calculating the area under the plasma concentration time curves (AUC) and comparing them with pharmacokinetic data obtained from marketed formulation.

The formulated fast-acting sublingual tablet has potential to be a valuable addition to the store of drugs for breakthough pain. The technique could also be useful for substances other than piroxicam where a rapid onset of effect is desirable. However, the new sublingual tablet system would probably be less useful for hydrophilic drug molecules, since this group of drugs will not undergo sufficiently rapid absorption across the sublingual mucosa to effectively utilize the advantages of rapid disintegration and drug dissolution that are built into this system.

Pharmacokinetic parameters estimated following the oral administration of piroxicam and its marketed product were (Table 7) viz; elimination rate constant (Kel) for piroxicam was found to be 0.014 h-1 and the corresponding biological half life (t1/2) of piroxicam obtained in the present study is 50.15 and is in good agreement with earlier reported value of 40 h (Table 7).

The absorption rate constant (Ka) was found to be 44.17 h-1, following oral administration of piroxicam. Piroxicam was found to be absorbed slowly when given orally and a peak serum concentration (Cmax) of 0.79 μg/ml was observed at 24 h following administration. All the pharmacokinetic parameters of absorption table 7.30 namely Ka, Cmax, Tmax, percent absorbed to various times and AUC (Figure 18) indicated rapid absorption and higher bioavailability of piroxicam when administered. Higher Cmax and shorter Tmax values were observed with these products when compared to those of marketed piroxicam formulation.

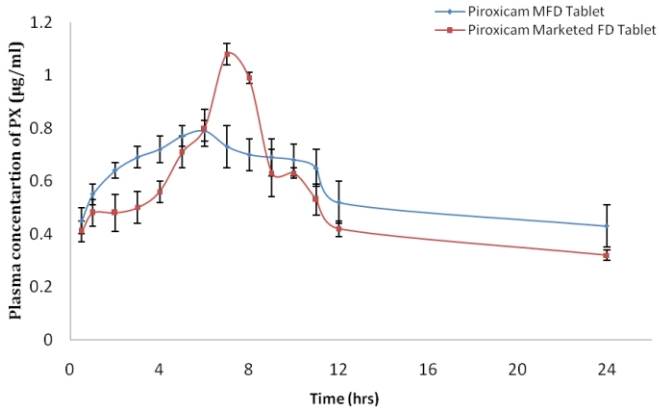

Figure18. Plasma drug concentration vs. time curves for sublingual administration of piroxicam (0.3 mg/kg dose) formulations.

By assuming the plasma drug levels to be the same as the corresponding blood drug levels, the total body clearance of the drugs (Clt) could be estimated. This is the ratio of the dose to the AUC of the blood drug level after IV/oral administration. The Clts of calculated from the sublingual administration were 0.02 L/h/Kg and 0.04 L/h/Kg, respectively. In the case of marketed piroxicam formulation, Ka was only 17.54 h-1.

AUC (extent of absorption) was also much higher in the case of formulated piroxicam tablet when compared to marketed formulation. [AUC]0-24h was 22.87μg/ml/h and 17.82 μg/ml/h for formulated and marketed tablet (Figure 19). The relative bioavailability of the sublingual tablet was 194. Thus, the results of pharmacokinetic studies indicated rapid and higher oral absorption of piroxicam with retention in sublingual cavity when administered as tablet.

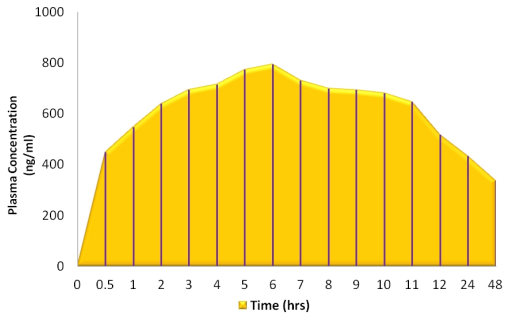

Figure 19. Area under the cure after sublingual administration of piroxicam 0.3 mg/kg

The sublingual tablet is based on tabulated interactive mixtures consisting of a water-soluble carrier, a fine particulate drug (piroxicam) and a bioadhesive component. The results from the in vitro test of content uniformity showed that the drug was homogeneously mixed and that only minor segregation had occurred during tablet processing (i.e. mixing and tableting). After single dose administration, plasma concentrations of piroxicam were obtained within 10 minutes, with no second peak corresponding to possible gastro-intestinal absorption. The approximate absorption and bioavailability of piroxicam was 80%. This suggests that less than 20% of the dose was swallowed, which could at least in part be attributed to the addition of the bioadhesive component. The technique could also be useful for substances other than piroxicam where a rapid onset of effect is desirable. However, the new sublingual tablet principle will probably be less useful for hydrophilic drug molecules since this group of drugs will not undergo sufficiently fast absorption over the sublingual mucosa to effectively utilise the advantages of rapid disintegration.

