ORIGINAL ARTICLE

High-amylose maize starch as a novel film former to develop oral films with excellent mechanical properties: A preliminary study

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Abstract

Aim: The study involved the development and optimization of the fast-dissolving oral films of salbutamol sulfate using high-amylose maize starch (HAMS) as a novel film former by comparison with the HPMC E50 (hydroxy propyl methyl cellulose) films. The high aqueous solubility, low dose, and low molecular weight of salbutamol sulfate make it best suited for oral dissolving films, thereby possible to enhance patient compliance in pediatrics and geriatrics. **Materials and Methods:** The HPMC E50 and HAMS films were prepared by solvent-casting technique. The casted films were optimized using the design of experiments employing 2^2 factorial designs with replicates separately. The concentration of HAMS/HPMC and crospovidone were considered as independent variables and the responses being tensile strength (TS), percentage elongation at break, and disintegration time. **Results and Discussion:** HAMS films exhibited good mechanical properties due to high TS and greater percentage elongation than the HPMC E50 films. Both the films disintegrated within a minute with no significant differences. X-ray diffraction studies exposed that starch with high-amylose content has a greater crystalline domain and this may be attributed to the maximum TS of the formulated HAMS oral films. *In vitro* drug dissolution profiles of HAMS and HPMC E50 films at the end of 10 min were found to be 96.98% and 88.25%, respectively. **Conclusion:** From this study, it is evident that HAMS can be utilized as the promising film-forming polymer in the development of fast-dissolving oral films.

Key words: Amylose starch, oral films, salbutamol sulfate, solvent-casting technique

INTRODUCTION

Bronchial asthma is characterized as a chronic inflammatory disease of the airways which lead to difficulty in breathing, chest congestion, and anxiety. Bronchodilators such as beta-2 sympathomimetics were commonly employed for the treatment of bronchial asthma.

Asthmatic patients especially pediatrics and geriatrics were facing difficulty in taking traditional dosage forms such as tablets, capsules due to fear of choking, big size of tablet or capsule, and unpleasant taste and smell. Aerosol systems remain precise but unable to bring the definite dose of the drug. Similarly, they need additional support for handling metered dosage inhalers. There are lots of obstacles for maintaining the stability of the dosage form such as microbial contamination, chemical instability which leads to low therapeutic efficacy.[1] Hence, these patients require special attention while designing drug delivery of the particular medicament.[2,3] To overcome the above problem, we need to shift the conventional dosage form to oral film technology. Oral films can be defined as the dosage form placed on the mouth to release the medicament very rapidly without the need for water or chewing. They are more advantageous due to the larger surface area and extreme vascularization of the oral mucosa resulting in fast disintegration and also the dissolution of the oral film.[4,5] The drugs undergoing first-pass hepatic metabolism are much benefitted by means of bypassing it when given as oral films.

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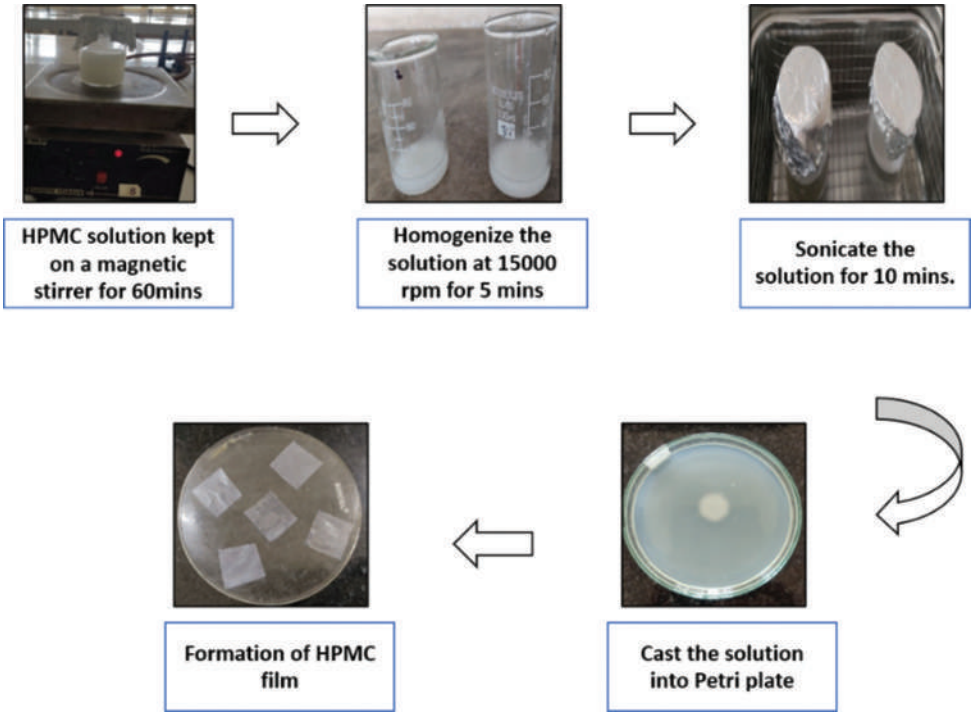

