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Original Article

Fast Dissolving Oral Film of Piroxicam: Solubility Enhancement by forming an Inclusion Complex with β-cyclodextrin, Formulation and Evaluation

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ABSTRACT

Objective: Piroxicam is a long-acting potent nonsteroidal anti-inflammatory drug (NSAID) which has a very low solubility in Gastrointestinal (GI) fluids results in poor bioavailability after oral administration. The present investigation aimed to formulate and evaluate fast dissolving oral films containing piroxicam to overcome solubility and bioavailability problems thereby to facilitate the convenience of pediatric and geriatric patients. **Method:** The inclusion complexes of piroxicam with β-cyclodextrin were prepared. *In vitro* dissolution study was performed to fix the ratio with better dissolution rate. The selected inclusion complex was then utilized for the preparation of fast dissolving oral films by solvent casting method using sodium CMC/chitosan as film-forming agents, sodium starch glycolate/crospovidone as super disintegrating agents. PEG 400 used as a plasticizer. Formulations (F1-F12) were prepared and evaluated for their physicochemical properties. *In vitro* disintegration, dissolution and permeation studies were also carried out. **Results:** Formulation F2 showed the minimum *in vitro* disintegration time (14.94±3.06 s), formulation F9 showed the maximum *in vitro* disintegration time (36.66±1.05 s). The formulations F6 and F4 showed better drug release of 94.4% and 92.9% respectively. Better drug permeation of 96.65% was obtained from the formulation F6 in 40 s. **Conclusion:** The study concluded that the fast dissolving films achieved quicker onset of action compared to the conventional preparations. The formulation found promising to obtain better therapeutic efficiency.

Key words: Fast dissolving film, Inclusion complex, β-cyclodextrin, Piroxicam.

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INTRODUCTION

The oral route of drug administration is the most frequently used and acceptable among the various drug administration routes due to its simplicity and convenience, which improve patient compliance. Peroral dosage forms can be distinguished as solid or liquid oral dosage forms. The solid dosage forms include pills, capsules, granules and powders, while the liquid dosage forms include solutions, suspensions or emulsions offering more advantages over the solid dosage forms. These liquid dosage forms also exhibit some disadvantages such as dose inaccuracy, microbiological instability and found inadequate in masking the taste. In the early 19th century the fast dissolving tablets were designed to overcome these problems associated with the liquids dosage forms.[1] Fast dissolving tablets disintegrate within 60 s when placed in the oral cavity without administration with the water or chewing the tablet. However, due to certain disadvantages such as solid physical form, psychological fear of swallowing, chewing, friability of wafer-like porous and low pressure moulded tablet etc. A new technology was developed as a mouth dissolving film.[2]

Fast dissolving oral disintegrating films (ODFs) are the most advanced form of oral solid dosage forms gives rapid absorption and instant bioavailability of drugs after quick release due to high blood flow and permeability of oral mucosa. These are thin films with an area of 2-8 cm^2 and drugs can be incorporated up to a single dose of 30 mg. These ODFs contain active ingredient embedded in a matrix of film-forming polymers that disintegrate within a few seconds after oral administration in saliva, even without chewing. Larger surface area of the film promotes rapid disintegration and dissolution in the oral cavity. The oromucosally absorbed drug enters the systemic circulation without undergoing first-pass hepatic metabolism hence the bioavailability of drug can be significantly greater than the conventional tablet dosage forms. Moreover, patient compliance will be more in the patients facing difficulty in swallowing and chewing.[3] Fast dissolving oral films are useful in paediatric, geriatric, bedridden patients. These are also beneficial in some of the conditions such as diarrhoea, sudden allergic attacks and also useful when the local action is desired such as local anaesthetic for toothaches, oral ulcers, cold sores or teething.[4-6]

Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam class used to relieve the symptoms of painful, inflammatory conditions like arthritis.[7] Piroxicam works by preventing the production of endogenous prostaglandins which are involved in the mediation of pain, stiffness, tenderness and swelling.[7] Its activity is largely attributable to a central mechanism not mediated by the opi-atergic system as it is not antagonized by naloxone.[8-10] One of the major problems with this drug is it has a very low aqueous solubility (0.023 mg/ml), which results in poor bioavailability after oral administration.[11,12] Hence there is a need to increase the solubility of piroxicam and also to formulate a suitable dosage form in order to increase the bioavailability. For the effective management of arthritis and osteoarthritis especially in the case of

geriatric patients, therefore it is desirable to formulate piroxicam in the form of fast dissolving oral films for the easy and effective drug delivery.

