ORIGINAL ARTICLE

Formulation and Development of Fast Dissolving Oral Film of a Poorly Soluble Drug Piroxicam with Improved Drug Loading Using Mixed Solvency Concept and its Evaluation

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Abstract

Aim: The aim of the present research work is to explore the application of mixed solvency to formulate and develop a fast dissolving oral film of piroxicam with improved drug loading utilizing the mixed-solvency concept. **Materials and Methods:** All solubilizers sodium benzoate, polyethylene glycol (PEG) 400, and polyvinylpyrrolidone (PVP) K30 were weighed accurately and transferred in a 100 ml beaker. Then, warm and demineralized water sufficient to dissolve the solubilizers were added. After complete dissolution of solubilizers, 200 mg of piroxicam was dissolved in the above solution, and temperature was maintained at 55–60°C so as to facilitate the evaporation of water. Then, this viscous mass was poured on the already prepared backing layer (having polymer ratio polyvinylalcohol [PVA] 14000: PVP K 30 [40:60] and 5% w/w PEG 400 as plasticizer) in Petri plate and spread with spreader. The prepared film was dried in an oven at 40°C for 24 h. The prepared films were kept in desiccators and used for further studies. **Results and Discussion:** On the basis of solubility studies, the blend containing PVP14000 + PEG 400 + SB (13.3:13.3:13.3) was selected. For formulation development, backing layer containing polymer ratio PVA 14000:PVP K 30 (40:60) was found to be most appropriate. PEG 400 5% w/w provides faster dissolution of the prepared backing layer as well as better tensile strength. FD 8 batch showed better evaluation results and was taken as the optimized batch. Dissolution profiles of piroxicam pure drug, optimized fast dissolving oral film, fast dissolving oral film with perforations and marketed dispersible tablet (Pirox DT) were compared and results showed that dissolution rate of piroxicam from fast dissolving oral film was similar to marketed dispersible tablet (Pirox DT). **Conclusion:** From all the above studies, it was concluded that the approach of mixed solvency is novel, safe, cost-effective, and user-friendly. It also eliminates the problem of toxicity associated with high concentration of single solubilizers. Hence, it may be employed in dosage form development of drugs where fast onset of action is desired. It may also enhance the bioavailability associated with poor dissolution of drug.

Key words: Fast dissolving oral film, mixed solvency concept, piroxicam

INTRODUCTION

Fast dissolving oral film, a new delivery system for the oral delivery of drugs, was developed based on the technology of the transdermal patch. It consists of a very thin oral strip, which releases the active ingredient immediately after uptake into oral cavity. In contrast to other existing, rapidly dissolving dosage forms, which mainly consist of lyophilizates; the fast dissolving film can be produced with the manufacturing process that is competitive with the manufacturing cost of conventional tablets.[1]

A huge number of different drugs can be formulated with this platform technology. Innovative products may increase therapeutic possibilities on the following indication:

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Pediatrics (antitussive, expectorant, antiasthmatics, etc.), gastrointestinal disease and nausea (e.g., due to cytostatic therapy), pain (e.g., migraine), and CNS (e.g., ant parkinsonism therapy).

Fast dissolving oral film is a thin film, with an area of 5–10 cm^2 containing an active ingredient. The immediate dissolution, in water or saliva, respectively, is reached through a special matrix from water-soluble polymers.[2-5]

A typical composition contains the following excipients:

Drug	1–25%
Water-soluble polymers	40–50%
Plasticizers	0–20%
Fillers, colors, flavors, etc.	0–40%

The fast-dissolving oral film can also be prepared by any one or combination of the following methods: [6] Casting and solvent evaporation method, hot melt extrusion, solid dispersion extrusion, and coating method.

Mixed solvency

Maheshwari[7-29] proposed the concept of mixed-solvency and proved that all substances whether liquids, solids, or gases may enhance the solubility of poorly soluble drugs. He has carried out solubility studies on poorly-water soluble drug salicylic acid (as a model drug). Solubility studies were carried in the solutions containing hydrotropic agents (urea and sodium citrate), cosolvents (glycerin, propylene glycol, and polyethylene glycol (PEG) 300 and PEG 400), and water-soluble solids (PEG 4000 and PEG 6000) individually as well as in 10 randomly prepared blends keeping total concentration constant, i.e., 40%. Results showed that seven out of 10 blends produced a synergistic effect on solubility enhancement.