Conclusion

With this new sublingual tablet system, an optimal exposure of active substance to the dissolving fluids in the mouth is combined with bioadhesive retention of the drug in the oral cavity, resulting in rapid sublingual absorption where intestinal absorption is thus essentially avoided. The new sublingual tablet system could also be useful for substances other than piroxicam where a rapid onset of effect is desirable. This formulation predicts the relationship between mucoadhesiveness and fast disintegration of the tablets. Formulated tablet fulfilled the requirements of the assay, uniformity of dosage units, and stability of pH values. Visually, all samples remained stable and did not exhibit signs of instability thoughout the year of. It was having the potential advantages over conventional dosage forms, with improved patient compliance, convenience, permeability, dissolution stability, bioavailability and rapid onset of action. The sublingual tablet is based on tabulated interactive mixtures consisting of a water-soluble carrier, a fine particulate drug (piroxicam) and a bioadhesive component. The result from the physicochemical characterization suggests that FTIR and DSC data showed no interaction between piroxicam and excipients. Content uniformity showed that the drug was homogeneously mixed and that only minor segregation had occurred during tablet processing (i.e. mixing and tableting). A Box Behnken design was performed to study the effect of formulation variables and results revealed that, the amount of Mannitol. MCC and SCC affected significantly the response variables. An observed response was in close accord with the predicted values of the optimized formulation and consequently demonstrates the feasibility of the optimization procedure in the development of sublingual tablets.

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Conflicts of interest

The author declares no competing interests.

References

[1]. Parakh SR, Gothoskar AV. A review of mouth dissolving technologies. Pharm Technol. 2003; 23:92–100.

[2]. Alderborn G. Tablets and compaction. In: Aulton, M.E. (Ed). Pharmaceutics: The science of dosage form design. Churchill Livingstone: New York, 2002; 2: 397-440.

[3]. Ajay B. Solanki. Formulation and optimization of piroxicam proniosomes by 3-factor, 3-level box-behnken design. AAPS PharmSci Tech. 2007; 8:43-49.

[4]. Harry G. Brittain. Profiles of drug substances, excipients, and related methodology. Elsevier Science (USA). 2002;15: 47-51

[5]. Bredenberg S, Nyström C. In vitro evaluation of bioadhesion in particulate systems and possible improvement using interactive mixtures. J Pharm Pharmacol. 2003; 55: 169-77.

[6]. Heeb HL, R. Chun. Single dose pharmacokinetics of piroxicam in cats. J Vet Pharmacol Therap. 2003; 26: 259–63.

[7]. Kate VK, Payghan SA; Effect of bioadhesion and permeability on dissolution behavior of piroxicam mucoadhesive fast disintegrating tablet. Inventi Rapid: Pharm Tech. April-June 2013, 2013:2: (http://www.inventi.in/Article/ppt/751/13.aspx)

[8]. Collet J, Moreton C. Modified-release peroral dosage forms. In: Aulton, M.E. (Ed). Pharmaceutics: The science of dosage form design. Churchill Livingstone: New York, 2002; 2: 289-305.

[9]. Reddy LH, Ghosh B, Rajneesh B. Fast dissolving drug delivery system: A review of the literature. Ind J Pharm Sci. 2002; 64; 4: 1-3.

[10]. Nystrom C, Malmqvist K. Studies on direct compression of tablets. I. The effect of particle size in mixing finely divided powders with granules. Acta Pharm Suec. 1980; 17: 282–87.

[11]. Kate VK, Payghan SA. Physicochemical Evaluation of mannitol based mucoadhesive fast disintegrating tablet for rapid absorption of piroxicam. Inventi Rapid: Pharm Tech. July - September 2013, 2013:3 (http://www.inventi.in/Article/ppt/761/13.aspx)

[12]. European Pharmacopoeia. Council of Europe, Stransbourg Cedex, France. 1997:3: 127-35.

[13]. Misha DN, Bindal M, Singh SK, Kumar SGV. Rapidly disintegrating oral tablets of valdecoxib. Ind J Pharm Sci. 2005; 67: 685-87.

[14]. S Velmurugan, B Deepika, K Nagaraju, S Vinushitha. Formulation and in-vitro evaluation of buccal tablets of piroxicam. Int J of Pharm Tech Res. 2010; 2: 1958-68.

[15]. Fiese EF, Hagen TA. Preformulation. In: Lachman L, Lieberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy. Varghese publishing house, Mumbai. 1987; 3:171-96.

