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Original Article

DESIGN, DEVELOPMENT AND OPTIMIZATION OF MOUTH DISSOLVING TABLET OF AMBRISENTAN USING DESIGN EXPERT SOFTWARE

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ABSTRACT

Objective: The rationale of the current work is to design, develop and optimize of mouth dissolving tablet of ambrisentan to treat hypertension.

Methods: Sodium starch glycolate and crospovidone were used as the super disintegrants in the direct compression method to create nine ambrisentan mouth-dissolving tablet formulations. Wetting time, drug content, *in vitro* disintegration time, dispersion time, and dissolution time were all assessed for the produced formulations.

Results: Based on the results obtained, formulation F6 containing 30 mg of crospovidone exhibited good wetting time, dispersion time, disintegration time and drug release. The hardness of formulations AS1 to AS9 was found to be in the range of 2.5 to 3.11 Kg/cm^2. The friability of formulations AS1 to AS9 was found to be less than 1%. A water absorption ratio was performed for ensuring the moisture sorption and water uptake properties of super disintegrants. The *in vitro* drug release of formulation AS6 containing a concentration of Crospovidone 30 mg, shows 91.30% drug release respectively at the end of 12 min.

Conclusion: The mouth-dissolving tablets of ambrisentan were successfully designed, developed, and fabricated. It can be reasonably concluded that the AS6 batch of mouth-dissolving tablets of ambrisentan with 30 mg of crospovidone exhibited maximum cumulative drug release in 12 min.

Keywords: Superdisintegrants, Ambrisentan, Crospovidone, Optimization, Mouth dissolving tablet

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INTRODUCTION

Mouth-dissolving drug delivery systems (MDDDS) are a new class of formulations that combine the benefits of traditional tablet and liquid dosage forms while also providing additional benefits over both of the older dosage forms [1]. They allow both the ease of ingesting offered by a liquid formulation and the convenience of a tablet formulation [2]. Compared to the main alternative, oral liquids, MDDDS has the luxury of offering far more precise dosing [3]. This type of formulation is specifically made for patients who have dysphagia, are elderly, young, bedridden, traveling, or are psychotic and unable to swallow standard oral medications. For dysphagic, pediatric, and geriatric patients with swallowing issues, MDDDS are the most practical dosage forms since they dissolve/disintegrate quickly when placed in the mouth [4]. They are a fantastic choice for travelers and people who are bedridden because they do not require water for administration. Psychotic individuals cannot conceal them in the mouth since they simply disappear when put there. Due to the line extension of the current formulation, these medications not only improve patient compliance but also generate significant profits for the makers [1, 3].

A persistently raised blood artery pressure is a defining feature of hypertension, also known as high or rising blood pressure. Every part of the body receives blood via the veins from the heart. With each beat, the heart pumps blood into the vessels [5]. Blood pressure is produced as a result of the heart's pumping action on the walls of blood vessels (arteries). When the pressure is greater, the heart must use more effort to pump blood. Hypertension, a serious medical disease, can increase your risk of having heart, brain, kidney, and other issues. The disorder affects more than a billion people worldwide-roughly 1 in 4 men and 1 in 5 women-and is a substantial cause of premature death. The fact that low-and middle-income countries account for two-thirds of cases of hypertension is partially attributable to the increase in risk factors in those populations over the past few decades. The current work aims to design, develop, and fabricate a mouth-dissolving tablet of ambrisentan to treat hypertension [5].

MATERIALS AND METHODS

Materials

The active pharmaceutical ingredient Ambrisentan was procured from MSN laboratories, Hyderabad. The other excipients, such as magnesium stearate, purified talc, and mannitol, were procured from SD Fine Chemicals (Mumbai). Sodium starch glycolate and crospovidone sodium were purchased from Prerana Enterprises (Ahmednagar), and lactose was purchased from Research fine chem industries (Mumbai).

Methods

Experimental design

3^2 full factorial design was employed for optimization of polymer-plasticizer ratio. This design involved conducting experimental trials in all nine feasible combinations while evaluating each of the two components at three different levels. Crospovidone polymer amount (X1) and SSG plasticizer amount (X2) were considered independent variables, and each factor was examined at levels of-1, 0, and+1. Table 1 lists the independent variable levels that were used as well as the entire factorial design layout of the variables. In table 2, the various mouth-dissolving tablet compositions are listed [6].

Table 1: Independent variables design

Factor	The level used, actual (coded)		
Independent variables	**Low (-1)**	**Medium (0)**	**High (+1)**
X1 = Concentration of polymer (mg)	20	30	40
X2 = Concentration of plasticizer (mg)	5	10	15

Table 2: Design layout of 3^2 factorial designs [7]

Formulation batches	X_1	X_2
AS1	−1	−1
AS2	0	−1
AS3	+1	−1
AS4	−1	0
AS5	0	0
AS6	+1	0
AS7	−1	+1
AS8	0	+1
AS9	+1	+1

Where 1 is the high value, −1 is the low value, and 0 is the center value for the factors X1 and X2. X1: amount of Crospovidone, X2: amount of SSG

Table 3: Composition of 3^2 factorial design batches of fast-dissolving tablets

S. No.	Ingredients (mg)	AS1	AS2	AS3	AS4	AS5	AS6	AS7	AS8	AS9
1	Ambrisentan	5	5	5	5	5	5	5	5	5
2	SSG	5	5	5	10	10	10	15	15	15
3	Cross povidone	20	30	40	20	30	40	20	30	40
4	Mag. Stearate	1	1	1	1	1	1	1	1	1
5	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6	Lactose	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

Procedure for preparation of Mouth dissolving tablet

Ambrisentan MDT tablets were prepared using the direct compression process and a super disintegrating agent, such as cross povidone [8, 9]. The medicine, super-disintegrant, diluents, and sweetening agent were properly combined after being screened using a 40-mesh screen. Talc and SSG were mixed and then screened through an 80-mesh screen. Thus, the powder obtained was compressed into tablets on 8 station punch rotary tablet compression machine. For tableting, a biconvex punch with a 6 mm diameter was employed [10].

