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FORMULATION AND CHARACTERIZATION OF RACECADOTRIL ORALLY DISINTEGRATING TABLETS USING DESIGN EXPERT

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ABSTRACT

Racecadotril is primarily used to treat diarrhoea which acts as a peripherally acting enkephalinase inhibitor. Racecadotril gets rapidly converted to thiorphan which interacts specifically with active site of enkephalinase to produce potent blockade of enzyme, thereby preventing inactivation of endogenous opioid peptides, resulting in fast disintegration and enhanced drug release. Sublimation method was used to prepare orally disintegrating tablets of formulations F1 to F11. The preliminary trials were done using the super disintegrant avidone and sublimating agent camphor. Optimization of racecadotril orally disintegrating tablets (F1 to F11) were done by optimizing independent variables such as concentration of super disintegrant and sublimating agent (avidone as 0.5, 2.75 and 5% and camphor as 5, 10 and 15%) and dependent variables like disintegration time, percent friability and percent drug release. Optimization was done using Design export 13 software by Central composite design from Response surface methodology. ANOVA elucidates the impact of independent variables on dependent variables. In preliminary studies, it was found that, apart from avidone, formulations containing avidone and camphor combinations shown fast disintegration and increased percent drug release. The optimized formulation F6 (using Design expert software) having 5% avidone and 15% camphor showed disintegration time of 4 sec, percent friability of 0.63% and 99.31% drug release. The optimized formulations were characterized using Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and Powder X-Ray diffraction (PXRD) studies which showed that there was no interaction between drug

and excipients of formulation. Based on disintegration and dissolution studies, the optimized formulations were subjected to stability studies and had indicated good stability.

Keywords: Sublimation, Disintegration, Optimization, Quality by design (QbD), Central Composite design, Friability

INTRODUCTION

Oral disintegrating tablets (ODTs) are solid oral dosage forms which quickly disintegrate in few seconds, when placed in the oral cavity. They are used due to their better patient compliance and acceptance, compared to conventional oral dosage forms **[1]**. Racecadotril is an antidiarrheal drug which acts a peripherally acting enkephalinase inhibitor. It has anti-secretory effect, which reduces secretion of water and electrolytes into the intestine. It is used as a complementary treatment when acute diarrhoea cannot be treated casually and is administered in adults and infants greater than 3 months of age. Racecadotril gets rapidly converted to thiorphan which interacts specifically with active site of enkephalinase to produce potent blockade of enzyme, thereby preventing inactivation of endogenous opioid peptides released by sub-lingual neurons. Recommended dose is 10mg, 30mg, 50mg and 100mg sachets. The peak plasma levels are attained in an hour and half-life of the drug is 3 hours **[2]**.

Design of Experiments (DOE) is an active means in direction to optimise the formulation with the least possible runs and identify the factors that have the great impact on formulated tablets **[3]**. The relationship between factors and responses (independent and dependent variables) noticed by DOE and the variability in responses were determined. The aim of the study is to formulate Orally Disintegrating Tablets of Racecadotril to improve rapid onset of action, bioavailability, solubility and have quick disintegration **[4]**.

MATERIALS AND METHODS

Racecadotril was gifted by Srivar Pharma, Tirupati, India. SMCC HD 90, Avidone were supplied as a gift sample from Natco Pharma Ltd, Hyderabad, Telangana, India. camphor, mannitol, talc and magnesium stearate were supplied from SD Chem Fine, Hyderabad, India. All solvents and excipients used were of analytical grade. Double distilled water was used throughout the experiment.

The opening trials were conducted on nine possible combinations of camphor, ammonium bicarbonate and thymol as sublimating agents, each of which was included in three different formulations at concentrations of 5%, 10%, and 15%, in addition to other excipients. Out of all three sublimating agents at different percentages, 10% of camphor in combination with super disintegrant showed best result based on

disintegration time, percent friability and percent drug release. Further optimization of Racecadotril oro dispersible tablets was completed by optimizing independent variables in two levels like concentration of super disintegrant (0.5, 2.75 and 5%) and sublimating agent (5, 10 and 15%) were performed by estimating dependent variables as disintegration time, percent friability and percent drug release by using Central composite design from Response surface methodology using Design Expert 13 software. Racecadotril oro dispersible tablets were formulated with eleven possible combinations (F1 to F11) was shown in **Table 1**. This optimization showed how independent variables affected dependent variables by ANOVA **[5]**. Therefore, 5% avidone, and 10% camphor were taken as fixed points for further optimization. These responses were assessed using a statistical model which includes two-factor interactive polynomial term.

Sublimation method

Racecadotril orally disintegrating tablets were formulated by direct compression method by including sublimating agent. SMCC HD 90 (binder), avidone (super disintegrant), camphor (sublimating agent), mannitol (sweetening agent and diluent), talc (glidant), magnesium stearate (lubricant). Precise amount of active ingredients and all additives were homogenously blended using geometric dilution after passing through sieve no 22 (standard sieve size) and finally magnesium stearate and talc were added for lubrication and triturated well. The blended material was compressed on 8mm standard concave punch using 16 station rotary tablet punching machine (Cadmach). The total weight of the formulation was made up to 130mg was shown in **Table 1 [5]**.

In this technique, a sublimating agent camphor is used to produce porous racecadotril tablets by direct compression technique. The compressed tablets were heated for 40-60°C in hot air oven for one hour. Due to evaporation of camphor, highly porous structures are created. High porosity is a vital characteristic of tablets formulated by this method. The resulting tablets, will achieve fast disintegration in saliva **[6]**.

