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Formulation and Evaluation of Orally Disintegrating Tablets of Captopril Using Natural Super Disintegrants

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A B S T R A C T

Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and children. Orally Disintegrating tablets constitute an innovative dosage form that overcomes the problems of swallowing and provides a quicksetof action. The purpose of this study was to formulate and evaluate an orally Disintegrating Tablet (ODT) containing captopril while using croscarmellose sodium, crospovidone and two natural superdisintegrants: karaya gum and natural agar. For the preliminary study 12 batches were prepared. A 3^2 full factorial design was applied to optimize the formulation and 9 batches were prepared and evaluated. From the preliminary study it was found that ODTs containing karaya gum showed a better disintegration time and hence it was considered for further studies.

According to the Results of optimized batches, the best concentration of superdisintegrant and binder were obtained. Karaya gum in the concentration of 9% w/w with Avicel PH 102 in25% w/w gave rapid disintegration in 25sec and showed 100% drug release within 5 minuteso it was concluded that orally disintegrating tablets of captopril can be successfully formulated using karaya gum.

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Introduction

Captopril is a sulfhydryl-containing angiotensin-converting enzyme inhibitor which is used in management of hypertension, heart failure and myocardial infarction [1]. The maximum effect of captopril is obtained within one to two hours after administration of the oral doses;[1, 2] this delay in beginning of action limits the value of captopril in treatment of hypertension crisis or acute heart failure [3].highly elevated blood pressure occurred in hypertension crisis, if not treated, can result in severe damages or even death in a short period of time. In this case, reduction of blood pressure within minutes is crucial [4]. Buccal route is a useful method of administration when rapid start of actions is desired. The ease of usage, patient compliance and improved bioavailability are other advantages of this route [5]. It has been reported that buccal administration of captopril is an effective and safe method of lowering arterial blood pressure in patients with hypertensive emergencies [6-8]. Based on previous researches, more rapid attainment of plasma concentration and more rapid beginning of pharmacological effect have been observed after buccal administration of captopril in comparison with the oral route [3, 9]. Hence, formulation of an orally disintegrating tablet containing captopril could be considered as an appropriate method to obtain suitable clinical effects. Orally disintegrating tablets (ODT) require rapid disintegration and absorption of drugs to produce a rapid beginning of action. ODTs are in dosage forms, which disintegrate in patient's mouth within a few seconds without the need of water, or chewing; some drugs are absorbed from the mucosal lining of mouth, pharynx and esophagus when they pass along with saliva. This may help to enhance the bioavailability of drugs, hence administrating a less dose [10]. Polysaccharides such as karaya gum derived from *"sterculiaurens"* (sterculiaceae family) and Natural agar derived from red algae *"Gelidiumamansii"* have been investigated as tablet disintegrants [11, 12]. The innovative part of this study in comparison with studies already performed on Captopril is that in this study natural superdisintegrants were used and if their superiority was to be proven compared to semi-synthetic superdisintegrants it would be a big step forward because natural superdisintegrants are safer, more biodegradable, better compressible, easier to prepare and cheaper and these advantages can boost the production of ODTs [13].

Experimental design, also called design of experiments (DOE), is an approach in development and optimization of drug delivery devices; by this method, it is feasible to obtain the desired formulation as quickly as possible while avoiding unnecessary experiments [14-16]. The major advantage of this method to develop pharmaceutical formulations is that the potential factors could be studied simultaneously, systematically and quickly. By using design of experiments, the effect of each formulation factor on each response can be evaluated and critical factors can be identified based on statistical analysis. When the formulation and manufacturing process of a pharmaceutical product is optimized by a systematic approach such as DOE, scale-up and process validation can be very efficient because of the efficiency of the formulation and manufacturing process [16].

In a full factorial experiment, which is suitable for pharmaceutical formulations, the independent factors are the components of a formulation and the response is dependent on the relative proportions of each ingredient [17, 18]. It involves changingthe formulation compositions and exploring how such changes will affect the properties of the formulation [19].