Evaluation of Mouth dissolving tablet

Pre-compression parameters

Bulk density

2 gm of granules were precisely weighed after passing through a 20# sieve and then transferred to a 10 ml graduated cylinder. Without compacting, the powder was carefully leveled and the apparent unsettled volume (V0) was read. The apparent bulk density in gm/ml was calculated using the following formula [11]:

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk volume}} \ldots\ldots (1)$$

Tapped density

The sample was weighed accurately. 2 grams of granules were taken after passing through a 20# sieve and placed into a 10 ml graduated cylinder. The sample container was then subjected to mechanical tapping, as it was raised and allowed to fall under its own weight using a mechanically tapped density tester at a nominal rate of 100 drops. Following this, the tapped volume was measured to the nearest graduated unit. The formula below was employed to determine the tapped bulk density in gm/ml [12]:

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume}} \ldots\ldots\ldots (2)$$

Carr's Index

Carr's compressibility index was used to calculate the powder blend's compressibility index. It was a straightforward test to determine a powder's BD, TD, and rate of packing down. The following is the formula for Carr's Index [13]:

$$\text{Carr}'\text{s index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped volume}} \times 100 \ldots\ldots (3)$$

Hausner's ratio

The flowability of a powder or granular substance can be measured using Hausner's ratio [12].

$$\text{Hausner}'\text{s Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \ldots\ldots (4)$$

Angle of repose

The angle of repose of the powder was calculated via the funnel technique. It was stuffed with the carefully proportioned powder combination. The height of the funnel was set such that the tip just touched the top of the powder mixture. The funnel was left propped open, allowing the powder combination to flow through and across the top. The diameter of the powder cone was measured, and the angle of repose was calculated using the equation below [11].

$$\boldsymbol{\theta} = \text{Tan}^{-1}\frac{h}{r} \ldots\ldots\ldots (5)$$

Where h and r are the height and radius of the powder cone, respectively [14].

Post-compression parameters

Tablet thickness

Tablet thickness is a crucial element in both duplicating appearance and counting with filling machinery. The uniform thickness of the tablets is used as a counting mechanism by some filling equipment. Micrometer was used to measure thickness [13].

Weight variation

Twenty tablets were chosen at random from each formulation, and their average weight was calculated. Individual tablets were then weighed and compared to the mean weight [15].

Friability

For assessing the friability, Roche friabilator was utilized. Twenty tablets was be precisely weighed before being inserted in the 25 rpm-revolving tumblers. After four minutes, the tablets was be weighed and the % weight loss was be calculated [16].

$$\%\ \text{Friability} = \frac{\text{initial wt.of tablets} - \text{Final wt.of tablet}}{\text{Initial wt.of tablets}} \times 100 \ldots\ldots\ldots (6)$$

Hardness

The tablets' crushing strength was determined using a Monsanto hardness tester. Three tablets were randomly sampled from each formulation batch, and the average reading was recorded [17].

Wetting time

12 cm × 10.75 cm of double-folded tissue paper was placed in a 9 cm-diameter Petri dish containing 9 ml of buffer solution pH 6.8. On the paper, a tablet was inserted and the time required for

complete wetness was recorded. Three tablets were chosen at random from each formulation, and the average wetting time was recorded [18].

Water absorption ratio (%)

Two-folded tissue paper was placed in a tiny Petri dish holding 6 milliliters of water. On the paper, a tablet was placed, and the time required for complete soaking was measured. The moistened tablet was afterward weighed. R, the water absorption ratio, was calculated using the following equation [19]:

$$R = 10\ (Wa/Wb) \ldots\ldots (7)$$

Where,

Wb is the weight of the tablet before water absorption

Wa is the weight of the tablet after water absorption.

Disintegration time

The disintegration time of each formulation was determined using tablet disintegration testing equipment. Six tablets were inserted individually in each tube of disintegration testing equipment with simulated saliva, followed by the placement of discs. The time required for the full tablet to dissolve was recorded [20, 21].

Drug content

Twenty tablets were weighed and ground into a powder. The powder corresponding to 10 mg of Ambrisentan was dissolved in 100 ml of 0.1N HCl, filtered with Whatman filter paper No. 42, diluted appropriately, and analyzed for drug concentration at 287 nm using a UV-Visible spectrophotometer (UV 160-Shimadzu, Japan) [22].

Dissolution test

The release of MDT was measured using USP type 2 dissolution testing equipment (paddle method). The dissolution test was conducted with 900cc of 0.1N HCl at 37.5 °C and 100 revolutions per minute. At various time intervals, samples of the solution were removed from the dissolution equipment and replaced with fresh dissolution media. At 287 nm, the absorbance of these solutions was measured. Derived from an equation derived from a standard curve [23].

***In vitro* drug release study**

In vitro, dissolving has been validated for the development of oral dosage forms. It is used to predict *in vivo* tablet dissolving. The *in vitro* release of mouth-dissolving tablets was measured using apparatus I of the USP XXIII tablet dissolution test apparatus. The dissolution equipment utilized a phosphate buffer with a pH of 6.8 (900 ml) and a temperature of 37.1 °C. At various intervals, 10 ml samples were extracted and the volume of media was maintained by adding fresh media to the chamber. At 287 nm, the aliquots were analyzed spectrophotometrically for Ambrisentan [24].

FTIR spectral analysis

Through the use of an FTIR spectrophotometer, the FTIR spectra of pure drug, physical mixture, and formulation F3 (after storage under accelerated circumstances) were recorded. The samples were scanned between 4000 and 500 cm^{-1} [25].

Differential scanning calorimetry (DSC) studies

DSC analysis was used to compare the melting enthalpy, glass transition temperature, and interactions of the medication Ambrisentan (pure drug) with Excipients. The investigation was conducted with DSC Q1000 TA equipment. Approximately 2-5 mg of sample was put in standard aluminum pans and scanned from 5 °C to above its melting point at a rate of 10 °C/min with dry nitrogen (flow rate 50 ml/min) as the effluent gas [26].