Precompression Tests

Preceding to compression, the powder blends must be estimated for their angle of repose, bulk and tapped density and from these values Carr's compressibility index and Hausner's ratio should be measured and shown **Table 2 [7]**.

Post Compression Tests

Weight Variation

Twenty tablets were randomly chosen from each preparation and weighed using digital weighing balance (BL- 220H/Shimadzu). Then the mean ±SD were estimated **[8]**.

Thickness

Ten tablets from each formulation are selected randomly and their thickness was determined using a digital screw gauge micrometer. The mean ±SD were measured **[9]**.

Hardness

The crushing strength of fast dissolving tablets was measured (kgs/cm^2) using the Monsanto hardness tester **[10]**.

Content Uniformity

Twenty tablets were randomly selected from every formulation and pulverized into a fine powder. An amount equivalent to 50mg of Racecadotril was weighed and dissolved in small quantity of acetone, sonicate for 15 minutes using ultra sonicator (Bio-Technics) and dilute with the same to get 50ml. Filter this solution and further dilutions were done to get 5 µg/ml in acetate buffer pH 4.5 containing 1%w/v sodium lauryl sulphate and measure the absorbance at 231nm using UV-visible spectrophotometer (UV LAB INDIA) against acetate buffer pH 4.5 containing 1%w/v sodium lauryl sulphate as blank **[11]**.

Friability

The friability of orally disintegrating tablets was calculated using (Analab friability) test apparatus. Twenty preweighed tablets were placed in a friabilator attached to a motor rotating at 25 rpm speed for 4 minutes. The tablets were then dedusted, reweighed and percentage loss was estimated **[12]**.

$$\%Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

In-vitro disintegration time

The test was performed using disintegration test apparatus (DBK). Six tablets were taken and placed in basket assembly which is immersed in 500ml of acetate buffer pH 4.5 containing 1%w/v sodium lauryl sulphate at 37±0.5°C. Time taken for tablets to disintegrate completely into smaller particles were noted **[13]**.

In vitro release Studies

The in vitro dissolution studies were carried out using USP Dissolution test apparatus Type II (Paddle method) (Electrolab)). The apparatus is rotated at 100 RPM speed for 60 minutes at 37±0.5°C using 900ml of pH 4.5 acetate buffer containing 1%w/v sodium lauryl sulphate as dissolution medium was poured in the vessels.10 ml of samples were collected at predetermined intervals and replaced with fresh buffer of equal volume in to the vessels, filtered through 0.45µm pore size (PVDF filter) and analysed using UV-visible spectrophotometer (LAB INDIA/UV 3200, India) at 231 nm wavelength. The released amount of drug from the tablets at different time intervals was measured using racecadotril standard graph **[14]**.

Characterization of Racecadotril orally disintegrating tablets

Characterization studies of placebo (tablet), racecadotril orally disintegrating tablet

formulation and standard racecadotril were carried out using FTIR-ATR spectrophotometer (Bruker), DSC (DSC 6, Perkin Elmer, USA) and PXRD (XRD x' pert PRO MPD PAN Analytical, USA) **[15]**.

Stability Studies

The finalized formulation was subjected to stability studies as per ICH guidelines. The samples were packed in aluminium foil and stored the formulation at 40±2°C/ 75±5% RH in stability chamber up to 3 months. For every 30 days' time intervals, analyse the samples for disintegration time, percent friability and percent drug release **[15]**.

RESULTS:

Standard graph of Racecadotril

Weigh accurately about 50mg of racecadotril working standard and transfer to 50ml volumetric flask, dissolved and diluted up to the mark with acetone. From this take 5ml and diluted to 0.50ml with pH 4.5 acetate buffer containing 1%w/v sodium lauryl sulphate. Further dilutions were done using acetate buffer pH 4.5 containing 1%w/v sodium lauryl sulphate to get 1,2,3,4,5 and 6 µg/ml of racecadotril. The absorbances of all the solutions was measured using UV-visible spectrophotometer (LAB INDIA/UV 3200, India) at 231nm respectively shown in **Figure 1**.

Preliminary trials

The trials were conducted on nine possible combinations of camphor, ammonium bicarbonate and thymol as sublimating agents, each of which was included in three different formulations at concentrations of 5%, 10%, and 15%, in addition to other excipients. Out of all three sublimating agents at different percentages, camphor in combination with super disintegrant showed best result. From the above trials, camphor was found to be best sublimating agent. Further nine tablet formulations were prepared by varying the concentration of camphor from 5 % to 15% along with other excipients. The optimized formulation of ODT's of racecadotril was shown in **Table 1**.

All the formulations were evaluated for micromeritic properties and exhibited good flow properties. The various flow properties were represented in **Table 2**. The results indicate angle of repose ranged from 31.25° to 34.23°, Carr's compressibility index ranging from 11 to 15 percent and Hausner's ratio from 1.11 to 1.17.

The results from post compression parameters revealed that all the designed tablet formulations were of uniform weight with acceptable weight variation and thickness. The hardness ranging from 4.0±0.29 to 4.17±0.5 kg/cm^{2}and friability ranged from 0.63 to 0.93% of all formulations which shown good mechanical resistance. The content uniformity for all nine formulations were within the

acceptable limits, in the range of 98.2±0.51 to 101.2±0.23% was shown in **Table 3**.

The percentage drug release for all nine formulations F1 to F9 were ranged from 82.3 to 99.31% in 10 min. The formulation F6 showed DT of 4 sec, friability of 0.63% and showed highest percent drug release of 99.31% at 10min interval.