MATERIALS AND METHODS

Materials

Piroxicam drug was obtained as a gift sample from Shreya Life Sciences Pvt. Ltd., Aurangabad. Other chemicals used were of analytical grade. Demineralized water was used in the study.

Preparation and optimization of backing layer

For the preparation of backing layers (Table 1), about 50 ml of 7.5% w/v aqueous solutions of individual polymers (polyvinyl alcohol [PVA] 14000 and polyvinylpyrrolidone [PVP] K 30) were prepared using magnetic stirrer (slight heating was required in case of PVA 14000). 20 ml solutions of each polymer combinations were made by taking the volume of individual polymeric solutions. Glycerin was added as a plasticizer in all polymeric solutions (5% w/w of total polymers). Then, volume of plasticized polymeric solutions was made up to 30 ml with DM water to achieve polymeric concentration, 5% w/v. Backing layers of different combinations of PVA 14000 and PVP K 30 were cast in plastic Petri plates (98 mm in diameter) as it provides about 20 mg dry weight per 6 cm^2. These casted films were dried in hot air oven at 40°C for 24 h and then stored in desiccator. These prepared backing layers were evaluated for their film properties, namely uniformity of thickness, dissolution time, folding endurance, hydration ratio, and tensile strength.

Evaluation of backing layer

Uniformity of thickness

Thickness of each prepared backing layers was measured using a micrometer (Digimatic Micrometer, Mitutoyo, Tokyo, Japan) with the sensitivity of 10 µ, at five locations (center and four corners), and the mean thickness was calculated. Samples with air bubble, nicks, or tears were excluded from such evaluation.

In vitro dissolution time

There may be some chances of polymeric residue of backing layers after complete dissolution of the drug deposit layer from bilaminated fast dissolving oral film. Hence, backing layers containing different polymer ratios of PVA 14000 and PVP K 30 were evaluated for *in vitro* dissolution time. This dissolution study was conducted in modified USP XXIII apparatus (paddle over disk) at 50 rpm, using 900 ml 0.1 N HCl and 300 ml simulated saliva fluid (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8.00 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.8) as dissolution media. The temperature was maintained at 37 ± 0.5°C. The time taken for complete dissolution of the polymeric backing layer was noted as the *in vitro* dissolution time.

Determination of hydration ratio

Hydration ratios of prepared backing layers were determined gravimetrically. The film sample (6 cm^2) was weighed and placed on a pre-weighed stainless steel wire mesh with average sieve size opening of 200 µ. The screen was then submerged in a Petri dish containing 20 ml DM water. Increase in weight of the film was determined at regular intervals until a constant weight was obtained. The hydration ratios of films were calculated according to the following equation:

$$\text{Hydration ratio} = \frac{Wt - W_0}{W_0}$$

W_o = Weight of the film at zero time, and
W_t = Weight of the film at time t

Table 1: Composition of different polymeric combinations for backing layer

Backing layer	Polymer ratio PVA 14000: PVP K 30	Volume of individual polymer solution (ml)		Glycerin (mg)
		PVA 14000	PVP K 30	
BL1	100:00	20	-	75
BL2	80:20	16	4	75
BL3	60:40	12	8	75
BL4	40:60	12	8	75
BL5	20:80	4	16	75
BL6	00:100	-	20	75

PVA: Polyvinyl alcohol, PVP: Polyvinylpyrrolidone, PVA: Polyvinyl alcohol

Table 2: Calibration curve of piroxicam in different media

Media	Regression equation	Correlation coefficient
D.M. water (at 358 nm)	y=0.0417x+0.0097	R^2 = 0.9997
Simulated Saliva fluid (pH 6.8) (at 358 nm)	y=0.0352x+0.0252	R^2 = 0.9993
0.1 N HCl (at 333 nm)	y=0.0777x+0.0063	R^2 = 0.999

