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Research Article

FORMULATION OPTIMIZATION AND EVALUATION OF MOUTH DISSOLVING FILM OF APREPITANT

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ABSTRACT

Objectives: The aim of the present research is to prepare mouth dissolving film of aprepitant used in the prevention and treatment of post-operative nausea and vomiting.

Methods: The MDF was prepared using Kollicoat IR, PEG 400, and spraying technique. Formulation was optimized by central composite design. Compatibility study was carried out using Fourier-transform infrared and differential scanning calorimetry. The films were evaluated for thickness, folding endurance, weight variation, disintegration time, dissolution studies, drug content, and *in vitro* diffusion test.

Results: From the results, it was found that there was no drug excipient interaction. The prepared optimized batch AP2 showed disintegration time 18 sec, highest dissolution rate 101.53%, drug diffused 39.58 mg/cm^2 within 10 min and also passes all the physicochemical parameters. It was concluded that plasticizer PEG 400 plays a very much important role in the preparation of aprepitant MDF.

Conclusion: MDF of aprepitant was found to be a better option in the prevention and treatment of post-operative nausea and vomiting by the way of fast onset of action for patient convenience and compliance. In the near future, the MDF market will expand very fastly to treat various diseases.

Keywords: Aprepitant, Kollicoat IR, PEG-400, Mouth dissolving film, Spraying technique, Central composite design.

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INTRODUCTION

Oral delivery is currently the gold standard in the pharmaceutical industry, where it is regarded as the safest, most convenient, and most economical method of drug delivery having the highest patient compliance. However, the problem associated with oral route of administration is first-pass metabolism, drug degradation in variable pH condition of gastrointestinal tract, inadequate absorption, slow onset of action, and drawbacks related to particular class of patients which includes geriatric, pediatric, and dysphagia patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. To overcome these issues, fast dissolving drug delivery systems are gaining considerable attention. Fast disintegrating drug delivery systems are an alternative to tablets, syrups, and capsules, for pediatric and geriatric patients who rapidly disintegrate and dissolve in saliva and then easily swallowed without the need of water which is a major benefit over conventional dosage form. It consists of a fast dissolving tablet and fast dissolving film. Moreover, FDTs usually have insufficient mechanical strength, so careful handling is required. To protect the dosage form and to overcome such problems, new technology was developed as fast dissolving oral films [1-6].

Mouth dissolving films are the most advanced form due to more flexibility and comfort. It improves the efficacy of the drug by dissolving within a minute in the oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability. MDF is a postage stamp size polymeric film which contains active pharmaceutical ingredient and excipients. When placed on the patient's tongue it rapidly disintegrates/disperse and releases the drug when it comes in contact with saliva, with an *in vitro* disintegration time of approximately 30 s or less.

Post-operative nausea and vomiting (PONV) is one of the complex and significant problems in anesthesia practice, with a growing trend toward ambulatory and daycare surgeries. It is a common complication of surgery and anesthesia. Although it is rarely fatal, PONV is unpleasant and associated with patient discomfort and dissatisfaction with their perioperative care. Patients have reported that avoidance of PONV is of greater concern than avoiding post-operative pain. PONV is also associated with delayed discharge from the recovery room and prolonged hospital care and, therefore, increases health-care costs. Morbidity associated with PONV includes wound dehiscence, dehydration, electrolyte disturbance, interference with nutrition and, more rarely, esophageal rupture (Boerhaave syndrome) or aspiration pneumonitis. Aprepitant is an antiemetic chemical compound that belongs to a class of drugs called substance P antagonists. It mediates its effect by blocking the neurokinin 1 receptor. Aprepitant is useful in the prevention of acute and delayed chemotherapy-induced nausea and vomiting and for prevention of PONV. It was approved by the FDA in 2003. Aprepitant may also be useful in the treatment of cyclic vomiting syndrome [7].

The drug belongs to BCS Class IV (low solubility and low permeability). There is a need to improve the solubility and dissolution rate of the drug. The micellar solubilization technique was used to improve the solubility and dissolution rate of the drug. In which sodium lauryl sulfate was used in the concentration of 1% w/v. SLS is an ionic surfactant. The most important property of surfactant is the formation of micelles in solution, which have particular significance in medicine because of their ability to enhance the solubility of poorly, water-soluble drugs. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. The use of surfactants to improve the dissolution of lipophilic drugs in an aqueous medium.

MATERIALS AND METHODS

Aprepitant was obtained as a gift sample from Glenmark, Sikkim, India. Kollicoat IR is obtained as a gift sample from Transchem, Bhiwandi, Mumbai, India. PEG-400, Citric acid, aspartame, raspberry red, and vanilla flavor were purchased from Jinendra Scientific, Jalgaon, India.

Compatibility studies

Identification of drug and polymer by Fourier-transform infrared (FTIR)

Started the instrument and initialise the software. Fixed the ATR unit in the compartment and cleaned the surface of the crystal using solvent, set the process parameter such as number of scans, resolution, and wavelength range. Background scan was taken. Placed the sample on the crystal and pressure was applied to have proper contact between crystal and sample. The sample was scan. Generated spectrum was analyzed.

Identification of drug and polymer by differential scanning calorimetry (DSC)

3–5 mg of sample was weighed on weighing balance. Crimped the sample pan with lead using crimping tool. Put reference and sample pan in the DSC detector. TAWS collection monitor software was opened and set the temperature program. Gave the details related to sample in file information and started the program. After the program is over, the obtained thermogram was analyzed.

Preparation of standard curve of aprepitant in phosphate buffer pH 6.8 containing 1% SLS

10 mg of aprepitant was weighed and dissolved in phosphate buffer pH 6.8 containing 1% SLS and volume was made up to 100 ml in a volumetric flask to get 100 µg/ml solution. From this solution, 0.2 ml solution was pulled out and diluted up to the 10 ml by phosphate buffer ph 6.8 containing 1% SLS to get 2 µg/ml solution, likewise 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, and 12 µg/ml solutions were prepared. The absorbance of each solution was measured at 210 nm using UV-visible spectrophotometer (Shimadzu-1800) and phosphate buffer pH 6.8+1% SLS used as a reference standard, and the standard curve was generated.