OPTIMIZATION BY CENTRAL COMPOSITE DESIGN

To evaluate the response, with two-factor interactive polynomial statistical model terms in the systems was used.

$Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1^2 + b_5 X_2^2 + b_6 X_1 X_2^2 + b_7 X_1^2 X_2 + b_8 X_1^2 X_2^2$

Where Y is dependent variable, b_0 is intercept, which is the average response for eleven runs shown in **Table 1**. b1 and b2 are evaluated coefficients for factors (X1 and X2). Correlation between all independent and dependent variables, before the treatment of regression and was expressed as correlation coefficient shown in **Table 4**.

DISINTEGRATION TIME:

Disintegration time was found to be between 4 to 33 seconds from F1 to F9 formulations. The minimum DT of 4 sec was found in F6 formulation which contains 5% avidone (super disintegrant) and 10% camphor (sublimating agent). The model is significant, as shown by the 102.03 model F-value **(Table 5)**.

FRIABILITY:

Friability was found to be between 0.63 to 0.93% from F1 to F9 formulations. The minimum percent friability 0.63% was found in F6 formulation which contains 5% avidone (super disintegrant) and 10% camphor (sublimating agent). The model is significant, as shown by the 76.57 model F-value **(Table 6)**.

PERCENT DRUG RELEASE

Percent drug release was found to be between 82.3 to 99.31% from F1 to F9 formulations. The maximum drug release is 99.31% and was found in F6 formulation containing 5% avidone (super disintegrant) and 10% camphor (sublimating agent). The model is significant, F-value was shown as 59.90 **(Table 7)**.

CHARACTERIZATION OF RACECADOTRIL ODT'S

FT-IR spectra of placebo (tablet), racecadotril standard and racecadotril tablet shown in **Figure 7**. The pure racecadotril exhibits characteristic peaks at 1079 cm^{-1} (C-O bond stretching), and racecadotril standard exhibits characteristic peaks at 1642.55 cm^{-1}indicating amide (N-H stretching), 1685.07 cm^{-1} shows ketone (C=O stretching), 1725.95 cm^{-1} shows ester bonding and between 1750-2000 cm^{-1} exhibiting aromatic overtone region.

Differential Scanning Calorimetry (DSC)

The thermo tropic behaviour and the physical states of the drug in orally disintegrating tablets were obtained from the

DSC thermo grams of placebo (tablet), racecadotril ODT tablet formulation (F6) and standard racecadotril. It was shown from **Figure 8** that the onset of peak for standard racecadotril was found at 76.57°C, and a sharp intensive peak at 80.86°C was observed. Whereas in racecadotril ODT tablet formulation the onset of peak was noticed at 74.03°C and sharp intensive peak at 78.53°C and no peak is observed between 74°C to 81°C for placebo tablet formulation as shown in **Figure 8**. This shows that there were no polymorphic changes in the racecadotril ODT formulation.

Powder X-Ray diffraction study (PXRD)

The pure drug showed numerous characteristic high intensity diffraction peaks indicating the crystalline nature of racecadotril shown in **Figure 9**. The peak at about 18.37(2Ɵ) corresponds to main peak in standard racecadotril at about 18.43(2Ɵ). This shows that the crystallinity of racecadotril was not changed in standard racecadotril and racecadotril ODT formulation.

Evaluation of stability studies

The optimized formulation was subjected to stability studies by storing F6 formulation at 40±2°C/ 75±5% RH in stability chamber for three months at thirty days' time interval where, disintegration time, percent friability and percent drug release were assessed. The optimized formulations are stable and did not show much difference in any of the parameters as shown in **Table 8**.

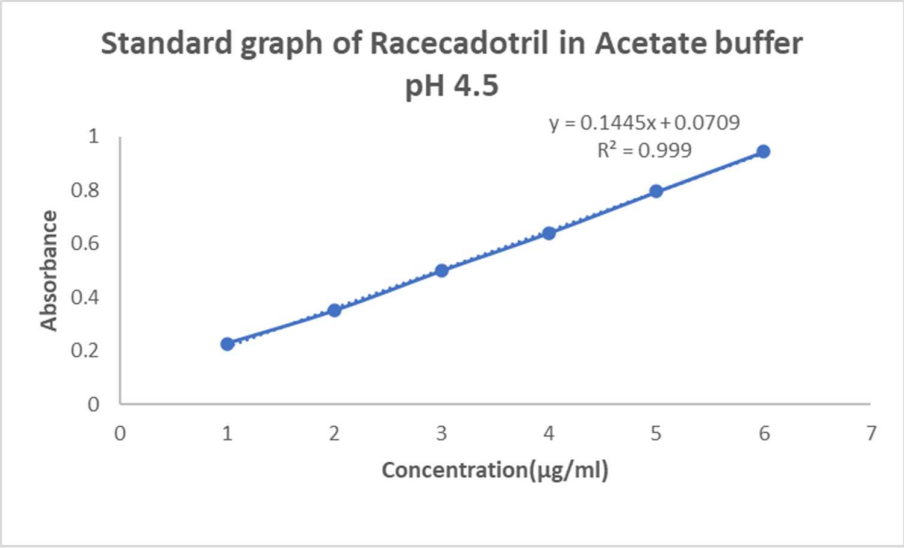

Figure 1: Standard graph of Racecadotril in Acetate buffer pH 4.5

Table 1: Factorial design formulations of Racecadotril orally disintegrating tablets

