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Formulation And Evaluation: Rapid Dissolving Oral Film of Piroxicam to Improve Solubility by Creating an Inclusivity Complex With B-Cyclodextrin

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Abstract

Objective: After oral administration, piroxicam, a long-acting, powerful nonsteroidal anti-inflammatory medication (NSAID), has limited bioavailability due to its extremely low solubility in gastrointestinal (GI) fluids. The goal of the current study was to develop and assess piroxicam-containing fast-dissolving oral films in order to address issues with solubility and bioavailability and improve patient convenience for both elderly and pediatric patients. Method: Piroxicam and α-cyclodextrin inclusion complexes were made. To determine the ratio with the best dissolving rate, an in vitro dissolution study was conducted. Using sodium CMC/chitosan as film-forming agents and sodium starch glycolate/crospovidone as super disintegrating agents, the chosen inclusion complex was then used to create fast-dissolving oral films via the solvent casting method. Plasticizer PEG 400 is utilized. Formulations (F1–F12) were made and their physicochemical characteristics assessed. Studies on disintegration, dissolution, and penetration were also conducted in vitro. Results: The in vitro disintegration time was lowest for formulation F2 (14.94±3.06 s) and highest for formulation F9 (36.66±1.05 s). Better drug release was demonstrated by formulations F6 and F4, with respective rates of 94.4% and 92.9%. In 40 seconds, the formulation F6 produced better drug penetration of 96.65%. In comparison to the traditional preparations, the study found that the fast dissolving films exhibited a faster commencement of effect. The formulation was shown to have the potential to improve therapeutic efficacy.

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

INTRODUCTION

Because of its ease of use and convenience, which enhance patient compliance, the oral route of drug administration is the most popular and widely accepted of the different drug administration routes. Solid and liquid oral dose forms are two types of peroral dosage forms. Pills, capsules, granules, and powders are examples of solid dosage forms; solutions, suspensions, and emulsions are examples of liquid dosage forms, which have additional benefits above solid dosage forms. These liquid dosage forms also have several drawbacks, including inability to cover flavor, microbiological instability, and dose inaccuracy. The fast-dissolving tablets were created in the early 1800s to address these issues with liquid dosage forms. When fast dissolving tablets are placed in the oral cavity without being chewed or administered with water, they dissolve in 60 seconds. However, because of some drawbacks, including the solid physical shape, the psychological anxiety of chewing and swallowing, the low pressure-molded tablet's friability, and the wafer-like porous form, etc. A mouth-dissolving film was created using a novel technology.

Because of the high blood flow and permeability of the oral mucosa, fast dissolving oral disintegrating films (ODFs), the most sophisticated type of oral solid dosage forms, provide rapid absorption and instant bioavailability of medications after quick release. These are 2–8 cm2 thin films that can contain up to 30 mg of medication in a single dose. Even without chewing, the active ingredient in these ODFs dissolves in saliva within a few seconds after oral administration thanks to a matrix of film-forming polymers. In the oral cavity, a larger surface area of the film facilitates faster dissolution and disintegration. The medicine's bioavailability can be substantially higher than that of traditional tablet dosage forms because the orally absorbed drug enters the systemic circulation without going through first-pass hepatic metabolism. Furthermore, those who have trouble eating and swallowing will be more compliant. Pediatric, elderly, and bedridden patients can benefit from fast-dissolving oral films. These are also helpful for certain disorders like diarrhea, acute allergic reactions,

and when a local anesthetic is needed for toothaches, oral ulcers, cold sores, or teething.
A member of the oxicam class of nonsteroidal anti-inflammatory drugs (NSAIDs), piroxicam is used to treat the symptoms of inflammatory, painful diseases including arthritis. By inhibiting the synthesis of endogenous prostaglandins, which mediate pain, stiffness, tenderness, and swelling, piroxicam works. Since naloxone does not counteract it, its activity is primarily due to a central mechanism that is not mediated by the opiatergic system. This drug's extremely low aqueous solubility (0.023 mg/ml) is one of its main issues, since it leads to poor bioavailability following oral administration. Therefore, in order to improve the bioavailability, it is necessary to make piroxicam more soluble and to create an appropriate dose form. Piroxicam should be developed as fast-dissolving oral films for convenient and efficient drug delivery in order to effectively treat osteoarthritis and arthritis, particularly in older patients. By generating an inclusion complex with β-cyclodextrin (β-CD), piroxicam's solubility was attempted to be improved in the current work. The resulting fast-dissolving films were then developed and assessed.