Materials and Methods

The active ingredient, captopril, was purchased from Exir pharmaceutical company (located in Iran); The other materials used for tablets preparation,experimental design and statistical evaluation of the data are as follows: Croscarmellose, Crospvidone (macleod's Pharmaceuticals-India), Karaya gum, Natural agar (Nutriroma-India), Aspartame (Fluka, Switzerland), Avicel PH102, Talc, Magnesium stearate, Mannitol (Merck, Germany). Design Expert Version 8 (state-Ease Inc., Minneapolis).

Preparation of Preliminary batches

To create the preliminary batches of orally disintegrating tablets of captopril drug, mannitol, Avicel PH102, Superdisintegrants, talc and magnesium stearate were used. Mannitol was used as filler and also to impart a cooling sensation in mouth. Avicel PH102 was used as a binder because of its binding property.Superdisintegrantswere used with Different concentrations. All ingredients were passed through a 250 μm mesh. The ingredients were mixed

using a glass mortar and pestle for 5 minutes according to table 1. Magnesium stearate and talc were added in the final step and mixing continued for one minute. This blend was subjected to the analysis of pre-compression parameters including: Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio [20, 21]. The blend was compressed on 8mm (diameter) flat punches on a single punch tableting machine (ErwekaAR 4100,Germany). The tablets were evaluated for weight variation, friability, hardness and in vitro disintegration time.

Table 1. Formulation of preliminary batches

Ingredients (mg)	A_1	A_2	A_3	B_1	B_2	B_3	C_1	C_2	C_3	D_1	D_2	D_3
Captopril	25	25	25	25	25	25	25	25	25	25	25	25
Agar	5	7.5	10	-	-	-	-	-	-	-	-	-
Croscarmellose	-	-	-	5	7.5	10	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	5	7.5	10	-	-	-
Karaya gum	-	-	-	-	-	-	-	-	-	5	7.5	10
Avicel PH102	40	40	40	40	40	40	40	40	40	40	40	40
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Mannitol	122	119.5	117	122	119.5	117	122	119.5	117	122	119.5	117
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Pre-compression parameters

Angle of repose (θ)

Angle of repose is defined as the maximum angle possible between the surface of a pile of powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose: $\tan\theta = h/r$

$\theta = \tan^{-1} (h/r)$ Where, θ is the angle of repose, h stands for the height of the pile and r represents the radius of the base of the pile

Bulk density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Tap density

Tap density is defined as the mass of a powder divided by the tapped volume.

Carr's compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = TD-BD/TD×100

Hausner's ratio

It is determined by comparing the tapped density to the bulk density using the following equation:

Hausner's ratio = tapped density / bulk density.

Evaluation of tablet properties

Weight variation

The test was performed according to specifications given in the USP, 2006, on 20 tablets. The maximum acceptable limit for 200 mg tablets (125-324 mg) is ± 7.5% deviation of an individual mass from the average mass [22].

Friability

Tablet friability was measured using the Roche Friabilator on ten tablets of each batch [22]. The friability was determined as the percentage in mass loss according to this Equation:

$F=W_A-W_B/W_A\times100$

Where f stands for Friability, W_A for Initial weigh (g) and W_B for Final weight (g).Tablets with friability of below one percent are acceptable.

Hardness

The crushing strength of tablets was measured by a Monsanto Hardness Tester.

Disintegration test

The in vitro disintegration studies were carried out using a Digital Tablet Disintegration test Apparatus (Erweka ZT- Germany). One tablet was placed in each of the six tubes of the basket assembly and then disk was added to each tube. This assembly was then suspended in a one-liter beaker containing water with its temperature being maintained at 37±2°C. The basket was then moved up and down through a distance of 5 to 6 cm, at the frequency of 28 to 32 cycles per minute. The time required for complete disintegration of the tablet was recorded [22].