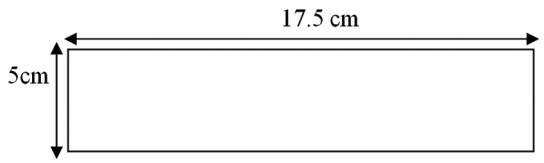
Methods

Preparation of mouth dissolving film of aprepitant by spraying technique

All the ingredients were weighed properly. Weighed Kollicoat IR was dissolved in 5 ml of distilled water under the constant stirring until the solution becomes clear. Remaining excipients such as aspartame and citric acid were dissolved in the above polymeric solution under constant stirring up to the formation of clear solution. Aprepitant was dissolved in sufficient quantity of ethanol and transferred the same into the polymeric solution. Raspberry red was dissolved in a little amount of water, then added into the polymeric solution under constant stirring to get a homogenized solution. Then, vanilla flavor was added under constant stirring for 5–10 min.

Above solution was added in a spraying gun and frequently sprayed the solution on the rectangle glass plate and intermittently dried using hot air blower at a temperature 30–35°C. The dried film was peeled off from the glass plate. Then, the film was cut into the desired size and shape (2.5×3.5 cm) and evaluated. Prepared mouth dissolving films of aprepitant are presented in Fig. 1.

Calculation of aprepitant loaded in the film



Surface area of TLC plate = Length×Height
= 5×17.5 = 87.5 cm^2

Each film surface area = 2.5×3.5
= 8.75 cm^2

8.75 cm^2 contain = 40 mg aprepitant

Therefore, 87.5 cm^2 contain = 400 mg aprepitant

Aprepitant is a highly insoluble drug, after adding 400 mg of drug in 900 mg Kollicoat IR, film reduces its elasticity and tensile strength, and the prepared film was not easily peelable and brittle in nature. Hence, increased the concentration of Kollicoat IR from F2 to F7 batches but the problem was not solved and hence decided to add plasticizer (PEG 400) to enhance the elasticity as well as strength of the film. The data are reported in Table 1.

Based on preliminary trials, two factors and three levels central composite design was employed by using design expert software to study the effect of independent variables on dependent variables. Thirteen runs were generated, among which one formulation was repeated four times then for the repeated formulation considered one formulation for further study and hence study was done on nine formulations. The data are reported in Table 2.

Evaluation parameters for aprepitant MDF

Weight variation test

The cast film was cut at different places and the weight of each film was checked with the help of an electronic weighing balance and the average weight was calculated [8].

Thickness test

The thickness of the film was measured by digital Vernier caliper at different position of the film (four corners and one center), and the average thickness was calculated [9].

Folding endurance

The folding endurance is expressed as the number of folds (number of times of film is folded at the same plain) required breaking the specimen or developing visible cracks. This gives an indication of the brittleness of the film. A small strip of 4 cm^2 was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed [10].

Surface pH

The film to be tested was placed in a Petri dish and moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the film and allowed to equilibrate for 1 min [11].

In vitro wetting time

A circular tissue paper was cut as per the size of the Petri plate. 1.1% w/v methylene blue solution was prepared and added to the Petri plate. The film was placed into the Petri plate. The time required for the dye to appear on the surface of the film was noted as the wetting time. *In vitro* wetting time of aprepitant film is presented in Fig. 2 [11].

In vitro disintegration test

A film of 2.5 cm×3.5 cm was cut and was put in the beaker containing 50 ml distilled water. The time when the film was completely disintegrated noted as disintegration time. The standard value of disintegration time is 5–30 s for the mouth dissolving film as per CDER [8,12].

Drug content

The drug content of all the optimized batches was determined by UV-Spectrophotometric method. For this, 2.5 cm×3.5 cm film from each batch was cut and dissolved in 100 ml of phosphate buffer pH 6.8+1% SLS. Then, from this solution, 1 ml was pulled out and diluted to 50 ml with the same solvent. Then, the solution was filtered through Whatman filter paper. The resulting solution was measured

spectrophotometrically at 210 nm. The drug content was calculated using the following formula.

$$\text{Drug content} = \frac{\text{Test absorbance}}{\text{Standard absorbance}} \times \text{Standard dilution} \times \text{Test dilution} \times 100$$

Moisture uptake

It was determined by placing aprepitant MDF (2.5 cm×3.5 cm) in a desiccator for 24 h to ensure the complete drying of the film before the actual test. 500 ml saturated solution of sodium chloride was poured in a desiccator. The film was then weighed in dry form and further placed the Petri plate containing MDF in a desiccator whose relative humidity was maintained at 75% for 1 week. The percentage relative humidity in the desiccator was measured using a digital hygro thermometer. Then, after the 1 week, aprepitant MDFs were reweighed and percentage weight increased due to moisture uptake was noted.

$$\text{Percentage of moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

In vitro drug release test

In vitro drug release study was carried out using a dissolution apparatus USP type II (paddle). The volume of dissolution medium 300 ml phosphate buffer pH 6.8+1% SLS used. The temperature was maintained at 37°C±0.5°C, and 50 RPM was set. Samples were withdrawn at suitable time intervals of 1 min–10 min and replaced with an equal amount with the same dissolution medium. The percentage drug release was determined by measuring the absorbance in UV spectrophotometer at 210 nm. Percentage DR was calculated using the following formula,

$$\%\ DR = \frac{\text{Test absorbance}}{\text{Standard absorbance}} \times \text{Standard dilution} \times \text{Test dilution} \times \frac{\text{Purity}}{\text{Label claim}}$$

In vitro diffusion studies

In vitro diffusion study was carried out using three-stage modified Franz diffusion cell having an internal diameter 2.5 cm. The cellophane membrane was mounted between the donor and the receptor compartment. In the donor compartment, MDF of aprepitant was placed. Receptor compartment filled with 20 ml of simulated salivary fluid of pH 6.8 containing 1% sodium lauryl sulfate, which was maintained at 37°C±2°C, and hydrodynamics was maintained using a magnetic stirrer. Samples (2 ml) were withdrawn from the receptor compartment (phosphate buffer pH 6.8+1% SLS) at suitable time intervals of 1 min and replaced with an equal amount in the receptor compartment with same diffusion medium. The percentage amount of drug diffused in the receptor compartment was determined by measuring the absorbance in UV spectrophotometer at 210 nm [13,14].

RESULTS AND DISCUSSION

Ultraviolet spectroscopy analysis

It was observed that the concentration range of 2-12 µg/ml obeyed the beers-lamberts law. The correlation coefficient was found to be R^2=0.999. Slope was found to be 0.036. The calibration curve of aprepitant is presented in Fig. 3.

Compatibility studies

Compatibility study by FTIR and DSC

The compatibility study between aprepitant and its physical mixtures with formulation excipients was carried out using FTIR spectrometer and is presented in Figs. 4-6.