Formulation code	Racecadotril (mg)	SMCC HD 90 (mg)	Avidone (mg)	Camphor (mg)	Mannitol (mg)	Talc (mg)	Magnesium stearate(mg)	Total weight(mg)
F1	40	73.15	0.65	6.5	8	1	0.7	130
F2	40	70.23	3.57	6.5	8	1	0.7	130
F3	40	67.3	6.5	6.5	8	1	0.7	130
F4	40	66.65	0.65	13	8	1	0.7	130
F5	40	63.73	3.57	13	8	1	0.7	130
F6	40	63.73	3.57	13	8	1	0.7	130
F7	40	63.73	3.57	13	8	1	0.7	130
F8	40	60.8	6.5	13	8	1	0.7	130
F9	40	60.15	0.65	19.5	8	1	0.7	130
F10	40	57.23	3.57	19.5	8	1	0.7	130
F11	40	54.3	6.5	19.5	8	1	0.7	130

Table 2: Micromeritic properties of Racecadotril tablet formulations

Formulation code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (%)	Hausner's ratio
F1	34.23±0.02	0.29±0.01	0.27±0.01	12±0.21	1.13±0.02
F2	32.08±0.05	0.26±0.01	0.38±0.01	14±0.28	1.11±0.00
F3	31.66±0.03	0.34±0.01	0.21±0.01	11±0.26	1.15±0.01
F4	33.57±0.06	0.29±0.01	0.29±0.01	13±0.05	1.16±0.02
F5	32.68±0.01	0.20±0.01	0.36±0.01	15±0.27	1.12±0.00
F6	33.11±0.00	0.25±0.01	0.34±0.01	11±0.24	1.14±0.01
F7	32.45±0.02	0.32±0.01	0.20±0.01	12±0.22	1.11±0.02
F8	31.25±0.06	0.31±0.01	0.37±0.01	14±0.48	1.17±0.00
F9	34.12±0.05	0.23±0.01	0.22±0.01	13±0.21	1.15±0.01

Results are expressed as Mean ± SD(n=3)

Table 3: Post-compression tests of odt by sublimation method

Formulation code	Weight Variation (mg)**	Thickness (mm)**	Hardness (kg/cm^2) *	Content Uniformity (%) **	Disintegration time (sec)*	Friability (%) **
F1	130.2±0.21	2.94±0.11	4.17±0.5	98.2±0.51	33±0.03	0.93±0.11
F2	131.3±0.31	2.91±0.24	4.0±0.3	99.3±0.24	28±0.05	0.84±0.15
F3	133.5±0.52	2.92±0.33	4±0.29	98.5±0.33	22±0.11	0.72±0.21
F4	132.2±0.23	2.90±0.41	4.1±0.0	100.3±0.41	13±0.07	0.73±0.23
F5	133.1±0.51	2.93±0.15	4.17±0.5	99.4±0.11	8±0.13	0.66±0.33
F6	130.4±0.44	2.91±0.25	4.0±0.5	101.2±0.23	4±0.21	0.63±0.25
F7	132.3±0.12	2.90±0.31	4.17±0.0	98.6±0.27	28±0.32	0.78±0.18
F8	133.2±0.54	2.92±0.26	4.0±0.29	100.4±0.31	17±0.23	0.72±0.17
F9	130.5±0.51	2.91±0.54	4±0.5	99.6±0.25	11±0.31	0.69±0.24

***Results are expressed as Mean ± SD(n=6); **Results are expressed as Mean ± SD(n=20).**

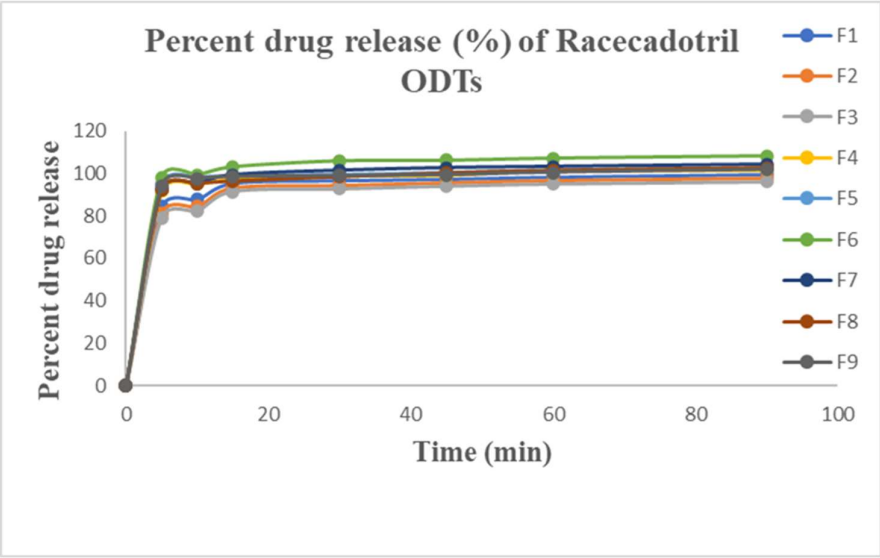

Figure 2: Percent drug release of racecadotril ODT's

Table 4: Independent variables and dependent variables of racecadotril orally disintegrating tablets using central composite design

Std	Run	Independent Variables		Dependent Variables		
		A: Conc of super disintegrant	B: Conc of camphor	DT	Friability	Drug Release
		%	%	sec	%	%
6	1	5	10	4	0.63	99.31
11	2	2.75	10	8	0.67	98.03
10	3	2.75	10	8	0.66	98.03
4	4	5	15	11	0.69	97.8
1	5	0.5	5	33	0.93	87.7
7	6	2.75	5	28	0.84	84.4
5	7	0.5	10	13	0.73	95.03
9	8	2.75	10	8	0.66	98.03
2	9	5	5	22	0.72	82.3
3	10	0.5	15	28	0.78	93.32
8	11	2.75	15	17	0.72	95.03