Figure 1: Preparation of HPMC E50 oral films

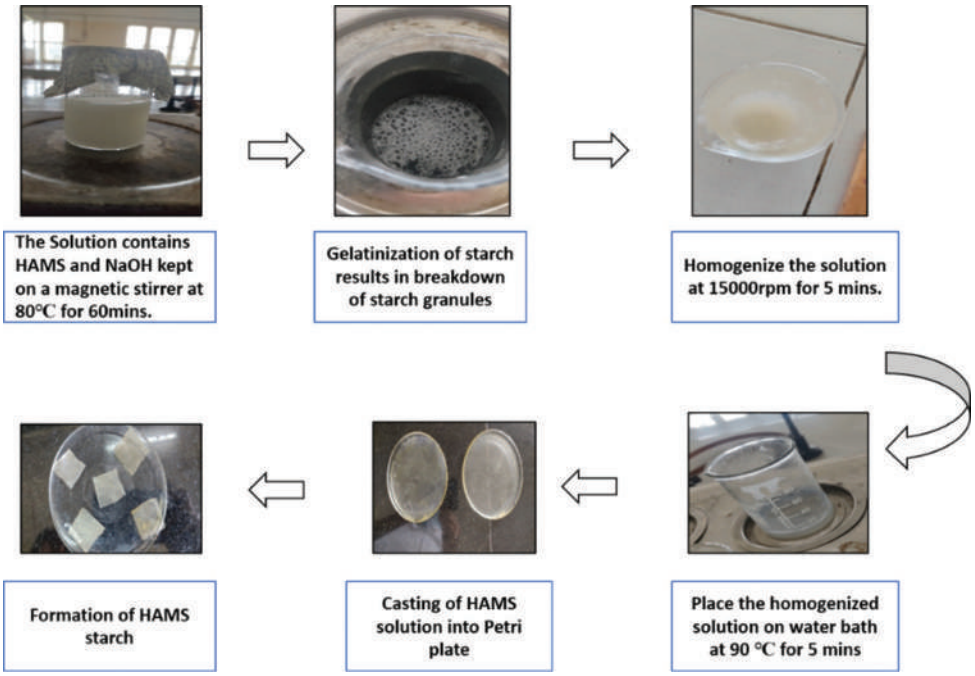

Figure 2: Preparation of HAMS oral films

Salbutamol sulfate is a bronchodilator, especially utilized as a drug for treating acute and chronic bronchial asthma.[6] Mostly, it is available as an inhalational route, but it is not widely suitable for the pediatric, geriatric population. Due to low dose, low molecular weight, and high-water solubility, it would be suitable for the formulation of fast-dissolving oral films (FDOFs).

The formulation of FDOFs is highly influenced by film-forming agents. The most commonly employed film-forming agents are hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, starch, pullulan, and chitosan.[7] The polymer employed in the preparation of oral films may be employed alone or in combination to get the required properties of the film to avoid damage during transportation.[2] It should be non-toxic, with sufficient peer, shear, and tensile strength (TS). Plasticizer aids to expand the film flexibility and, thus, reduces the brittle nature of the film. Glycerol and sorbitol are a few examples of plasticizers in the preparation of oral films.

Starch is mainly composed of two components, amylose, and amylopectin. Amylose is a linear polymer connected together to 1,4-D-glucosidic bonds, while amylopectin has a large molecular weight and it has branching of the 1,4 -D-linked chains that occur to 1,6-D-glucosidic bonds. High-amylose maize starch (HAMS) is a genetically modified starch, widely employed in the food industry. HAMS comprises more than 70% of amylose and was procured from corn kernels using a refinement process. Due to its high-amylose content, it can yield strong, flexible films with good TS.[8,9] Many studies have been carried out to investigate the efficacy of HAMS as a film former in the coating, alone or in combination with other polymers such as ethyl cellulose, chitosan, and pectin.[10,11] Their findings have demonstrated that HAMS is an excellent film-forming material as they possess greater amounts of linear chains and form stable networks by hydrogen bond.[12,13] Hence, the present study would involve the investigation of HAMS as a film-forming agent in the formulation of fast-dissolving oral films by comparing with the films made from HPMC E 50.

MATERIALS AND METHODS

Salbutamol sulfate IP was gifted by Medopharm, Bangalore, Karnataka. HPMC E50 was procured from LobaChemie laboratory reagents, Mumbai, India. HAMS was gifted by Roquette Pharma ltd, Mumbai, India. Glycerin and D-sorbitol from LobaChemie Pvt. limited, Mumbai, citric acid from Hi-pure Chem industries, Chennai. Crospovidone (CP) was obtained from yarrow Chem products, Mumbai, India. Distilled water was utilized all over the experiment.

Solvent-Casting Technique[14]

Preparation of salbutamol sulfate oral film

Briefly, this technique involves, solubilizing the film-forming agent in a solvent such as water or any volatile solvent, and also involved in the addition of drugs, and other excipients to form a uniform homogeneous solution. The resulting solution or suspension is kept aside for a few minutes to remove the bubbles and then cast on molds such as glass and polytetrafluoroethylene. The casted solution/suspension is dried and then peeled to obtain the film. Oral films of salbutamol sulfate were formulated by solvent-casting technique employing HPMC E 50 and HAMS. The composition of FDOFs of salbutamol sulfate is shown in Table 1. The Preparation of HPMC E 50 and HAMS oral films were presented in Figures 1 and 2 respectively.

Drug-Polymer Compatibility

Fourier-transform infrared (FTIR) study

The drug and the other excipients were recorded by the potassium bromide (KBr) pellet method using FTIR spectrophotometer Model 15.[15,16] Physical mixtures of drug and excipients were prepared as KBr pellets by compressing at 6 ton/nm2. The wavelength ranges were selected between 400 and 4000 cm^{-1}.

Preliminary Screening Studies

To establish the low and high level of the independent variables in DoE, initially, a total of 8 trial formulations (F1 to F8) containing varying amounts of HPMC E50, HAMS, and CP were prepared and characterized. Based on these results, the levels of the variables were set for further optimization in DoE.

Characterization

Thickness

It is important to regulate the uniformity of thickness, because it is directly related to the precision of the drug in the film. The thickness was determined using a micrometer screw gauge at the center, and edges of prepared films. All the experimental values are carried out in triplicates and the mean value was noted.[17]

Weight variation

Oral films of salbutamol sulfate were weighed by electronic digital balance and the average weight of the prepared films was taken.[18,19]

Folding endurance

The oral film flexibility mainly depends on folding endurance value. It was calculated by repeated folding of the oral film at the same place till the film breaks. The total number of times that the oral film is folded without breaking is calculated as the folding endurance value.[18,20]

Content uniformity

Films of size 1 × 1 cm^2 were taken in the standard flask and diluted appropriately with distilled water to obtain a concentration of 10 µg/ml. The diluted solutions were determined at 276 nm using UV-Visible spectrophotometry and the absorbance of the solution was noted. Then, the drug content was determined.

