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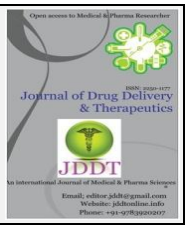

Open Access Research Article

Formulation and development of vaginal films of poorly water soluble drug, metronidazole, using mixed solvency concept and their evaluations

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ABSTRACT

Aim: To deliver antibacterial therapy in an efficacious way, film dosage form has been proposed for drug delivery in vagina which can overcome bioavailability issues of poorly water soluble drugs. The present research work is aimed to explore the application of mixed solvency concept to increase solubility of poorly water soluble drug, metronidazole. **Materials and Methods:** Metronidazole, a slightly soluble drug in water was tried to be solubilized by employing the combination of solubilizers like niacinamide, sodium benzoate, sodium caprylate, caffeine and urea to endeavour its fast dissolving film formulations. The procured sample of drug was characterized by UV, IR and DSC studies. The formulations were evaluated for various properties of film such as thickness, folding endurance, surface pH, disintegration time and thin layer chromatography. Stability studies of vaginal films of metronidazole were performed for ten weeks at room temperature, and refrigerated conditions. **Results and Discussion:** It was found that 97.54% and 97.58% of drug was remaining after stability study at respective temperatures in batch F1 and 98.53% and 96.57% in batch F4.**Conclusion:** It was concluded that the approach of mixed solvency concept is novel, safe, cost-effective and user friendly. It also eliminates the problem of toxicity associated with high concentration of water-soluble solubilizers. So, it may be employed in dosage form development of drugs with poor solubility to overcome bioavailability issues.

Keywords: Solubility, metronidazole, vaginal films, mixed solvency concept.

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INTRODUCTION

The female genital tract consists of cervix and vagina. The vagina is extremely flexible, bent canal that is approximately 15 cm long in which posterior wall is larger than frontal wall because of presence of cervical portion of genital tract which is further connected to vestibule. A healthy reproductive woman has an acidic vaginal pH. There is a natural balance of aerobic and anaerobic microbes in vagina.[1] The vagina consists of numerous microbes that exist in equilibrium, and their presence is influenced by various factors such as pregnancy, menstruation, hygiene and infection. Microbes include bacteria, yeast and viruses, in which the vagina is dominated by Lactobacillus species. Lactobacillus helps to prevent such growth of unwanted harmful microbes by various mechanisms such as stimulating the immune system, maintaining the vaginal pH, production of antimicrobial substance such as hydrogen peroxide that acts against pathogens and further competing with other microbes for nutrients. The reduction in lactobacilli results in change in pH of vagina which can lead to other bacterial infections such as development of bacterial vaginosis.[1,2] Bacterial vaginosis (BV) occurs as most widely recognized vaginal disorder affecting prolific, premenopausal and pregnant ladies, with a frequency rate extending from 5% to 50 %. BV is depicted by an excess of strict or facultative anaerobic microbes and a decrease of lactobacilli especially those involved in hydrogen peroxide production. Female with BV normally account for vaginal inconvenience.[3] The symptoms of BV include: 1) an increase in fluid discharge from vagina that has common "fishy" smell. 2) The colour of discharge is usually milky white or gray. 3) Burning sensation and itching while urination.[4] Diagnosis test include: **The presence of clue cells** (20% of cells as clue cells specify the positivity of test), **Vaginal discharge (**milky white or gray discharge), **Whiff test (**Fishy odour noted after addition of 10% of potassium hydroxide) **OSOM BV Blue test (**based on detection of elevated activity of sialidase within the vaginal fluid, blue or green colour indicates that the sample is positive for BV).[5] Its treatment include oral or vaginal antimicrobials such as metronidazole or clindamycin, and

probiotics. But conventional dosage forms have certain limitations such as lower bioavailability (oral formulations), leakage, and inappropriate drug release, prolong duration of action (vaginal formulations). These limitations are overcome by advanced topical drug delivery system such as vaginal film, which is a type of polymeric drug delivery system that could be applied without using an applicator.[6] Vaginal films are designed to get rapid dispersion or dissolution of API that come in contact with vaginal fluid forming a smooth, viscous, and bio-adhesive gel. As vaginal fluid have some water content so it favours absorption of drugs having certain solubility in water. But for drugs having poor solubility, formulation strategies has to be applied to enhance the solubility.[7-13] To enhance the solubility of the drug, there are several methods available, such as changing the pH, using cosolvents, using dielectric solvents, using surface active agents, complexation, hydrotropic solubilisation, mixed hydrotropy and mixed solvency. Mixed solvency concept plays an important role to enhance the solubility.