MATERIALS AND METHODS

The piroxicam, β-cyclodextrin, sodium CMC, chitosan, crospovidone, sodium starch glycolate, and citric acid were supplied by Yarrow Chem in Mumbai, India. PEG 400 was supplied by Loba Chemie Pvt Ltd of Mumbai, India. All of the chemicals and reagents used were of analytical purity.

Compatibility study by FTIR

The method of matching Fourier Transform Infrared (FTIR) spectra was employed to find any potential chemical interactions between the medication and polymers. Pure drugs and physical drug-polymer combinations were among the samples. To create dry pellets, a suitable amount of potassium bromide was added. The FTIR spectrophotometer (Jasco FTIR 4100, Japan) was then used to scan the pellets from 4000 to 400 cm-1. Peak matching was used to find any appearance or disappearance of peaks in the FTIR spectra of physical mixes and the pure drug spectrum.

Preparation of inclusion complex of piroxicam with β-cyclodextrin

By kneading the physical mixture of piroxicam: β-CD in several ratios (1:0.5 (IC1), 1:1 (IC2), and 1:2 (IC3) in a mortar with a methanol and water mixture (1:1), inclusion complexes were created. After that, a pestle was used to completely knead the wet mixture until it had the consistency of paste. Following room temperature drying, the dry sample was run through sieve #80 and kept in a desiccator until it was needed again.

Evaluation of Inclusion Complex

Drug content and in vitro drug release

25 mg of the inclusion complex was placed in a 50 ml volumetric flask, dissolved in methanol, and then appropriately diluted with a pH 6.8 phosphate buffer. A UV spectrophotometer (Shimadzu UV-1201, Japan) was then used to analyze the solution after it had been filtered via Whatman filter paper at 350 nm. Using USP dissolving testing device type-II (EDT-08Lx, Electrolab, Mumbai, India), the in vitro drug release investigation was conducted. Approximately 100 milligrams of piroxicam was added to 900 milliliters of the dissolving media (pH 6.8). A paddle speed of 50 rpm and a temperature of 37±0.5°C were maintained. At predetermined intervals, the 5 ml sample was removed, and the sink state was maintained by replacing it with an equivalent volume of fresh medium. A UV spectrophotometer was used to detect absorbance at 350 nm after the extracted material had been filtered and appropriately diluted with phosphate buffer pH 6.8.

Formulation of Fast Dissolving Film of Piroxicam

Using chitosan or sodium CMC, a film-forming polymer, the solvent casting process was used to create the fast-dissolving piroxicam films. The inclusion complex containing piroxicam was integrated into the polymeric solution after the predicted amount of polymer was introduced to a 3/4 volume of water while being constantly stirred. After that, crospovidone or sodium starch glycolate was added to the polymeric solution and forcefully

agitated. Following the addition of PEG 400 and citric acid, the final volume was adjusted with distilled water to reach 15 ml. A petri dish with an area of 69.362 cm2 was filled with the resultant bubble-free viscous solution, which was then heated to 40ºC for 24 hours. Table 1 lists the ingredients of Piroxi-cam oral films. The 2x2 cm films, which contained 10 mg of piroxicam, were wrapped in aluminum foil and kept in a desiccator until they were needed again.