Table 3: Composition of different polymeric combinations for backing layer

Backing layer	Polymer ratio PVA14000:PVPK 30	Volume of individual polymer solution (ml)		Glycerin (mg)
		PVA 14000	PVP K 30	
BL1	100:00	20	-	75
BL2	80:20	16	4	75
BL3	60:40	12	8	75
BL4	40:60	12	8	75
BL5	20:80	4	16	75
BL6	00:100	-	20	75

PVA: Polyvinyl alcohol, PVP: Polyvinylpyrrolidone, PVA: Polyvinyl alcohol

Table 4: *In vitro* dissolution time of prepared backing layers

Backing layers	Dissolution time (min)	
Batch no	0.1 HCl (min)	Simulated saliva fluid (pH 6.8) (min)
BL1	More than 5 min	More than 6
BL2	3–4	3–4
BL3	2–3	2–3
BL4	<1	<1

Folding endurance

For determination of folding endurance, three films of each composition of size 6 cm^2 (2 cm × 3 cm) were cut using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of three readings and standard deviation was obtained.

Tensile strength

Tensile strength of the prepared backing layers was evaluated using tensile strength tester equipment equipped with a 50-kg load cell (Fibratech, Rookree). Backing layer in the dimension of 50 mm × 10 mm and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the lower clamp at a rate of 2.0 mm/s to a distance of 10 cm. The force was measured when the films were broken.

Selection of plasticizer

For the selection of plasticizer, three batches of backing layers were prepared with a fixed concentration (10% w/w of polymer) of three different plasticizers, namely propylene glycol, glycerin, and PEG 400 taking polymer combination PVA 14000:PVP K 30 (40:60). All three prepared batches were studied for the evaluation parameters, namely thickness, dissolution time, folding endurance, and tensile strength.

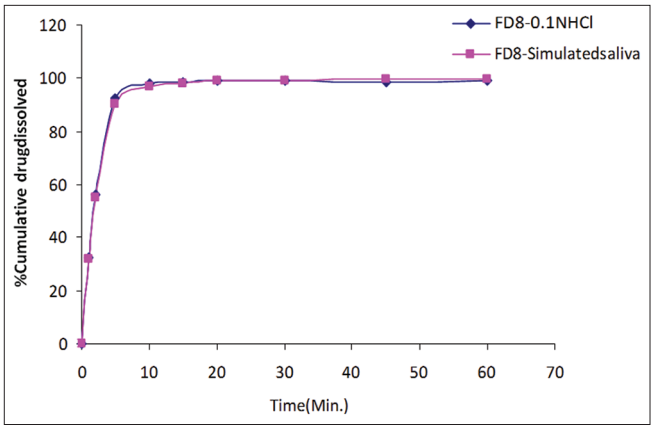

Figure 1: Dissolution profiles of batch FD8

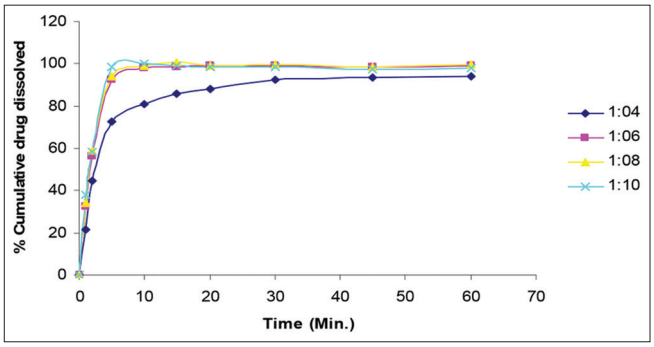

Figure 2: Dissolution profiles of different batches of fast dissolving films containing different drug:solubilizer ratio in 0.1 HCl