Table 5: Results of ANOVA for predicting disintegration time (Y1)

Source Sum of	Sum of Squares	df	Mean Square	F-value	p-value	
Model	960.58	3	320.19	102.03	<0.0001	significant
A-Conc. of super disintegrant	228.17	1	228.17	72.71	<0.0001	
B-Conc. of camphor	121.50	1	121.50	38.72	0.0004	
B^2	610.91	1	610.91	194.68	<0.0001	
Residual	21.97	7	3.14			
Lack of Fit	21.97	5	4.39			
Pure Error	0.0000	2	0.0000			
Cor Total	982.55	10				

Table 6: Results of ANOVA for predicting percent friability (Y2)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0783	4	0.0196	76.57	< 0.0001	significant
A-Conc of super disintegrant	0.0267	1	0.0267	104.35	< 0.0001	
B-Conc of camphor	0.0150	1	0.0150	58.70	0.0003	
AB	0.0036	1	0.0036	14.09	0.0095	
B^2	0.0330	1	0.0330	129.13	< 0.0001	
Residual	0.0015	6	0.0003			
Lack of Fit	0.0015	4	0.0004	11.00	0.0851	not significant
Pure Error	0.0001	2	0.0000			
Cor Total	0.0798	10				

Table 7: Results of ANOVA for predicting percent drug release (Y3)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	351.59	4	87.90	59.90	< 0.0001	significant
A-Conc of super disintegrant	1.88	1	1.88	1.28	0.3007	
B-Conc of camphor	168.01	1	168.01	114.50	< 0.0001	
AB	24.40	1	24.40	16.63	0.0065	
B^2	157.29	1	157.29	107.20	< 0.0001	
Residual	8.80	6	1.47			
Lack of Fit	8.80	4	2.20			
Pure Error	0.0000	2	0.0000			
Cor Total	360.39	10				

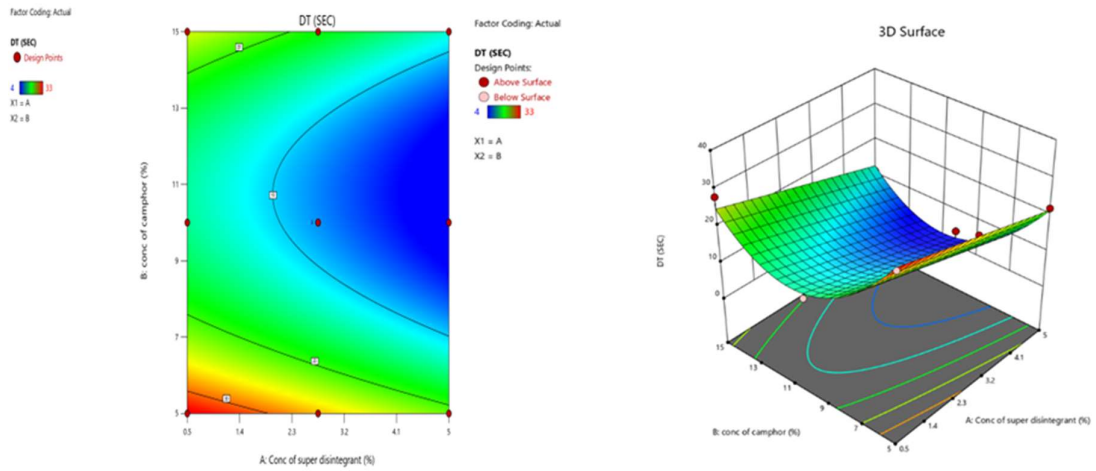

Figure 3: Super disintegrant and sublimating agent in relation to DT in 3D surface response graph

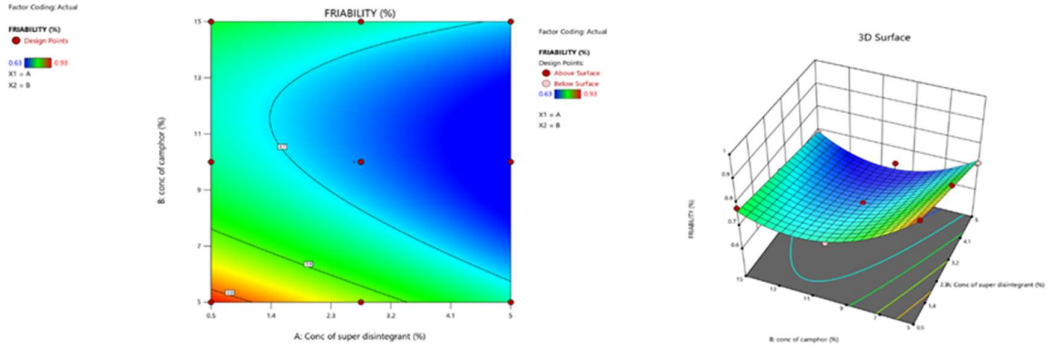

Figure 4: Super disintegrant and sublimating agent in relation to percent friability in 3D surface response graph