Evaluation of Piroxicam Fast Dissolving Film

A screw gauge (Kayco India Ltd., Delhi, India) was used to measure the rapid dissolving film's thickness (2×2 cm). Each film's thickness was measured and computed in triplicate at three separate locations. Fast dissolving film measuring 2 x 2 cm was cut into tiny pieces and put into a graduated glass-stoppered flask with roughly 100 ml of phosphate buffer at a pH of 6.8 in order to assess content homogeneity. A motorized shaker was used to shake the flask for four hours. Following appropriate dilutions with phosphate buffer of pH 6.8, the solution was filtered, and the absorbance at 350 nm was measured using a UV spectrophotometer to determine the amount of medication present. After calculating the individual and average weights of the 2x2 cm films in triplicate using an electronic analytical balance (Essae Teraoka, Japan), weight variation was computed. Oral film was put on a petri dish, soaked with 0.5 ml of distilled water, and left for 30 seconds in order to measure the surface pH. The pH was determined by touching the oral film's surface with the electrode of a pH meter (Systronics, Mumbai, India). The process was carried out three times. The bottom clamps of the tensile strength apparatus (F.4026, Instron Ltd., Japan) were moveable, whereas the upper clamps were permanent. The force at tearing and elongation were recorded while the 6x2 cm film sample was clamped between the two clamps. To assess the film, two mechanical characteristics—tensile strength and % elongation—were calculated. Folding endurance was measured by repeatedly folding a 4x2 cm material in the same spot until cracks were visible. The 4 cm2 piece of film was cut off, precisely weighed, and stored in a desiccator with fused anhydrous calcium chloride. The film was taken out after 24 hours, weighed once more, and the percentage of moisture content was determined.

***In vitro* Disintegration**

One tube of the disintegration apparatus IP (ED-2L, Electrolab, Mumbai, India) was filled with the film size (2×2 cm) needed for dosage administration, and a disc was positioned on the tube's surface. The apparatus was run until the film dissolved while the assembly was suspended in a beaker filled with a pH 6.8 phosphate buffer. The in vitro disintegration time was the amount of time needed for the film to break down.

***In vitro* Drug Release**

The USP XXIII type-I dissolution apparatus (EDT-08Lx, Electrolab, Mumbai, India) was used for the dissolving investigations. It was run at 37±0.5°C and 50 rpm with a 300ml medium of phosphate buffer with a pH of 6.8. Every 2x2 cm film that was set on a basket was immersed in the dissolving solvent and agitated. At intervals of 0, 20, 30, 40, 60, 80, 100, 120, and 140 seconds, samples were taken out, and the same volume of new medium was added. After passing through 0.45 µm Whatman filter paper, the extracted samples were examined at 350 nm using a UV spectrophotometer.

***In vitro* Permeation**

The Franz diffusion cell, which has an interior diameter of 2.5 cm, was used to investigate in vitro permeability through cellophane membrane. The donor and receptor compartments were separated by a cellophane membrane. The receptor compartment was filled with 100 milliliters of pH 6.8 phosphate buffer that was kept at 37±0.5°C. The donor compartment contained a single 2x2 cm film that had been moistened with a few drops of phosphate buffer with a pH of 6.8. Five milliliters of phosphate buffer with a pH of 6.8 were added to the donor compartment. At predetermined intervals, a 1 ml sample was taken out of the receptor compartment, and each time the same volume of new media was added. By utilizing a UV spectrophotometer to measure the absorbance at 350 nm, the proportion of piroxicam that

permeated was ascertained.

RESULTS

Compatibility Study by FTIR

S=O stretching at 3640.95 cm-1, C=C stretching at 1586.16 cm-1, and two C=O stretches at 1586.16 cm-1 and 1726.94 cm-1, respectively, were used to characterize the FTIR spectra of the pure medication. The FTIR spectra of medication mixes containing polymers also showed all of the distinctive infrared peaks associated with the pure drug piroxicam. Figure 1 displays the FTIR spectrum overlay.