Full factorial design

$A3^2$ full factorial design was adopted to optimize the variables. In this design 2 Factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations [15]. The amounts of binder, Avicel PH102 (X_2) and the amounts of karaya gum (X_1) were selected as independent variables. The batches were formulated according to the formula given in table2. Pre compression parameters were evaluated; then the optimized batches were evaluated for weight variation, friability, hardness, in vitro disintegration time, content uniformity, in vitro Dissolution study and %drug release in 5 minutes (Q_{T5}). The friability, Disintegration time and %drug release Q_{T5} were selected as dependent variables.

Content Uniformity

Twenty randomly selected tablets from each batch were finely powdered and powder equivalent to 25mg of captopril was accurately weighted and transferred to 100 ml volumetric flasks containing 50 ml of 0.1N HCl. The flasks were shaken to completely mix the contents. The volume was made up to the mark with 0.1 N HCl and filtrate was suitably diluted and captopril content was estimated at 218 nm using a double beam UV visible spectrophotometer [22].

In vitro Dissolution studies

Dissolution studies were performed for the optimized formulation, employing USP 24 type II apparatus (paddle method, Erweka DT 6R Germany) at the Rotating speed of 50 rpm and phosphate buffer solution pH 6.8 (900 ml) at 37±0.5 °C was used as dissolution medium [22].

Samples (5 ml) were withdrawn at predetermined time intervals quickly and the volume replaced by fresh dissolution medium, pre-warmed to 37 ±0.5°C. The drug concentration was determined spectrophotometrically at 218 nm using UV spectrophotometer (shimadzu 1800-Germany).

Table 2. Formulation using 3^2 full factorial design

Ingredients (mg)	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9
Run	8	1	6	3	9	7	4	5	2
Captopril	25	25	25	25	25	25	25	25	25
Karaya gum	5	12.5	20	5	12.5	20	5	12.5	20
Avicel PH102	30	30	30	50	50	50	70	70	70
Aspartame	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Mg. Stearate	3	3	3	3	3	3	3	3	3
Mannitol	124	116.5	109	112	104.5	97	92	84.5	77
Total weight	200	200	200	200	200	200	200	200	200

Results

Preliminary batches

Powder flow properties

Powder flow properties were analyzed. It was observed that all formulations showed good flow properties with Carr's index ranging from 10.34 to 18.51 and Hausner's ratio below 1.25 which indicated good compressibility and flow ability. Results are shown in Table 3.

Table 3. Powder flow properties of preliminary batches

F.NO	Angle of Repose θ	Bulk density g/cm^3	Tap density g/cm^3	Carr's Index	Hausner's Ratio
A_1	29.02	0.415	0.532	21.99	1.28
A_2	28.25	0.430	0.522	16.35	1.19
A_3	30.12	0.432	0.540	17.62	1.21
B_1	31.06	0.430	0.522	17.62	1.21
B_2	32.08	0.435	0.520	16.35	1.19
B_3	28.78	0.415	0.532	21.99	1.28
C_1	32.08	0.415	0.532	21.99	1.28
C_2	28.45	0.435	0.525	17.14	1.20
C_3	29.67	0.432	0.540	20.00	1.25
D_1	28.85	0.425	0.515	17.48	1.21
D_2	29.67	0.435	0.522	16.67	1.20
D_3	31.06	0.430	0.524	17.94	1.22

Tablet properties

Orally disintegrating tablets were prepared using the direct compression method. All of the formulations passed the weight variation test. The hardness of all tablets was found in the range of 3.3-3.9 kg/cm^2. Friability was found to be below 1% which was an indication of good resistance of the tablets. Disintegration times were different between formulations, and the formulations containing karaya gum had less disintegration time; according to these results karaya gum was selected for optimization studies. The results of these evaluations are shown in table 4.

Optimized batches

Powder flow properties

The powder flow properties of the optimized batches were also studied and from the observation it was concluded that the optimized batches showed good powder flow properties with good compressibility. The results are shown in table 5.