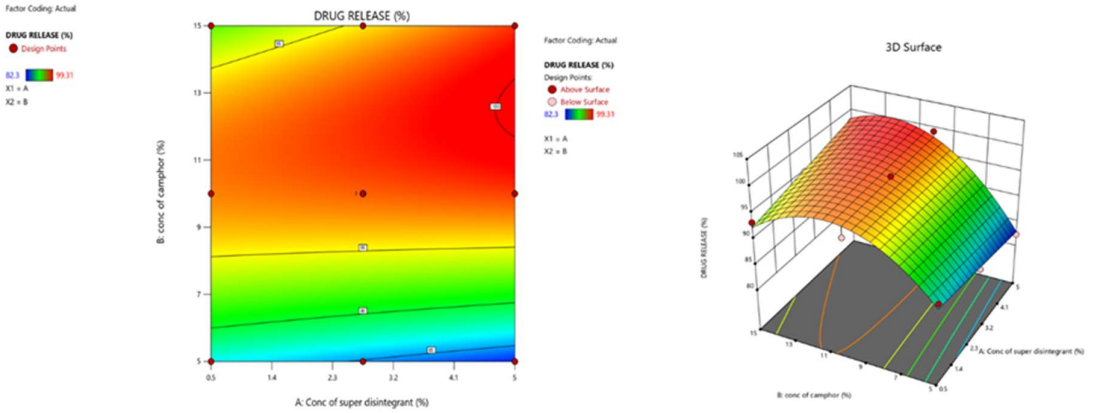

Figure 5: Super disintegrant and sublimating agent in relation to percent drug release in 3D surface response graph

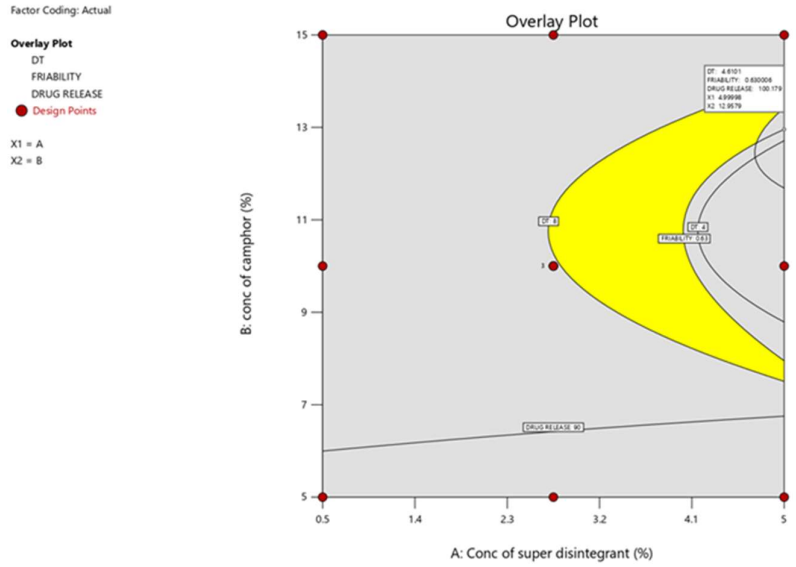

Figure 6: Overlay plot

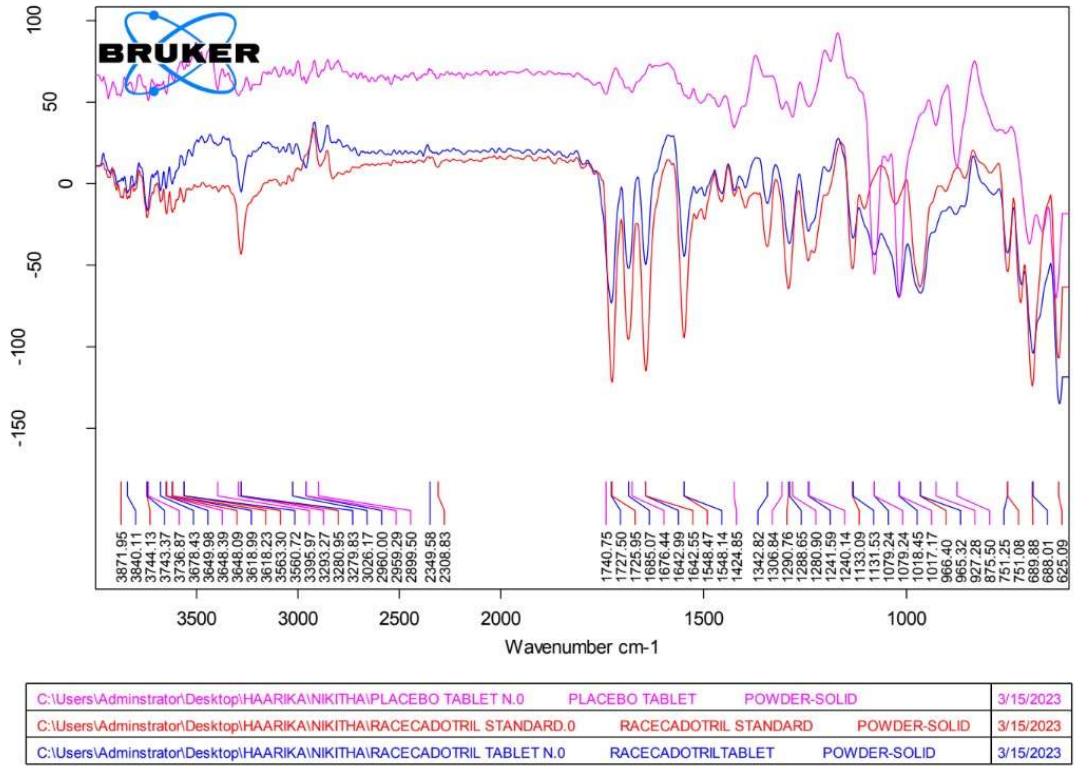

Figure 7: FT-IR spectra of placebo (tablet), racecadotril ODT tablet formulation and standard racecadotril