Mixed Solvency Concept

As per the mixed solvency concept proposed by Maheshwari R.K., each and every substance present in the universe has got solubilizing property i.e. all the liquids, gases and solids possess solubilizing power. As per his statement, each substance is solubilizer. A concentrated aqueous solution containing various water soluble substances may act as good solvent for poorly water soluble drugs.[14] By combining various excipients, additive and synergistic solvent actions are expected which has advantage of reducing the toxicities. For a desired solubility enhancement, a single solubilizer may prove toxic for human being but the combination of different excipients in safe smaller concentrations solves the problem of toxicity for same desired solubility of drug.[15-30]

In present research work mixed solvency concept has been employed to formulate vaginal film of poorly water soluble drug, metronidazole.

2.0 MATERIALS AND METHODS

2.1 Materials: Metronidazole was obtained as a gift sample from Schon pharmaceutical Limited, Indore.

2.2 Estimation of metronidazole:

2.2.1 UV spectropholometric analysis of metronidazole using 0.1 N HCl

A solution of 10µg/ml of metronidazole in 0.1 N HCl was scanned between 200 to 400 nm on a double beam UV/Visible spectrophotometer (Shimadzu 1700). The UV spectrum of metronidazole drug sample is shown in figure 1.

2.2.2 IR analysis of drug sample:

Metronidazole drug powder was compressed into a pellet along with KBr (KBr pellet technique) using Shimadzu hydraulic press. The FTIR spectrum of drug was recorded in the wave number region of 450-4000 cm^{-1} on a FTIR spectrophotometer (Shimadzu 8300) and presented in figure 2.

2.2.3 DSC analysis of drug sample:

The DSC study was performed on a Pyris 6 DSC (Jade DSC) differential scanning calorimeter with thermal analyzer. Accurately weighed samples (about 3 mg of samples) were placed in a sealed aluminum pan, before heating under nitrogen flow (20 ml/min) at a scanning rate of 20°C per min from 25 to 350° C. An empty aluminum pan was used as reference. The DSC spectrum of metronidazole drug sample is shown in figure 3.

2.3 Determination of solubility of metronidazole in different solvent medium

Solubility studies in different solvent mediums were carried out by adding an excess amount of drug metronidazole in 5 ml of respective medium and keeping the screw capped tubes containing these solutions, on a mechanical shaker at room temperature for 12 hrs, so that equilibrium solubility can be achieved and solutions were allowed to equilibrate for 24 hrs undisturbed. Then, the solutions were filtered through Whatman grade 41 filter. One ml of the filtrate was suitably diluted with the respective medium. The absorbances of the solutions were measured at 320 nm on a double beam UV/Visible spectrophotometer (Simadzu-1700) against respective reagent blanks. The results are recorded in table 2.

2.4 Study of interference of additives in UV spectrophotometric estimation of metronidazole

For determination of interference of additives in the spectrophotometric estimation of metronidazole, the absorbances of solution containing drug (20µg/ml) alone and solution containing drug (20µg/ml) and excipient (2000µg/ml) were recorded against respective reagent blank at 320 nm and results are shown in table 3. A UV-visible recording spectrophotometer (Shimadzu 1700) with 1 cm matched silica cells was employed for spectrophotometric determinations.