In the present work, an attempt was made to enhance the solubility of piroxicam by forming an inclusion complex with β-cyclodextrin (β-CD) and then formulated in the form of fast dissolving films and evaluated.

MATERIALS AND METHODS

Materials

Piroxicam, β-cyclodextrin, sodium CMC, chitosan, crospovidone, sodium starch glycolate and citric acid were procured from Yarrow Chem, Mumbai, India. PEG 400 was purchased from Loba Chemie Pvt Ltd., Mumbai, India. All chemicals/reagents used were of analytical grade.

Methods

Compatibility study by FTIR

Fourier Transform Infrared (FTIR) spectra matching approach was used for the detection of possible chemical interactions between the drug and polymers. Samples included pure drug and physical mixtures of drug and polymers, were mixed with a suitable quantity of potassium bromide to form dry pellets. Pellets were then scanned from 4000 to 400 cm^{-1} using FTIR spectrophotometer (Jasco FTIR 4100, Japan). The FTIR spectra of physical mixtures were compared with the pure drug spectrum and peak matching was done to detect any appearance or disappearance of peaks.[13]

Preparation of inclusion complex of piroxicam with β-cyclodextrin

Inclusion complexes were prepared by kneading method by wetting the physical mixture of piroxicam: β-CD in different ratios 1:0.5 (IC1), 1:1 (IC2) and 1:2 (IC3) in a mortar with methanol and water mixture (1:1). The wet mass was then kneaded thoroughly with a pestle to obtain a paste-like consistency. The mass was then dried at room temperature and the dry sample was passed through sieve #80 and stored in a desiccator until further use.[14]

Evaluation of Inclusion Complex

Drug content and in vitro drug release

Inclusion complex (25 mg) was taken in a 50 ml volumetric flask and dissolved in methanol and diluted suitably with phosphate buffer of pH 6.8. Then the solution was filtered through a Whatman filter paper and analysed using a UV spectrophotometer (Shimadzu UV-1201, Japan) at 350 nm. The *in vitro* drug release study was carried out using USP dissolution testing apparatus type-II (EDT-08Lx, Electrolab, Mumbai, India). Inclusion complex (~100 mg of piroxicam) was taken in 900 ml of the dissolution medium (Phosphate buffer of pH 6.8). The temperature was maintained at 37±0.5°C and the paddle speed was set at 50 rpm. The sample (5 ml) was withdrawn at specific time intervals and an equal volume of fresh medium was replaced to maintain the sink condition. The sample withdrawn was filtered and diluted with phosphate buffer pH 6.8 suitably before the analysis and absorbance was measured using a UV spectrophotometer at 350 nm.[15]

Formulation of Fast Dissolving Film of Piroxicam

The fast dissolving films of piroxicam were prepared by solvent casting technique using film forming polymer sodium CMC or chitosan. The calculated amount of polymer was added in a 3/4th volume of water with continuous stirring and the inclusion complex containing piroxicam was incorporated in the polymeric solution. Sodium starch glycolate or crospovidone was then added to the polymeric solution and stirred vigorously. Then citric acid and PEG 400 were added and the final volume was adjusted up to 15 ml with distilled water. The resulting bubble-free viscous solution was cast on a petri dish (area of 69.362 cm^2) then kept in a hot air oven at 40°C for 24 h. The composition of piroxicam oral films are given in Table 1. The films were cut into the size of 2×2 cm containing 10 mg of piroxicam were wrapped in an aluminium foil and stored in a desiccator until further use.[16,17]