Table 4. Tablets properties of preliminary batches

F.NO	Weight variation Mean±SD	Friability%	Hardness (kg/cm^3)	In vitro D.T. (sec)
A_1	200.15±3.85	0.49	3.44±0.01	72±1.42
A_2	199.75±3.32	0.47	3.32±0.04	54±1.36
A_3	200.8±3.47	0.43	3.39±0.03	49±1.21
B_1	201.20±3.64	0.47	3.60±0.04	48±2.15
B_2	200.94±2.79	0.44	3.65±0.02	43±2.13
B_3	201.55±2.18	0.44	3.81±0.06	39±1.81
C_1	200.35±3.70	0.48	3.42±0.02	55±2.19
C_2	200.30±3.54	0.46	3.75±0.05	44±2.77
C_3	203.45±3.87	0.45	3.62±0.03	38±1.35
D_1	200.75±3.31	0.43	3.72±0.04	48±1.35
D_2	201.05±4.01	0.42	3.26±0.05	38±1.88
D_3	199.60±2.52	0.41	3.59±0.02	35±1.25

Table 5. Powder flow properties of optimized batches

F.NO	Angle of Repose θ	Bulk density g/cm^3	Tap density g/cm^3	Carr's Index	Hausner's Ratio
A_1	29.58	0.435	0.521	16.50	1.19
A_2	28.20	0.432	0.520	16.92	1.20
A_3	30.10	0.431	0.523	17.59	1.21
A_4	31.08	0.430	0.525	18.10	1.22
A_5	31.06	0.434	0.522	16.85	1.20
A_6	30.50	0.430	0.521	17.46	1.21
A_7	30.40	0.437	0.526	16.92	1.20
A_8	31.02	0.430	0.524	17.93	1.21
A_9	30.60	0.433	0.527	17.83	1.21

Tablet properties

Orally disintegrating tablets were prepared by direct compression method in 8mm (diameter) flat punches on a single punch tableting machine (ErwekaAR 4100, Germany). Total of nine optimized formulations were prepared using three different levels of Avicel PH102 and karaya gum in the manner described above. All of the formulations passed the weight variation test and the content uniformity test. The hardness of all the tablets was found in the range of 3.4-3.8 kg/cm^2.

The result of friability, in vitro disintegration time and percent drug release Q_{T5} are shown in table 6. The graphs showing drug release are given in figures 1, 2 and 3.

