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Development and characterization of Fast Dissolving Film of Chitosan embedded Famotidine Using 3^2 Full Factorial Design Approach

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Abstract

The aim of the present study was to develop a fast dissolving film (FDF) of taste masked inclusion complex of Famotidine (FMT) using film forming polymer. FDFs were prepared by solvent casting method applying 3^2 full factorial design. Response surface methodology (RSM) was used to optimize the independent variables like chitosan as a film forming polymer and PEG-400 as a plasticizer for dependent variable i.e. *in vitro* drug release (DR).The developed FDFs were characterized for film thickness, disintegration time, FTIR, DSC, XRD, and FESEM analysis.The developed FDFs of FMT were transparent, elegant, smooth and homogenous. Physicochemical characterization of FDFs showed no interaction between the drug and film forming polymer. The drug content was found in the range of 96.05 to 102% and disintegration time was found in pharmacopeial limit, which was less than 1 min. *In vitro* drug release study showed that approximately 82% drug release within 5 min.

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Keywords: Famotidine, Film forming polymer, RSM, Drug release, fast dissolving films

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1. Introduction

On the basis of Biopharmaceutical Classification System (*BCS*), poorly water soluble drugs can be considered as class II or Class IV drugs. Drug having low water solubility and low bioavailability have been categorized under BCS Class II drugs, once these drugs are dissolved, they rapidly absorbed over the biological membrane such as the gastrointestinal tract. After oral administration these drugs having slow dissolution rate in gastrointestinal tract result in low oral bioavailability due to the poor aqueous solubility [1-4]. Therefore increasing the solubility or dissolution rate of class II drugs can improve the oral bioavailability [5-7].

Famotidine (FMT) is H_2-receptor antagonist, potent histamine having low oral bioavailability and bitter taste. FMT is used for the treatment of ulcers like peptic ulcer and to treat, prevent heartburn due to acid indigestion and sour stomach caused by eating or drinking certain foods or drinks [8-10]. Some of the patients groups, particularly paediatrics and elderly patients may have swallowing problems of the conventional solid dosage form such as tablets and capsules. This leads to the prolonged duration of action and patient's non-compliance, which can be solved through the development of orally disintegrating dosage forms that disintegrate in the saliva and are swallowed without water [11-14].The main objective of this work was to develop fast dissolving film of taste masked inclusion complex of Famotidine using chitosan (CH), biodegradable, film forming polymer. Chitosan is the best known natural polymer used for its versatile applications in pharmaceutical industry. Along with general applications as binder, diluents, wetting agent, disintegrant, preparation of hydrogels, and improvement of dissolution of poorly soluble drug substances. Chitosan has been used to develop fast mouth dissolving film due to its superdisintegrant property [15, 16].

2. Materials and Methods

2.1 Materials

Famotidine and chitosan were obtained as a gift sample from Lupin Ltd., Pune, India and India Sea Foods, Kochi respectively. Polyvinyl pyrrolidone K-30 (PVP K-30) and Crosscarmellose Sodium (CCS) were obtained as a gift sample from Nanhang Industrial, P.R. China and Cellulose Pharma Chem., Jalgaon, India, respectively. (2-Hydroxy propyl) –β-Cyclodextrin (HP-β-CyD), Aspartame and citric acid were purchased from HIMEDIA® laboratories Pvt. Ltd. (Mumbai, India). All other chemicals and reagents were of analytical grade and used as provided.

2.2 Methods

2.2.1. Experimental design

Before application of the design, a number of trials were conducted to determine the formulation parameters and conditions at which the process resulted to fast dissolving film (FDFs). To optimize the formulation a 3^2 full factorial design was applied for the preparation of FDFs using Design-Expert® Software (Stat-Ease Inc., Minneapolis,) which allows evaluation by nine experiments in order to limit the number of experiments. Response surface methodology (RSM) was used for the analysis of results. The effect of two factors were studied such as CH (A, % w/w) as a film forming agent and PEG-400 as a plastisizer (B, % w/v) with respect to drug were selected as independent variables. Statistical models were used to evaluate the effect of independent variables on the dependent variable (Y, %). The significance of the model was determined by the comparisons of statistical parameters, and the best model (suggested) was decided based on higher values of R^2 and model p-value (should be less than 0.05) [17,18].