Evaluation of Piroxicam Fast Dissolving Film

The thickness of the fast dissolving film (2×2 cm) was determined by using a screw gauge (Kayco India Ltd., Delhi, India). The thickness of each film at three different places was determined and calculated in triplicate. To determine content uniformity, fast dissolving film of size (2×2 cm) was cut into small pieces and transferred into a graduated glass-stoppered flask containing about 100 ml of phosphate buffer of 6.8 pH. The flask was shaken for 4 h in a mechanical shaker. The solution was filtered and the amount of drug present was determined by measuring the absorbance using UV spectrophotometer at 350 nm after suitable dilutions with phosphate buffer of pH 6.8. Weight variation was calculated after determining the individual and average weights of the films of size (2×2 cm) using an electronic analytical balance (Essae Teraoka, Japan), performed in triplicates. To determine the surface pH oral film was placed in a petri dish and moistened with 0.5 ml of distilled water and kept for 30 s. The pH was measured by bringing the electrode of the pH meter (Systronics, Mumbai, India) in contact with the surface of the oral film. The procedure was performed in triplicate. The tensile strength apparatus (F.4026, Instron Ltd., Japan) had upper fixed and the lower movable clamps. The film sample (6×2 cm) was clamped between the two clamps and the force at tearing and elongation were noted. Two mechanical properties, namely, tensile strength and percentage elongation were computed for the evaluation of the film. Folding endurance was determined by taking the film size of (4×2 cm) and repeatedly folding at the same place till visible cracks appear. The film of 4 cm^2 area was cut out and weighed accurately and kept in a desiccator containing fused anhydrous calcium chloride. After 24 h the film was removed and weighed again and % moisture content was calculated.[18]

In vitro Disintegration

The film size (2×2 cm) required for dose delivery was placed into one tube of disintegration apparatus IP (ED-2L, Electrolab, Mumbai, India) and a disc was placed at the surface of the tube. The assembly was suspended in a beaker containing phosphate buffer of pH 6.8 and the apparatus was operated until the film disintegrated. The time required for breakdown of the film was noted as *in vitro* disintegration time.[19]

In vitro Drug Release

The dissolution studies were carried out using USP XXIII type-I dissolution apparatus (EDT-08Lx, Electrolab, Mumbai, India) at 37±0.5°C and 50 rpm using phosphate buffer of pH 6.8 (300ml) medium. Each film with dimension (2×2 cm) placed on a basket was submerged into dissolution medium and stirred. Samples were withdrawn at 0, 20, 30, 40, 60, 80, 100, 120 and 140 s time intervals and the same amount of the fresh medium was replaced. The samples withdrawn were filtered through 0.45 µm Whatman filter paper and were analysed using a UV spectrophotometer at 350 nm.[20]

In vitro Permeation

In vitro permeation through cellophane membrane was studied using the Franz diffusion cell of the internal diameter of 2.5 cm. The cellophane membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with 100 ml of phosphate buffer of pH 6.8 which was maintained at 37±0.5°C. One film of dimension (2×2 cm) which was previously moistened with few drops of phosphate buffer of pH 6.8 was placed in the donor compartment. The donor

compartment was filled with 5 ml of phosphate buffer of pH 6.8. From the receptor compartment, 1 ml sample was withdrawn at definite time intervals and the same amount of fresh medium was replaced each time. The percentage of piroxicam permeated was determined by measuring the absorbance using UV spectrophotometer at 350 nm.[21]

RESULTS

Compatibility Study by FTIR

The FTIR spectra of pure drug were characterized by two C=O stretches at 1586.16 cm^{-1} and 1726.94 cm^{-1} respectively indicated the presence of two -O atoms, S=O stretching at 3640.95 cm^{-1}, C=C stretching at 1586.16 cm^{-1}. All the characteristic IR peaks related to pure drug piroxicam also appeared in the FTIR spectra of mixtures of drug with polymers. Overlay of FTIR spectra is shown in Figure 1.