The physical mixture of aprepitant and excipients was subjected to FTIR to identify any interaction between them. There was no appearance or disappearance of any characteristic peak of the aprepitant, which confirms the absence of chemical interaction between aprepitant and carrier. Hence, the excipient Kollicoat IR, which was observed to be compatible with aprepitant, was selected for further development of the formulation.

Compatibility studies by DSC

An endothermic peak was observed for the aprepitant at 253.39°C, and an endothermic peak was observed for the Kollicoat IR at 216.49. In

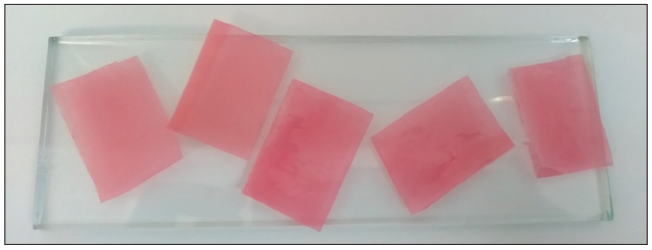


Fig. 1: Mouth dissolving film of aprepitant

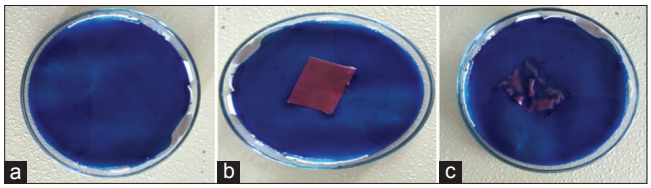


Fig. 2: (a-c) *In vitro* wetting time of aprepitant MDF

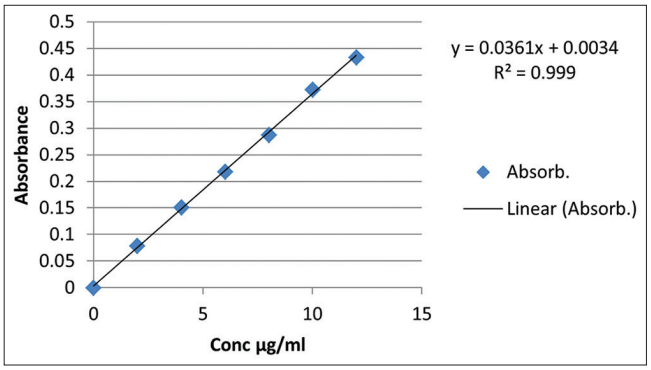


Fig. 3: Calibration curve of aprepitant

Table 1: Preliminary trial batches of aprepitant mouth dissolving the film

S. No.	Ingredient	Batches						
		F1	F2	F3	F4	F5	F6	F7
1	Aprepitant	40	40	40	40	40	40	40
2	Kollicoat IR	90	90	130	160	160	160	160
3	PEG-400	-	-	-	-	-	-	0.01
4	Croscarmellose sodium	-	-	-	-	11.82	-	-
5	Crospovidone	-	-	-	-	-	11.996	-
6	Aspartame	9	9	10	10	10	10	10
7	Citric acid	12	12	15	15	15	15	15
8	Raspberry red	2.0	3.0	3.0	3.5	3.5	3.5	3.5
9	Vanilla flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10	Ethanol	-	q.s	q.s	q.s	q.s	q.s	q.s
11	Distilled water	1	1	1	1	1	1	1

*All quantities are expressed for (2.5 cm×3.5 cm) 8.75 cm^2 film in mg except PEG-400, ethanol, flavor, and water in ml. PEG: Polyethylene glycol

