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FORMULATION DEVELOPMENT OF FAST DISSOLVING FILM

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ABSTRACT

Conventional vaginal delivery systems are somewhat effective; however, they still offer several disadvantages which we need to encounter in order to deliver anti-fungal therapy in an efficacious way. Disadvantages associated are leakage and messiness as in case of creams and gel, uncomfortable, efficacy is quite low as gels may not provide an exact dose because of non-uniformity and leakage, poor patient compliance, prolonged duration of therapy, low bioavailability, drug release pattern is inappropriate On the basis of film properties, 20% v/v concentration of glycerine was optimized and used in further studies of formulation development. On the basis of evaluation parameters 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. The % cumulative drug release of optimized batches F1 and F4 in simulated vaginal fluid were found to be 99.82% and 99.77% in 60 minutes respectively. The developed film of metronidazole was found to be stable for ten weeks.

INTRODUCTION

Generally vaginal films are manufactured by solvent casting technique which is a six step process. In this process initially the film mass is prepared either by dissolution or dispersion of the API and other excipients which are required in the formulation, in a suitable solvent. During homogenization and mixing step the air may get entrapped in the film mass which can be eliminated by sonication process. The prepared film mass is then poured onto a plane and smooth surface so as to allow the film mass to distribute uniformly which will lead to efficient evaporation of solvent. The process of drying occurs either at room temperature or it can be accelerated by heating directly in ovens. After drying the film mass, cutting of films takes place. An alternate method of preparing individual film is by directly pouring the film mass in individual film molds. Different kinds of films may be designed having varying

configuration and dimensions to get the required therapeutic effect. At the final stage, packaging is done which provides stability during storage for future use and for further analysis.[8]

The formulation of vaginal films include the drug (API) and excipients such as polymers which are generally water soluble, plasticizers, colouring and flavouring agents. The property of selected polymer is that it should be safe, non-irritant, devoid of any leachable impurity, have good wettability and spreading property, provide easy peelability to films, with good tensile strength; and provide economic manufacturing and packaging of films. Various polymers used in formulation are polyethylene glycol, polyacrylates, polyvinyl alcohol, and cellulose derivates. Polymer selection should be done carefully because its molecular weight can influence the properties of the film like disintegration time and mechanical strength. The plasticisers are included in formulation because they (e.g., glycerine, polyethylene glycol) provide flexibility to the film and provide them adequate texture. Disintegrating agents are used to enhance dissolution speed example veegum, cross-linked PVP, crosscarmellose sodium.

Preparation of aqueous solutions of excipients

For the preparation of different composition of excipients (% w/v), caffeine, HP beta cyclodextrin, PVP K 25(film forming polymer), PEG 4000, propylene glycol, PEG 200, PEG 400, glycerine etc. were weighed/measured and taken in a volumetric flask and about 100 ml of D.M. water was added in this flask and was shaken to achieve complete dissolution of excipients. Then volume was made up to 100 ml by D.M. water. Glycerine and propylene glycol were used for development of fast dissolving film since the drug was having better solubility in the compositions containing these excipients as compared to other excipients. On the basis of solubility studies, compositions containing four excipients were selected for further studies because of low individual toxicity of excipients and achieved desired required solubility of drug (40mg/ml).

Water soluble polymers are used as film forming polymers. For the development of fast dissolving film, water soluble polymer is one of the most important ingredients. Polymer properties affect the properties of film. HPMC- hydroxy propylmethyl cellulose, PVA- polyvinylalcohol, CMC- carboxymethyl cellulose.

Preparation of single film 0.6ml composition was taken in a 5ml vial to which accurately weighed 20mg 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.

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. HPMC E-5 was taken in further studies because it gave better film properties compared to other polymers used to prepare the film.

Table: Evaluation of film properties.

S.No.	Polymer	Physical appearance of film	
		A1	A2
1	HPMC-E5	Transparent, flexible	Hazy, flexible
2	HPMC-E50	Transparent	Translucent
3	Sodium alginate	Opaque, Powdered on scrapping	Opaque, cracked
4	PVA	Transparent	opaque
5	Gelatin	Yellowish, translucent, cracked	Yellowish, hazy, hard, brittle
6	CMC	Opaque, hard, non-foldable	Opaque, brittle

HPMC - hydroxy propylmethyl cellulose, PVA - polyvinylalcohol, CMC - carboxymethyl cellulose.

Optimization of Polymer Concentration

Three batches of selected polymer (HPMC E-5) having different concentrations were prepared, casted and their film properties were studied. On the basis of selection factors, 20%

w/v concentration of HPMC E-5 was selected and was used in further formulation development studied.

Selection of Plasticizer

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

Table: Effect of different plasticizers in polymeric casted film.

S.No.	Plasticizer (20%v/v)	Polymer (20%w/v)	Appearance		Folding endurance	
			A1	A2	A1	A2
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	---	---

Result and Discussion- On the basis of film properties and effect of plasticizer in polymeric film, glycerine was selected, it shows better results compared to other plasticizers.

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 composition 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. On the basis of film properties, 20% v/v concentration of glycerine was optimized and used in further studies of formulation development.

Method of preparation of fast dissolving film

500 mg metronidazole was accurately weighed and dissolved in 8ml of respective solubilizer composition 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.

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 diluted with demineralised water and then analysed in U.V. at 320nm and absorbance was noted against reagent blank (using placebo).

b) % Drug content determination

It was determined by taking one- half of film by weight (metronidazole 20mg) in 1000 ml volumetric flask and dissolved in about 900ml demineralised water and then volume was made upto 1000 ml with demineralised water. Then absorbance of this solution was noted at 320 nm and then from it the concentration of drug in whole film was calculated and % drug content with respect to 40mg/ 12.0736 cm^2 was calculated.

% drug content= (practical value/ theoretical value) × 100

c) 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.

d) 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.

Table: Evaluation of formulated film batches.

S. No.	Batch	Thickness (average of 5 different positions)	Folding endurance (number)	pH	Disintigration time (sec)
1.	F1	0.07	162	4.60	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

Table: 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

On the basis of evaluation parameters 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. So batches F1 and F4 were taken as optimized batches and dissolution profile of batches F1 and F4 were shown in figure 28 below.

The % cumulative drug release of optimized batches F1 and F4 in simulated vaginal fluid were found to be 99.82% and 99.77% in 60 minutes respectively.

CONCLUSION

The blends of solubilizers of total strength 40% w/v were used in selected final blends to get sufficiently expected solubilities. The maximum synergistic effect was observed in the blend containing sodium benzoate, niacinamide, urea, sodium caprylate, and caffeine. For the development of fast dissolving film, different film forming polymers, plasticizers were tested. According to the mechanical properties, pH and disintegration time of film, they were selected and optimized. From selected and optimized ingredients, six batches of fast dissolving film containing 4mg dose of drug per 3.5×3.5 cm^2 were developed and evaluated for thickness, folding endurance, pH, disintegration time, in-vitro dissolution profile.

Amongst all the batches, F1 and F4 batches of prepared fast dissolving film showed better invitro 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 by reducing the area of film. 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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