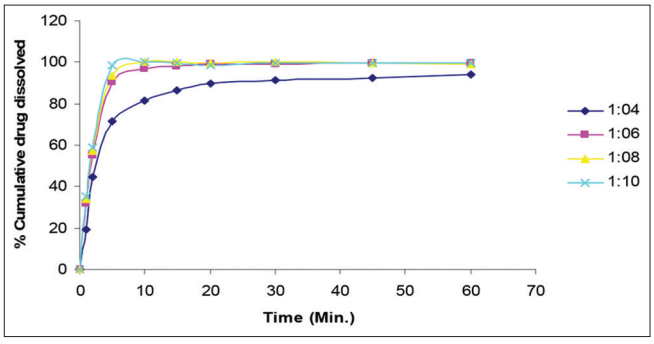

Figure 3: Dissolution profiles of different batches of fast dissolving films containing different drug:solubilizer ratio in simulated saliva

Optimization of plasticizer concentration

For the optimization of plasticizer concentration, three batches of backing layers with varied concentration (5, 10, and 15 % w/w of polymer) of PEG 400 were prepared taking polymer combination PVA 14000:PVP K 30 (40:60). All three prepared batches were studied for the evaluation parameters, namely thickness, dissolution time, folding endurance, and tensile strength.

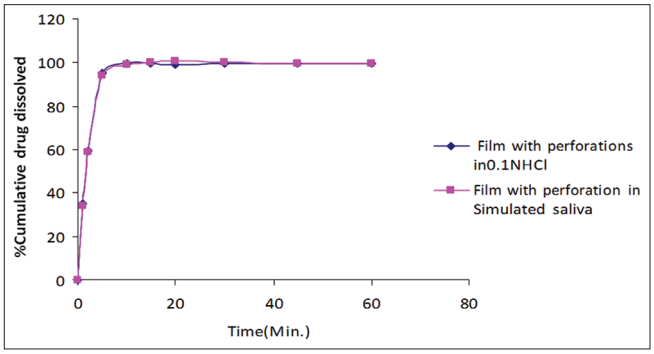

Figure 4: Dissolution profiles of fast dissolving oral film with perforations

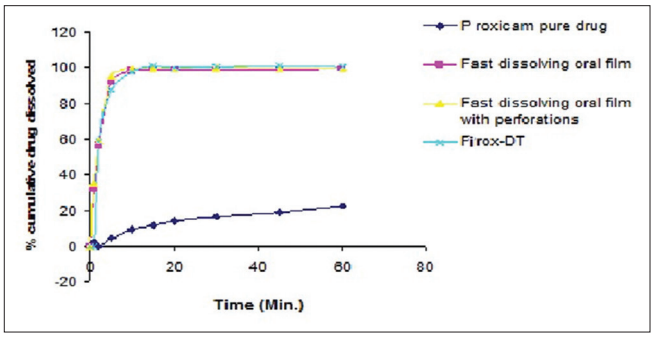

Figure 5: Comparative account of dissolution studies of piroxicam pure drug, fast dissolving oral film, fast dissolving oral film with perforations and marketed tablet formulation (Pirox DT)

Table 5: Hydration ratios of prepared backing layers

Batch	Hydration ratio with time		
	1 (min)	2 (min)	5 (min)
BL1	2.13	4.12	4.26
BL2	1.94	3.87	3.79
BL3	1.79	3.79	3.81
BL4	2.02	4.29	4.31

Weight adjustment of backing layer

Weight of backing layer (in relation to thickness) is of good concern from the point of view of its mechanical strength and dissolution time. For the weight adjustment, three different batches of backing layers were prepared having polymer ratio PVA 14000:PVP K 30 (40:60), and 5% w/w PEG 400 as a plasticizer.

Preparation and optimization of fast dissolving drug layer

Selection of water-soluble carriers for formulation of fast dissolving drug layer

For selection of appropriate water-soluble carriers that have good solubilizing capacities for piroxicam the solubilities

Table 6: Folding endurance, tensile strength, and mean thickness of the prepared backing layers

Backing layers batch	Folding endurance (numbers)	Tensile strength (Kg/cm²)	Mean thickness (μm)
BL1	>300	1.12	20
BL2	>300	1.03	10
BL3	>300	0.98	10
BL4	>300	0.97	10

Table 7: Evaluation of backing layers containing different plasticizers

Backing layers	Polymer ratio PVA 14000: PVP K 30	Plasticizer (10% w/w)	Mean thickness (μm)	Dissolution time (s)	Folding endurance (numbers)	Tensile strength (Kg/cm²)
BL7	40:60	Glycerin	10	60	>300	0.91
BL8	40:60	PG	10	55	>300	0.97
BL9	40:60	PEG 400	10	45	>300	0.98