In Vitro Disintegration (Petri Dish Method)

The disintegration of the prepared oral films can be determined by the Petri dish method. The formulated film was kept in a Petri dish comprising 2 ml of saline phosphate buffer. The time at which the film breaks or disintegrates was noted.[5,6]

Surface pH

It is necessary to determine the surface pH of the oral films to detect any irritation produced by the film in the oral cavity. Initially, the film was kept in a Petri plate consisting of 1 ml distilled water; then, the electrode remains placed on

Table 1: Composition of fast-dissolving oral films of salbutamol sulfate

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Salbutamol sulfate	80	80	80	80	80	80	80	80
HPMC E50	350	400	450	500	-	-	-	-
HAMS	-	-	-	-	600	800	1000	1200
Glycerol	1.5 ml	1.5 ml	1.5 ml	1.5 ml	-	-	-	-
Sorbitol	-	-	-	-	120	120	120	120
Citric acid	40	40	40	40	40	40	40	40
Mannitol	20	20	20	20	20	20	20	20
Crospovidone	20	30	40	50	20	30	40	50
Distilled water	30	30	30	30	30	30	30	30

the film's surface for a time interval of 1 min, and pH was noted.[17]

Mechanical Property

The mechanical property was assessed using stable microsystem testing apparatus (TA XT Texture Analyzer). Oral formulated film of size 70 mm × 40 mm, should be free from any air bubbles, and were placed between two clamps positioned at a distance of 50 mm.

TS and percentage elongation at break (PE) were computed for the estimation of the oral film.[12] TS is the extreme stress that was applied to a particular point at which the oral film breaks and can be determined from the following equation.[21]

Tensile strength = Force at break/Initial cross-sectional area of the sample

PE

When stress was applied to an oral film, the sample gets stretched. It is the deformation of the film before it gets cracked due to stress. It can be obtained by the following equation:

Percentage elongation at break = Final length–Initial length/Initial length × 100

In vitro Dissolution Studies

In vitro release of salbutamol sulfate oral films was determined using USP type II dissolution apparatus (paddle). The dissolution medium (900 ml, saline phosphate buffer pH 6.4) was kept at 37 ± 0.5°C with constant paddle rotation at 50 rpm. The drug release of salbutamol sulfate FDOF was determined by withdrawing the samples at regular intervals and replenishing them with the fresh medium of a buffer that was kept at the same temperature. Finally, the samples were filtered through a filter paper and then the absorbance was measured in a UV spectrophotometer at 276 nm.[21]

X-ray Diffraction (XRD) Studies

XRDs were obtained for the best FDOFs sample using X-ray diffractometer (3rd generation Empyrean, Malvern Paralytical multipurpose diffractometer with Multicore Optics). It is capable of a large variety of measurements from powders to thin films on a single instrument, without much manual intervention. X-Ray sources such as Cu Kα (λ = 1.54 Å) and Mo Kα (λ =0.71 Å) were utilized for this study.[9] The area of the crystalline peak diffraction relative to the total area of the diffractogram was taken as a measure of the relative crystallinity.

Optimization Using Design of Expert (DoE)

The 2^2 factorial designs were employed for the optimization of fast-dissolving oral film of salbutamol sulfate. The independent and dependent variables of these experimental designs are shown in Table 2. To maximize the power of the experiment design, replicates were made, eight runs for the different concentrations of polymer, and CP was carried out.[22] The responses were analyzed using analysis of variance (ANOVA) and the parameters were evaluated by a polynomial equation.

RESULTS AND DISCUSSION

In the present study, solvent-casting technique were employed due to ease of preparation and also economical. The prepared oral films were transparent and flexible.

Drug Polymer Compatibility Study

FTIR spectroscopy study was assessed to check the compatibility of drugs with other excipients by the potassium bromide pellet press method. It was observed from the spectra that there was no interference of functional groups of the drug and excipients and the FTIR values are summarized in Table 3. Peaks of physical mixtures of HAMS and other excipients were shown that the symmetrical bending was observed.[15,23] Thus, it can be reported, that the drug and

physical mixtures of polymers are compatible with each other. The spectra are presented in Figure 3.

Thickness and Weight Variation

The mean thickness of the oral films ranges from 0.138 ± 0.01 to 0.20 ± 0.03 mm. It shows that all formulated oral films have a uniform thickness; also, HAMS produces thin films than that of HPMC E50. The thickness of fast-dissolving oral films of salbutamol sulfate was found to be in the optimum range, and also, it provides flexibility.[4] The average weight variation ranges from 118 ± 0.3 to 136 ± 0.2 mg and it shows that all prepared oral films were within the limits.

Folding Endurance

Folding endurance of all formulated oral film ranges from 185 ± 1.22 to 197 ± 2.48 folds indicated that all FDOFs were found to be excellent flexibility and it was established that amount of film-forming agent increases, the folding endurance also increases.[18] Furthermore, the choice of plasticizer influences the folding endurance of fast-dissolving oral films.