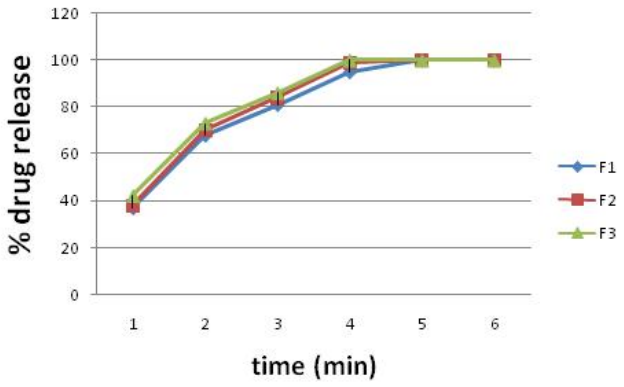

Fig. 1. % drug release of batches A1 to A3

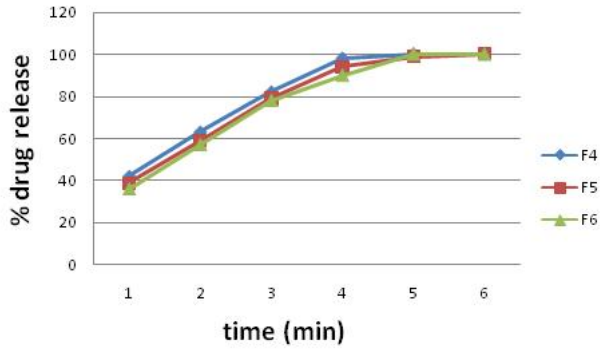

Fig. 2. % drug release of batches A4 to A6

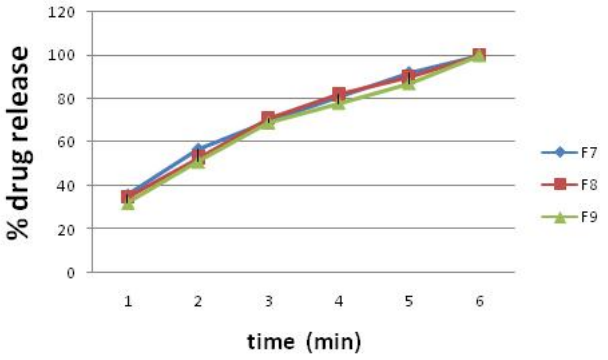

Fig. 3. % drug release of batches A7 to A9

Data Analysis

A response surface model factorial design with 2 independent variables at 3 different levels was used to study the effects on dependent variables. The dependent variables obtained from various levels of the 2 independent Variables (X_1 and X_2) were subjected to multiple regressions to yield a second-order polynomials equation.

Polynomials Equations

Disentegration time = + 30.78 - 8.50X_1 -9.17X_2 + 1.25X_1X_2 + 1.83X_1^2 + 4.83X_2^2

%Friability = 0.36 + 0.028X_1 - 0.093X_2

%drugrelease = +100.66 – 0.35X_1 – 5.00X_2 – 0.35 X_1X_2 – 0.85 X_1^2 – 4.23X_2^2

The interaction effect between X_1 and X_2 are shown in Response surface plot Figures 4, 5 and 6.

Table 6. Tablets properties of optimized batches

F.NO	Weight variation Mean±SD	Friability%	Hardness kg/cm^2	In vitro D.T (sec)	Content Uniformity (mg)	%Drug Release Q_{T5}
A_1	201.5±1.50	0.40	3.55±0.02	55±1.28	25.28±0.84	100.90
A_2	197.5±1.85	0.55	3.41±0.05	48±1.34	25.39±1.05	101.29
A_3	199.35±1.48	0.46	3.55±0.03	35±1.38	25.57±1.24	100.40
A_4	200.65±1.35	0.35	3.59±0.04	41±1.45	25.48±1.43	100.30
A_5	198.80±1.75	0.31	3.65±0.04	30±1.41	25.09±1.32	99.35
A_6	201.35±1.40	0.36	3.71±0.06	25±1.39	25.44±0.92	100.63
A_7	200.55±1.35	0.25	3.58±0.02	37±1.32	25.15±1.14	90.82
A_8	199.45±1.47	0.25	3.62±0.03	24±1.25	25.02±1.55	92.89
A_9	200.85±1.56	0.35	3.70±0.05	22±1.49	25.54±0.86	88.90