Evaluation of Inclusion Complex of Piroxicam with β-Cyclodextrin

It was determined that the prepared complexes had a drug content of 90.73±0.56% (IC1), 91.67±0.63% (IC2), and 90.32±0.83% (IC3). Figure 2 displays the results of an in vitro dissolution research of inclusion complexes and the pure medication piroxicam. The IC2 (1:1) and IC3 (1:2) complexes completely dissolved in 200 s, while the IC1 (1:0.5) complex only displayed a 64.83 % release at the end of 200 s. About 98.71% of the medication was released in 180 seconds when Complex IC2, which had a 1:1 ratio of drug to β-CD, demonstrated a quicker rate of breakdown.

Evaluation of Fast Dissolving Film of Piroxicam

Using chitosan (Table 1) or sodium CMC as a polymer, 12 formulations were created. The fast-dissolving films F1 through F12 had low standard deviation values and ranged in thickness from 0.29±0.04 mm to 0.46±0.09 mm. The lowest thickness, 0.29±0.04 mm, was displayed by formulation F1, while the highest thickness, 0.46±0.09 mm, was displayed by formulation F9. All of the formulations' content uniformity was determined to be between 84.3±0.41% and 96.05±1.34%. The films' average weight was determined to be between 97.33±1.69 mg and 146.66±2.05 mg. The lowest weight, 97.33±1.69 mg, was displayed by formulation F1, while the highest weight, 146.66±2.05 mg, was displayed by formulation F9. The films F1 through F12 had surface pH values between 6.61±0.01 and 6.88±0.04. Table 2 shows the findings of the surface pH, weight fluctuation, film thickness, and content uniformity studies for each formulation. The films F1 to F12 were found to have tensile strengths between 4.1±0.02 and 5.6±0.07 N/cm2. The minimum tensile strength was 4.1±0.02 N/cm2 for formulation F1, while the maximum tensile strength was 5.6±0.07 N/cm2 for formulation F12. Films F1 through F12 had elongations ranging from 8.81±1.17% to 31.33±2.18 %. Formulations F9 and F5 displayed the maximum percent elongation of 31.33±2.18 % and 30.50±2.24 %, respectively, whereas formulation F2 displayed the lowest percent elongation of 8.81±1.17%. The films F1 through F12 had folding endurances ranging from 200±1.69 to 212±3.17. While formulation F12 demonstrated a better folding endurance of 212±3.17, formulation F1 demonstrated a lower folding endurance of 200±1.69. The films F1 through F12 had moisture contents ranging from 1.26±043% to 2.49±0.35%. The moisture content of formulations F5 and F9 was high, but that of formulations F2 and F4 was low. Table 3 displays the results of a study on tensile strength, percentage elongation, folding endurance, and moisture content.

***In vitro* Disintegration**

All of the films broke up quickly. The films F1 through F12 were found to have disintegration times ranging from 14.94±3.06 s to 36.66±1.05 s. The lowest in vitro disintegration time, 14.94±3.06 s, was displayed by formulation F2, while the maximum, 36.66±1.05 s, was displayed by formulation F9.

***In vitro* Drug Release**

Figures 3 and 4 show the outcomes of in vitro drug release experiments. At the conclusion of 100 seconds, rapid drug dissolution was seen in the cases of F6 containing 6% w/v of crospovidone, which released 94.4%, and F4 containing 2% w/v of crospovidone, which released 92.90%. F5 containing 4% w/v of crospovidone showed slow drug dissolution, releasing 92.71% at the end of 120 seconds, while F9 containing 6% w/v of sodium starch glycolate showed 96.51% at the end of 140 seconds. T90% of the films F1 through F12 were

found to range from 90.28 s to 120.83 s. The minimum T90% was 90.28 s for formulation F6, while the maximum T90% was 120.83 s for 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)

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

Formulation code	Tensile Strength (N/cm2)	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)