Where, PG: propylene glycol, PVA: Polyvinyl alcohol, PVP: Polyvinylpyrrolidone, PVA: Polyvinyl alcohol

Table 8: Evaluation of backing layers containing different concentrations of PEG 400

Backing layers	Polymer ratio PVA 14000: PVP K 30	PEG 400 (%w/w)	Mean thickness (μm)	Dissolution time (s)	Folding endurance (numbers)	Tensile strength (Kg/cm²)
BL10	40:60	5	10	60	>300	0.98
BL11	40:60	10	10	55	>300	0.97
BL12	40:60	15	10	45	>300	0.91

PVA: Polyvinyl alcohol, PVP: Polyvinylpyrrolidone, PVA: Polyvinyl alcohol

Table 9: Evaluation of backing layers of different weights

Backing layer	Polymer ratio PVA 14000: PVP K 30	Mean thickness (μm)	Weight per 6 cm² (mg)	Dissolution time (s)	Folding endurance (numbers)	Tensile strength (Kg/cm²)
BL13	40:60	10	10	45	>300	0.80
BL14	40:60	10	15	48	>300	0.93
BL15	40:60	10	20	60	>300	0.97

PVA: Polyvinyl alcohol, PVP: Polyvinylpyrrolidone, PVA: Polyvinyl alcohol

of piroxicam in aqueous blends containing different compositions from among different solubilizers such as sodium benzoate, sodium acetate, sodium citrate, urea and niacinamide, glycerin, propylene glycol, PEG 200, PEG 300, PEG 400, and PEG 600, and PVP K 30 were measured keeping total concentration of solubilizers constant 40% w/v. An excess amount of piroxicam was added to 5 ml of these solutions in volumetric flasks, and the volumetric flasks were shaken on mechanical shaker for 12 h so that equilibrium solubility can be achieved and solutions were allowed undisturbed to equilibrate for 24 h. Then, solutions were centrifuged at 2000 rpm for 5 min in a centrifuge (Eppendorf) and then, solutions were filtered through Whatman grade 41 filters. Aliquots were suitably diluted with DM water and analyzed using UV spectrophotometer at 358 nm against corresponding reagent blanks.

Preparation of fast dissolving drug layer

All solubilizers [Table 11] except the drug were weighed accurately and transferred in a 100 ml beaker. Then, minimum quantity of warm, demineralized water sufficient to dissolve the solubilizers was added (lesser the amount of water lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely during removal of water). Dissolution of the solubilizers was facilitated by agitation of a Teflon coated magnetic rice bead on a high-speed magnetic stirrer. After complete dissolution of solubilizers, 200 mg of piroxicam was dissolved in the above solution, and temperature was maintained in the range of 55–60°C so as to facilitate the evaporation of water. As evaporation proceeded, the speed of rice bead automatically decreased, and it stopped stirring when most of the water was

Table 10: Equilibrium solubility of piroxicam in different aqueous blends of solubilizers

Blends of solubilizers	Total concentration (% w/v)	Solubilizer ratio	Solubility (% w/v)	Solubility enhancement ratio
PVP+P2+SB	40	13.3:13.3:13.3	1.518	225.026
PVP+P3+SB	40	13.3:13.3:13.3	1.291	191.351
PVP+P4+SB	40	13.3:13.3:13.3	1.533	227.175
PVP+P6+SB	40	13.3:13.3:13.3	1.298	192.426

Where, SB: Sodium benzoate, P2: PEG 200, P3: PEG 300, P4: PEG 400, P6: PEG 600 and PVP: PVP K 30

Table 11: Composition of different fast dissolving drug layers

Batch	Compositions			
	Piroxicam (mg)	Sodiumbenzoate (mg)	PEG 400 (mg)	PVP K 30 (mg)
FD1	200	100	250	850
FD2	200	100	300	800
FD3	200	100	350	750
FD4	200	150	250	800
FD5	200	150	300	750
FD6	200	150	350	700
FD7	200	200	250	750
FD8	200	200	300	700
FD9	200	200	350	650
FD10	200	250	250	700
FD11	200	250	300	650
FD12	200	250	350	600
FD13	200	300	250	650
FD14	200	300	300	600
FD15	200	300	350	550

PVP: Polyvinylpyrrolidone, PVA: Polyvinyl alcohol

evaporated. Then, this viscous mass was poured on already prepared backing layer in Petri plate and spread with a spreader. The prepared film was dried in an oven at 40°C for 24 h. The prepared films were kept in desiccators and used for further studies.