Table 2: Variables of 2^2 Factorial experimental design

Code	HPMC E50	HAMS
X1	Concentration of HPMC	Concentration of HAMS
X2	Crospovidone	Crospovidone
Y1	Tensile strength	Tensile strength
Y2	Percentage elongation at break	Percentage elongation at break
Y3	Disintegration time	Disintegration time

Table 3: Report of Fourier transform infrared spectra of physical mixtures of HPMC E 50 and HAMS polymer

Peak	HPMC E 50 (cm^{-1})	HAMS (cm^{-1})
OH stretching	3525	3398
C - O stretching ether bond	1153	1171
C = C Stretching alkane group	1624.12	1707
C-H bending aromatic benzene ring	1067	1391
C-H stretching aldehyde group	3448.84	3433

Content Uniformity and Surface pH

The obtained absorbance for the drug content value was correlated with the standard graph. The content uniformity ranges from 91–96 ± 2.14% which was in the acceptable range of IP. Surface pH of the films ranges from 6.39–6.90 ± 0.2. As the surface pH of FDOF was close to the pH of the oral cavity (6.5), it can be suggested that the films would not have irritation when administered. Thus, it would be compatible with the oral mucosa region of the buccal cavity.[19]

In Vitro Disintegration Time

FDOFs should disintegrate within a minute for quick onset of action. All the films exhibited rapid disintegration with no significant differences. Faster disintegration of the oral film was due to the addition of super disintegrate which aids in quick penetration of water into the oral film.[5] Thus, it indicates that the prepared oral film was able to release the medicament quickly for the enhanced onset of action thereby increasing the patient's compliance.

Mechanical Properties

The formulated oral film has excellent flexibility and should bear high TS ranges from 110.12 to 375.9 N/m for HPMC E 50 and 319.5–1593.6 N/m for HAMS polymer and PE ranges from 25.3 to 60.23% for HPMC E50 and 37.5–132.5% for HAMS film-forming agent[24] and the respective constraints are shown in Table 5. Similarly, the increase in the concentration of film-forming agents and the superdisintegrate increases the mechanical properties of the FDOFs. Thereby, the polymer and superdisintegrant has a direct positive impact on the flexibility and stretch ability of the oral films of salbutamol sulfate.[25,26]

In Vitro Dissolution Studies

All the formulated oral films were able to dissolve and release the drug at maximum in saline phosphate buffer pH 6.4 used as a dissolution medium. HPMC E 50 oral films were showed maximum drug release of 88.5%, while HAMS films showed

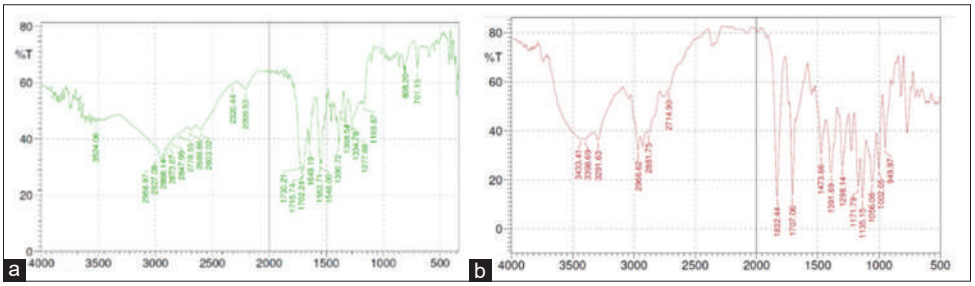

Figure 3: Fourier-transform infrared spectra of physical mixtures (a) HPMC E50 (b) HAMS

Table 4 : Results of dependent variables of HPMC E 50 and HAMS for experimental design

RUNS	X1 (Coded Value)	X2 (Coded Value)	TS (N/m)		PE (%)		DT (s)	
			HPMCE50	HAMS	HPMC E50	HAMS	HPMC E50	HAMS
1	+	−1	264.65	773	25.34	37.5	55	62
2	+	−1	204.1	727	37.5	92.5	52	64
3	+	+1	375.9	1341.8	30.8	85.9	42	59
4	+	+1	350.5	1593.6	117.5	132.5	41	58
5	*	+1	127.2	441.59	60.23	82.5	53	57
6	*	+1	136.14	423.56	56.2	95.4	55	58
7	*	−1	127.45	350.2	53.3	55.6	61	65
8	*	−1	110.12	319.5	42.5	78.2	59	62

maximum drug release of 96% at the end of 10 min. This showed that the HAMS oral film has an improved dissolution rate than HPMC E 50 films,[27] and also, it was influenced by the concentration of the film-forming and superdisintegrant incorporated into the oral films and *in vitro* dissolution profile graph is shown in Figure 4. All the values of preliminary studies are described as mean ± SD, as shown in Table 6.

Preliminary Screening Studies

XRD studies

XRD spectra of the HAMS powder and oral film are compared. It can be concluded that both the diffractograms show a similar pattern with a slight difference in intensity of the peaks. XRD spectrum peaks are shown in Figure 5. The study showed that the HAMS powder and the HAMS oral films exhibited characteristic peaks of B and V polymorphs at 17.09°, 19.60°, 22.18° (2θ), and 5.62°, 15.50° (2θ), respectively,[16] and the values are presented in Table 7. It is evident from the study that starch with high-amylose content has a greater crystalline domain and this may be attributed to the maximum TS of the formulated HAMS oral films. The relative crystallinity of the HAMS oral films is slightly more than the HAMS powder and it can be due to the recrystallization of the starch granules after gelatinization.[26]

Validation of the Experimental Design

The prepared films necessity to be robust to avoid any rupture during processing and administration. Furthermore, the mechanical properties, such as TS and extensibility, greatly influence the film's property, and hence, they were considered as dependent variables in DoE.[25,28] In turn, these properties vary depending on the concentration of the film-forming polymer. The results of dependent variables of HPMC E50 and HAMS for the experimental designs were shown in Table 4.