Evaluation of Inclusion Complex of Piroxicam with β-Cyclodextrin

The percentage drug content of prepared complexes was found to be 91.73±0.56 % (IC1), 91.67±0.63 % (IC2) and 90.32±0.83 % (IC3). *In vitro* dissolution study data of the pure drug piroxicam and inclusion complexes are shown in Figure 2. The complete dissolution of complexes occurred within 200 s in case of IC2 (1:1) and IC3 (1:2) complexes, whereas IC1 (1:0.5) complex showed only a release of 64.83 % at the end of 200 s. Complex IC2 containing 1:1 ratio of drug and β-CD showed faster dissolution rate, about 98.71 % of the drug was released within 180 s.

Evaluation of Fast Dissolving Film of Piroxicam

12 formulations were prepared using sodium CMC or chitosan (Table 1) as a polymer. The thickness of the fast dissolving films F1 to F12 varied from 0.29±0.04 mm to 0.46±0.09 mm with low standard deviation values. Formulation F1 showed the lowest thickness of 0.29±0.04 mm and formulation F9 showed the highest thickness of 0.46±0.09 mm. The content uniformity for all the formulations was found to be in the range of 84.3±0.41 % to 96.05±1.34 %. The average weight of the films was found to be in the range of 97.33±1.69 mg to 146.66±2.05 mg. Formulation F1 showed the lowest weight of 97.33±1.69 mg and formulation F9 showed the highest weight of 146.66±2.05 mg. The surface pH of the films F1 to F12 was ranging from 6.61±0.01 to 6.88±0.04. Film thickness, content uniformity, weight variation and surface pH study results of all the formulations are depicted in Table 2. The tensile strength of the films F1 to F12 was found to be in the range of 4.1±0.02 N/cm^2 to 5.6±0.07 N/cm^2. Formulation F1 showed the minimum tensile strength of 4.1±0.02 N/cm^2 whereas formulation F12 showed the maximum tensile strength of 5.6±0.07 N/cm^2. The percentage elongation of films F1 to F12 ranged between 8.81±1.17 % to 31.33±2.18 %. Formulation F2 showed the lowest percent elongation of 8.81±1.17 % and formulation F9 and F5 showed the highest percent elongation of 31.33±2.18 % and 30.50±2.24 % respectively. Folding endurance of the films F1 to F12 ranged from 200±1.69 to 212±3.17. Formulation F1 showed lower folding endurance of 200±1.69 whereas formulation F12 showed higher folding endurance of 212±3.17. The % moisture content of the films F1 to F12 ranged from 1.26±043 % to 2.49±0.35 %. F5 and F9 formulation showed high % moisture content while F2 and F4 showed low % moisture content. Tensile strength, percentage elongation, folding endurance and % moisture content study result data is shown in Table 3.

In vitro Disintegration

All films were disintegrated rapidly. The disintegration time of the films F1 to F12 was found to be in the range between 14.94±3.06 s to 36.66±1.05 s. Formulation F2 showed the minimum *in vitro* disintegration time, i.e., 14.94±3.06 s and formulation F9 showed the maximum *in vitro* disintegration time, i.e., 36.66±1.05 s.

In vitro Drug Release

Results of *in vitro* drug release studies are depicted in Figure 3 and 4. Rapid drug dissolution was observed in case of F6 containing 6 % w/v of crospovidone which released 94.4% followed by F4 containing 2 %w/v of crospovidone which released 92.90 %, at the end of 100 s. Slow drug dissolution was observed in F5 containing 4 % w/v of crospovidone which released 92.71 % at the end of 120 s and F9 containing 6 % w/v of sodium starch glycolate which released 96.51 % at the end of 140 s. It was observed that $T_{90\%}$ of the films F1 to F12 varied from 90.28 s to 120.83 s. Formulation F6 showed minimum $T_{90\%}$ of 90.28 s and maximum $T_{90\%}$ of 120.83 s was observed in formulation F9 (Table 4).

Table 1: Composition of piroxicam oral films.