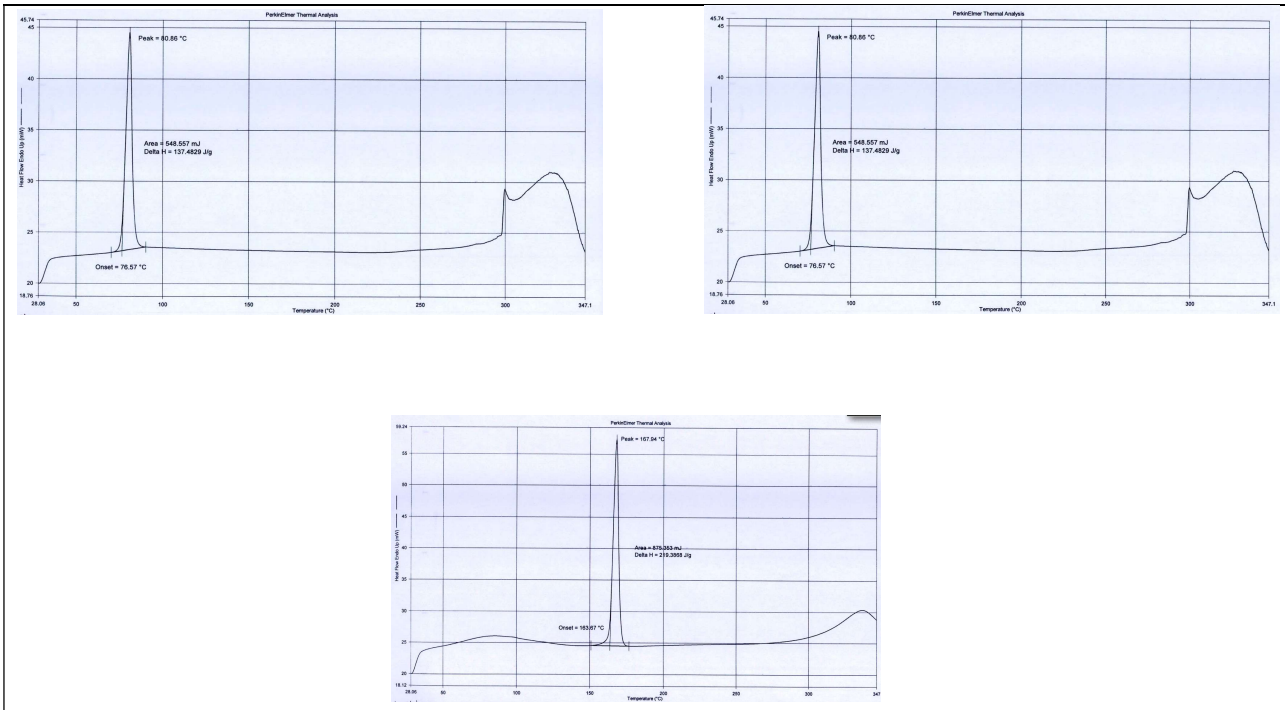

Figure 8: DSC curves of standard racecadotril, racecadotril ODT formulation and placebo

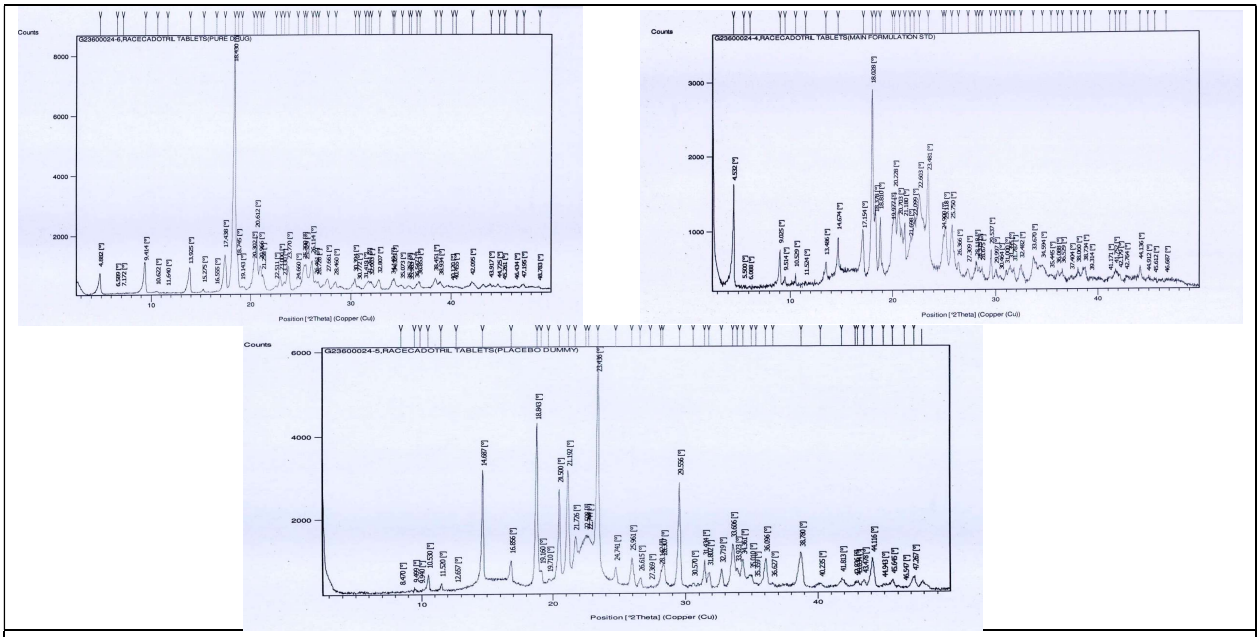

Figure 9: XRD patterns of standard racecadotril, racecadotril ODT formulation and placebo