The responses were analyzed using ANOVA and polynomial models which include interaction and quadratic terms. The

Table 5: Constraints of the responses of the experimental designs of fast-dissolving oral films of salbutamol sulfate

Coded value	Actual value HPMC E50 (mg)	Actual value HAMS (mg)
*	300	600
+	500	1200
−1	20	20
+1	50	50

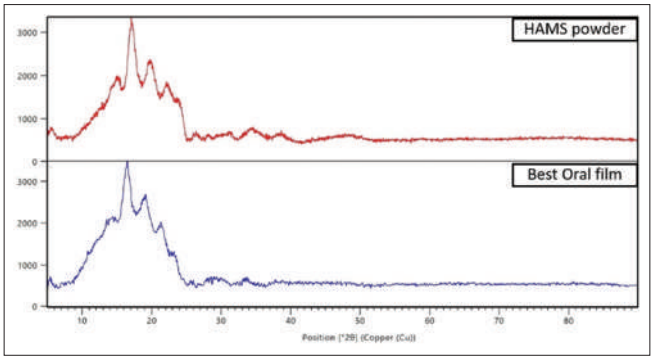

Figure 4: XRD spectrum for HAMS powder and optimized oral film

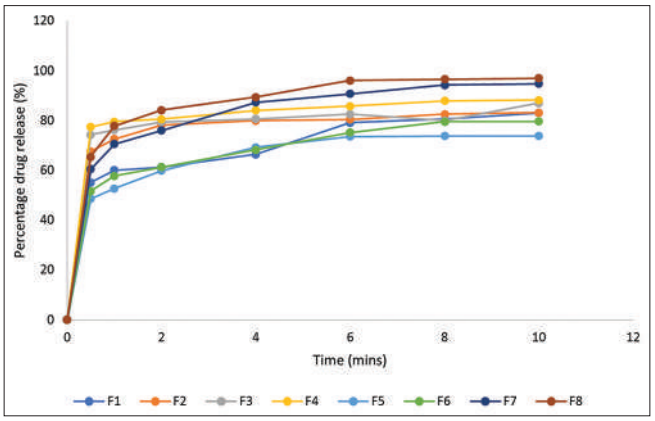

Figure 5: *In vitro* dissolution profile of oral films of salbutamol sulfate using HPMC E 50 and HAMS

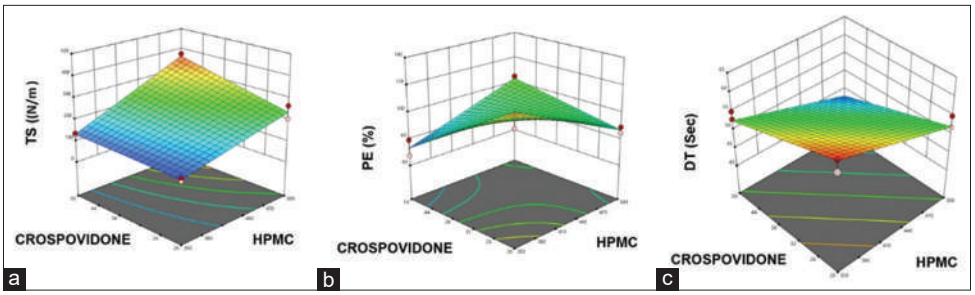

Figure 6: Response surface plot of factorial variable on tensile strength (a), percentage elongation at break (b), and disintegration time (c) for HPMC E 50

Table 6: Characterization of fast-dissolving oral films of salbutamol sulfate

Formulation code	Thickness (mm)	Folding endurance	Weight variation (mg)	Content uniformity (%)	Surface pH	DT (s)
F1	0.23 ± 0.03	185 ± 4.72	136.5 ± 0.2	92 ± 0.02	6.45 ± 0.05	49.6 ± 0.081
F2	0.20 ± 0.02	190 ± 4.35	126.5 ± 0.3	94 ± 0.01	6.39 ± 0.02	54 ± 0.35
F3	0.19 ± 0.01	180 ± 4.86	131.7 ± 0.23	91 ± 0.03	6.44 ± 0.03	48 ± 1.81
F4	0.20 ± 0.03	192 ± 1.58	135.2 ± 0.4	93 ± 0.01	6.46 ± 0.05	42 ± 0.23
F5	0.16 ± 0.03	193 ± 1.52	124 ± 0.1	93 ± 0.03	6.51 ± 0.2	62 ± 0.70
F6	0.135 ± 0.03	190 ± 2.51	118 ± 0.2	94 ± 0.01	6.90 ± 0.3	59.3 ± 1.78
F7	0.142 ± 0.02	187 ± 2.51	128 ± 0.5	95 ± 0.03	6.89 ± 0.3	55 ± 0.35
F8	0.138 ± 0.01	197 ± 4.16	118.2 ± 0.3	96 ± 0.3	6.49 ± 0.02	58.33 ± 1.08

*n=3

Table 7: Report of X-ray diffraction studies of HAMS oral powder and HAMS oral film (best formulation)

Content	HAMS Powder	HAMS Oral film
No. of Peaks	5	5
Area of crystalline peaks	22544.24	11068.08
Peak value	17.09°, 19.60°, 22.18° (2θ)	5.62°, 15.50° (2θ)
Crystallinity index	39.02	40.68

model adequacy was checked by residual analysis. These were produced for each response variable and the polynomial equation[29] for the experimental design is generally represented as follows.

$$Y = \beta_0+\beta_1X_1+\beta_2X_2+\beta_1\beta_2X_1X_2$$

Where Y is the dependent variable, b0 is the arithmetic mean of the eight runs and b1 is the coefficient for the corresponding factor.

For HPMC E 50 Films

The polynomial equations obtained in analysis for the TS, PE, and disintegration time which are summarized as,

TS = 211.93+86.74 X1+35.39X2+28.89 X1X2
PE = 97.35–2.32 X1–9.14 X2+17.21 X1X2
DT = 52.38–4.88 X1–4.63 X2–1.37 X1X2

A positive sign of the coefficient for X1 and X2 specifies that the increase in the concentration of HPMC E 50 and CP increases the TS which can be confirmed with its R^2 value of 0.9706. The negative signs in the equations of PE and DT denote that the increasing concentration of independent variables might decrease the elasticity of the film and result in faster disintegration.[22] ANOVA for 2 FI model values is tabulated in Table 8, and ANOVA for a linear model for both polymers is shown in Table 9. The interaction effect of the two variables was found to be significant on the TS of the film than PE. The above regression analysis findings were well established by the results of ANOVA. 2FI and linear model were found to be significant models with $P < 0.05$ for TS, PE, and DT respectively. Furthermore, the lack of fit for the linear model being not significant.[30] The corresponding response surface plots are presented in Figure 6.