Formulation code	Ingredients							
	Inclusion Complex equivalent to 173mg of drug (mg)	Sodium CMC (mg)	Chitosan (mg)	Sodium starch glycolate (mg)	Crospovidone (mg)	Citric Acid (mg)	PEG 400 (ml)	Distilled water upto (ml)
F1	364	1250		50		100	0.2	15
F2	364	1250		100		100	0.2	15
F3	364	1250		150		100	0.2	15
F4	364	1250			50	100	0.2	15
F5	364	1250			100	100	0.2	15
F6	364	1250			150	100	0.2	15
F7	364		1250	50		100	0.2	15
F8	364		1250	100		100	0.2	15
F9	364		1250	150		100	0.2	15
F10	364		1250		50	100	0.2	15
F11	364		1250		100	100	0.2	15
F12	364		1250		150	100	0.2	15

Table 2: Film thickness, drug content, average weight and surface pH of fast dissolving films containing piroxicam.

Formulation code	Film Thickness (mm)	Drug Content (%)	Average Weight (mg)	Surface pH
F1	0.29±0.04	88.45±0.96	97.33±1.69	6.61±0.01
F2	0.32±0.069	96.05±1.34	112.00±3.09	6.65±0.03
F3	0.31±0.08	88.1±1.38	134.66±3.29	6.78±0.08
F4	0.43±0.12	94.5±0.92	98.33±1.24	6.79±0.05
F5	0.40±0.04	84.3±0.41	113.33±1.69	6.81±0.05
F6	0.36±0.08	88.7±1.93	130.66±2.49	6.72±0.03
F7	0.44±0.12	93.3±1.88	101.66±2.86	6.88±0.04
F8	0.37±0.08	92.5±2.12	115.66±1.69	6.83±0.06
F9	0.46±0.09	86.5±0.96	146.66±2.05	6.64±0.05
F10	0.43±0.12	87.3±0.41	102.54±1.86	6.66±0.08
F11	0.39±0.08	86.2±0.92	109.86±1.22	6.69±0.03
F12	0.36±0.04	91.01±1.37	138.67±2.81	6.67±0.09

Values are mean ± SEM (n=3)

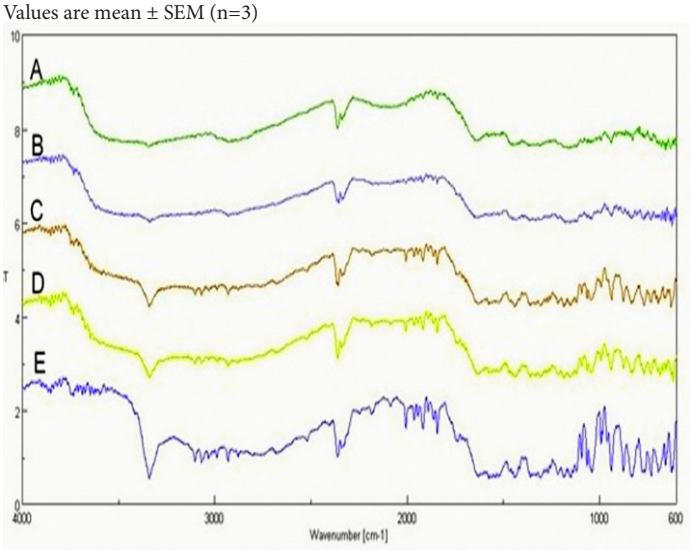

Figure 1: Overlay FTIR Spectra; Piroxicam (A), piroxicam+ betacyclodextrin (B), piroxicam+ betacyclodextrin+ sodium CMC (C), piroxicam+ betacyclodextrin+ chitosan (D) and piroxicam+ betacyclodextrin+ chitosan+s odium CMC (E).

In vitro Permeation

In *in vitro* drug permeation study, the formulation F6 containing 6 % w/v of crospovidone showed better drug permeation of 96.65 % in 40 s, formulation F4 containing 2 % w/v crospovidone showed drug permeation of 99.13 % in 45 s, formulation F2 containing 4 % w/w of sodium starch glycolate and formulation F7 containing 2 % w/w of sodium starch glycolate showed drug permeation of 98.08 % and 97.39 % respectively at the end of 45 s. The results obtained from the *in vitro* permeation studies are depicted in Figure 5 and 6.