Statistical analysis

The data were analyzed using GraphPad Prism 5.0 and displayed as mean (SD) (GraphPad Software, Inc., San Diego, CA, USA). Using Design Expert software Version 13.0, the formulation was optimized. Using ANOVA, a difference below the probability threshold of P-value = 0.05 was calculated.

RESULTS AND DISCUSSION

RESULTS

Drug-excipient compatibility study

FTIR spectral analysis

The FTIR spectra of the pure drug and physical mixture (Pure drug+Excipient) were recorded using an FTIR spectrophotometer (Shimadzu IRxross). The samples were scanned over a range of 4000-500 cm^{-1} [27].

Differential scanning calorimetry (DSC) studies

The DSC thermogram of the Ambrisentan tablet physical mixture is depicted in fig. 7 and 8.

Post-compression parameters of MDT

The post-compression parameters of formulations AS1 to AS9, such as hardness, friability, weight variation, wetting time, disintegration time, water absorption ratio, and drug content, are given in tables 5 and 6.

***In vitro* dissolution study of MDT**

The % cumulative drug release (% CDR) profile of formulation AS1 to AS7 is shown in fig. 5.

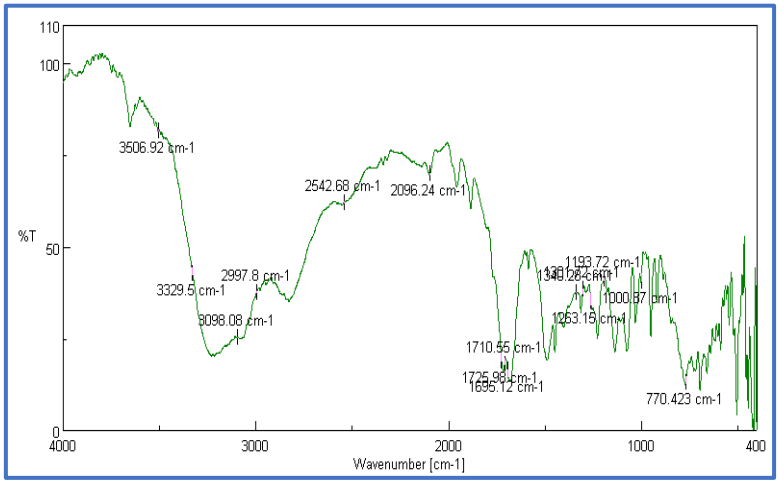

Fig. 1: IR spectra of extract (Ambrisentan)

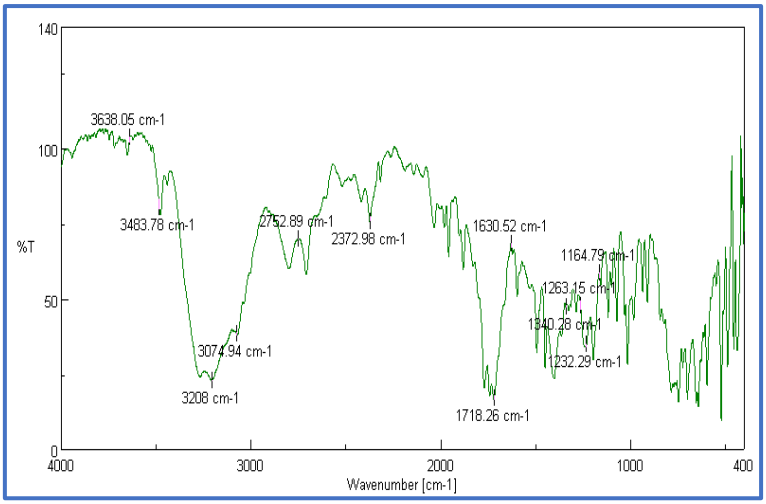

Fig. 2: IR spectra of pure extract+excipients

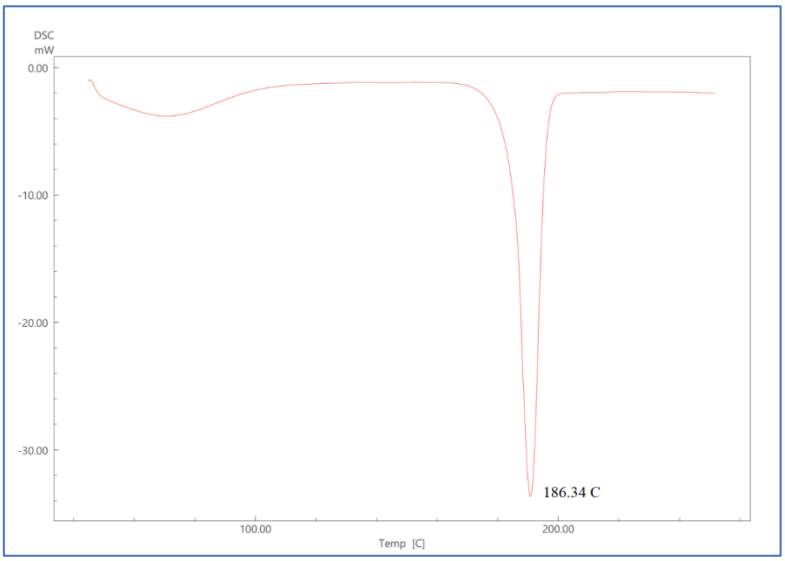

Fig. 3: DSC of pure drug (Ambrisentan)

