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Original Research Article

FORMULATION AND CHARACTERIZATION OF FAST DISSOLVING ORAL FILM OF AN ANTIEMETIC DRUG APREPITANT

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ABSTRACT

This study aimed to develop and characterize fast dissolving oral films (FDOFs) of the antiemetic drug Aprepitant to enhance its solubility and dissolution rate, thereby improving its bioavailability and therapeutic efficacy. Aprepitant, a BCS Class II drug, was formulated into FDOFs using different polymer ratios. The films were evaluated for general appearance, thickness, weight, mechanical properties, disintegration time, drug content, and *in-vitro* drug release. The optimized formulation (F7) exhibited excellent transparency, optimal thickness (51±5 µm), and appropriate weight (115±3 mg). It demonstrated the highest folding endurance (245±4 times), shortest disintegration time (36±4 seconds), and rapid drug release (99.65% cumulative release at 10 minutes). The drug release kinetics followed a first-order model (r^2 = 0.999), indicating a concentration-dependent release mechanism. The results confirm that FDOFs of Aprepitant can significantly enhance its solubility and dissolution rate, offering a promising alternative to conventional oral dosage forms for improved patient compliance and efficacy in managing nausea and vomiting.

Key Words: Aprepitant, Fast Dissolving Oral Films (FDOFs), Solubility enhancement Dissolution rate**,** Antiemetic drug

INTRODUCTION

Nausea and vomiting are common symptoms associated with various conditions such as chemotherapy, surgery, and motion sickness. Aprepitant, an antiemetic drug, is widely used to manage these symptoms, particularly in chemotherapy-induced nausea and vomiting (CINV). However, conventional oral dosage forms of aprepitant, such as tablets and capsules, may present challenges like delayed onset of action and difficulty in swallowing, especially for patients experiencing nausea. To overcome these limitations, the development of fast dissolving oral films (FDOFs) offers a promising alternative. FDOFs are thin strips that rapidly disintegrate in the mouth without the need for water, providing a convenient and efficient drug delivery system (Bala *et al.,* 2013; Arya *et al.,* 2010). Fast dissolving oral films have gained significant attention due to their ease of administration, rapid onset of action, and improved patient compliance. These films are particularly beneficial for pediatric, geriatric, and dysphagic patients who have difficulty swallowing conventional solid dosage forms (Seager, 1998; Kunte & Tandale, 2010). Moreover, FDOFs enhance the bioavailability of drugs by facilitating their direct absorption through the oral mucosa, bypassing the first-pass metabolism (Peh & Wong, 1999).

The formulation of FDOFs involves the incorporation of the drug into a polymeric matrix, which dissolves or disintegrates upon contact with saliva (Dixit & Puthli, 2009).

Various polymers, plasticizers, sweeteners, and flavoring agents are used to optimize the film's mechanical properties, taste, and patient acceptability (Bhowmik *et al.,* 2009). Aprepitant's poor solubility and bioavailability necessitate the use of solubilizing agents or techniques to enhance its dissolution rate and therapeutic efficacy in FDOFs (Singh *et al.,* 2008).

The objective of this study is to formulate and characterize fast dissolving oral films of aprepitant to improve its solubility, dissolution rate, and patient compliance. The study will involve the selection of suitable polymers and excipients, preparation of the films using the solvent casting method, and evaluation of their physicochemical properties, drug content, dissolution profile, and stability.

MATERIALS AND METHODS

Formulation development of fast dissolving oral film of Aprepitant

Drug (Aprepitant) containing fast dissolving films were fabricated by the solvent casting method. HPMC is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely HPMC K4, and HPMC K15 were evaluated as film formers. For the fabrication of films, glycerin was used as a humectant. PEG 400 is also reported as lubricant and solubilizer. Therefore PEG 400 along with glycerol was also used for fabrication of films. Apart from these film formers, SSG (Sodium starch glycolate), CP (Crospovidone) and CCS (croscarmellose sodium) alone or in combination with each other along with other excipients were tried. Citric acid for saliva stimulating agent and mannitol as sweeteners used to fabricate the films. The composition of various formulations is given in Table 1. The polymer was soaked in water for 30 min or heated in water bath to 80° to get a clear solution. Then a plasticizer was added to it and mixed so as to get homogeneous solution. This solution was then casted onto glass moulds (15*5cm) and was dried in hot air oven at 45° for 24 h.