For HAMS films,

The regression analysis was carried out similar to HPMC E 50 films and the polynomial equations for the responses were as follows.

TS = 746.15+362.71X1+203.84 X2+155.01 X1X2
PE = 180.68+30.06X1–4.52 X2–20.01 X1X2
DT = 60.63–0.1250 X1–2.63X2+0.3750X1X2

Table 8: Report of analysis of variance for 2 FI model of optimized fast-dissolving oral film of salbutamol sulfate

Polymer	Source	Sum of squares	df	Mean square	F-value	*P*-value	
HPMC (TS)	Model	76883.87	3	25627.96	44.02	0.0016	Significant
HPMC (PE)	Model	3081.19	3	1027.06	13.06	0.0156	Significant
HAMS (TS)	Model	1.577	3	5.257	62.96	0.0008	Significant
HAMS (PE)	Model	10594.49	3	3531.50	7.06	0.0447	Significant

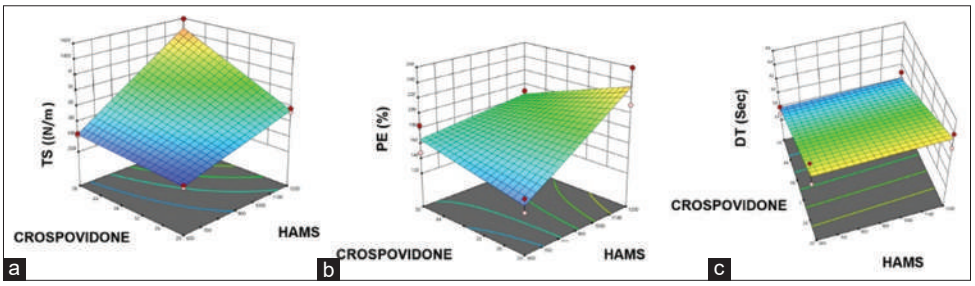

Figure 7: Response surface plot of factorial variable on tensile strength (a) percentage elongation at break (b), and disintegration time (c) for HAMS

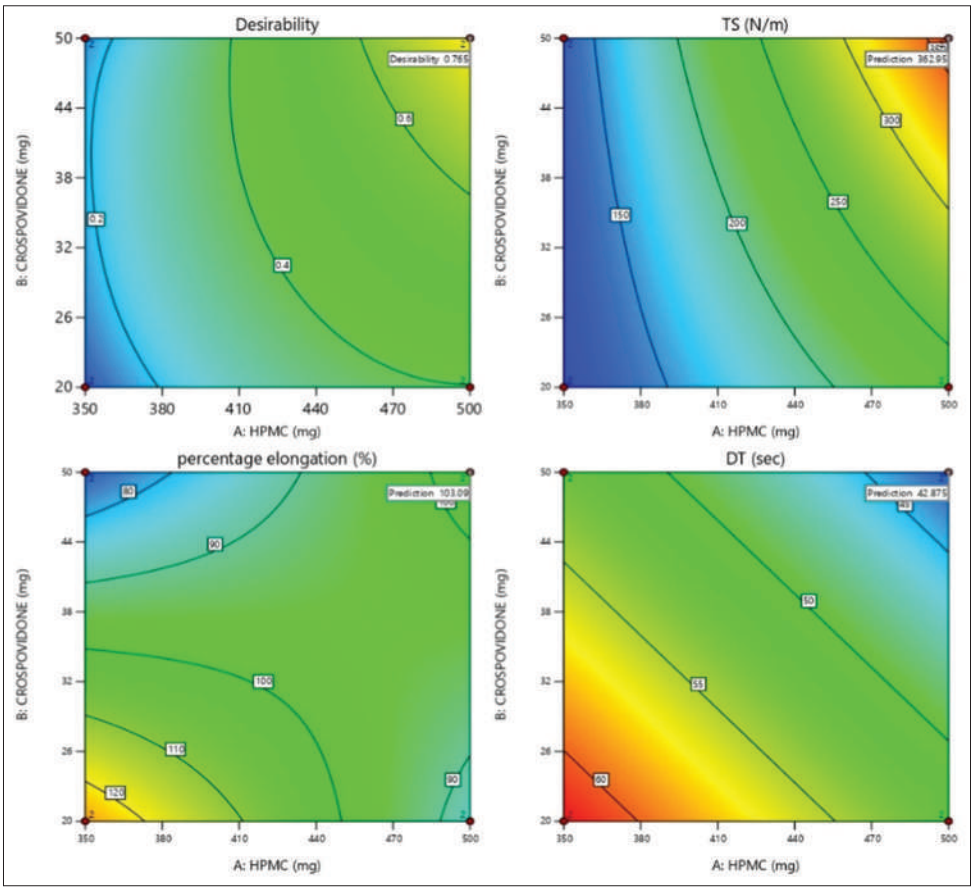

Figure 8: Desirability graph (HPMC E50 oral films)

The coefficient values in the equation reveal that an increase in the concentration of HAMS has a positive effect on the TS and PE of the films. The change in HAMS concentration has shown the least influence on the DT of the films. DT of the films has been influenced by the concentration of CP. Furthermore, CP has exhibited a positive effect on the TS of the films. The change in the amounts of HAMS and CP has an interactive effect mainly on the TS and PE of the film rather than DT. All these findings were well correlated with the ANOVA results. 2FI model was considered as the significant model with $P = 0.0008$ and 0.0447 for TS and PE, respectively. As the DT was not found to be affected by