DISCUSSION

The IR peaks obtained in the spectra of each physical mixture correlated with the peaks of the drug spectrum. Hence, it was concluded that all the polymers used were compatible with the drug and did not lead to a stability problem when used in the formulation. Piroxicam inclusion complexes with β-CD were prepared by kneading method to enhance the

Table 3: Tensile strength, percentage elongation, folding endurance and % moisture content of fast dissolving films containing piroxicam.

Formulation code	Tensile Strength (N/cm^2)	Percentage elongation (%)	Folding endurance	% moisture content (%)
F1	4.5±0.01	9.75±2.07	200±1.69	1.61±0.54
F2	5.4±0.02	8.81±1.17	205±2.05	1.36±0.58
F3	4.8±0.03	18.83±2.29	207±3.09	1.87±0.47
F4	4.7±0.09	22.75±2.07	209±2.82	1.26±0.43
F5	5.2±0.04	30.50±2.24	204±1.24	2.32±0.37
F6	5.5±0.02	12.83±1.35	208±0.94	1.49±0.49
F7	5.2±0.21	15.75±1.96	205±2.86	1.67±0.81
F8	4.8±0.04	27.91±2.45	211±0.47	1.96±0.41
F9	4.5±0.03	31.33±2.18	212±1.24	2.49±0.35
F10	5.1±0.05	21.37±1.18	206±1.57	1.41±0.38
F11	5.6±0.07	26.23±2.26	208±2.28	2.19±0.46
F12	4.5±0.01	28.03±2.08	212±3.17	1.49±0.52

Values are mean ± SEM (n=3)

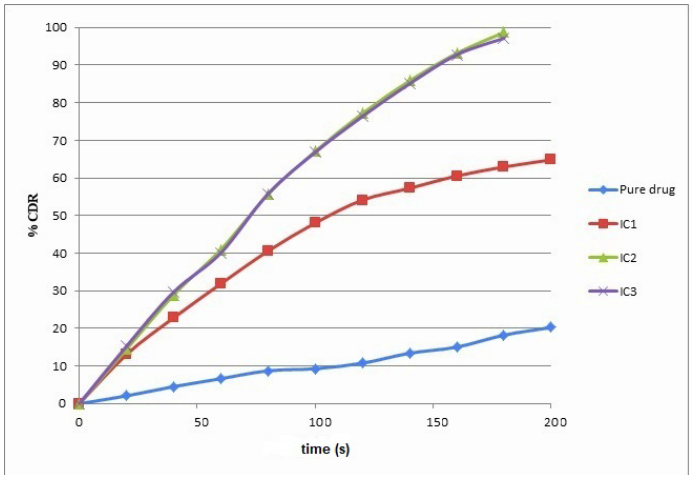

Figure 2: *In vitro* release pattern of piroxicam and its inclusion complexes with β-CD.

Table 4: *In vitro* disintegration time and $T_{90\%}$ of fast dissolving films containing piroxicam.

Formulation code	*In vitro* disintegration time (s)	$T_{90\%}$ (s)
F1	17.40±1.62	100.8±0.59
F2	14.94±3.06	100±0.46
F3	25.23±2.02	100.33±0.76
F4	28.12±1.49	90.61±0.91
F5	34.55±0.57	110.35±0.84
F6	20.75±1.28	90.28±0.71
F7	22.36±1.18	100.21±0.43
F8	31.11±2.01	110.14±0.62
F9	36.66±1.05	120.83±0.79
F10	26.80±1.82	90.91±0.83
F11	22.51±2.09	100.25±0.94
F12	27.60±3.05	110.07±0.57

Values are mean ± SEM (n=3)