2.2.2. Preparation of the Inclusion Complex

Naik et al prepared Inclusion complex of FMT with HP-β-CyD and PVP K-30 by Lyophilisation method which was described in earlier publication [19]. Briefly, accurately weighed quantity of HP-β-CyD (1 mM) and PVP K-30 (1% w/v) were dissolved in 25 mL of distilled water to get a clear solution. Then the drug (1 mM) was dispersed in the aqueous solution of HP-β-CyD and PVP K-30 and stirred for 24 hours at room temp. Immediately after stirring, Freeze drying was performed by using a programmable freeze dryer (Lyophilizer, Make M/s Labogen Aps, Denmark).

2.2.3. Formulation of Fast Dissolving Film

Fast Dissolving Film (FDFs) of FMT were prepared by solvent casting method [20], according to the design given in Table 1. Solution –I was prepared by dissolving CH and PEG-400 in 2% aqueous solution of acetic acid and was allowed to stirred for 2 hours. After 2 hours, for removal of the entrapped air bubbles solution was kept for 1 hour at room temperature in crescent condition Solution-II was prepared by dissolving the specific proportion of Complex (equivalent to 10 mg dose), Aspartame as a sweetening agent, and CCS as a superdisintegrant, citric acid, tween-80 and vanilla flavor in distilled water. Solution-I and solution-II were mixed and stirred for 2 hours. Then the solution was casted on mercury and dried for 12 hours. The film was removed from the casting material and cut according to the size required for testing (1cm ×1cm area).

Table 1. Variables in a 3^2 full factorial design

A = amount of CH (%) and B = amount of PEG (%) in combination and response Y=DR (%)

Independent variables	Level used (actual, coded)			
	Low actual	High actual	Low coded	High coded
A	50	70	-1.000	1.000
B	0.10	0.40	-1.000	1.000
Experimental Run	Independent variables			Dependent variable
	A	**B**		**Y**
1	50.00	0.10		70.42
2	60.00	0.10		75.60
3	70.00	0.10		73.12
4	50.00	0.25		96.71
5	70.00	0.25		92.56
6	50.00	0.40		76.61
7	60.00	0.40		77.93
8	70.00	0.40		65.23
9	60.00	0.25		98.57

2.3. Physicochemical Characterisation of FDFs

Drug polymer interactions were studied by using a FTIR spectrophotometer (Shimadzu, FTIR-8400). X-ray diffraction analysis of samples was carried out by X-ray diffractometer (D8 Advance, Bruker) with Cu Kα radiation (λ=1.54060 A°). Thermal behaviour of the sample was determined by Differential Scanning Calorimetry (DSC-60, Shimadzu & 821, Mettler Toledo). Surface morphology of the film was analysed by Field Emission Scanning Electron Microscope (Hitachi, Model-S4800, Type -II).

FDFs was also characterised for Thickness, *in vitro* disintegration time, Drug content uniformity and for *In-Vitro* drug release studies. The *in vitro* disintegration time was carried out in phosphate buffer (pH=6.8). Drug release studies of the FDFs were carried out in a 900 ml dissolution medium of phosphate buffer pH 4.5 and in salivary pH 6.8 by using Tablet Dissolution Tester Apparatus, Type-II (Paddle method, Electrolab, TDT 06) at 37±0.5º C and at paddles speed of 50 rpm. 5 ml sample was withdrawn from the dissolution apparatus at different time intervals (1, 5, 10, 15, 20, 30, 60 min) and filtered through a membrane filter. The withdrawn sample was replenished with 5mL of fresh media to maintain the sink condition. The drug content was determined at 265 nm by double beam ultraviolet spectrophotometer (Hitachi, U-2900).

3. Results and discussions

The quadratic mathematical model (suggested) generated by 3^2 factorial design was used to evaluate the response.