2.5 Formulation development of vaginal film:

2.5.1 Solubilizer selection

For the preparation of different blends of solubilizers (% w/v), niacinamide, sodium citrate, caffeine, HP beta cyclodextrin, PVP K 25 (film forming polymer), PEG 4000, propylene glycol, PEG 200, PEG 400, and glycerine were used. Total solute concentration was varied up to 40% w/v concentration and the % solubility of drug (metronidazole) was calculated. To decrease the individual concentration of solubilizers as well as individual toxicity of solubilizers, combinations of solubilizers in blend were used to increase the solubility of drug in various ratios. Solubility studies in different aqueous systems of solubilizers were carried out by equilibrium solubility method. The results of solubility studies are shown in table 4.

2.5.2 Polymer selection

For the development of fast dissolving film, HPMC E5, HPMC E50, sodium alginate, PVA, gelatine, CMC were used as film forming polymer (table 5). Blend composition NM:SB:UR:SC =15:10:10:5 (B1) and NM:SB:UR:CF =15:10:10:5 (B2) were selected for film formulation. (NM-Niacinamide, SC-Sodium caprylate, UR-Urea, SB-Sodium benzoate, CF-Caffeine)

Procedure for preparation of single film:

0.8ml blend was taken in a 5ml vial to which accurately weighed 40mg drug was added and covered with the closure then the vial was shaken well to dissolve the drug. Then 0.2 ml plasticizer (glycerine) and 200mg polymer was added to above solution and it was mixed properly using vortex mixer. Then, the film solution was kept undisturbed for 5 hours so as to remove the entrapped air bubble and for proper swelling of the polymer. Then the film solution was poured over a glass petridish and kept for drying at room temperature for 24 hrs.

2.5.2.1 Evaluation of casted polymeric film

a) Folding endurance

Folding endurance was determined by repeatedly folding the film at the same position until it breaks. The number of times the films can be folded without breaking is termed as the folding endurance value.

b) Thickness

The thickness of film was determined by the use of micrometer (Digimatic micrometer, Mitutoyo, Tokyo, Japan) at five locations (centre and four corners) and mean thickness was calculated.

2.8.2.2 Optimization of polymer concentration

Three batches of selected polymer (HPMC E-5) having different concentrations were prepared, casted and their film properties were studied. Results are shown in table 6.

2.5.3 Selection of plasticizer

Five batches of HPMC E-5 with different plasticizers (table 7) having concentration 20% v/v were prepared and casted, after proper drying the films were scrapped out and their film properties were studied.

2.5. 3.1 Optimization of plasticizer concentration

Several batches of HPMC E-5 with different concentration range 10%-20% of selected plasticizer glycerine were prepared by adjusting the blend concentration according to the concentration of selected plasticizer so as to get 100% v/v film solution. Then, the prepared batches were evaluated for film properties (table 8).

2.5.4 Optimized batch formula

According to the preliminary studies and studies of selection of excipients, 6 batches were optimized.

Table 1: Optimized blend for formulation development

S.No.	Batch code	Blend (8ml)	HPMC E5 (polymer) concentration	Glycerine (plasticizer) concentration	Drug used for 10ml film solution
1.	F1	B1	15%w/v	20%v/v	500mg
2.	F2	B1	17%w/v	20%v/v	500mg
3.	F3	B1	20%w/v	20%v/v	500mg
4.	F4	B2	15%w/v	20%v/v	500mg
5.	F5	B2	17%w/v	20%v/v	500mg
6.	F6	B2	20%w/v	20%v/v	500mg

2.5.4.1 Method of preparation of fast dissolving film:-

500 mg metronidazole was accurately weighed and dissolved in 8ml of respective solubilizer blend taken in a vial of 20ml capacity. Then, 20% v/v glycerine (as plasticizer) and respective concentration (15% or 17% or 20%w/v) of HPMC E-5 (as film forming polymer) were added and properly mixed using vortex mixer. The preparation was placed undisturbed for 5 hrs (for removal of entrapped air bubble and proper swelling of polymer) and then 5ml of prepared film solution was pipetted out and it was uniformly spread over glass petridishes and then kept for drying at room temperature for 24 hrs. After proper drying, films were cut into desired calculated dimension i.e. 3.5×3.5 cm^2 in which 40mg of metronidazole was present. At last they were wrapped in aluminium foils with sealing plastic bags and stored for further evaluations of films.