Table 8: Effect of storage of optimized formulation F6 at 40±2°C/ 75±5% RH

Formulation code F6/ day	Disintegration time (sec)	Friability (%)	Percent drug release (%)
1st day	4.60±0.12	0.62±0.14	100.18±0.21
30th day	4.59±0.22	0.61±0.33	100.16±0.32
60th day	4.59±0.15	0.61±0.25	100.18±0.15
90th day	4.60±0.13	0.62±0.21	100.16±0.11

DISCUSSION

Racecadotril ODT's were prepared by sublimation method using avidone as super disintegrant and camphor as sublimating agent. Avidone swells without gelling, a property which is advantageous for developing ODT's where gelling can delay the dissolution process. When force is applied, polymer deforms upon contact with fluids where via capillary action, increases tablet porosity which facilitates wicking of liquid into tablet bed. Thus, causes rapid disintegration hence avidone was selected as a super disintegrant. In this tablet formulations SMCC HD 90 consists of MCC and colloidal silicon dioxide was used as a free-flowing diluent. Mannitol was used as a diluent owing to its sweet taste and imparts a cooling sensation in mouth because of its negative heat of solution. Talc and magnesium stearate were used as flow promoters. These factorial design formulations showed good flow properties.

The disintegration time which is the most important parameter, needs to be optimized in mouth dissolving tablets to get the optimized formulation with less disintegration time. As concentration of super disintegrant increases, DT will decrease. A combination of super disintegrant (avidone, 5%) and sublimating agent (camphor, 10%) results in high porosity which lead to decreasing in wetting time due to capillary action along with wicking action of super disintegrant, bringing about rapid disintegration. The percentage drug release for all nine formulations F1 to F9 were ranged from 82.3 to 99.31% in 10 min. The formulation F6 showed DT of 4 sec, friability of 0.63% and 99.31% drug release at 10min interval, hence it was considered as optimized formulation.

The drug with excipient compatibility was confirmed by FTIR, DSC and XRD. The FTIR studies reveal that drug with excipient are compatible with each other. The substantial changes in the IR absorption bands were not observed in drug in ODT formulation compared with pure drug. DSC and XRD studies reveal that there was no interaction between the drug and excipients. Based on disintegration and dissolution studies the optimized F6 formulation was subjected to stability studies and showed good stability.

Analysis of variance for disintegration time, friability and percentage drug release was performed. The coefficients X_1 (Avidone) and X_2 (Camphor) showed significant effect ($P<0.05$) on selected responses.

The response surface plots for dependent variables disintegration time, friability and percent drug release were generated and the effect of independent variables, X_1 and X_2 on the responses was studied.

The effect of formulation variables on disintegration time can be described by the

model equation, Y1 (disintegration time) = $+8.20-6.17X_1-4.50X_2+14.97X^2$. The negative sign for coefficient X_1 and X_2 indicated that as the concentration of avidone and camphor increased, DT decreased (R^2= 0.9776) indicating good correlation between independent and dependent variables. The term with ($P<0.01$) was considered significant.

Friability can be described by the model equation, Y2 (friability)= $+0.67-0.0667X_1-0.0500X_2+0.0300X_1X_2+0.1100X^2$, the negative sign for coefficient X_1 suggests increase in concentration of super disintegrant. Initially as the concentration of camphor increases, friability decreases followed by a slight increase in friability within the pharmacopeial acceptable limits. The effect of independent variables on friability was significant ($P<0.01$) and indicates good correlation (R^2=0.9808).

The model equation for percentage drug release was Y3 (% drug release) = $+97.69+0.5600\ X_1+5.29X_2+2.47X_1X_2-7.59X^2$, the positive sign for X_1 and X_2 indicated that as the concentration of super disintegrant and camphor increased, percentage drug release also increased. R^2 value of 0.9756 for percent drug release indicated good correlation between independent and dependent variable. The term with ($P<0.01$) was considered significant.

Results from stability studies of F6 formulation at 40±2°C/75±5% RH in stability chamber for three months at 30 days' time interval analysed for disintegration time, percent friability and percent drug release. The optimized F6 formulation were stable and did not show much variation in any of the above parameters.

CONCLUSION

Racecadotril orally disintegrating tablets were developed to give fast release and to have better patient compliance. Different formulations of racecadotril orally disintegrating tablets from F1 to F11 were prepared by sublimation technique. In preliminary trials, it was found that, apart from super disintegrant, the formulations containing camphor as sublimating agent showed best disintegration time and better drug release. Further optimization of racecadotril orally disintegrating tablets (F1 to F11) was done by optimizing independent variables such as concentration of super disintegrant (0.5, 2.75 and 5%) and concentration of sublimating agent (5,10 and 15%) and assessing dependent variables such as disintegration time, percent friability and percent drug release by using Central composite design from Response surface methodology. Combination of variables was suggested by software with a desirability function of 0.92 which is satisfactory as reaching 1. The optimized formulation (F6)

exhibited a disintegration time of 4 sec, percent friability of 0.63% and 99.31% drug release. It was recommended that the generated models would work well for orally disintegrating tablets optimization.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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