$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 AB + \beta_4 A^2 + \beta_5 B^2 \quad \text{(I)}$$

Where, β_0 is the intercept; β_1 to β_5 are the estimated coefficient obtained from the observed experimental value of *Y*; *A* and *B* are the coded levels of the factor. The coefficient corresponding interaction (AB) and the quadratic effects (A^2B^2) were determined from the results of the experiments. Results of all the nine experiments carried out are summarized in Table 1. A study showed that the formulation parameters had an influence on the drug release of FMT in FDFs. The polynomial model described the correlation between the formulation variables and the response could be represented by the following equation.

$$Y= 99.23 - 2.14A + 0.10B -3.52AB -4.92A^2 -22.79B^2 \quad \text{(II)}$$

The equation represents the quantitative effects of factor (A & B) on the response (Y). Table 2 showed the model summary statistics of responses. Table 3 showed the coefficient estimate and p values of each factor for the measured responses. Significant values indicated in bold faces. The quadratic model showed a best fit for the response Y due to the highest R^2 value for response 0.9963. Significant factors affecting the response Y was A (p-value =**0.0225**), which is less than p<0.05[21-22].

Table 2. Model summary statistics of response, Y= % DR

Response	Model	Predicted R^2	Adjusted R^2	Std. R^2	PRESS	dev.	*p*-value	Significance
	Linear	0.0235	-0.3020	-1.1528	2516.94	13.79	0.9321	-
	2FI	0.0659	-0.4945	-3.2835	5008.06	14.78	0.6539	-
Y	**Quadratic**	**0.9963**	**0.9900**	**0.9585**	**48.53**	**1.21**	**0.0003**	**Suggested**
	Cubic	0.9992	0.9933	0.8472	178.62	0.99	0.4740	-

Table 3. ANOVA for Response Surface Quadratic Model for the Dependent variable (Y)

Factors	Y (%DR)		
	Coefficient of estimate	Standard Error	*p*-value
A-CH	-2.14	0.49	**0.0225**
B-PEG	0.10	0.49	0.8448
AB	-3.52	0.60	**0.0100**
A^2	-4.92	0.85	**0.0103**
B^2	-22.79	0.85	**0.0001**

Table 4. Experimental and predicted values of the response

Response	Run	Experimental value	Predicted value	Residual	Predicted (%) error*
	1	70.42	70.02	0.40	0.56
	2	75.60	76.33	-0.73	-0.96
	3	73.12	72.79	0.33	0.45
	4	96.71	96.44	0.27	0.27
Y	5	92.56	92.17	0.39	0.42
	6	76.61	77.27	-0.66	-0.86
	7	77.93	76.54	1.39	1.78
	8	65.23	65.96	-0.73	-0.01
	9	98.57	99.23	-0.66	-0.66

*Percent prediction error = (Experimental value − predicted value)/experimental value×100

Table 4 showed the experimental and predicted value for the response. Therefore, it can be concluded that the model is best suitable because of the difference between experimental and predicted value is very low.

FTIR spectra and XRD patterns of FMT, CH, CYD, PVP, FL (FDF) and COMPLEX of optimized formulation are shown in Fig.1 & Fig.2 Famotidine consists of guanidine, thiazole, thioether and sulfamoyl parts. The spectral position of NH_2 groups in guanidine and sulfamoyl depends upon bonded atom or groups to NH_2 group. However, its stretching vibrations generally give rise to bands in the region 3550–3250 cm^{-1}, which is disappeared from the spectrum of the inclusion complex. The band observed at 1491 cm^{-1} is assigned to the C=N stretching vibration of thiazole ring. Further, a shift in the position of the C = N stretching bands in the region of 1528-1636 cm^{-1} is observed in the IR spectrum of the complex. These spectral changes may have resulted from the inclusion of famotidine within the cavity of HP-β-CyD and the dissociation of the intermolecular hydrogen bonds of famotidine between the guanidine nitrogen and thiazole nitrogen through this complexation [23]. There is no major interaction was found between the drug and polymer in the complex and film.