2.5.4.2 Evaluation parameters:-

a) In-vitro release studies

Release study of metronidazole film containing 40mg drug was performed by setting an assembly in which the film was placed in the beaker containing 30 ml of simulated vaginal fluid on a magnetic stirrer at 50 rpm. Five ml of dissolution media was withdrawn at regular intervals and fresh media was replaced immediately after withdrawal of sample. The sample was filtered and suitably diluted with demineralised water and then analysed in U.V. at 320nm and absorbance was noted against reagent blank (using placebo). Drug release is graphically represented in figure 4.

b) Surface pH

Film was taken and placed in a glass petridish containing 5 ml of simulated vaginal fluid. After wetting of the film, the surface pH of the film was checked by using pH electrode.

c) Disintegration time

10ml of demineralised water was placed in a beaker and one film was added on the surface of the water and it was shaken briskly. The time was measured until the film was dissolved completely.

d) Thin layer chromatography (TLC) analysis

TLC analysis was done to check any drug-solubilizer interaction (table 10). Acetone was used as solvent for preparation of standard solution of drug and test solution was prepared in aqueous blend of solubilizers. The mobile phase consisted of a mixture of 80 volumes of chloroform, 10 volumes of diethylamine, 10 volumes of ethanol, and 1 volume of water.

e) Stability study of optimized batches F1 and F4: Stability study of optimized film formulation was carried out for 10 weeks at 2-8°C (refrigerator) and 25°C±2°C (room temperature).

3.0 RESULTS AND DISCUSSION

3.1 Drug characterization:

3.1.1 UV spectrophotometric analysis of metronidazole: The UV spectrum of metronidazole drug sample was scanned between 200 to 400 nm. λ_{max} of metronidazole was found to be 277 nm which is same as reported in literature.

3.1.2 IR analysis of drug sample: The FTIR spectrum of drug sample had shown identical peaks as reported in reference sample of metronidazole.