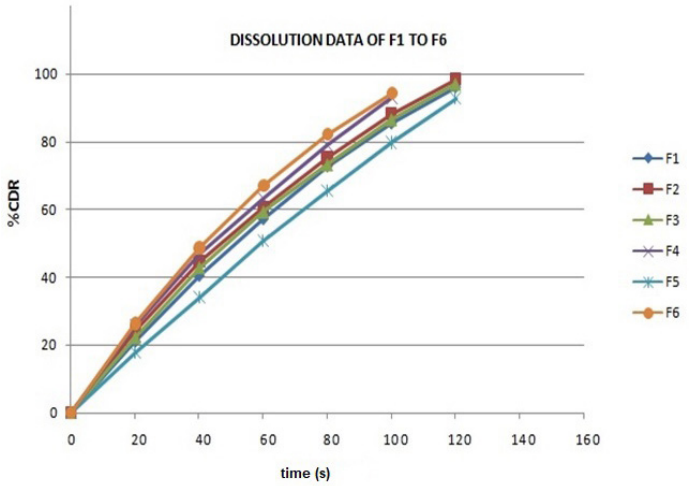

Figure 3: *In vitro* dissolution of F1 to F6 formulations.

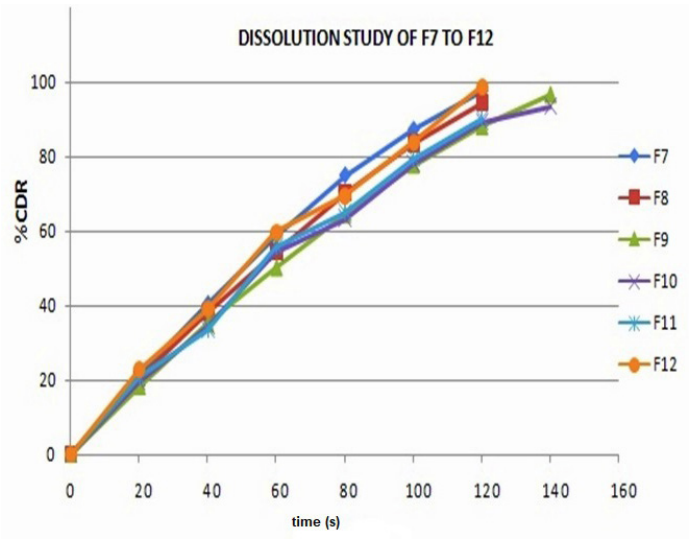

Figure 4: *In vitro* dissolution of F7 to F12 formulations.

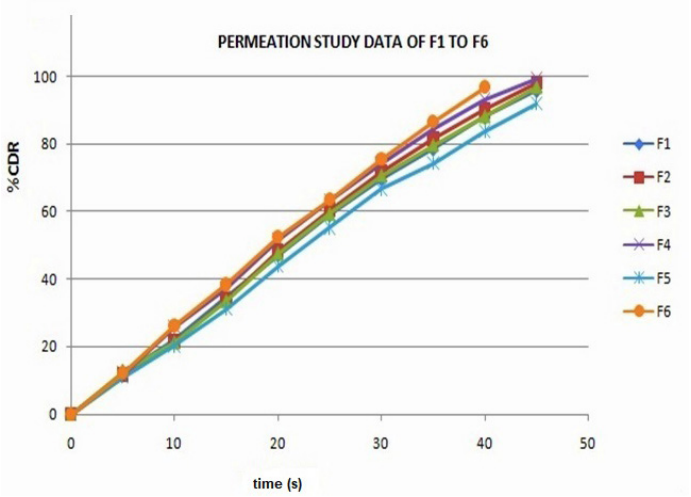

Figure 5: *In vitro* permeation pattern of F1 to F6 formulations.