XRD patterns of pure FMT shows the intense peak of crystallinity, whereas decrease in the peak intensity in complex shows amorphous nature of the drug. Intense peak of crystallinity was found in the XRD pattern of chitosan, whereas XRD pattern of film show some intense peak with semi crystalline nature in comparison to pure FMT, which indicates that FMT completely embedded in the chitosan. Slightly amorphous nature of the FMT in film is also responsible for the faster dissolution rate, which leads to the increase in bioavailability of FMT [24]

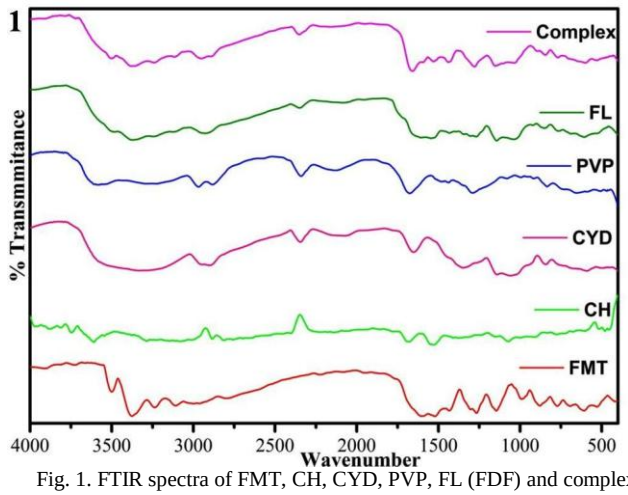

Fig. 1. FTIR spectra of FMT, CH, CYD, PVP, FL (FDF) and complex

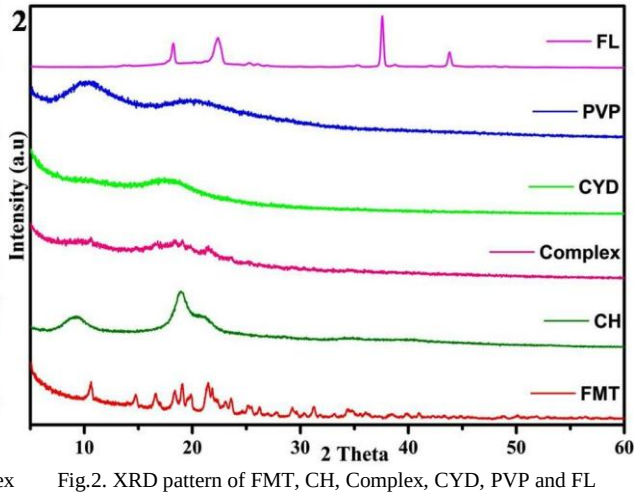

Fig.2. XRD pattern of FMT, CH, Complex, CYD, PVP and FL

Fig.3. shows the DSC thermo grams of FMT, CH and chitosan embedded film (FL). DSC scan of FMT shows Sharp endothermic peak at 163.5 ºC, which is corresponding to the melting point of FMT. Thermogram of film shows sharp single endothermic peak with low intensity, which indicate the homogeneity of the film with the polymer and other film components. The melting point of the FMT in the chitosan film was shifted slightly below the 163.5 ºC due to the physical interaction of FMT and CH, which interrupt the rearrangement of polymer chain due to intermolecular forces [25].

Surface morphology of the pure FMT and film was shown in Fig.4. FESEM study revealed that the pure FMT was in crystalline form. Chitosan film of FMT shows uniform distribution of drug in film with porous nature. The pores on the surface of the film are responsible for the fast release of the drug from film.

Thickness of the film was found in the range of 8±0.42µm to 10±0.78µm and drug content ranges from 96.05 to 102%, which was in specified limit. Disintegration time of the FDFs was found 14 sec and completely disappeared in 1.5 minute in salivary pH.