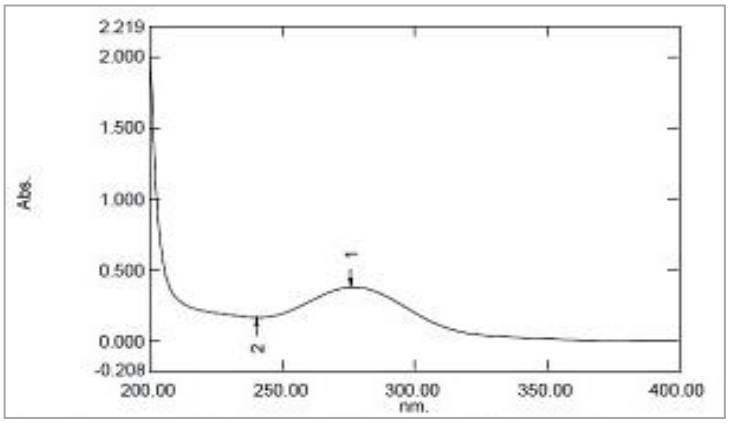

Figure 1: UV spectrum of metronidazole drug sample in 0.1M HCl

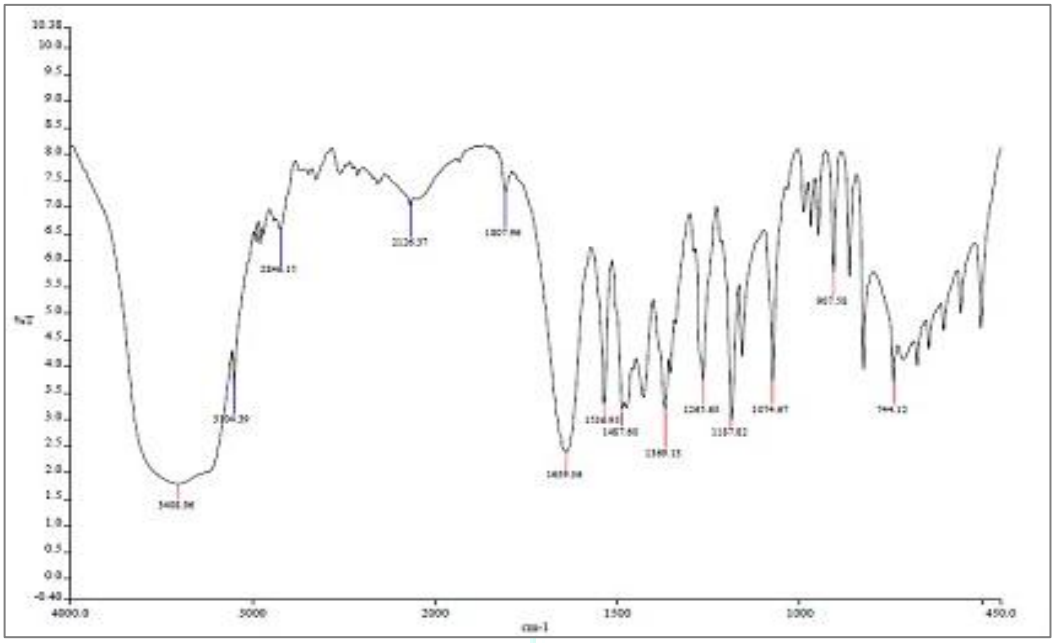

Figure 2: IR spectra of metronidazole

3.1.3 DSC analysis of drug sample: The DSC spectrum of metronidazole was same as reported in literature.

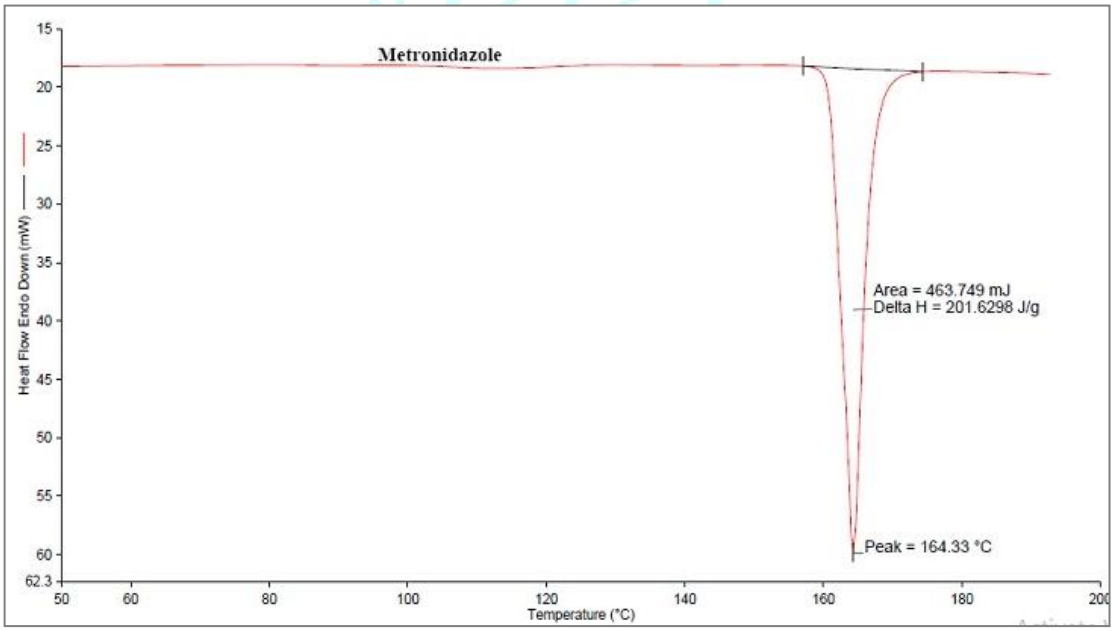

Figure 3: DSC spectrum of metronidazole drug sample

3.2 Determination of solubility of metronidazole in different solvent medium:

Table 2: Solubility data of metronidazole in different solvent medium

S. No.	Solvent systems	Solubility (mg/ml)	Inference
1.	Demineralized water	9.8	Slightly soluble
2.	Citrate buffer (pH 4.4)	9.3	Slightly soluble

3.3 Study of interference of additives in UV spectrophotometric estimation of metronidazole: Observing the results from table 3 of drug-excipients interference study, it was concluded that there is nearly no interference in UV spectrophotometric analysis of metronidazole due to excipients.