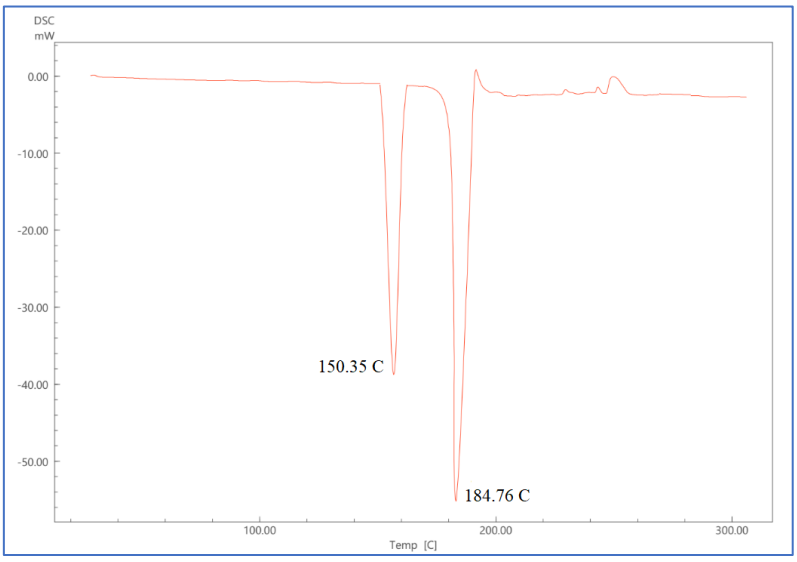

Fig. 4: DSC of pure drug+excipients

Table 4: Results of pre-compression parameters

F. code	Bulk density	Tapped density	% Carr's index	Hausner's ratio	Angle of repose
AS1	0.63±0.025	0.54±0.78	8.42±3.22	1.185±0.96	22.63±3.45
AS2	0.55±0.041	0.69±0.64	7.46±2.34	1.084±0.78	21.63±3.14
AS3	0.65±0.025	0.68±0.34	7.94±2.14	1.078±0.89	22.32±2.45
AS4	0.57±0.024	0.64±0.96	7.74±1.47	1.087±0.96	22.84±3.66
AS5	0.63±0.078	0.66±0.79	8.56±1.98	1.114±0.94	22.96±3.47
AS6	0.68±0.096	0.59±0.93	6.42±1.46	1.144±0.91	22.98±2.14
AS7	0.58±0.063	0.63±0.88	9.06±2.45	1.091±0.90	22.83±2.36
AS8	0.59±0.015	0.61±0.36	7.44±1.23	1.096±0.88	23.75±2.45
AS9	0.57±0.014	0.59±0.78	8.36±2.34	1.083±0.87	23.96±2.96

Values are expressed in mean±SD (n=6).

Table 5: Post-compression parameters of MDT

Batch No.	Hardness (Kg/cm^2)	Weight variation (mg)	Wetting time (sec)
AS1	2.53±0.29	99.14±0.01	559.56±2.08
AS2	2.56±0.29	102.12±0.01	1051±1.52
AS3	2.61±0.17	95.74±0.01	1544±4.35
AS4	2.69±0.29	99.12±0.00	546.5±1.52
AS5	2.76±0.29	102.82±0.00	1045.7±1.52
AS6	2.87±0.17	100.21±0.00	1541.25±1.00
AS7	3.11±0.17	100.78±0.01	540.5±1.00
AS8	2.61±0.17	95.74±0.01	1037±1.52
AS9	2.69±0.29	99.12±0.00	1529.75±4.35

Values are expressed in mean±SD (n=6).

Table 6: Post compression parameters of MDT

Batch No.	Disintegration time (sec)*	Friability (%)	Water absorption ratio (%)*	Drug content (%)
AS1	59.56±2.08	0.75	66.48	98.30±0.26
AS2	51±1.52	0.71	72.16	99.50±0.43
AS3	44±4.35	0.69	74.35	98.21±0.36
AS4	46.5±1.52	0.64	78.54	98.32±0.53
AS5	45.7±1.52	0.55	83.74	98.83±0.42
AS6	41.25±1.00	0.49	86.92	99.38±0.33
AS7	40.5±1.00	0.43	88.52	99.54±0.74
AS8	37±1.52	0.71	72.16	99.50±0.43
AS9	29.75±4.35	0.69	74.35	98.21±0.36

*Values are expressed in mean±SD (n=6).

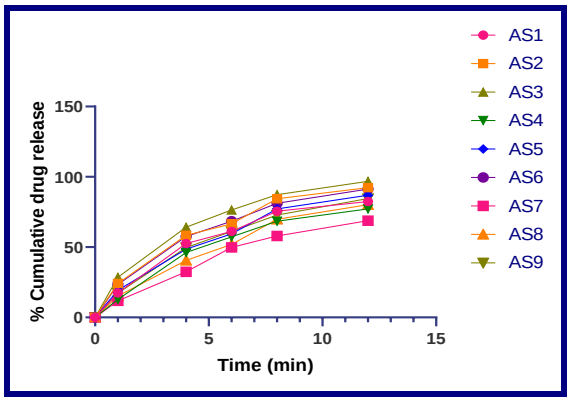

Fig. 5: A plot of *in vitro* % CDR of MDT

Table 7: ANOVA of quadratic models for Y1 (Type III–Partial)

Source	Sum of squares	df	Mean square	F-value	p-value	
Model	548.16	5	109.63	13.76	0.0279	significant
A-Crosspovidone	373.04	1	373.04	46.82	0.0064	
B-SSG	166.01	1	166.01	20.83	0.0197	
AB	5.78	1	5.78	0.7259	0.4568	
A^2	1.44	1	1.44	0.1806	0.6995	
B^2	1.89	1	1.89	0.2378	0.6592	
Residual	23.9	3	7.97			
Cor Total	572.07	8				

Abbreviation: ANOVA, analysis of variance.