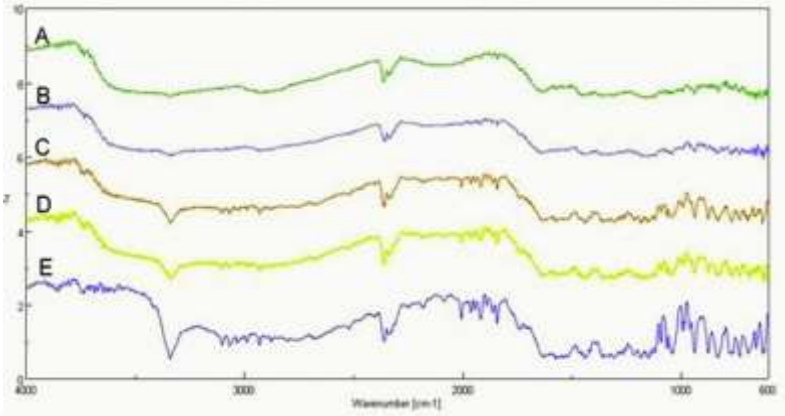

Figure 1: Overlay FTIR Spectra; Piroxicam (A), piroxicam+ betacyclodextrin (B), piroxicam+ betacyclodextrin+ sodium CMC (C), piroxicam+ betacyclo- dextrin+ chitosan (D) and piroxicam+ betacyclodextrin+ chitosan+s odium CMC (E).

***In vitro* Permeation**

The formulation F6 with 6% w/v crospovidone demonstrated superior drug penetration of 96.65% in 40 seconds, formulation F4 with 2% w/v crospovidone demonstrated drug penetration of 97.13% in 45 seconds, formulation F2 with 4% w/w sodium starch glycolate, and formulation F7 with 2% w/w sodium starch glycolate demonstrated drug penetration of 98.08% and 97.39%, respectively, at the conclusion of 45 seconds. Figures 5 and 6 show the findings from the in vitro permeation investigations.

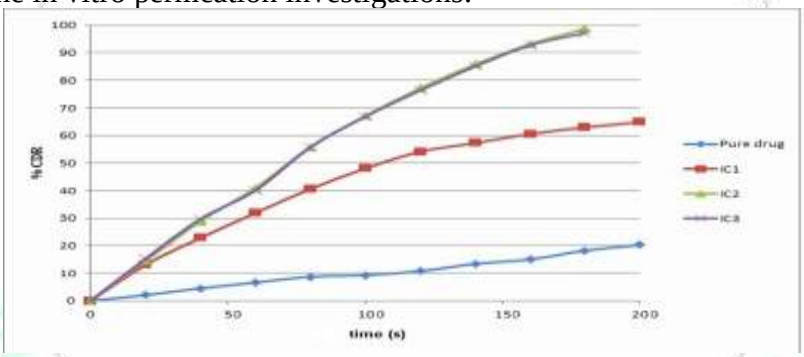

Figure 2: In vitro release pattern of piroxicam and its inclusion complexes with β-CD.

Table 4: In vitro disintegration time and T90% of fast dissolving films con- taining piroxicam.

Formulation code	In vitro disintegration time (s)	T90% (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)

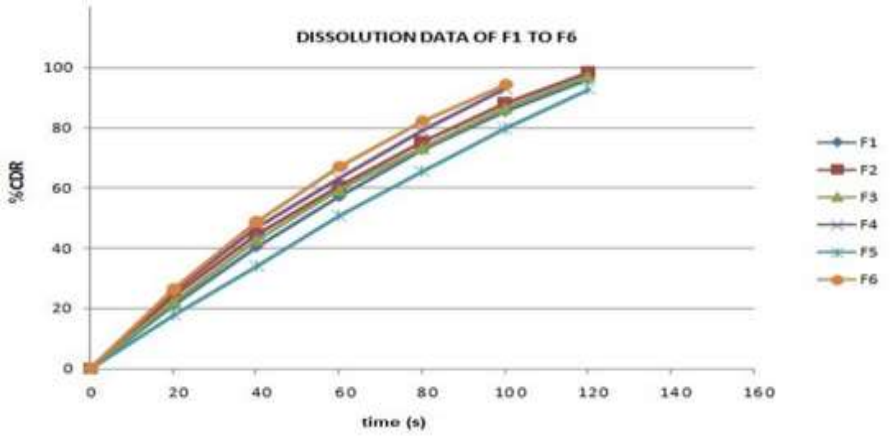

Figure 3: In vitro dissolution of F1 to F6 formulations.