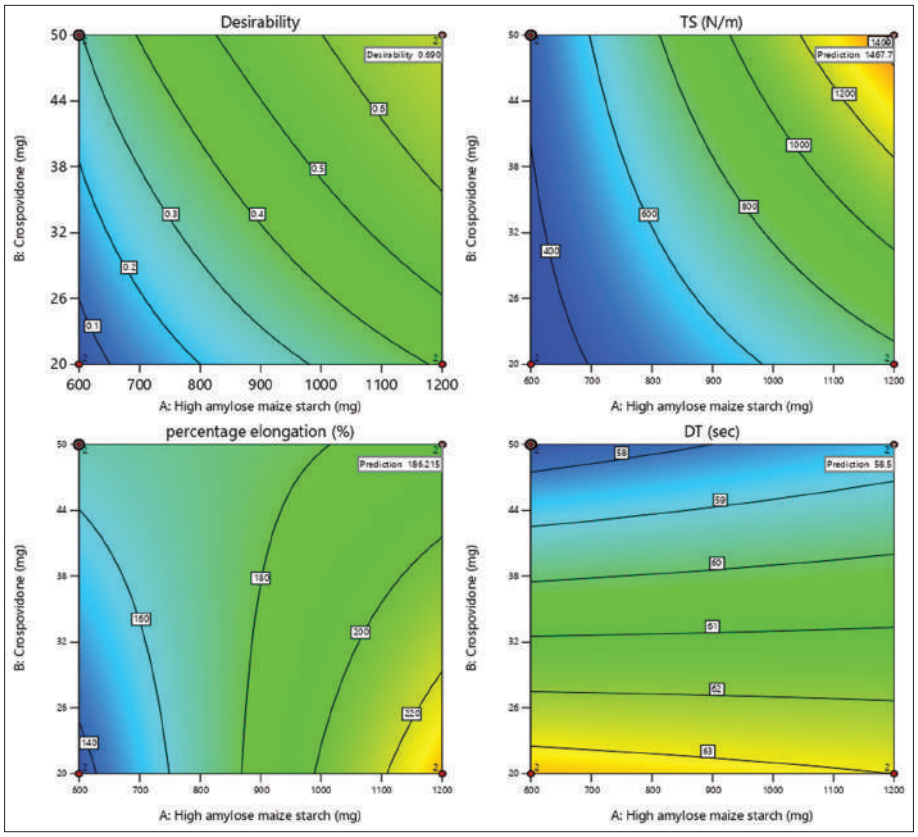

Figure 9: Desirability graph (HAMS oral films)

Table 9: Report of analysis of variance for linear model of optimized fast-dissolving oral films of salbutamol sulfate

Polymer	Source	Sum of squares	df	Mean square	F-value	*P*-value	
HPMC (DT)	Model	376.38	3	25627.96	43.64	0.0016	Significant
HPMC (DT)	Model	55.25	2	27.62	13.06	0.0067	Significant

Table 10: Desirability table for optimized fast-dissolving oral films of salbutamol sulfate

Polymer	HPMC E50	CP	TS	PE	DT	Desirability
HPMC E50	500.000	50.000	362.950	103.090	42.875	0.865
HAMS	1200.000	50.000	1467.700	186.215	58.125	0.903

the interaction of variables, so, it fits the linear model with $P = 0.0008$ and lack of fit being non-significant.[30] The corresponding response surface plots are shown in Figure 7.

Desirability Graph

The desirability function is exploited to discover the finest batch among the formulation. In both cases, a high concentration of polymer and super disintegrate shows optimized solution of desirability 0.865 and 0.903 for HPMC E50 and HAMS, respectively, and it is shown in Table 10. The desired optimum concentration of HPMC E 50 and HAMS was formulated and assessed for thickness, folding endurance, weight variation, uniformity of content, and surface pH, mechanical properties such as TS, PE, *in vitro*

Table 11: Characterization of optimized best formulation of fast-dissolving oral films of salbutamol sulfate

Characterization	HPMC E50	HAMS
Weight Variation	139 mg	116.5 mg
Folding Endurance	195 folds	198 Folds
Thickness	0.31 mm	0.135 mm
In vitro Disintegration	49 s	55 s
In vitro drug release	88.5%	96.9%
Tensile strength	352.2 N/m	1478.1 N/m
Percentage Elongation at break	114%	142%
Surface pH	6.48	6.55
Content Uniformity	92%	96%

disintegration, and *in vitro* dissolution studies.[22,30] All the values are within the limit and the values are tabulated in Table 11. The desirability graph for optimized HPMC E50 and HAMS Oral films were represented in Figures 8 and 9 respectively.

CONCLUSION

FDOFs of salbutamol sulfate were formulated using HAMS as a film-forming agent by solvent-casting technique and compared with HPMC E50. The study has demonstrated the film-forming ability of HAMS, a natural, and biodegradable polymer. HAMS films were found to have similar *in vitro* disintegration, dissolution characteristics, and improved mechanical properties as that of the HPMC E 50 films. XRD study of the HAMS films confirmed the crystallinity of the polymer which might have contributed to the excellent mechanical property of the formulated HAMS oral films. The factors influencing film formation and the optimized film formulation were established by factorial experimental design.

Therefore, HAMS was found to be a promising novel film-forming polymer in the development of fast-dissolving oral films. Further, the study can be substantiated by investigating the role of plasticizer on the mechanical properties of the films and the stability of the films. Thus, the oral film was a promising tool for developing salbutamol sulfate as an oral film, thereby enhancing patients' compliance and fast onset of action.