[16]. Gohel M, Patel M. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS Pharm Sci Tech. 2004; 5: 33-36.

[17]. Khayyam , S, Patwekar, S., S. A. Payghan; Dissolution and Stability Enhancement of Poorly Water Soluble Drug – Lovastatin by Preparing Solid Dispersions; Asian Journal of Biomedical and Pharmaceutical Sciences. 2011; 1: 24-31.

[18]. Lewis GA, Mathieu D. Pharmaceutical experimental design, Marcel Dekker, New York. 1999; 210-20.

[19]. Rippie, E. Compression of solids and compressed dosage forms. In: Encyclopedia of Pharmaceutical Technology. Swarbrick J., Marcel Dekker Inc. NY. 1990; 3: 149-66.

[20]. Lachman L, Lieberman HA, Kaling JL. The theory and practice of industrial pharmacy, 3rd ed., Lea & Febiger, Philadelphia USA, 1991; 318-21.

[21]. Ziya B, Cetin T. Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: In vitro and in vivo evaluation; Eur J of Pharm Biopharm. 2011; 78: 499–05.

[22]. Hisakadzu Sunada, Yunxia B. Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technology. 2002; 122: 188–98.

[23]. Rele RV, Sawant SA Warkar CB. Simple spectrophotometric methods for determination of piroxicam in pharmaceutical formulation, Int J Chem Tech Research. 2010; 2: 2173-76.

[24]. Bredenberg S, Margareta Duberg. In vitro and in vivo evaluation of a new sublingual tablet system for rapid oromucosal absorption using fentanyl citrate as the active substance. Eur J Pharm Sci. 2003; 20: 327–34.

[25]. Gohel M, Patel M. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS Pharm Sci Tech. 2004; 5: 33-36.

[26]. Adolfsson A, Nystrom C. Tablet strength, porosity, elasticity and solid state structure of tablets compressed at high loads. Int J Pharm. 1996; 132: 95-106.

[27]. Supriya C. Patil, S.A Payghan, J.I. Disouza; Formulation and Evaluation of Oral Disintegrating Tablet of Lornoxicam; International Journal of Pharmaceutical & Bio. Archieves; 2011; 2(5): 1518-1523.

[28]. Kate VK, Payghan SA, Shinde AJ. Effect of aging conditions on the dissolution stability of piroxicam mucoadhesive fast disintegrating tablet, Inventi Rapid: NDDS. April - June 2013,2013:2

[29]. Kate VK, Payghan SA. Development of directly compressible mucoadhesive fast disintegrating sublingual tablet system of piroxicam using 3 factor 3 level box behnken design. Asian journal of biomedical and pharmaceutical sciences. 2013; 03: 1-6.

[30]. Lade Milind, Payghan SA, Tamboli ZJ. Polymer based wafer technology: a review International Journal of Pharmaceutical & Biological Archives. 2013;4: 1060-74.

[31]. Gurdale M.S. Lade M. S., Payghan S. A. Disouza J. I; Fast dissolving HPMC E5 based oral film for rapid absorption of Metoprolol Tartrate, European Journal of Pharmaceutical and Medical Research. 2014; 1: 75-91

[32]. Eun-Seok Park, Yu Cui, Bum-Jin Yun, In-Ja Ko. Transdermal delivery of piroxicam using microemulsions. Arch Pharm Res. 2005; 28: 243-48.

[33]. Kate VK, Payghan SA, Shinde AJ. Single dose pharmacokinetics of mucoadhesive fast disintegrating sublingual tablet of piroxicam in rabbits. Inventi Impact: Pharmacokinetics & Pharmacodynamics. July-Sep-2013: 3 (http://www.inventi.in/Article/pkd/97/13.aspx)

[34]. Ziya Bayrak, Cetin Tas. Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: In vitro and in vivo evaluation. Eur J Pharm Biopharm. 2011; 78: 499–05.

[35]. Rasetti-Escargueil C, Grangé V. Pharmacokinetic profiles of two tablet formulations of piroxicam. Int J Pharm. 2005; 295:129–34.

[36]. Shinde SM, Payghan SA. Physiochemical assessment of pharmaceutical salt Forms: a quality attribute. International Research Journal for Inventions in Pharmaceutical Sciences. 2014; 2: 46-53.

[37]. Payghan SA, Shivastava DN, Toppo E. Potential of solubility in drug discovery and development. Oct- 2008 http://www.pharmainfo.net/reviews/potential-solubility-drug discovery - and-development

[38]. AS Jirage, VS Baravkar, VK Kate, SA Payghan. Poly-β-hydroxybutyrate: intriguing biopolymer in biomedical applications and pharma formulation trends. International Journal of Pharmaceutical & Biological Archives. 2013; 4: 1107-18.