Table 3: Drug-excipient interference study

Drug	Excipient	Drug conc. (µg/ml)	Solubilizer conc. (µg/ml)	Lambda max (nm)	Absorbance
Metronidazole	-	20	-	320	1.037
Metronidazole	Sodium benzoate	20	2000	320	1.045
Metronidazole	Niacinamide	20	2000	320	1.041
Metronidazole	Urea	20	2000	320	1.043
Metronidazole	Sodium caprylate	20	2000	320	1.040
Metronidazole	Caffeine	20	2000	320	1.038
Metronidazole	PVP K 25	20	2000	320	1.041

3.4 Formulation development of vaginal film:

3.4.1 Solubilizer selection

Table 4: Solubility of drug in aqueous solutions containing various solubilizers

S.No.	Aqueous blend of solubilizers	Concentration (%w/v)	Solubility (mg/ml)	Solubility (%w/v)	Solubility enhancement ratio
1	DM water	---	9.80	0.98	---
2	PG	15	12.47	1.25	1.27
3	Glycerine	15	11.82	1.18	1.20
4	PEG 200	15	10.00	1.00	1.02
5	PEG 400	15	10. 12	1.01	1.03
6	PVP K 25	10	11.47	1.15	1.17
7	Urea	20	17.61	1.76	1.79
8	Sodium benzoate	20	27.94	2.79	2.48
9	Niacinamide	20	30.88	3.09	3.15
10	Sodium caprylate	20	15.14	1.51	1.54
11	PG:NM	20:20	34.07	3.41	3.47
12	PG:SB	20:20	26.19	2.62	2.67
33	PG:SC	20:20	19.11	1.91	1.94
14	GLY:NM	20:20	31.09	3.11	3.17
15	GLY:SC	20:20	16.66	1.67	1.70
16	GLY:SB	20:20	25.94	2.59	2.64
17	NM:SB	20:20	53.64	5.36	5.46
18	UR:SB	20:20	48.15	4.82	4.91
19	UR:NM	20:20	44.62	4.46	4.55
20	NM:SB:UR	20:10:10	36.74	3.67	3.74
21	SB:SC:NM	10:20:10	27.49	2.75	2.80
22	NM:SB:SC	10:20:10	37.96	3.80	3.87
24	NM:SB:UR:PEG 4000	15:10:10:5	41.01	4.10	4.18
25	NM:SB:UR:HBC	15:10:10:5	39.25	3.93	4.01
26	NM:SB:UR:CF	15:10:10:5	52.38	5.24	5.34
27	NM:SB:UR:PVPK25	15:10:10:5	40.30	4.03	4.11
28	NM:SB:UR:SC	15:10:10:5	50.94	5.09	5.19

NM-Niacinamide, SC-Sodium caprylate, UR-Urea, SB-Sodium benzoate, CF-Caffeine, HBC-Hβ cyclodextrin.

3.4.2 Polymer selection: HPMC E-5 was taken in further studies because it gave better film properties (table 5) compared to other polymers used to prepare the film.

Table 5: Evaluation of film properties

S.No.	Polymer	Physical appearance of film		Folding endurance	
		B1	B2	B1	B2
1	HPMC-E5	Transparent, flexible	Hazy, flexible	167	183
2	HPMC-E50	Transparent	Translucent	103	118
3	Sodium alginate	Opaque, Powdered on scrapping	Opaque, cracked	---	---
4	PVA	Transparent	opaque	55	73
5	Gelatin	Yellowish, translucent, cracked	Yellowish, hazy, hard, brittle	----	---
6	CMC	Opaque, hard, non-foldable	Opaque, brittle	---	---

3.4.2.1 Optimization of polymer concentration: On the basis of selection factors (table 6), 20% w/v concentration of HPMC E-5 was selected and was used in further formulation development studies.