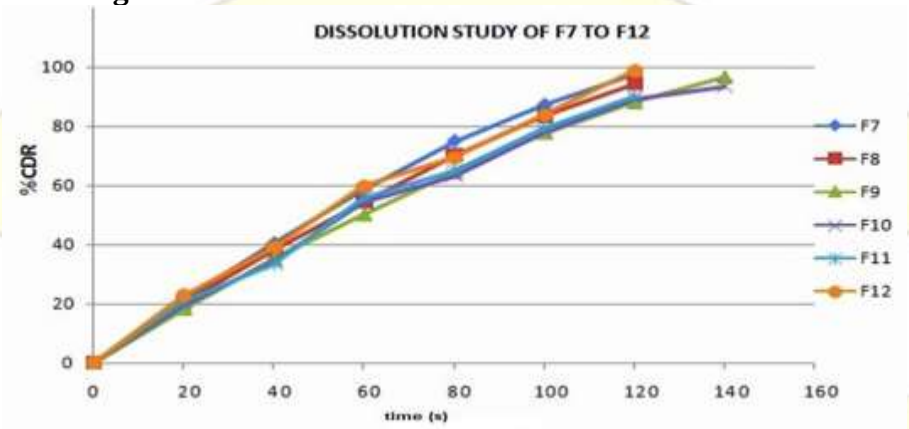

Figure 4: In vitro dissolution of F7 to F12 formulations.

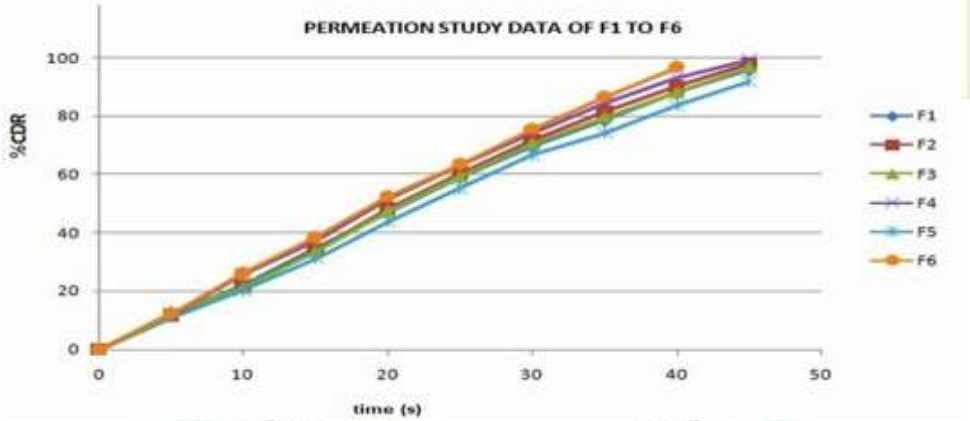

Figure 5: In vitro permeation pattern of F1 to F6 formulations.