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REFERENCES

1. Yir-Erong B, Bayor MT, Ayensu I, Gbedema SY, Boateng JS. Oral thin films as a remedy for noncompliance in pediatric and geriatric patients. Ther Deliv 2019;10:443-64.
2. Nagaraju T, Gowthami R, Rajashekar M, Sandeep S, Mallesham M, Sathish D, *et al*. Comprehensive review on oral disintegrating films. Curr Drug Deliv 2013;10:96-108.
3. SevincOzakar R, Ozakar E. Current overview of oral thin films. Turk J Pharm Sci 2021;18:111-21.
4. Pimparade MB, Vo A, Maurya AS, Bae J, Morott JT, Feng X, *et al*. Development and evaluation of an oral fat disintegrating anti-allergic film using hot-melt extrusion technology. Eur J Pharm Biopharm 2017;119:81-90.
5. Uddin M, Allon A, Roni MA, Kouzi S. Overview and future potential of fast dissolving buccal films as drug delivery system for vaccines. J Pharm Pharm Sci 2019;22:388-406.
6. Ngo HV, Tran P, Zhong L. Formulation and evaluation fast disintegrating film salbutamol sulfate using HPMC E15. J Phys Conf Ser 2019;10:1742-6592.
7. Pacheco MS, Barbieri D, da Silva CF, de Moraes MA. A review on orally disintegrating films (ODFs) made from natural polymers such as pullulan, maltodextrin, starch and others. Int J Biol Macromol 2021;178:504-13.
8. Zhai X, Gao S, Xiang Y, Wang A, Li Z, Cui B, *et al*. Cationized high amylose maize starch films reinforced with borax cross-linked nanocellulose. Int J Biol Macromol 2021;193:1421-9.
9. Menzel C, Andersson M, Andersson R, Vázquez-Gutiérrez JL, Daniel G, Langton M, *et al*. Improved material properties of solution-cast starch films: Effect of varying amylopectin structure and amylose content of starch from genetically modified potatoes. Carbohydr Polym 2015;130:388-97.
10. Hernandez-Perez P, Flores-Silva PC, Velazquez G, Morales-Sanchez E, Rodríguez-Fernández O, Hernández-Hernández E, *et al*. Rheological performance of film-forming solutions made from plasma-modified starches with different amylose/amylopectin content. Carbohydr Polym 2021;255:117349.
11. Meneguin AB, Cury BS, Evangelista RC. Films from resistant starch-pectin dispersions intended for colonic drug delivery. Carbohydr Polym 2014;99:140-9.
12. Zhang C, Chen F, Meng W, Li C, Cui R, Xia Z, *et al*. Polyurethane prepolymer-modified high content starch-PBAT films.Carbohydr Polym 2021;253:117168.
13. Chen J, Li X, Chen L, Xie F. Starch film-coated microparticles for oral colon-specific drug delivery. Carbohydr Polym 2018;191:242-54.
14. Kumria R, Nair AB, Al-Dhubiab BE. Loratidine buccal films for allergic rhinitis: Development and evaluation. Drug Dev Ind Pharm 2014;40:625-31.
15. Musale VP, Lifescience M, Limited P, Collage MP. Research article study of physicochemical compatibility of inhalation grade active ingredients with propellant HFA 134a by FTIR. Int J Pharm Sci Rev Res 2018;49:53-7.
16. Dankar I, Haddarah A, Omar FE, Pujola M, Sepulcre F. Characterization of food additive-potato starch complexes by FTIR and X-ray diffraction. Food Chem 2018;260:7-12.
17. Qurrat-Ul-Ain K, Siddique MI, Rasool F, Naeem M, Usman M, Zaman M. Development and characterization of orodispersible film containing cefixime trihydrate. Drug Dev Ind Pharm 2020;46:2070-80.
18. Cardelle-Cobas A, Madureira AR, Costa E, Barros R, Tavaria FK, *et al*. Development of oral strips containing chitosan as active ingredient: A product for buccal health. Int J Polym Mater Polym Biomater 2015;64:906-18.

19. Nalluri BN, Sravani B, Maheswari KM, Srianusha VS, Bramhini RS. Development and evaluation of mouth dissolving films of salbutamol sulfate. J Chem Pharm Res 2013;5:53-60.
20. Gupta B, Chaurasia U, Chakraborty P. Design and development of oral transmucosal film for delivery of salbutamol sulphate. J Pharm Chem Biol Sci 2014;2:118-29.
21. Pandey GS, Kumar R, Sharma R, Singh Y. Development and optimization of oral fast dissolving film of salbutamol sulphate by design of experiment. Am J PharmTech Res 2013;3:1-17.
22. Sudheer P, Shrestha S, Narayana KA. Amorphous solid dispersion based oral disintegrating film of Ezetimibe: Development and evaluation. Drug Metab Lett 2021;14:66-79.
23. Abdullah AH, Chalimah S, Primadona I, Hanantyo MH. Physical and chemical properties of corn, cassava, and potato starch. IOP Conf Ser Earth Environ Sci 2018;160:1755-315.
24. Alaei S, Omidi Y, Omidian H. *In vitro* evaluation of adhesion and mechanical properties of oral thin films. Eur J Pharm Sci 2021;166:105965.
25. Ashri LY, Abou El Ela AE, Ibrahim MA, Alshora DH, Naguib MJ. Optimization and evaluation of chitosan buccal films containing tenoxicam for treating chronic periodontitis: *In vitro* and *in vivo* studies: J Drug Deliv Sci Technol 2020;57:101720.
26. Domene-Lopez D, García-Quesada JC, Martin-Gullon I, Montalban MG. Influence of starch composition and molecular weight on physicochemical properties of biodegradable films. Polymers (Basel) 2019;11:1-17.
27. Bisharat L,Barker SA, Narbad A, Craig DQ. *In vitro* drug release from acetylated high amylose starch-zein films for oral colon-specific drug delivery. Int J Pharm 2019;556:311-9.
28. Rezaee F, Ganji F. Formulation, characterization, and optimization of captopril fast-dissolving oral films. AAPS PharmSciTech 2018;19:2203-12.
29. Imran AM, Sudhakar P, Altaf MA. Design and evaluation of optimized fast dissolving tablets. Int Res J Pharm 2018;10:31436-46.
30. Rigon RB, Goncalez ML, Severino P, Alves DA, Santana MH, Souto EB, *et al*. Solid lipid nanoparticles optimized by 2^2 factorial design for skin administartion: Cytotoxicity in NIH3T3 fibroblasts.Colloids Surf B Biointerfaces 2018;171:501.

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