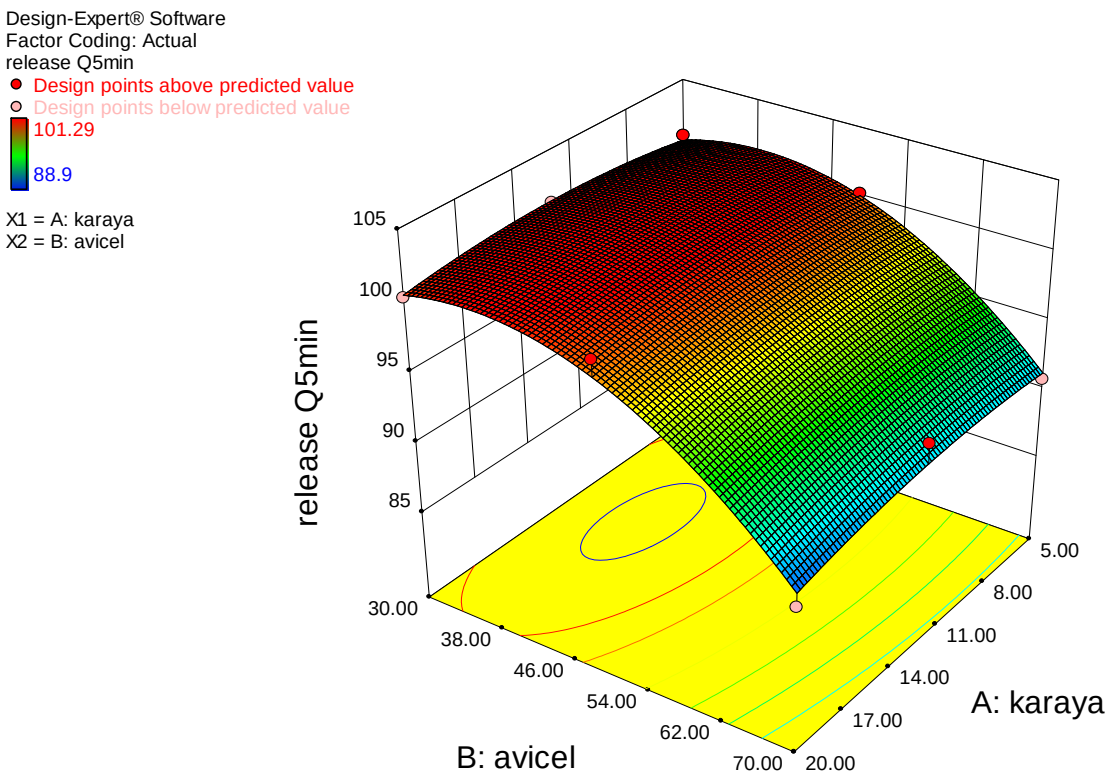

Fig. 4. 3D Surface response plot showing the effect of variables on % drug release Q5min.

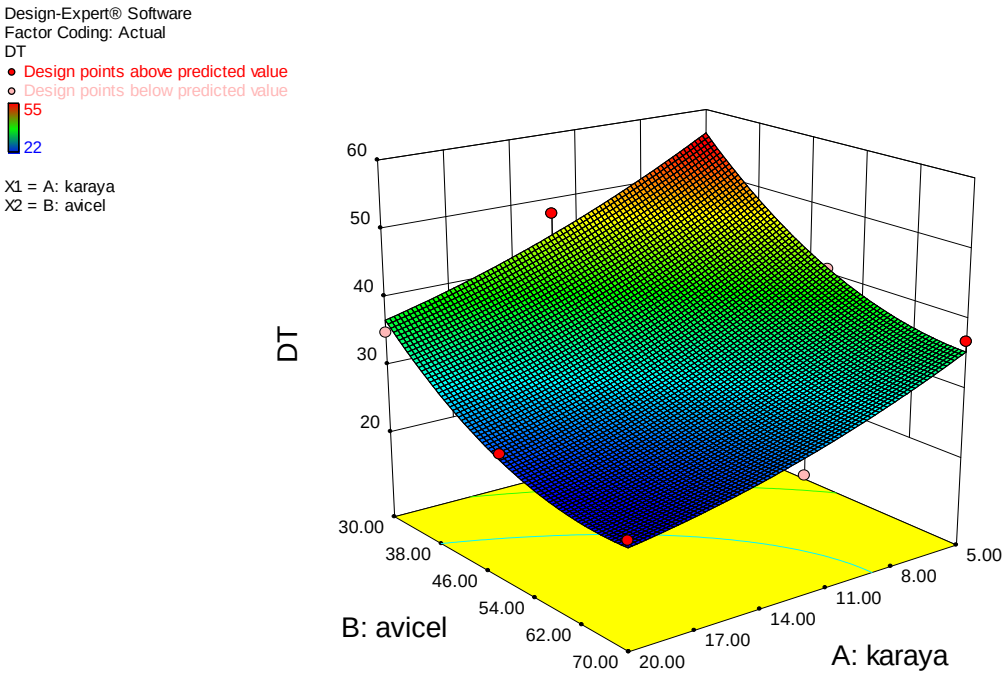

Fig. 5. 3D surface response plot showing the effect of variables on disintegration time.