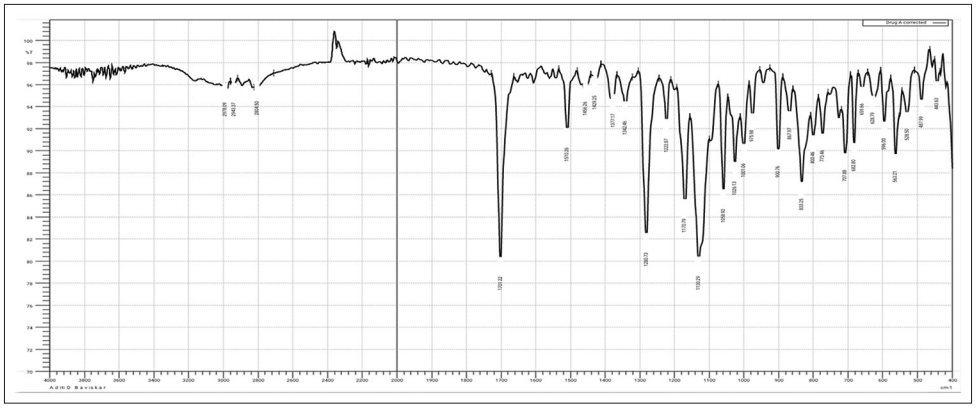


Fig. 4: Fourier-transform infrared spectrum of aprepitant

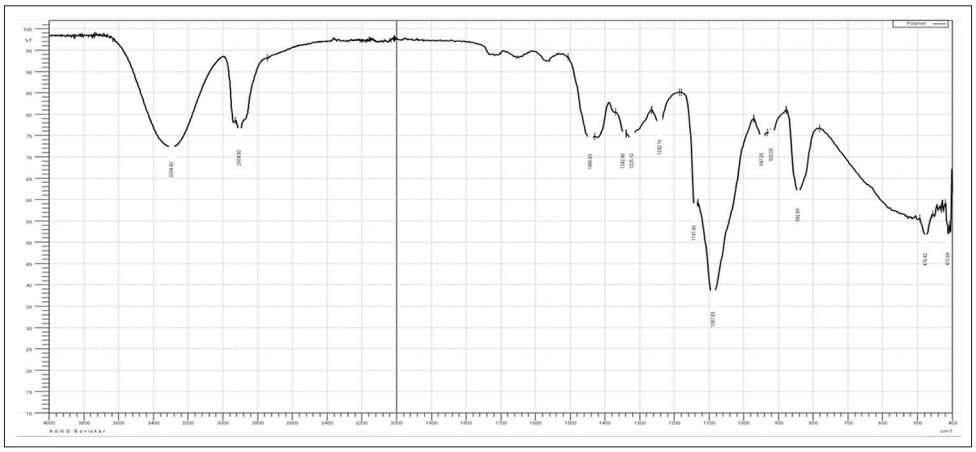


Fig. 5: Fourier-transform infrared spectrum of Kollicoat IR

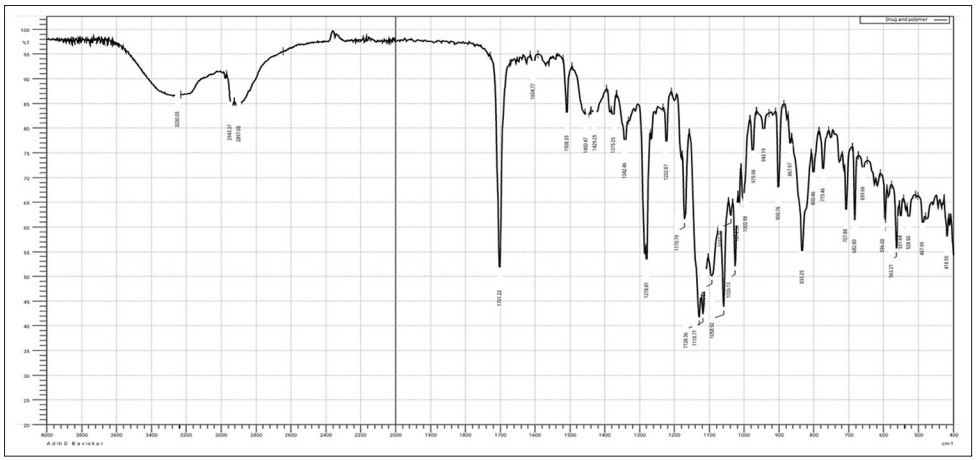


Fig. 6: Fourier-transform infrared spectrum of an overlay of aprepitant and Kollicoat IR

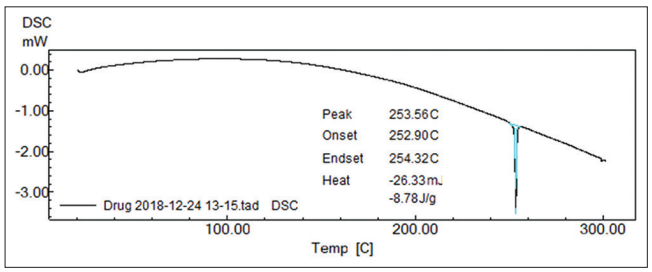


Fig. 7: Identification of aprepitant by differential scanning calorimetry

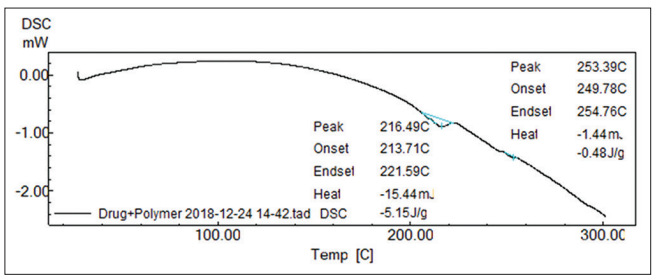


Fig. 8: Identification of overlay of aprepitant and Kollicoat IR by differential scanning calorimetry

Table 2: Composition of optimized batches of aprepitant mouth dissolving the film

S. No.	Ingredient	Batches								
		AP1	AP2	AP3	AP4	AP5	AP6	AP7	AP8	AP9
1	Aprepitant	40	40	40	40	40	40	40	40	40
2	Kollicoat IR	160	160	202.43	130	117.57	130	190	190	160
3	PEG-400	0.02	0.01	0.02	0.01	0.02	0.03	0.01	0.03	0.03
4	Aspartame	10	10	10	10	10	10	10	10	10
5	Citric acid	15	15	15	15	15	15	15	15	15
6	Raspberry red	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
7	Vanilla flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8	Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9	Distilled water	1	1	1	1	1	1	1	1	1

*All quantities are expressed for 8.75 cm^2 (2.5 cm×3.5 cm) film in mg except PEG-400 (polyethylene glycol), vanilla flavor, ethanol and water in ml. PEG: Polyethylene glycol

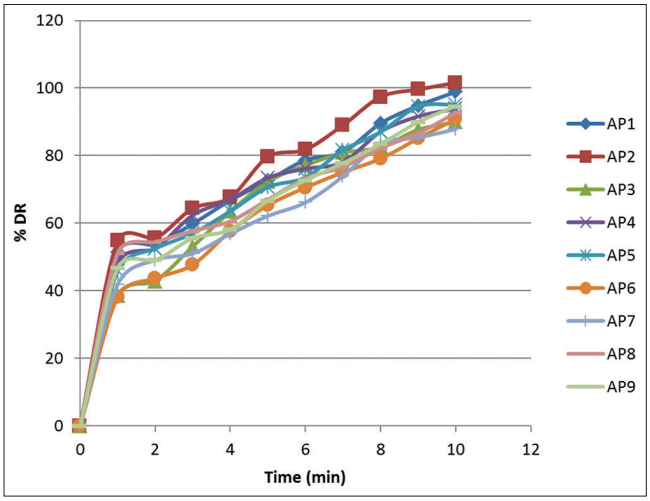


Fig. 9: Comparative *in vitro* drug dissolution profiles of aprepitant film (Batch AP1 to AP9)

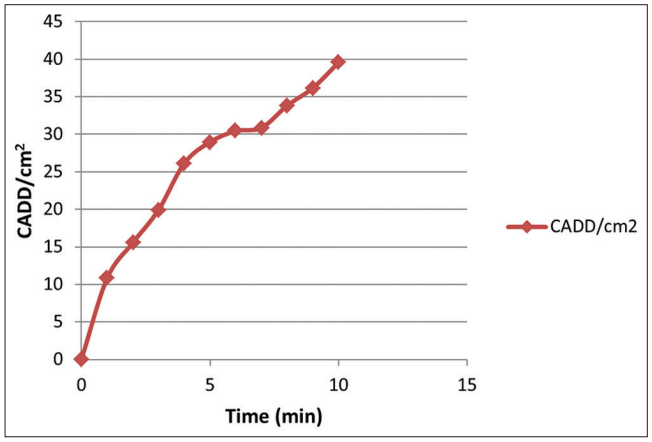


Fig. 10: *In vitro* drug diffusion study of optimized batch of aprepitant MDF (AP2)

DSC of aprepitant and Kollicoat IR, there was no any interaction and hence the aprepitant and Kollicoat IR were compatible with each other for further development of formulation. The spectrums were analyzed and interpreted in Figs. 7-8