Evaluation of bilaminated fast dissolving oral film

Drug content

The prepared fast dissolving oral films equivalent to 10 mg of piroxicam (6 cm^2) were accurately taken and transferred to a 500-ml volumetric flask. Approximately 300 ml of DM water was added, and flask was shaken to dissolve the film completely, and the volume was made up to the mark with DM water. Then, the solution was filtered through Whatman grade 41 filter paper and analyzed spectrophotometrically (Shimadzu A-160) at 358 nm against corresponding reagent blank. The analysis was carried out in triplicate, and drug contents were determined.

In vitro dissolution rate study

Films containing 10 mg of piroxicam were used in the *in vitro* dissolution study. Dissolution studies were conducted in modified USP XXIII apparatus (paddle over disk) at 50 rpm, using 900 ml of 0.1 N HCl and 300 ml of simulated saliva fluid (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8.00 g NaCl per liter of aqueous solution adjusted with phosphoric acid to pH 6.8) as dissolution media. The temperature was maintained at 37 ± 0.5°C. 10 ml sample was withdrawn at regular intervals and analyzed spectrophotometrically (Shimadzu A-160) at 333 nm (where dissolution media were 0.1 N HCl) and at 358 nm (where dissolution media were simulated saliva of pH 6.8). An equal amount of fresh dissolution media was replaced immediately after withdrawal of sample.

Uniformity of thickness

Thickness of each prepared film sample was measured.

Determination of hydration ratio

Hydration ratios of prepared fast dissolving oral films were determined.

Tensile strength

Tensile strength of prepared fast dissolving oral films was measured.

Folding endurance

Folding endurance of prepared fast dissolving oral films was measured.

The mean values of three readings and standard deviations were shown in Table 13.

Effect of perforations on drug dissolution rate of piroxicam from the bilaminated fast dissolving film

To study the effect of perforations on the drug dissolution from fast dissolving oral film, perforations were made on a bilaminated oral film containing formulation FD8, making

two perforations per cm^2 using 16-gauge needle. Drug content of the film was determined as perforations may cause the loss of some drug. Dissolution study was conducted taking films containing 10 mg of piroxicam in modified USP XXIII apparatus (paddle over disk) at 50 rpm, using 900 ml SGF and 300 ml simulated saliva fluid (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8.00 g NaCl per liter of aqueous solution adjusted with phosphoric acid to pH 6.8) as dissolution media. The temperature was maintained at 37 ± 0.5°C. 10 ml samples were withdrawn at regular intervals and analyzed spectrophotometrically (Shimadzu A-160) at 333 nm (when dissolution medium was 0.1 N HCl) and at 358 nm (when dissolution medium was simulated saliva pH 6.8). An equal amount of fresh dissolution media was replaced immediately after withdrawn of the sample.

Table 12: Drug content of piroxicam in bilaminated fast dissolving oral film

Fast dissolving drug layer batch	Drug content (mg/6 cm^2)	Hydration ratio with time (min)		
		1	2	5
FD1	10.083	2.13	4.12	4.26
FD2	9.866	1.94	3.87	3.79
FD3	9.600	1.79	3.79	3.81
FD4	9.999	2.02	4.29	4.31
FD5	10.241	1.93	3.95	3.74
FD6	9.805	1.74	3.54	3.70
FD7	10.241	2.31	4.11	4.06
FD8	9.842	1.98	3.73	3.75
FD9	10.108	1.69	3.62	3.71
FD10	9.854	1.49	3.45	3.51
FD11	9.805	1.51	3.24	3.31
FD12	10.253	1.32	3.20	3.31
FD13	9.842	1.22	3.42	3.41
FD14	9.926	1.29	3.29	3.22
FD15	10.023	1.23	3.32	3.10