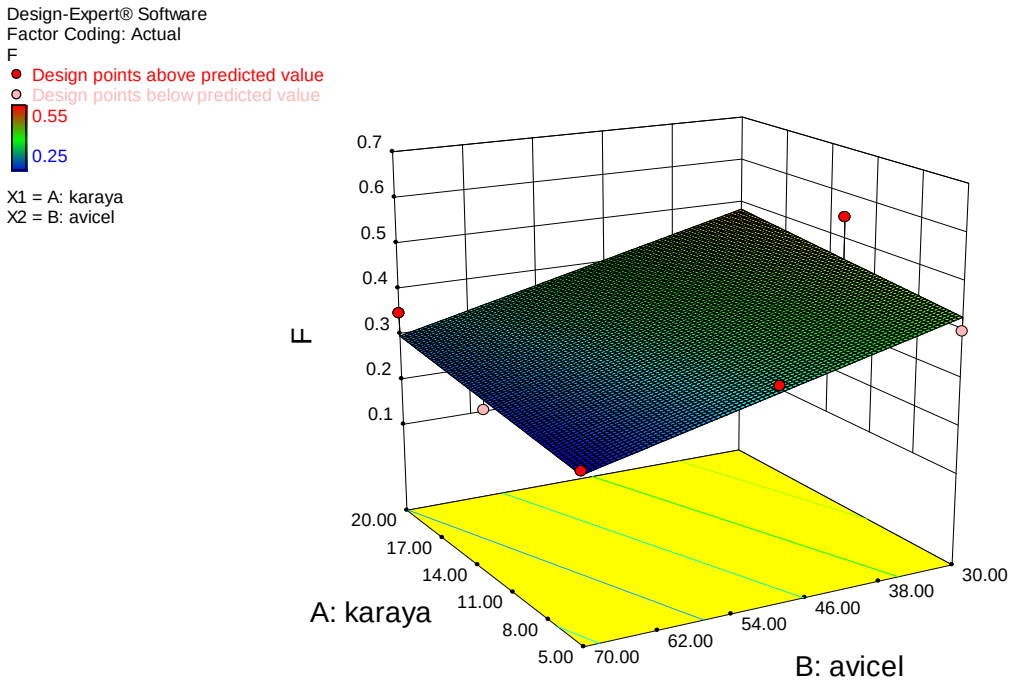

Fig. 6. 3D Surface response plot showing the effect of variables on % friability.

Targeting

The optimization of the orally disintegrating tablet was decided to target DT=25 sec, with Friability = 0.4% and drug Release Q_{T5} = 100%.

Optimized concentrations were obtained from the software is yellow area in overlay plot shown in figure 7. Comparative values of predicted and observed responses along with the formulation components are reported in table 7.