From the above results of aprepitant mouth dissolving film, it was observed that AP2 batch showed highest folding endurance which indicates prepared film having good flexibility and the surface pH was found to be 6.76±0.21 which is as similar as the pH of the oral cavity. The thicknesses of the prepared mouth dissolving films were found to be in the range of

Table 3: Evaluation parameters for optimized batches of mouth dissolving film of aprepitant

Batches	Mean±SD			
	Weight variation (mg)	Surface pH	Thickness (mm)	Folding endurance
AP1	0.144±0.002	6.94±0.12	0.15±0.01	222±4.58
AP2	0.112±0.004	6.76±0.21	0.13±0.01	250±3.46
AP3	0.146±0.004	6.88±0.22	0.15±0.02	175±4.42
AP4	0.152±0.003	6.85±0.41	0.15±0.03	231±5.21
AP5	0.154±0.001	7.08±0.31	0.17±0.01	198±3.54
AP6	0.155±0.005	6.99±0.11	0.17±0.05	125±2.28
AP7	0.154±0.002	6.84±0.23	0.18±0.02	189±4.25
AP8	0.153±0.002	7.02±0.42	0.19±0.02	193±5.52
AP9	0.172±0.005	7.11±0.44	0.19±0.03	197±2.11

*±SD (n=3). SD: Standard deviation

0.13 nm–0.19 nm. The AP2 batch showed 0.13±0.01 mm thickness, which is lowest than other batches, as the concentration of polymer increases the thickness of the film increases. Results are shown in Table 3.

Formulation AP2 showed better results with percentage moisture uptake and moisture content among all batches. AP2 batch showed 98.87% drug content, which is highest in all batches. Film disintegrate in 18.5±2.55 s and having wetting time 25.1±1.5 s which is lesser among all. From the results formulation, AP2 was selected as the best-optimized batch (Table 4).

By comparing all the formulations (AP1–AP9), it was concluded that formulation AP2 showed the highest drug release and hence selected as the best formulation (Fig. 9). Formulation AP2 showed maximum drug release of 101.53% at 10 min (Table 5).

The cumulative amount of drug diffused was plotted against time to obtain the diffusion profile. It was found that in 10 min, the entire quantity of the drug from the formulation diffused completely and hence indicated a good diffusion coefficient, which is essential for faster onset of action. The AP2 batch diffused 39.58 mg/cm^2 drug within 10 min. These data are reported in Table 6 and Fig. 10.

Optimization and data analysis/statistical analysis

On the basis of the preliminary trials, a two factor central composite design was employed to study the effect of independent variables, i.e., concentration of Kollicoat IR (X_1) and concentration of PEG 400 (X_2) on dependent variables *in vitro* drug release % (Y_1), disintegration time (Y_2), and folding endurance (Y_3) (Table 7). Analysis and optimization were done by Design-Expert Software (version 7.1.5, State-Ease Inc., Minneapolis, USA).

Optimization of dependent variables

Response 1 (in vitro drug release % Y_1)

Aprepitant used in PONV that requires fast effect, so percentage DR within 10 min considered as a suitable time for desired therapeutic effect. Therefore, percentage DR in 10 min forms important criteria

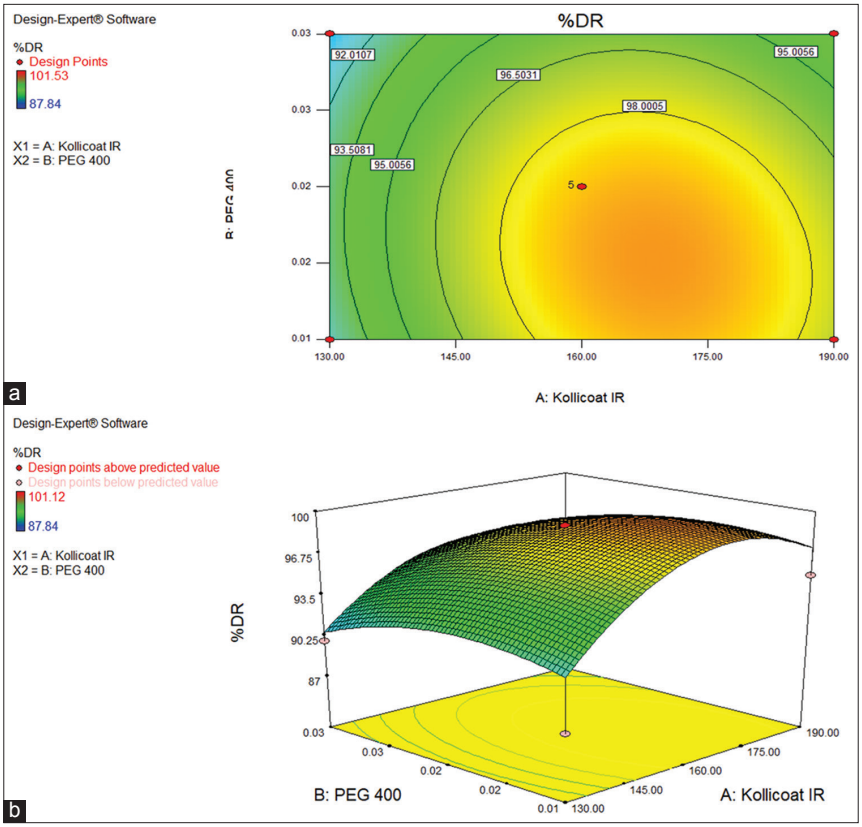


Fig. 11: (a) Contour plot for percentage DR of optimized formulation AP2. (b) Response surface plot for percentage DR of optimized formulation AP2