Table 8: Value of R^2 for disintegration time (Y1)

Parameters	Values	Parameters	Values
Std. Dev.	2.82	R^2	0.9582
Mean	43.92	Adjusted R^2	0.8886
C. V. %	6.43	Predicted R^2	0.4966
		Adeq Precision	11.4066

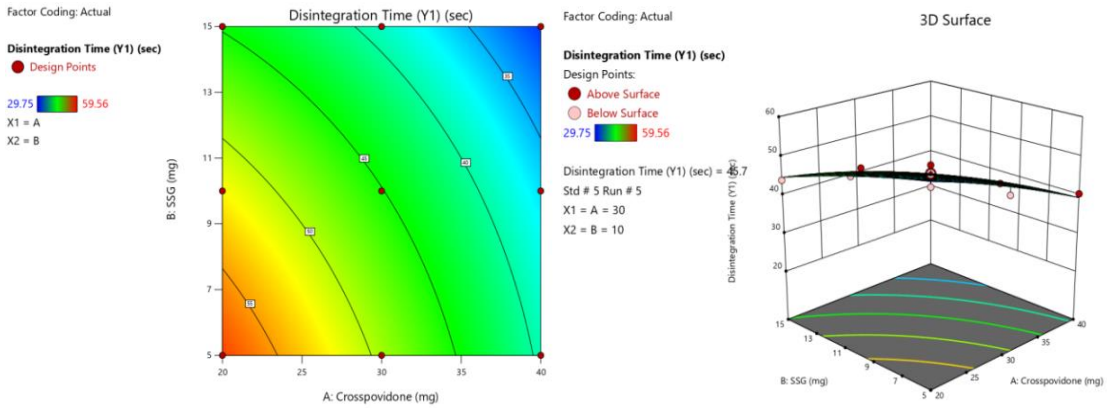

Fig. 6: 2D and 3D response surface plot showing the effect of the amount of cross povidone (X1) and SSG (X2) on disintegration time (Y1)

ANOVA of models for wetting time (Y2)

Table 9: ANOVA of quadratic models for Y2 (Type III–Partial)

Source	Sum of squares	df	Mean square	F-value	p-value	
Model	641.88	5	128.38	13.58	0.0284	**significant**
A-Crosspovidone	452	1	452	47.82	0.0062	
B-SSG	187.97	1	187.97	19.89	0.021	
AB	0.0992	1	0.0992	0.0105	0.9249	
A^2	1.59	1	1.59	0.1682	0.7093	
B^2	0.2158	1	0.2158	0.0228	0.8895	
Residual	28.36	3	9.45			
Cor Total	670.23	8				

Abbreviation: ANOVA, analysis of variance.

Table 10: Value of R^2 for wetting time (Y2)

Parameters	Values	Parameters	Values
Std. Dev.	3.07	R^2	0.9577
Mean	41.79	Adjusted R^2	0.8872
C. V. %	7.36	Predicted R^2	0.5607
		Adeq Precision	11.3742

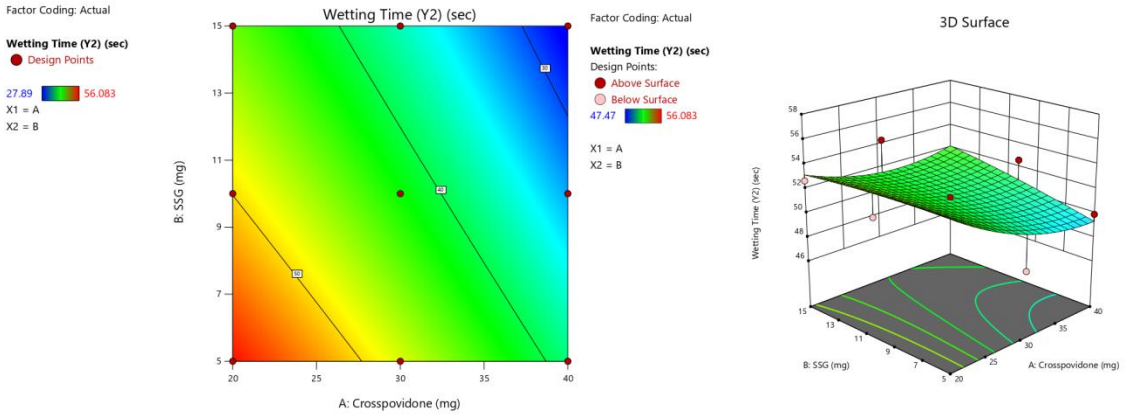

Fig. 7: 2D and 3D response surface plot showing the effect of the amount of cross povidone (X1) and SSG (X2) on wetting time (Y2)

ANOVA of models for drug release (Y3)

Table 11: ANOVA of quadratic models for Y3 (Type III–partial)

Source	Sum of squares	df	Mean square	F-value	p-value	
Model	8722.83	5	1744.57	851.57	<0.0001	**significant**
A-Crosspovidone	7526.98	1	7526.98	3674.12	<0.0001	
B-SSG	761.19	1	761.19	371.56	0.0003	
AB	161.01	1	161.01	78.59	0.003	
A^2	272.58	1	272.58	133.06	0.0014	
B^2	1.07	1	1.07	0.5224	0.5221	
Residual	6.15	3	2.05			
Cor Total	8728.97	8				

Abbreviation: ANOVA, analysis of variance.

Table 12: Value of R^2 for drug release (Y3)

Parameters	Values	Parameters	Values
Std. Dev.	1.43	R^2	0.9993
Mean	35.62	Adjusted R^2	0.9981
C. V. %	4.02	Predicted R^2	0.9919
		Adeq Precision	79.8904

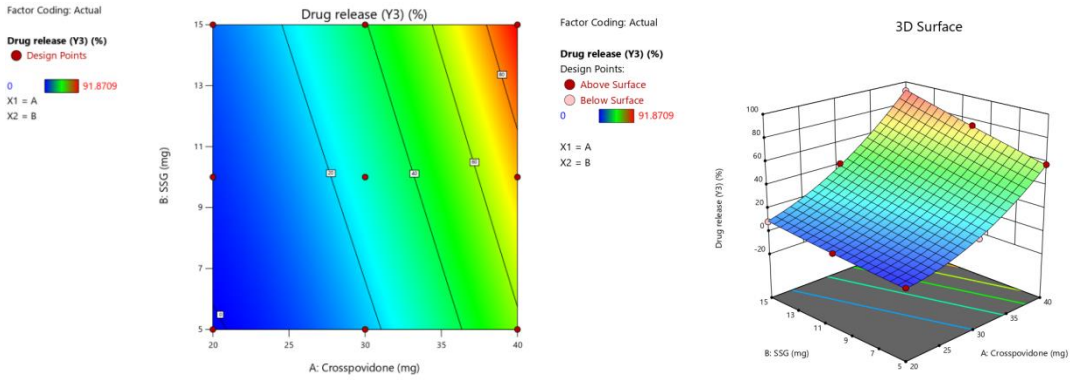

Fig. 8: 2D and 3D response surface plot showing the effect of the amount of crosspovidone (X1) and SSG (X2) on drug release (Y3)