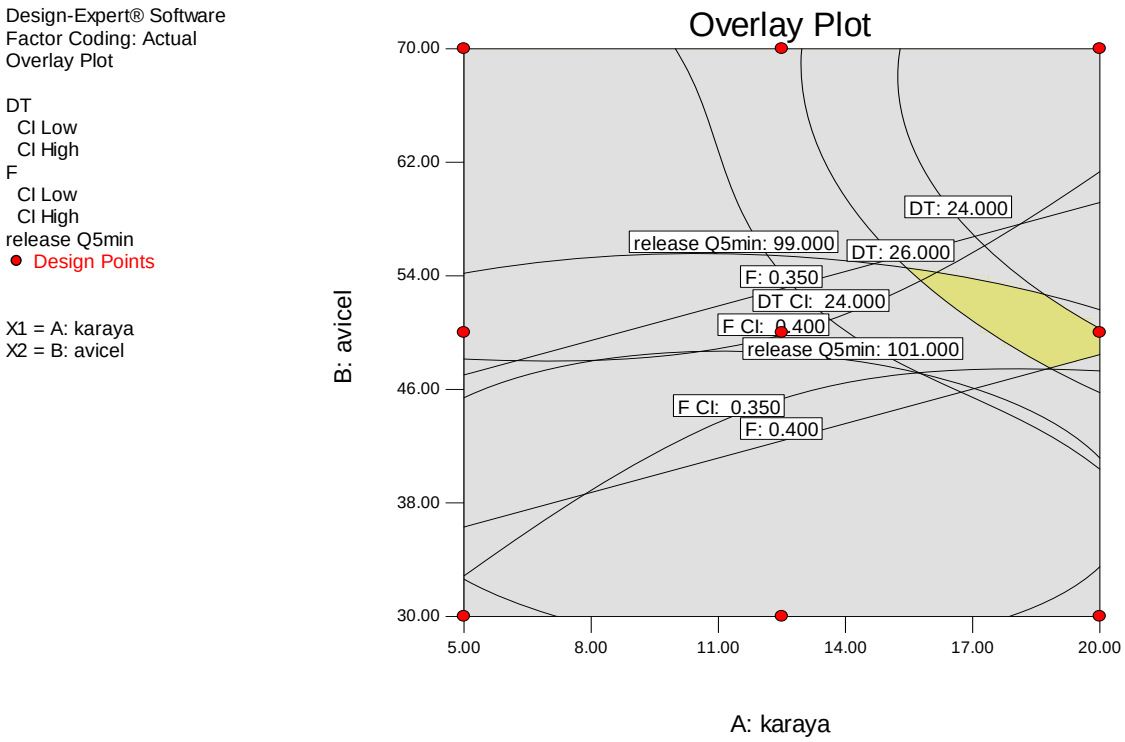

Fig. 7. The overlay plot showing the desired area of all three responses containing optimum formulations in yellow.

Table 7. Comparative value of predicted and observed Responses

F.NO	Karaya gum (mg)	Avicel (mg)	In vitro D.T (Sec)		% drug Release QT5		%Friability		Desirability
			Predicted	Observed	Predicted	Observed	Predicted	Observed	
O_1	18.49	49.38	25.4	25.2	100	100	0.40	0.39	1.00

Discussion

An optimized formulation of captopril orally disintegrating tablet was found and prepared in this study using the "Direct compression" method. Formulation and optimization procedures were facilitated using 3^2 full factorial designs. From previous studies in the field of ODT it was proven that between semi syntheticsuperdisintegrants, crospovidone and croscarmellose were more efficient, hence these two were chosen to be compared with natural superdisintegrants.Based on results obtained from analyzing the preliminary batches, due to a better disintegration time and Hausner's ratio in formulations containing Karaya gum, this superdisintegrant was used for further formulations.

About the friability test, it was observed that with increasing the Avicel PH102 the percentage of friability was decreased; however, changes in the quantities of Karaya gum had almost no effect on this matter.

On the other hand with increasing the percentage of Avicel PH102, amount and speed of drug release was decreased, hence to create a suitable response, an optimum limit inusing theAvicel PH102was found to have a proper amount of drug release and friability.

That is to say that changes made in quantities of Karaya gum had no effect on drug release because only the first few seconds of contact between the ODT and saliva are important and because the dissolution time is more than 5min it can't be effective.

About the test of disintegration time, it was observed that with increasing the amount of Karaya gum and Avicel PH 102, the disintegration time decreases, but for the purpose of not decreasing the amount of dissolution we can't exceed the optimum limit and we need to mention that increasing the amounts of Karaya gum more than the optimum limit won't decrease the time of disintegration anymore.

Conclusion

Finally this study argues that orally disintegrating tablets of captopril can be successfully formulated using karaya gum (a natural superdisintegrant) with concentration of 12% w/w as an alternative for semi synthetic superdisintegrants such as crospovidone and croscarmellose sodium.

Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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