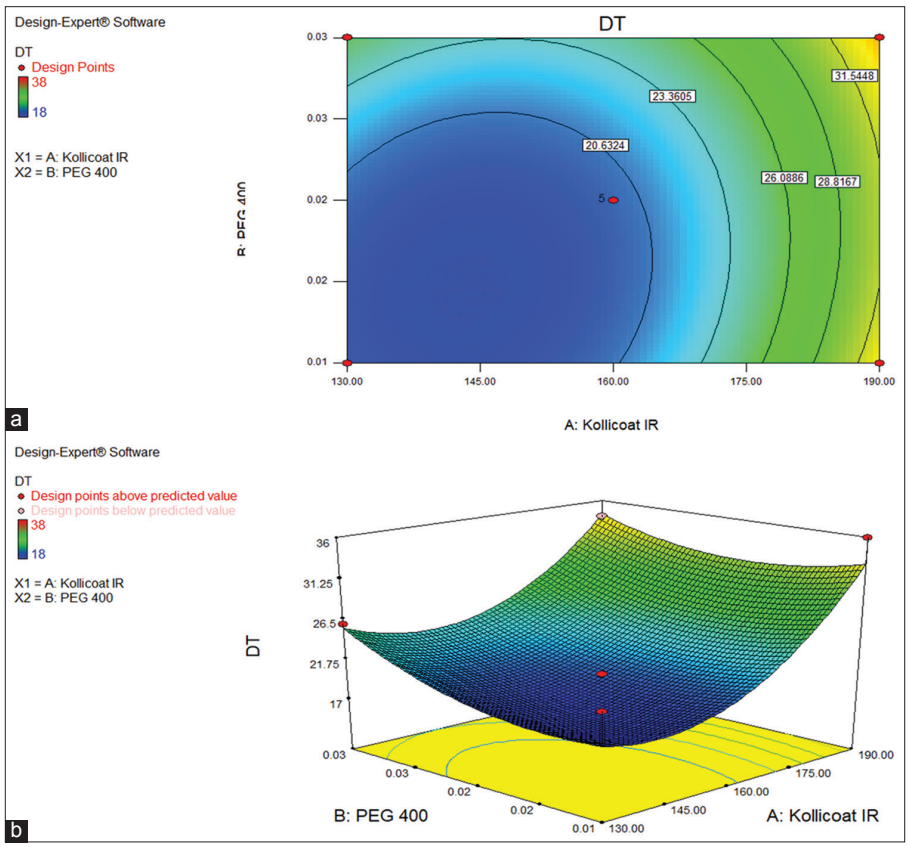


Fig. 12: (a) Contour plot for disintegration time of optimized formulation AP2. (b) Response surface plot for disintegration time of optimized formulation AP2

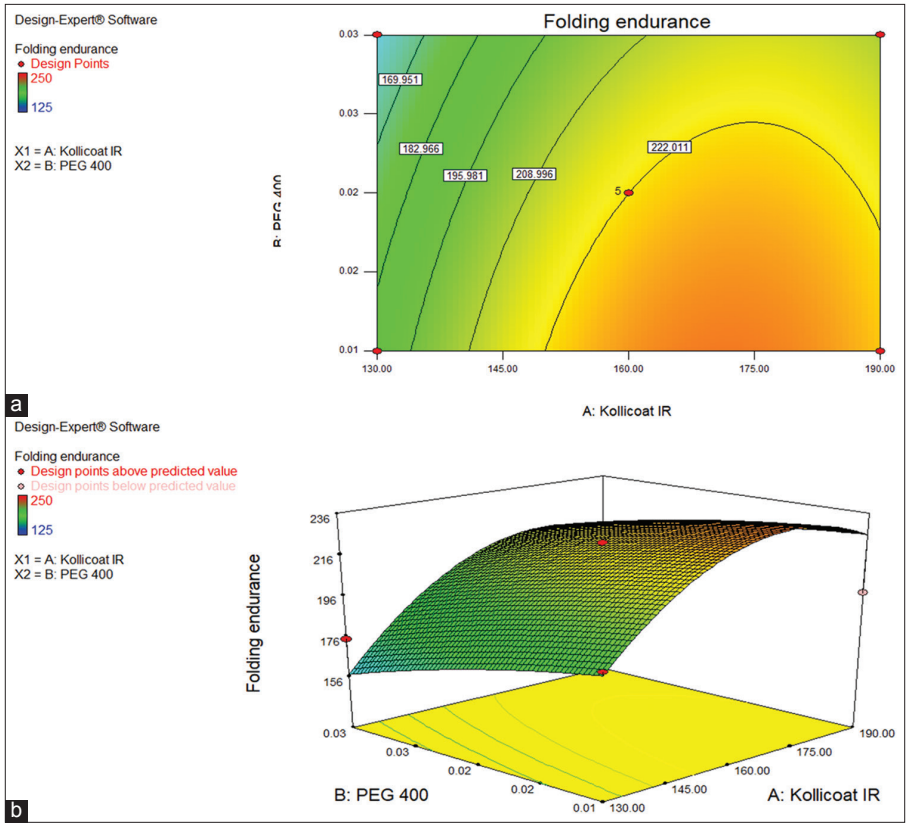


Fig. 13: (a) Contour plot for folding endurance of optimized batch AP2. (b) Response surface plot for folding endurance of optimized batch AP2

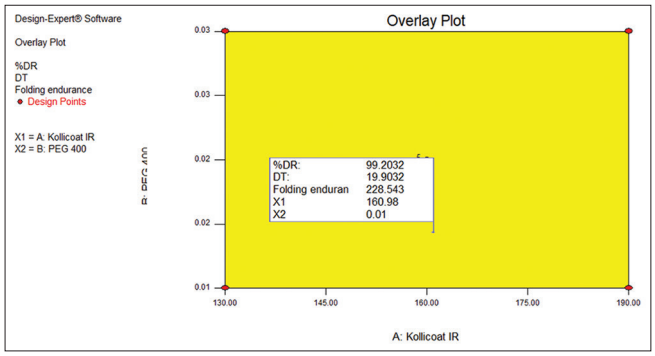


Fig. 14: Overlay plot showing compositions for optimized formulation AP2 and the predicted values for the responses Y1, Y2, Y3

and hence selected as the dependent variable for optimization. On applying central composite design, the quadratic model suggested by software and found significant with a model F value of 4.76 implies that the model is significant. There is only a 3.24% chance that a "Model F-value" this large could due to noise.

Values of "Prob > F" <0.0500 indicate model terms are significant. In this case, X_1^2 are significant model terms. Values >0.1000 indicate that the model terms are not significant.

Following quadratic equation could describe the % DR response,

$$Y_1 = +98.87+2.03\ X_1-1.37\ X_2-0.61\ X_1X_2-3.96\ X_1^2-1.60\ X_2^2$$

From the above quadratic equation, positive (+) sign of X_1 indicates that factor X_1 (concentration of Kollicoat IR) has positive effect on response Y_1 (% DR in 10 min) and negative (−) sign of X_2 indicates that factor X_2 (concentration of PEG 400) has a negative effect on response Y_1 (% DR in 10 min). That is percentage drug release in 10 min increases with increase in Kollicoat IR concentration and decreases with increase in PEG 400 concentration. The release of drug was found to be dependent on swelling property.