Evaluation of prepared Film

Thickness

The thickness of patches was measured at three different places using a vernier caliper (Mahajan *et al.,* 2011).

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated (Nagar *et al.,* 2014).

Folding Endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance (Pathan *et al.,* 2016).

Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight (Bhyan *et al.,* 2010).

Drug content analysis

The film taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and reacted by UV spectrophotometer at 276nm (Murata *et al.,* 2010).

Disintegrating time

The most important criteria of present work is that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent was done to minimize the disintegrating time. Three super disintegrating agent were selected for this work (Koland *et al.,* 2010).

In vitro dissolution study

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5°C with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was used (Schimoda *et al.,* 2009). Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 4, 6, 8, and 10 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved drug was determined using UV-Visible spectrophotometer at 276nm. The results were presented as an average of three such concentrations.

RESULTS AND DISCUSSION

The formulation and characterization of fast dissolving oral films (FDOFs) of the antiemetic drug aprepitant involved evaluating various parameters to ensure optimal performance and patient acceptability. The study aimed to enhance the solubility and dissolution rate of aprepitant, a BCS Class II drug, to improve its bioavailability and therapeutic efficacy.

The prepared films (F1-F9) were all transparent, indicating uniformity in their appearance. The thickness of the films ranged from 45 µm to 58 µm, with formulation F6 having the highest thickness (58±5 µm) and F1 the lowest (45±4 µm). The weight of the films varied from 105 mg to 120 mg, with F6 being the heaviest (120±2 mg) and F1 the lightest (105±6 mg). These variations in thickness and weight are within acceptable ranges, ensuring consistency in drug content and mechanical properties.

Folding endurance, disintegration time, tensile strength, percentage moisture content, and drug assay were evaluated for all formulations. Formulation F7 showed the highest folding endurance (245±4 times) and one of the shortest disintegration times (36±4 seconds), indicating good flexibility and rapid disintegration, which are desirable characteristics for FDOFs. The tensile strength of the films ranged from 0.32 kg/cm² (F3) to 0.85 kg/cm² (F4), reflecting the robustness of the films. The percentage moisture content was relatively consistent, ensuring stability and preventing brittleness. Drug content assay values were close to 100%, indicating uniform distribution of aprepitant within the films.

The *in-vitro* drug release profiles of formulations F1-F9 demonstrated varying degrees of cumulative drug release over a 10-minute period. Formulation F7 exhibited the fastest and most complete drug release, with

99.65% cumulative release at 10 minutes. This rapid release profile is beneficial for achieving quick onset of action, which is crucial for antiemetic drugs used to manage acute nausea and vomiting.

The drug release kinetics of the optimized formulation F7 was analyzed using various models. The regression coefficient (r^2) values indicated that the drug release from F7 followed first-order kinetics (r^2 = 0.999), suggesting that the rate of drug release is concentration-dependent. The Higuchi model (r^2 = 0.871) and Peppas model (r^2 = 0.918) also provided a good fit, indicating that the drug release mechanism involved both diffusion and erosion processes.

The comparative study of the regression coefficients for the optimized batch F7 confirmed that the first-order kinetic model was the best fit for describing the drug release profile. This implies that the release rate of aprepitant from the FDOFs is proportional to the remaining concentration of the drug, providing a controlled release mechanism suitable for managing symptoms of nausea and vomiting.