Table 6: Properties of different concentrations of HPMC E-5

S.No	Property of film	Polymer					
		HPMC E5 (20%)		HPMC E5 (25%)		HPMC E5(30%)	
		B1	B2	B1	B2	B1	B2
1.	Pourability	Easy	Easy	Difficult	Difficult	Non pourable	Non pourable
2.	Appearance	Transparent	Hazy	Transparent	Hazy	---	---
3.	Thickness	0.05 mm	0.07 mm	0.09 mm	0.10 mm	---	---

3.4.3 Selection of plasticizer: On the basis of film properties and effect of plasticizer in polymeric film (table 7), glycerine was selected, it shows better results compared to other plasticizers.

Table 7: Effect of different plasticizers in polymeric casted film

S.No.	Plasticizer (20%v/v)	Polymer (20%w/v)	Appearance		Folding endurance	
			B1	B2	B1	B2
1	Glycerine	HPMC E5	Tranparent, flexible, easily peelable	Translucent, flexible, easily peelable	170	182
2	Propylene glycol	HPMC E5	Translucent, less flexible	Hazy, less flexible	80	103
3	PEG 200	HPMC E5	Hazy, less flexible	Hazy, less flexible	73	94
4	PEG 400	HPMC E5	White, non flexible	White, non flexible	---	---

3.4.3.1 Optimization of plasticizer concentration: On the basis of film properties (table 8), 20% v/v concentration of glycerine was optimized and used in further studies of formulation development.

Table 8: Effect of different concentrations of selected plasticizers in properties of polymeric film

S.No.	Plasticizer concentration (glycerine)	Appearance		Thickness (mm)		Folding endurance	
		B1	B2	B1	B2	B1	B2
1.	10%v/v	Hazy, hard, brittle	White, hard, brittle	0.04	0.03	---	---
2.	15%v/v	Translucent, flexible	Hazy, flexible	0.04	0.05	70	96
3.	20%v/v	Transparent, highly flexible	Translucent, highly flexible	0.05 mm	0.07 mm	175	186

3.5 Evaluations of optimized batches – On the basis of evaluation parameters (table 9) of different batches of films, batch F1 and batch F4 were found to be more appropriate and gave better results as compared to other batches.

Table 9: Evaluation of formulated film batches

S.No.	Batch	Thickness (mm) (average of 5 different positions)	Folding endurance (number)	pH	Disintigration time (sec)
1.	F1	0.06	173	4.67	57
2.	F2	0.08	103	4.73	70
3.	F3	0.12	68	4.80	82
4.	F4	0.08	186	4.69	60
5.	F5	0.09	125	4.76	76
6.	F6	0.11	34	4.82	89

3.5.1 Thin layer chromatography (TLC) analysis:

Table 10: TLC analysis of pure metronidazole and in blend of solubilizers

S.No.	Mobile phase	R_f value			Inference
		Standard solution	B1	B2	
1.	Chloroform:diethylamine: ethanol:water = 80:10:10:1	0.921	0.923	0.921	No significant change in R_f value hence no interaction between drug and solubilizers

3.5.2 In-vitro release studies: The % cumulative drug release of optimized batches F1 and F4 in simulated vaginal fluid in 60 minutes were found to be 99.82% and 99.77%, respectively (table 11).

Table 11: In-vitro drug dissolution profile of fast dissolving metronidazole film in simulated vaginal fluid.