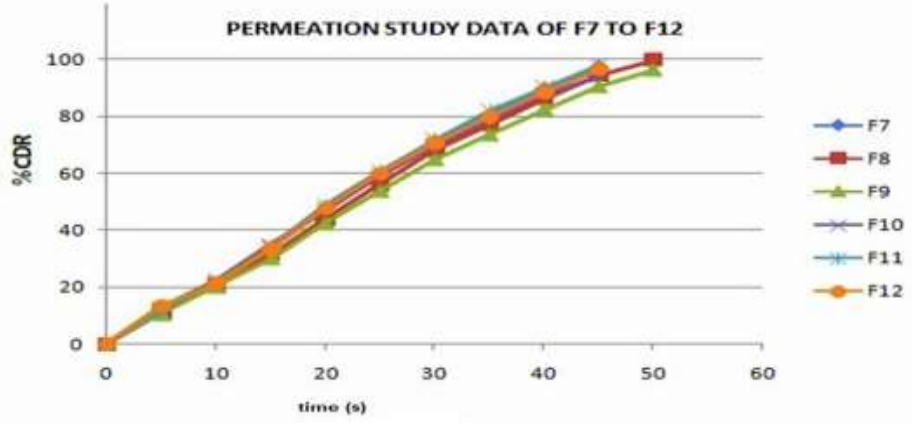

Figure 6: In vitro permeation pattern of F7 to F12 formulations.

DISCUSSION

Each physical mixture's spectra showed IR peaks that were correlated with the drug spectrum's peaks. As a result, it was determined that every polymer utilized in the formulation was safe for the medicine and did not cause any stability issues. To improve the drug's solubility, kneading was used to create piroxicam inclusion complexes with β-CD. The medication was uniformly distributed in all three of the produced inclusion complexes. The complexes' dissolution rate was shown to be higher than that of the pure drug, most likely as a result of the drug's production of water-soluble inclusion complexes with the β-CD. Formulation IC2, or the inclusion complex of piroxicam with β-CD (1:1 ratio), which was made using the kneading process, exhibited a faster rate of dissolution than the other inclusion complexes (Figure 2). Therefore, using the solvent casting approach, polymers like sodium CMC and chitosan as well as super disintegrants like sodium starch glycolate and crospovidone were chosen as excipients for the creation of fast dissolving films. The physico-chemical characteristics of each formulation were assessed. The concentration of the polymer determines the thickness of the fast-dissolving film. Here, the polymer concentration is maintained at a consistent level. Therefore, variations in the concentration of the super disintegrating agent determine the thickness of the rapid dissolving film. The lowest film thickness may be caused by a low concentration of the super disintegrating agent in F1 (2% w/v of sodium starch glycolate), while the highest film thickness may be caused by a high concentration of the super disintegrating agent in F9 (6% w/v of sodium starch glycolate). The findings of the content uniformity analysis verified that the medication was distributed uniformly throughout all formulations. Since the standard deviation of the percentage weight variation of each formulation was found to be within the pharmacopoeial limit, or ±7.5%, all of the films passed the weight variation test. The lowest weight of the film may have been caused by the super disintegrating agent's low concentration in F1 (2% w/v of sodium starch glycolate), while the maximum weight of the film may have been caused by the super disintegrating agent's high concentration in F9 (6% w/v of sodium starch glycolate). All formulations were found to have surface pH, tensile strength, percentage elongation, folding durability, and moisture content within a satisfactory range. The amount of moisture that passes through a film's unit area in a unit amount of time is known as moisture loss, and it shows how well a film can tolerate its physicochemical characteristics under typical circumstances. One crucial characteristic of fast-dissolving films is their rapid disintegration, which was demonstrated by all of the formed films (F1–F12). medication release experiments conducted in vitro verified that the medication was released from formulations quickly, with the F6 formulation releasing the drug more quickly than any other formulation. Because piroxicam is a member of BCS class II, it was found to permeate the membrane with ease. Thus, the in vitro permeation study's findings show that piroxicam is easily soluble and absorbed from fast-dissolving films.

CONCLUSION

In order to improve therapeutic efficacy and patient compliance, the solvent casting technique was effectively used to create the rapid dissolving oral films of piroxicam inclusion complexes. The results were positive and thought to be a good way to provide better action than traditional pills while still being easy to administer. Overall, it was determined that the preparation was easy, repeatable, and economical. Thus, it can be said that this drug delivery method has the ability to go around the limitations of the typical tablet formulations that are now on the market.

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