According to FIP/AAPS (Federation International Pharmaceutique/American Association of Pharmaceutical Sciences) guidelines, dissolution values of an early time point (e.g.≤5 min) can be used to establish the approximate baseline of taste for Fast dissolving tablets [8]. In vitro drug release profile of FMT and FDF are shown in Fig.5 a&b. From the *in-vitro* drug release, it was found that inclusion complex can mask the bitter taste of FMT by retarding the release of FMT in salivary pH=6.8 [17]. Fig.5a. showed the *in vitro* drug released study of optimised film formulation (Run 9) in phosphate buffer pH 4.5 showed approximately 82% drug released within 5 min and 98.57 % in 20 min. This might be due of the fact that Run 9 contained 60% CH, 0.25% PEG and 2% CCS. Chitosan along with CCS reduce the wetting time of the film, which leads to the fast disintegration of film in oral cavity, which is responsible for the faster drug released from the film. From the Fig.5b. dissolution profiles of taste masked FDFs as well as of control (pure drug), it was observed that the cumulative percentage drug released in phosphate buffer pH 6.8 was 0.42% in 1 min. while 2.9% in 5 min from FDFs of taste masked preparation. Whereas FDFs prepared with pure drug gives 6.12% in 1 min and 16.32 % in 5 min. This value is more than the FDFs of taste masked complex. This suggests that sufficient taste masking has been achieved and that the bitter taste of the drug will not be perceived while the film was in the mouth after oral intake.

3D response surface and 2D contour plots were constructed to visualize the effect of independent variables on response. 3D response surface plot gave the idea about interaction effects of the independent variables whereas visual representation of the values of responses was given by 2D contour plots. From the 2D contour plots and 3D response surface plot Fig.6. (a, b), it was observed that % DR of the FMT in FDF increases at optimum concentration of CH and PEG-400. As the concentration of CH and PEG-400 increases it reveals increase in dissolution rate but after certain limit, further increased in concentration it reflects the decrease in dissolution rate

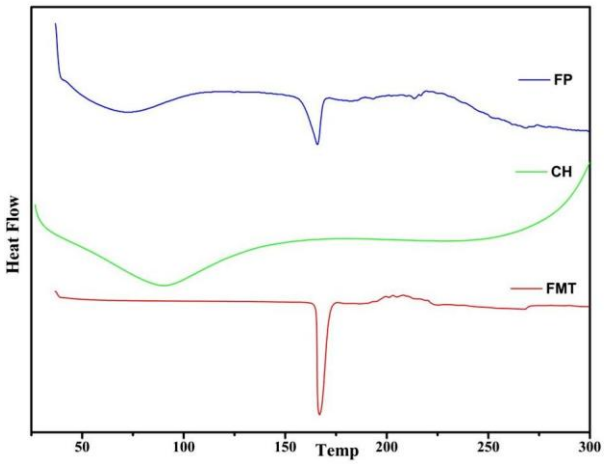

Fig. 3. DSC thermograms of FMT, CH and FL.