The contour plot and 3D response surface plots show the combined effect of concentration of Kollicoat IR and PEG 400 on percentage DR in 10 min. In this case, the results indicated that Kollicoat IR concentration had a more significant positive effect on response Y_1 than the negative effect of PEG 400 concentration. As the concentration of PEG 400 increases in the formulation more than 14% w/w of polymer, the water uptake capacity of the film decreases and a significant decrease in percentage DR in 10 min obtained at the same level of Kollicoat IR concentration with an increase in PEG 400 concentration. Formulation containing the lowest amount of PEG 400 (0.01 ml) got disintegrate first and thus enhance release rate of the drug. AP2 formulation contains the lowest amount of PEG 400 (0.01 ml) and medium amount of Kollicoat IR (160 mg) showed the highest amount of drug release in 10 min (Fig. 11).

Response 2 (in vitro disintegration time Y_2)

Disintegration time of the film varies from 20 s (batch 1) to 34 s (batch 9) for the selected independent factor combinations. The model F-value of 4.76 implies that the model is significant. There is only a 3.24% chance that a "Model F-value" this large could occur due to noise. Value of "Prob > F" < 0.0500 indicate that model terms are significant. In this case, X_1^2 are significant model terms. Values >0.1000 indicate that the model terms are not significant. Following quadratic equation could describe the disintegration time response,

$$Y_2 = +20.00+5.63\ X_1+1.89\ X_2-1.25\ X_1X_2+5.63\ X_1^2+2.38\ X_2^2$$

From the above quadratic equation, positive (+) sign of X_1 and X_2 indicates that factor X_1 (concentration of Kollicoat IR) and X_2

Table 4: Evaluation parameters for optimized batches of mouth dissolving film of aprepitant

Batches	Mean±SD			Drug content (%)	Wetting time (S), mean±SD
	Moisture content (%)	Moisture absorption (%)	Disintegration time (S)		
AP1	2.7±4.2	1.91±0.1	20.2±3.16	92.11	26.5±1.2
AP2	1.4±2.5	1.77±0.1	18.5±2.55	98.87	25.1±1.5
AP3	1.8±2.2	1.98±0.2	26.3±3.42	95.44	30.4±2.1
AP4	1.6±3.5	1.88±0.1	38.2±2.24	88.69	42.6±2.5
AP5	1.7±2.8	2.21±0.3	36.4±2.22	89.21	40.5±1.1
AP6	1.6±2.6	2.19±0.2	21.6±4.16	92.22	24.2±2.2
AP7	1.8±3.8	1.87±0.1	23.2±3.32	96.55	30.6±2.3
AP8	2.4±4.2	2.31±0.4	28.4±2.21	88.87	32.4±1.3
AP9	2.5±3.7	2.18±0.2	34.4±4.32	91.22	39.6±3.5

*±SD (n=3). SD: Standard deviation

Table 5: *In vitro* drug release study of optimized batches of mouth dissolving film of aprepitant

S. No.	Time (min)	AP1	AP2	AP3	AP4	AP5	AP6	AP7	AP8	AP9
1	1	51.32	54.85	38.56	48.11	45.87	38.06	41.88	51.14	46.76
2	2	53.72	55.57	42.88	52.46	52.48	43.66	49.08	54.44	49.04
3	3	59.84	64.38	53.11	62.38	57.01	47.72	51.03	57.72	55.54
4	4	66.77	67.66	63.47	67.01	63.54	57.66	56.88	60.61	58.15
5	5	72.58	79.63	72.31	73.42	70.68	65.31	62.14	66.98	66.68
6	6	78.68	81.80	77.12	76.13	73.55	70.55	66.14	73.31	72.70
7	7	81.03	89.01	80.81	78.08	81.62	75.08	73.88	76.66	77.80
8	8	89.55	97.38	82.54	87.07	87.01	79.12	83.60	82.24	83.38
9	9	94.77	99.60	87.67	91.60	94.54	85.08	85.33	86.61	89.94
10	10	98.87	101.53	89.86	93.87	95.09	90.89	87.84	92.67	94.66

Table 6: *In vitro* drug diffusion study of optimized batches of MDFs of aprepitant (AP2)

S. No.	Time (min)	Abs.	Conc. (µg/ml)	Total amount of drug diffused		CADD/cm² (CADD/unit area)	
				(µg)	(mg)	(µg/cm²)	(mg/cm²)
1	1	0.248	6.805	34,027.77	34.02	10,836.87	10.83
2	2	0.355	9.777	48,888.88	48.88	15,569.70	15.56
3	3	0.454	12.527	62,638	62.63	19,948.69	19.94
4	4	0.594	16.416	82,083.33	82.08	26,141.18	26.14
5	5	0.658	18.194	90,972.22	90.97	28,972.04	28.97
6	6	0.691	19.111	95,555.55	95.55	30,431.70	30.43
7	7	0.701	19.388	96,944.44	96.94	30,874.02	30.87
8	8	0.768	21.25	106,250	106.25	33,837.57	33.83
9	9	0.821	22.722	113,611.11	113.61	36,181.88	36.18
10	10	0.898	24.86	124,305.55	124.305	39,587.75	39.58

*CADD: Cumulative amount of drug diffused

Table 7: Results of optimized batches of aprepitant by central composite design

Run	Batch	Factor 1	Factor 2	Response variables		
		X1: Conc. of Kollicoat IR (mg)	X2: Concentration of PEG 400 (ml)	*In vitro* drug release (%)	Disintegration time (S)	Folding endurance (times)
1	AP1	160.00	0.02	98.87	20	222
2	AP2	160.00	0.01	101.53	18	250
3	AP3	202.43	0.02	89.86	26	175
4	AP4	130.00	0.01	93.87	38	231
5	AP5	117.57	0.02	95.09	36	198
6	AP6	130.00	0.03	90.89	21	125
7	AP7	190.00	0.01	87.84	23	189
8	AP8	190.00	0.03	92.67	28	193
9	AP9	160.00	0.03	94.66	34	197

Variable level	-α	Low (−1)	Medium (0)	High (+1)	+α
Kollicoat IR (mg)	117.57	130	160	190	202.43
PEG 400 (ml)	0.02	0.01	0.02	0.03	0.02