RESULTS AND DISCUSSION

On the basis of solubility studies, the blend containing PVP14000 + PEG 400 + SB in the ratio of 13.3:13.3:13.3 shown the highest solubility enhancement, and therefore, combination of these three solubilizers were selected to form the fast dissolving drug layer because of low individual toxicity of solubilizer and achieved desired required solubility of drug described in Table 10. For formulation development, backing layer of composition BL4 containing polymer ratio PVA 14000: PVP K 30 (40:60) was found to be most appropriate for the desired properties. Hence, the polymeric ratio PVA 14000:PVP K 30 (40:60) was taken as optimized polymer ratio on the basis of mechanical properties and disintegration time of backing layer as described in Tables 2-6. PEG 400 provides faster dissolution of the prepared backing layer as well as better tensile strength. PEG 400 5% w/w was taken as the optimized concentration of plasticizer. As described in Tables 7 and 8, the backing layer prepared of weight 15 mg per 6 cm^2 was found to be most appropriate for the desired properties as described in Table 9. For the preparation and optimization of fast dissolving film layer, fast dissolving drug layer of 15 formulae [Table 11] was prepared keeping

Table 13: Folding endurance, tensile strength, and mean thickness of different batches of fast dissolving oral film

Backing layer	Folding endurance (numbers)	Tensile strength (Kg/cm^2)	Mean thickness (μm)
FD1	72	1.24	60
FD2	126	1.13	60
FD3	163	1.06	70
FD4	69	1.21	60
FD5	112	1.11	60
FD6	139	1.02	70
FD7	65	1.20	70
FD8	106	1.12	70
FD9	125	1.00	70
FD10	22	1.21	70
FD11	49	1.09	70
FD12	65	0.98	70
FD13	16	1.15	70
FD14	1	1.08	70
FD15	22	0.92	70

Table 14: Evaluation of different batches of fast dissolving oral films

Batch	Drug: solubilizer ratio	Mean thickness (μm)	Folding endurance (numbers)	Tensile strength (Kg/cm²)
FD 16	1:4	50	122	0.98
FD 8	1:6	70	106	1.12
FD 17	1:8	80	91	1.21
FD 18	1:10	110	72	1.32

Table 15: Hydration ratio of different batches of fast dissolving oral films

Batch	Drug: solubilizer ratio	Hydration ratio with time (min)		
		1	2	5
FD 16	1:4	2.35	5.23	5.31
FD 8	1:6	1.98	3.73	3.75
FD 17	1:8	1.34	3.05	2.91
FD 18	1:10	1.12	2.88	2.70

the ratio of drug:solubilizers always, 1:6 and evaluated for their film properties and dissolution rate described in Tables 11-15. Among the 15 batches, FD 8 batch showed better evaluation results and was taken as the optimized batch. Dissolution profile of batch FD8 was presented in Figure 1. Dissolution studies of prepared fast dissolving oral film revealed that drug dissolution from fast dissolving oral film containing drug:solubilizer ratio 1:6 showed good folding endurance among all the prepared fast dissolving oral films. Hence, the 1:6 drug:solubilizers ratio was considered as optimized. Comparative dissolution profiles are shown in Figures 2-4. Effect of perforations (in the prepared film) on the dissolution of piroxicam from prepared film was also determined, and dissolution profiles of piroxicam pure drug, optimized fast dissolving oral film, fast dissolving oral film with perforations, and marketed dispersible tablet (Pirox DT) were compared in Figure 5. Results showed that dissolution rate of piroxicam from fast dissolving oral film was similar to marketed dispersible tablet (Pirox DT).

CONCLUSION

From all the above studies, it was concluded that the approach of mixed solvency is novel, safe, cost-effective, and user-friendly. It also eliminates the problem of toxicity associated with high concentration of single solubilizers. Hence, it may be employed in dosage form development of drugs where a fast onset of action is desired. It may also enhance the bioavailability associated with poor dissolution of the drug.

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