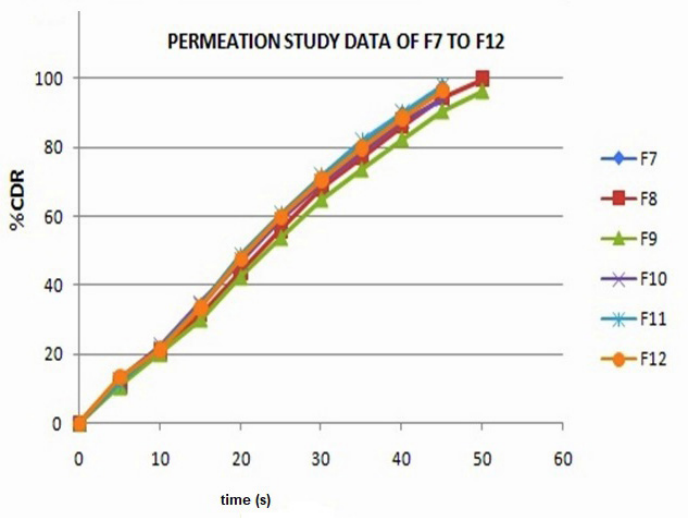

Figure 6: *In vitro* permeation pattern of F7 to F12 formulations.

solubility of the drug.[22] All three prepared inclusion complexes showed the uniform distribution of the drug. The dissolution rate of the complexes was found to be increased compared to pure drug probably due to the formation of water-soluble inclusion complexes of the drug with the β-CD.[23,24] Among the inclusion complexes prepared, formulation IC2, i.e., the inclusion complex of piroxicam with β-CD (1:1 ratio) prepared by the kneading method showed a faster dissolution rate (Figure 2). Therefore for the formulation of fast dissolving films polymers such as Sodium CMC and Chitosan and super disintegrants like sodium starch glycolate and crospovidone were selected as an excipient by solvent casting technique. All the formulations were evaluated for their physico-chemical parameters. The Thickness of fast dissolving film depends on the concentration of the polymer. Here the concentration of polymer is kept constant. Hence, the thickness of fast dissolving film depends on vary in concentration of the super disintegrating agent.[25] Low concentration of the super disintegrating agent in F1 (2 % w/v of sodium starch glycolate) may be the reason for the lowest thickness of the film and high concentration of the super disintegrating agent in F9 (6 % w/v of sodium starch glycolate) may be the reason for the highest thickness of the film.[26] Content uniformity study results confirmed the uniform distribution of the drug in all the formulations. All the films passed the weight variation test as the standard deviation of % weight variation of individual formulations was found to be within the pharmacopoeial limit, i.e., ±7.5 %. Low concentration of the super disintegrating agent in F1 (2 % w/v of sodium starch glycolate) may be the reason for the lowest weight of the film and high concentration of the super disintegrating agent in F9 (6 % w/v of sodium starch glycolate) may be the reason for the highest weight of the film.[27] The surface pH, tensile strength, percentage elongation, folding endurance and % moisture content of all formulations were found to be within the satisfactory range. Moisture loss is the quantity of moisture transmitted through the unit area of film in unit time indicates films ability to withstand its physicochemical properties under normal conditions.[28] All the formulated films (F1-F12) were disintegrated rapidly which is a very important property of fast dissolving films.[29] *In vitro,* drug release studies confirmed the fast release of the drug from formulations and F6 formulation released the drug faster compared to all other formulations. It was observed that piroxicam easily permeated across the membrane since it belongs to the BCS class II.[30] So, the result of *in vitro* permeation study indicates the easy solubilisation and absorption of piroxicam from fast dissolving film.

CONCLUSION

The fast dissolving oral films of piroxicam inclusion complexes were developed successfully via solvent casting technique with the intention of obtaining better therapeutic efficiency with patient compliance. Results obtained was found to be encouraging and considered suitable to obtain better action compared to conventional tablets with the convenience of administration. The overall preparation was found to be simple, reproducible and cost-effective. So, it can be concluded that this drug delivery system has the potential of overcoming the drawbacks of currently available conventional tablet formulations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

NSAID: nonsteroidal anti-inflammatory drug; **GI fluids:** Gastrointestinal fluids; **PEG 400:** polyethylene glycol 400; **ODFs:** Oral Disintegrating Films; **β-CD:** β-cyclodextrin; **USP:** United States Pharmacopeia; **Sodium CMC:** Sodium Carboxymethyl Cellulose; **UV:** Ultraviolet; **FTIR:** Fourier-transform infrared spectroscopy.

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