DISCUSSION

Fig. 3 and 4 display the results of an Ambrisentan and physical tablet mixture DSC thermogram. Ambrisentan's thermogram displayed an endothermic peak at 186.34 °C. The DSC thermogram for the physical tablet mixture with pure medication added peaks at 150.35 °C and 184.76 °C. FTIR spectrophotometer results of FT-IR interaction investigation between Ambrisentan and excipients in formulations showed in fig. 1 and 2. The pellets were introduced into FTIR spectra after being produced on a KBr press. The spectra were captured in the range of 4000 to 400 cm-1 in wave number. N-H Stretch 3376.07 cm-1, OH Bend 3506.92 cm-1, C-H Bend 2997.8 cm-1, C=O 1725.98 cm-1, and C=C Aromatic 1695.12 cm-1 are the main IR peaks seen in Ambrisentan. The fact that the identical peak is present in the physical combination supports the absence of any excipient interaction.

The formulations AS1 to AS9 were found to have angles of repose ranging from 21.633.14 to 23.962.96 and the Hausner's ratio was found to be less than 1.25 for each formulation. It was discovered that Carr's index was under 16%. Knowing the formulation's bulk and tapped densities is crucial for determining the blend's compressibility. It was observed that all of the formulations' tapped densities were higher than their respective bulk densities, indicating that all of the powders had good compressibility [28]. All of the batches' flow characteristics of the powdered mixture were found to be good and free-flowing (table 4). All pre-compression settings adhere to the IP standard. The range of 2.5 to 3.11 Kg/cm^2 was discovered for the hardness of formulations AS1 to AS9 [29]. The table formulations AS1 through AS9 were determined to have friability of less than 1%. As a result, it was accepted following I. P. 2010. The disintegration of tablets is the most crucial factor that needs to be adjusted in the creation of MDT tablets. The rapid disintegration of the MDT tablets may be explained by the water's speedier entry into the tablet's pores, which may have caused super disintegrants to expand and provide sufficient hydrodynamic pressure for rapid and total disintegration. Wetting time was employed as a measure to correlate with oral cavity disintegration time since it is directly related to the inner structure of the tablets and the hydrophilicity of the excipients [30]. Wetting time may be the cause of disintegration because the breakdown process of a tablet depends on wetting time, followed by disintegration.

Tables 5 and 6 provide the wetting time and disintegration time for formulations AS1 to AS9, which demonstrates that tablets dissolve quickly. To ensure the moisture sorption and water uptake capabilities of super disintegrants, a water absorption ratio was carried out. Table 6 lists the medication concentration and water absorption ratio for formulations AS1 to AS9. The formulation AS6 with a Crospovidone concentration of 30 mg displays the fastest disintegration time. Drug concentration was determined from the standard calibration curve and expressed as the cumulative percent of the drug dissolved in the formulations used in the *in vitro* drug release tests shown in fig. 5. Crosspovidone (CP) concentration was inversely related to tablet dissolving time. Variable CP concentrations were utilized to shorten the time. Drug release at low CP concentration was reported to be 91.30% after 12 min. As a result, it was discovered that the time for drug release decreased by up to 5 min from 12 min as the concentration of CP was increased from 20 to 30 mg. The *in vitro* drug release of formulation AS6, which contains a 30 mg concentration of crospovidone, shows a

respective drug release rate of 81.20% after 8 min. Thus, it was determined that higher Crospovidone concentrations result in improved medication release. Better medication release was achieved with the AS6 formulation.

The 2D and 3D disintegration time is shown in fig. 6. Table 7 shows a statistically significant model is one with a model F-value of more than 13, which is 13.76. An F-value of this magnitude has a 2.79 percent chance of being caused by noise. P-values under 0.0500 indicate that model terms are important. Important model terms in this situation include A and B. If the values are more than 0.1000, the model terms are likely not statistically significant. Model reduction may help if your model includes a lot of extraneous terms (apart from those required to maintain hierarchy).

It suggested that there was a linear relationship between the independent factors and the Y1 disintegration time. The value of Y1 grew when polymer X1 and X2 concentrations increased (disintegration time). The contour map, which indicates that the concentration of X1 and X2 was optimal for the desired Y1, makes it plain that the region around the blue zone was in that region. Surface Plot (3D) demonstrated that the tablet's disintegration time increased along with the amount of crospovidone used. However, as the value of crospovidone increased from a lower to a higher range, so did the matrix system's disintegration time. The surface plot (3D) led to the conclusion that the combined action of the polymer had a significant impact on the system's disintegration time; therefore, the concentration must be kept at its ideal level to provide the intended outcomes. The difference between the Predicted R^2 of 0.4966 and the Adjusted R^2 of 0.8886 is larger than 0.2, contrary to what would be expected. This might be a sign of a significant block effect or a problem with your model and/or data. Considerations include model reduction, response transformation, outliers, and others. Confirmation runs should be used to verify all empirical models (table 8). Adeq Precision measures the signal-to-noise ratio. A ratio of at least four is ideal. Your ratio of 11.407 indicates a strong enough signal. To navigate the design space, this paradigm is helpful [31].