S.No.	Time (min.)	% Cumulative drug release					
		F1	F2	F3	F4	F5	F6
1.	2	46.73	23.78	21.40	41.71	34.28	30.46
2.	5	67.79	44.63	34.81	47.81	48.82	49.60
3.	10	83.81	62.28	47.05	66.76	73.81	63.56
4.	15	94.36	69.27	52.03	81.55	85.81	91.91
5.	30	98.72	79.67	65.36	86.64	93.47	91.68
6.	45	99.61	91.68	73.71	94.77	94.56	84.60
7.	60	99.82	96.50	91.16	99.77	88.71	84.40

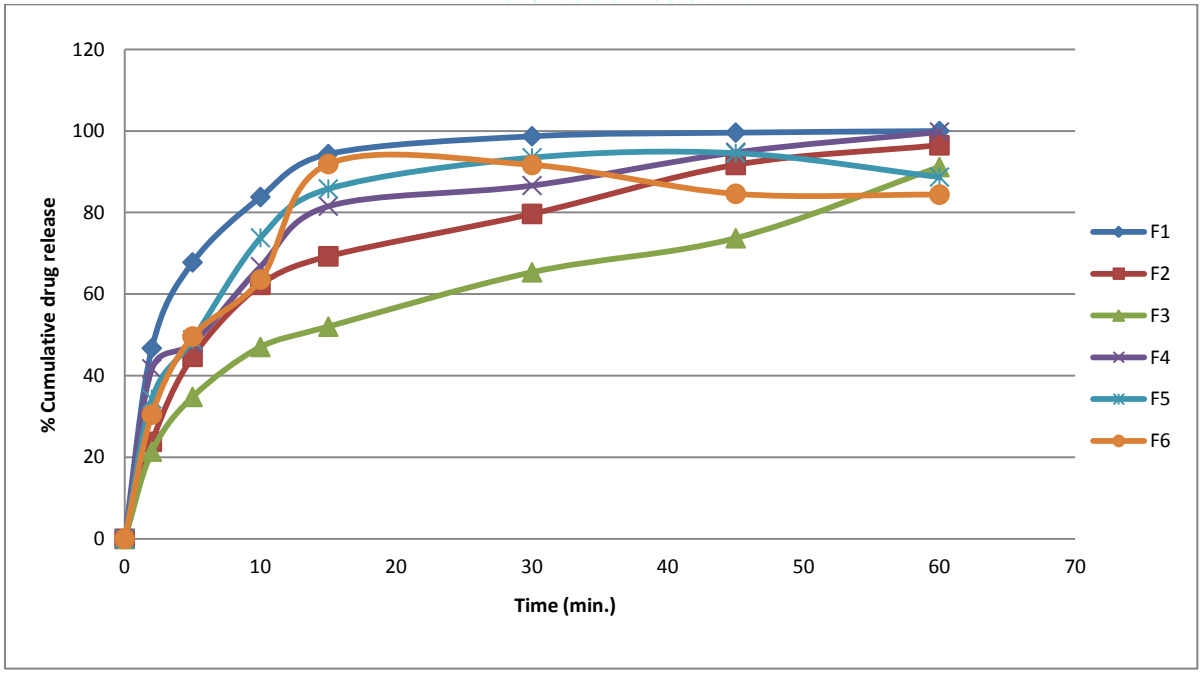

Figure 4: Graphical representation of % cumulative drug release in simulated vaginal fluid

3.5.3 Stability study of optimized batches F1 and F4:

The developed film of metronidazole was found to be stable for ten weeks at room temperature as well as refrigerated condition. It was found that 97.54% and 97.58% of drug was remaining after stability study at respective temperatures in batch F1 and 98.53% and 96.57% in batch F4.

4.0 CONCLUSION

In the present study, metronidazole, a slightly soluble drug in water was tried to be solubilized by employing the combination of physiologically compatible solubilizers to endeavour its fast dissolving formulations. Amongst all the batches, F1 and F4 batches of prepared fast dissolving films showed better in-vitro dissolution profile, disintegration time and were selected for stability studies. It was found to be stable for 10 weeks. The loading of drug got increased and hence the area of film was reduced. From all the above studies, it was concluded that the approach of mixed solvency concept is novel, safe, cost-effective and user friendly. It also eliminates the problem of toxicity associated with high concentration of water-soluble solubilizers. So, it may be employed in dosage form development of drugs where fast onset of action is required.

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