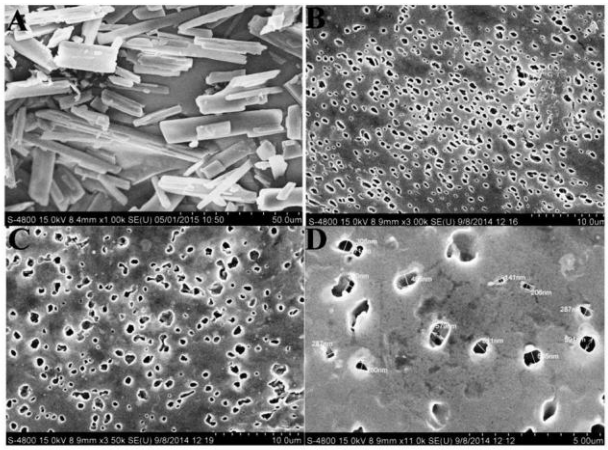

Fig. 4. FESEM images of (A) FMT, (B-D) FL

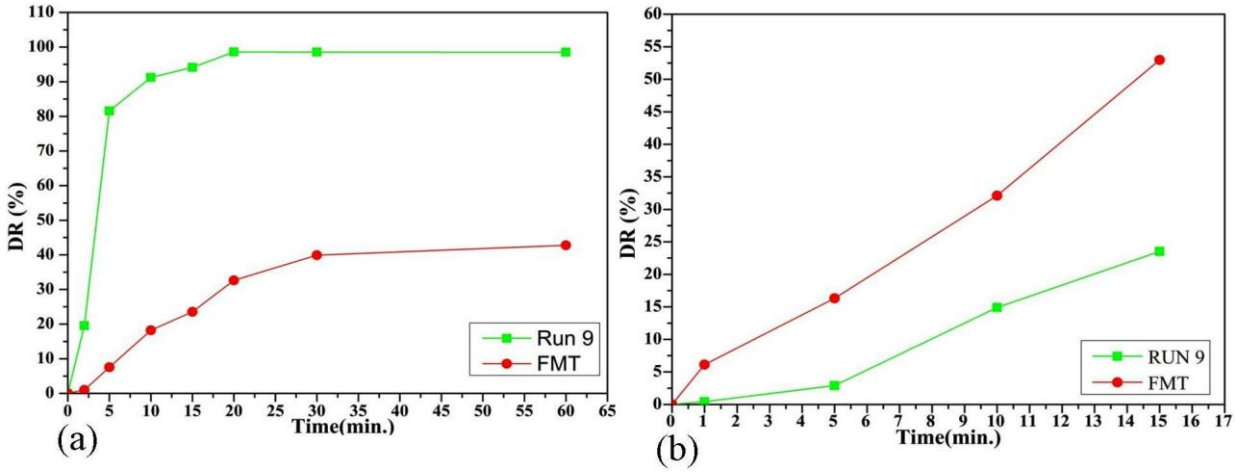

Fig. 5. %DR profile of FMT and RUN 9 in (a) pH=4.5, (b) pH=6.8

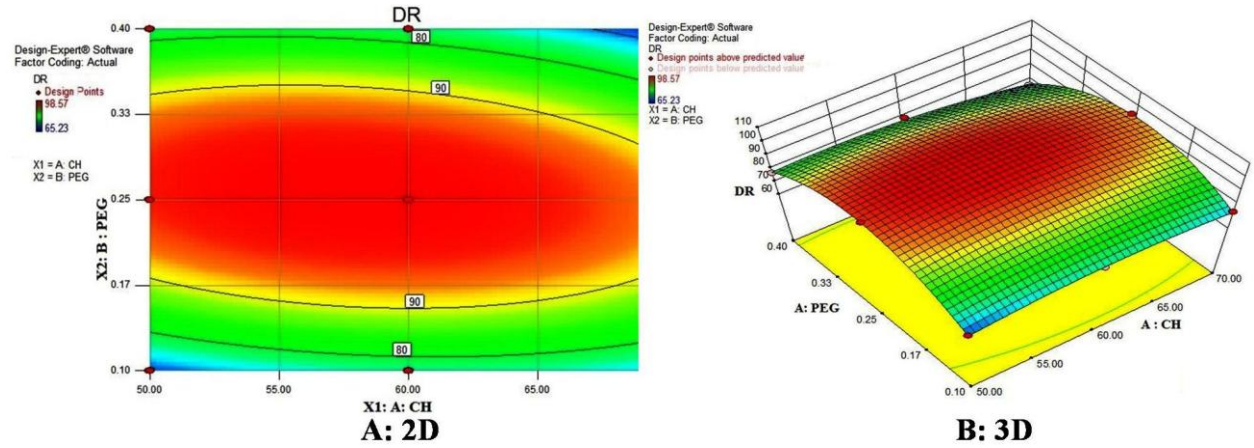

Fig. 6. (A) 2D response surface plot, (B) 3D response surface plot

4. Conclusion

In the present work, an approach was used for incorporating the inclusion complex of the poorly water soluble drug into fast dissolving film with the goal of faster dissolution rate. *In vitro* drug released study showed that approximately 82% drug released within 5 min in comparison to the pure drug. Effects of independent variables on dependent variables were screened out by applying response surface methodology. FTIR and DSC studies of the film confirmed the good compatibility between the drug and polymer. FESEM images confirm the uniform distribution of drug in the film with porous nature. These pores are responsible for the fast release of FMT from the film. From the study we can conclude that FDFs formulation could be an alternative approach for the delivery of various drugs for the paediatrics as well as elderly patients which having swallowing problems.

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