Final equation in terms of coded factors

Disintegration Time (Y1) =+45.13-7.88*A-5.26*B+1.2*AB-0.8483*A^2-0.9733*B^2

Final equation in terms of actual factors

Disintegration Time (Y1) =+74.993-0.52 *Crosspovidone-0.994 *SSG+0.0240* Crosspovidone *SSG-0.008483 *Crosspovidone^2-0.038933*SSG^2

Table 9 is despite the model being statistically significant, as shown by the Model F-value of 13.58. The likelihood that this F-value is the result of noise is 2.84 percent. Significant model terms are indicated by P-values lower than 0.05. Important model terms in this situation include A and B. If the values are more than 0.1000, the model terms are likely not statistically significant. Model reduction may help your model if it includes a lot of unnecessary words (apart from those required to maintain hierarchy) [10]. The response surface plot of Y2 (Wetting time) is displayed in fig. **7**.

Final equation in terms of coded factors

Wetting Time (Y2) =+42.16-8.68*A-5.6*B-0.1575*AB-0.8915*A^2+0.3285*B^2

Final equation in terms of actual factors

Wetting Time (Y2) =+71.739-0.30155 *Crosspovidone-1.28773 *SSG-0.00315 *Crosspovidone * SSG-0.008915 *Crosspovidone^2+0.01314*SSG^2

Table 10 shows the difference between the Predicted R^2 value of 0.5604 and the Adjusted R^2value of 0.8872, which is bigger than 0.2, and is larger than one may anticipate. This can indicate a significant block effect or a problem with your model and/or data. Considerations include model reduction, response transformation, outliers, etc. Confirmation runs should be used to validate all empirical models. Adeq Precision measures signal-to-noise ratio. The ideal ratio is more than four. Your ratio of 11.374 shows a strong enough signal. Using this paradigm was help you move around the design area [31].

Table 11 shows the model is implied to be significant by the Model F-value of 851.57. An F-value this large might happen to owe to noise only 0.01% of the time. Model terms are considered significant when the P-value is less than 0.0500. In this instance, key model terms were A, B, AB, and A2. Model terms are not significant if the value is higher than 0.1000. Model reduction may enhance your model if it has a large number of unnecessary terms (excluding those necessary to maintain hierarchy). The response surface plot of Y3 (Drug release) is displayed in fig. 8.

Final equation in terms of coded factors

Drug release (Y3) =+27.35+35.42*A+11.26*B+6.34*AB+11.67*A^2+0.7315*B^2

Final equation in terms of actual factors

Drug release (Y3) =+44.624-4.733*Crosspovidone-2.13914 *SSG+0.1268* Crosspovidone *SSG+0.116744* Crosspovidone^2+0.029259*SSG^2

The discrepancy between the Predicted R^2 of 0.9919 and the Adjusted R^2 of 0.9981 is less than 0.2, which is considered to be a reasonable agreement. The ratio of signal to noise is measured by Adeq Precision. A ratio of at least 4 is preferred. Your ratio of 79.890 shows a strong enough signal. To move around the design space, utilize this model (table 12).

CONCLUSION

It was concluded that Ambrisentan MDTs were successfully formulated using the direct compression approach. Superdisintegrants were utilized in the composition of the tablets' disintegration process. It leads to increased patient compliance and effective tablet therapy. The results indicated that a rise in the overall rate of cumulative drug release was correlated with an increase in the amount of various super disintegrants. The highest cumulative drug release was seen in 12 min for all nine formulations, including the AS6 formulation with 30 mg of crospovidone. Formulation AS6 additionally demonstrated a quick wetting time, good drug content, and quick disintegration. Therefore, we concluded that Ambrisentan MDTs with a formulated formulation could be one of the best options for the control of hypertension due to improved patient compliance and quick onset of action.

ABBREVIATION

FTIR-Fourier transforms infrared spectroscopy, DSC-Differential scanning calorimetry, MDT-Mouth dissolving tablet, SSG-sodium starch glycolate.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declared that the No conflict of interest for the given article.

REFERENCES

1. Garg A, Gupta MM. Mouth dissolving tablets: a review. J Drug Delivery Ther. 2013 Mar 15;3(2). doi: 10.22270/jddt.v3i2.458.
2. Jire DS, Gosavi NS, Badhe RB, Jagdale DH. Mouth dissolving tablet: a novel drug delivery system. Asian J Pharm Res. 2021 Aug 14;11(3):180-6. doi: 10.52711/2231-5691.2021.00033.