Table 1: Selection and optimization of film forming agents

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F8
Aprepitant	960	960	960	960	960	960	960	960	960
HPMC K4	50	100	150				25	50	75
HPMC K15				50	100	150	25	50	75
PEG-400	50	50	50	50	50	50	50	50	50
SSG	50	100	-	-	-	-	25	-	25
CCS	-	-	50	100	-	-	25	25	-
CP	-	-	-	-	-	-	-	25	25
Mannitol	50	50	50	50	50	50	50	50	50
Citric acid	30	30	30	30	30	30	30	30	30
DM water qs to (ml)	30	30	30	30	30	30	30	30	30

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 films present whole plate = 12
- Each film contains 80 mg of drug.
- 12 no. of films contains mg of drug = 80×12 = 12mg

The amount of Aprepitant added in each plate was approximately equal to 12mg.

Table 2: Evaluation of prepared film for general appearance, thickness and weight

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	45±4	105±6
F2	Transparent	49±3	108±7
F3	Transparent	52±5	109±5
F4	Transparent	47±6	108±4
F5	Transparent	53±4	112±7
F6	Transparent	58±5	120±2
F7	Transparent	51±5	115±3
F8	Transparent	52±3	118±7
F9	Transparent	56±2	114±4

***Average of three determination (n=3±SD)**

Table 3: Result of Folding Endurance, Disintegrating time, Tensile strength, Percentage Moisture Content and % Assay

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	195±5	63±2	0.65±4	7.12±3	96.65±0.12
F2	210±4	55±1	0.74±6	6.58±2	98.85±0.25
F3	225±7	48±2	0.32±2	7.95±4	96.65±0.36
F4	199±5	76±2	0.85±3	6.95±8	98.88±0.45
F5	236±6	63±3	0.79±5	7.12±5	97.78±0.21
F6	189±5	59±3	0.68±2	6.88±2	96.65±0.32
F7	245±4	36±4	0.73±2	6.95±4	99.45±0.47
F8	182±3	53±2	0.65±2	5.12±2	97.74±0.25
F9	168±4	54±2	0.74±4	6.98±3	96.65±0.44

Table 4: *In-vitro* drug release study of Formulation F1-F9

Time (Min.)	Cumulative % Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	23.65	25.65	27.85	22.65	25.65	38.85	39.85	35.65	34.65
2	46.65	49.96	52.32	43.36	48.98	43.36	63.32	55.65	55.56
4	53.32	63.32	65.65	50.47	53.32	56.65	88.98	69.98	69.85
6	69.98	75.85	78.98	64.45	69.98	79.98	96.66	82.25	76.65
8	82.25	89.98	93.32	80.36	84.45	86.65	98.85	91.74	90.32
10	89.78	93.32	94.77	86.65	89.98	92.45	99.65	93.74	95.65

Table 5: Results of *in-vitro* release Kinetics of optimized formulation F7

Time (min.)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0	39.85	1.60042833	60.15	1.779
2	1.414	0.301	63.32	1.80154091	36.68	1.564
4	2.000	0.602	88.98	1.9492924	11.02	1.042
6	2.449	0.778	96.66	1.98524679	3.34	0.524
8	2.828	0.903	98.85	1.99497667	1.15	0.061
10	3.162	1	99.65	1.9984773	0.35	-0.456

Table 6: Comparative study of regression coefficient for selection of optimized batch F7

Zero order		First order	Higuchi	Peppas model
r^2	0.762	0.999	0.871	0.918

CONCLUSION

The study successfully formulated and characterized fast dissolving oral films of aprepitant with enhanced solubility and dissolution rates. The optimized formulation F7 demonstrated excellent mechanical properties, rapid disintegration, and superior drug release profile. These characteristics make FDOFs a promising alternative to conventional oral dosage forms for improving the bioavailability and patient compliance of aprepitant. Further studies, including in-vivo evaluations, are recommended to confirm the clinical efficacy and safety of the developed films.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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