PEG: Polyethylene glycol

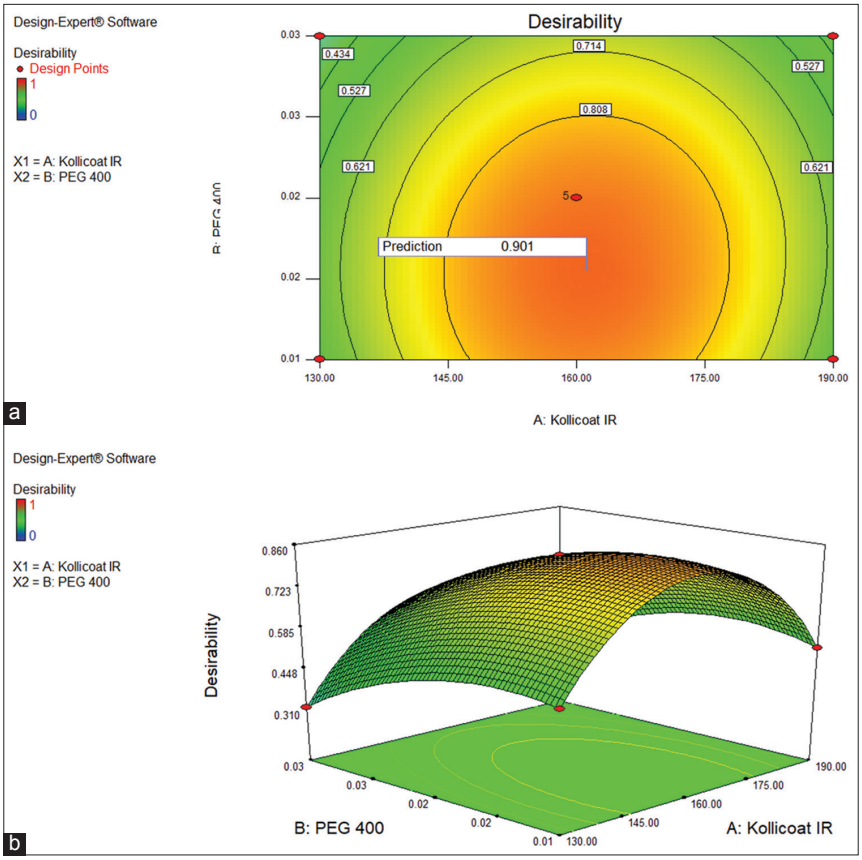


Fig. 15: (a) Contour graph for desirability of optimized formulation AP2. (b) Response surface graph for the desirability of optimized formulation AP2

(concentration of PEG 400) have positive effect on response Y_2 (*in vitro* disintegration time). That is, disintegration time decreases with an increase in Kollicoat IR and PEG 400 concentration. Kollicoat IR and PEG 400 directly related to disintegration time as they show good swelling due to its hydrophilic nature (Fig. 12). As the level of Kollicoat IR increases, the capacity of water uptake increases resulting in swelling.

Response 3 (folding endurance Y_3)

PEG 400 acts as a plasticizer and which is used in many of the pharmaceutical products due to its low human toxicity and desirable formulation properties. It is capable to improve the flexibility of the film and reduces the brittleness of the film. Plasticizers significantly improve the strip properties by reducing the glass transition temperature of the polymer and thus increase folding endurance. The model F-value of 5.28 implies that the model is significant. There is only a 2.50% chance that a "Model F-value" this large occurred due to noise. Values of "Prob. > F" <0.0500 indicate that model terms are significant. In this case, X_1 and X_1^2 are significant model terms. Values >0.1000 indicate that the model terms are not significant. Following quadratic equation could describe the folding endurance response (Y_3).

$$Y_3 = +222.00+22.61\ X_1-11.92\ X_2+3.25\ X_1X_2-24.50\ X_1^2-2.75\ X_2^2$$

From the above quadratic equation, positive (+) sign of X1 indicates that factor X1 (concentration of Kollicoat IR) has positive effect on response Y_3 (folding endurance) and negative (−) sign of X_2 (concentration of PEG 400) indicates that negative effect on response Y_3 (folding endurance). That is, folding endurance increases with increase in the concentration of X_1 (Kollicoat IR) and decreases with increase in the concentration of X_2 (concentration of PEG 400) above 14% w/w of the polymer (Fig. 13).

Selection of optimized batch

The overlay plot (Fig. 14) reflects that the yellow region of the area showed the area of interest (experimental region). From the overlay plot, it was found that the concentration of X_1 (Kollicoat IR) and concentration of X_2 (PEG 400) were same as that of the selected optimized batch from quadratic equations, contour plots, and response surface plot but there is somewhat variation in the responses of percentage % DR, DT, and folding endurance, which is negligible. From the results selected optimized batch was found to be AP2. The desirability of the optimized formulation AP2 was found to be 0.901, which is lies between 0-1 and it represents the closeness of a response to it's ideal value (Fig. 15). From the results selected optimized batch was found to be AP2.

CONCLUSION

Aprepitant is an antiemetic agent used in the treatment of post-operative nausea and vomiting. Aprepitant MDFs were prepared by spraying technique using Kollicoat IR and PEG 400. In the preliminary phase, attention was given to select the proper concentration of film forming agent (Kollicoat IR) and plasticizer (PEG 400) to develop a MDF. These selections were used to impart suitable folding endurance and flexibility to the films. On the basis of preliminary trials, two factors and three levels of central composite design were employed using design expert software to study the effect of independent variables, i.e., concentration of Kollicoat IR (X_1) and concentration of PEG 400 (X_2) on dependent variables that are *in vitro* percentage drug release (Y_1), disintegration time (Y_2), and folding endurance (Y_3). Preliminary trials indicated that 60–75% w/w level of Kollicoat IR and 10–14% plasticizer level in the film showed good results for mechanical properties and disintegration time. It was concluded that plasticizer PEG 400 plays a very much important role in the preparation of aprepitant MDF. Among all formulations optimized

AP2 batch showed good physicochemical parameters, the highest percentage of drug release, and less disintegration time. The *in vitro* release of the drug was found to be 101.53% within 10 min. The disintegration time was found to be 18 sec. It was found that in 10 min, the entire quantity of the drug from the AP2 formulation diffused completely and hence indicated a good diffusion coefficient, which is essential for fast onset of action. The AP2 batch diffused 39.58 mg/cm^2 drug within 10 min. It was concluded that MDF of aprepitant was found to be a better option in control/avoidance of post-operative nausea and vomiting by the way of fast onset of action for patient convenience and compliance. Among the plethora of avenues explored for drug releasing products, MDF is gaining much attention. In the near future, the MDF market will expand very fastly to treat various diseases.

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AUTHORS' CONTRIBUTIONS

The three authors contributed equally to this work.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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