3. Masih A, Kumar A, Singh S, Tiwari AK. Fast dissolving tablets: a review. Int J Curr Pharm Sci. 2017 Mar 1;9(2):8. doi: 10.22159/ijcpr.2017v9i2.17382.
4. Preeti AV, Agarwal V, Agarwal A. An overview on mouth dissolving tablet: from manufacturing and patented technique to quality control test. Asian J Pharm Clin Res. 2022 Nov 7:7-13. doi: 10.22159/ajpcr.2022.v15i11.46555.
5. Sharifi AM, Darabi R, Akbarloo N. Study of antihypertensive mechanism of Tribulus terrestris in 2K1C hypertensive rats: role of tissue ACE activity. Life Sci. 2003 Oct 24;73(23):2963-71. doi: 10.1016/j.lfs.2003.04.002, PMID 14519445.
6. Shukla D. Mouth dissolving tablets I: An overview of formulation technology. Sci Pharm. 2009 Mar 6;77(2):309-26. doi: 10.3797/scipharm.0811-09-01.
7. Iqbal H, Naz S, Ali H, Bashir L, Zafar F, Akram S. Formulation development and optimization studies of mouth dissolving tablets of tizanidine HCl. Pak J Pharm Sci. 2020 Jan 1;33(1 Suppl):245-51. PMID 32122855.
8. Sharma V, Chopra H. Formulation and evaluation of taste masked mouth dissolving tablets of levocetirizine hydrochloride. Iran J Pharm Res. 2012;11(2):457-63. PMID 24250469.
9. Jain SK, Shukla M, Shrivastava V. Development and *in vitro* evaluation of ibuprofen mouth dissolving tablets using solid dispersion technique. Chem Pharm Bull (Tokyo). 2010 Aug;58(8):1037-42. doi: 10.1248/cpb.58.1037, PMID 20686256.
10. Madgulkar AR, Bhalekar MR, Padalkar RR. Formulation design and optimization of novel taste masked mouth-dissolving tablets of tramadol having adequate mechanical strength. AAPS PharmSciTech. 2009;10(2):574-81. doi: 10.1208/s12249-009-9237-y, PMID 19440844.
11. Masareddy RS, Kadia RV, Manvi FV. Development of mouth dissolving tablets of clozapine using two different techniques. Indian J Pharm Sci. 2008 Feb 1;70(4):526-8. doi: 10.4103/0250-474X.44611, PMID 20046788.
12. Patel BP, Patel JK, Rajput GC, Thakor RS. Formulation and evaluation of mouth dissolving tablets of cinnarizine. Indian J Pharm Sci. 2010 Jul;72(4):522-5. doi: 10.4103/0250-474X.73930, PMID 21218071.
13. Dave V, Yadav S, Sharma S, Vishwakarma P, Ali N. Novel approach of aceclofenac fast dissolving tablet. Pak J Pharm Sci. 2015 Jan 1;28(1):37-41. PMID 25553683.
14. Patra S, Sahoo R, Panda RK, Himasankar K, Barik BB. *In vitro* evaluation of domperidone mouth dissolving tablets. Indian J Pharm Sci. 2010 Nov;72(6):822-5. doi: 10.4103/0250-474X.84607, PMID 21969764.
15. Nakamura S, Fukai T, Sakamoto T. Orally disintegrating tablet manufacture via direct powder compression using cellulose nanofiber as a functional additive. AAPS PharmSciTech. 2021;23(1):37. doi: 10.1208/s12249-021-02194-5, PMID 34950985.
16. Ghourichay MP, Kiaie SH, Nokhodchi A, Javadzadeh Y. Formulation and quality control of orally disintegrating tablets (ODTs): recent advances and perspectives. BioMed Res Int. 2021;2021:6618934. doi: 10.1155/2021/6618934, PMID 34977245.
17. Douroumis D. Orally disintegrating dosage forms and taste-masking technologies. Expert Opin Drug Deliv. 2011;8(5):665-75. doi: 10.1517/17425247.2011.566553, PMID 21438776.
18. Goel H, Rai P, Rana V, Tiwary AK. Orally disintegrating systems: innovations in formulation and technology. Recent Pat Drug Deliv Formul. 2008 Oct 31;2(3):258-74. doi: 10.2174/187221108786241660, PMID 19075912.
19. Comoglu T, Unal B. Preparation and evaluation of an orally fast disintegrating tablet formulation containing a hydrophobic drug. Pharm Dev Technol. 2015 Jan 1;20(1):60-4. doi: 10.3109/10837450.2013.862636, PMID 24295202.
20. Parkash V, Maan S, Deepika, Yadav SK, Hemlata, Jogpal V. Fast disintegrating tablets: opportunity in drug delivery system. J Adv Pharm Technol Res. 2011 Oct;2(4):223-35. doi: 10.4103/2231-4040.90877, PMID 22247889.
21. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. Crit Rev Ther Drug Carrier Syst. 2004;21(6):433-76. doi: 10.1615/critrevtherdrugcarriersyst.v21.i6.10, PMID 15658933.
22. Keshari A, Tripathi DPK, Srivastava A, Vishwas R. Formulation and evaluation of effervecent floating tablets of antidiabetic drug. J Drug Delivery Ther. 2015 Nov 15;5(6). doi: 10.22270/jddt.v5i6.1176.
23. Aher S, Saudagar R, Chaudhari D. Formulation and evaluation of taste masked fast dissolving tablet of prazosin hydrochloride. J Drug Delivery Ther. 2018 Jul 15;8(4). doi: 10.22270/jddt.v8i4.1785.
24. Siraj SN, Kausar SH, Khan GJ, Khan T. Formulation and evaluation of oral fast dissolving tablet of ondansetron hydrochloride by coprocess excipients. J Drug Delivery Ther. 2017 Sep 15;7(5). doi: 10.22270/jddt.v7i5.1498.
25. Rahane R, Rachh PR. A review on fast dissolving tablet. J Drug Delivery Ther. 2018 Sep 6;8(5):50-5. doi: 10.22270/jddt.v8i5.1888.
26. Kumar I, Chaudhary D, Thakur B, Pandit V. Formulation and evaluation of piroxicam fast dissolving tablets using direct compression and sublimation method. J Drug Delivery Ther. 2020 Jun 15;10(3-s):17-25. doi: 10.22270/jddt.v10i3-s.4063.
27. Singh R, Saxena S, Jain S. Formulation and evaluation of mouth dissolving tablet containing non-steroidal anti-inflammatory drug. Res J Pharm Technol. 2021;14(1):432-6. doi: 10.5958/0974-360X.2021.00078.0.
28. Kumar R, Patil S, Patil MB, Patil SR, Paschapur MS. Formulation evaluation of mouth dissolving tablets of fenofibrate using sublimation technique. Int J Chemtech Res CODEN. 2022;24(1):412–6.
29. Baviskar KD, Baviskar RD, Kanke PK, Patil KD. Formulation and evaluation of mouth dissolving tablet of lornoxicam using novel natural superdisintegrants. AJPTR 2020;10(1):44-54. doi: 10.46624/ajptr.2020.v10.i1.005.
30. Eisa AM, El-Megrab NA, El-Nahas HM. Formulation and evaluation of fast dissolving tablets of haloperidol solid dispersion. Saudi Pharm J. 2022;30(11):1589-602. doi: 10.1016/j.jsps.2022.09.002. PMID 36465849.
31. Dave V, Yadav RB, Ahuja R, Yadav S. Formulation design and optimization of novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques. Bull Fac Pharm Cairo Univ. 2017 Jun;55(1):31-9. doi: 10.1016/j.bfopcu.2016.12.001.