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Development and Characterization of Mouth Dissolving Tablet of Zolmitriptan

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ABSTRACT

Objective: To formulate and Characterize Mouth Dissolving Tablet of Zolmitriptan to produce the intended benefits. **Methods:** Tablets were prepared using a direct compression method employing superdisintegrants such as Kyron T-314, Crospovidone, Croscarmellose Sodium, and Sodium Starch Glycolate. Tablets of Zolmitriptan prepared using Kyron T-314 exhibited the least friability and disintegration time 35 seconds. To decrease the disintegration time further, a sublimation technique was used along with the superdisintegrants for the preparation of Mouth Dissolving Tablet (MDTs). The addition of camphor as a subliming agent lowered the disintegration time 10 seconds further, but the percent friability was increased. A 32 full factorial design was employed to study the joint influence of the amount of superdisintegrant (Kyron T-314) and the amount of sublimating agent (Camphor) on the percent of friability and the disintegration time. **Results:** The results of multiple linear regression analysis revealed that an effective MDT of Zolmitriptan requires higher percentages of Kyron T-314 and camphor should be used. The approach using the optimization technique helped to produce a detailed understanding effect of formulation parameters. An optimized formulation was found to have good hardness, wetting time, disintegration time. Release kinetic model study indicated that all the formulations follow zero order kinetics. It also indicated that batch F1, F2, F5 and F8 releases the drug at constant rate as well as fast rate as per the Weibull model which was also confirmed by Hixson-Crowell model. Stability studies indicated that there are no significant changes in hardness, Percentage friability, drug content and in-vitro disintegration time and cumulative percentage drug release. **Conclusions:** Thus, it was concluded that by adopting a systematic formulation approach, Zolmitriptan Mouth dissolving tablet could be formulated using superdisintegrants in combination with a vacuum-drying technique for improved therapeutic efficacy.

1. Introduction

In today's era many people are suffering from migraine. Migraine is a one sided throbbing headache followed by neurological and visual disturbances. Attack may prolong for long period. Patients routinely report the pain of an attack as being the most severe they have ever experienced [1].

Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. It has a selective action on serotonin receptors and is very effective in reducing migraine symptoms, including pain, nausea and photo or phonophobia. It is currently available as a conventional tablet, an oral disintegrating tablet and a nasal spray (2.5 mg and 5 mg per dose). The absolute bioavailability of zolmitriptan is up to 40% for both oral and nasal dosage forms. The faster clearance of the drug from the nasal cavity could explain the low bioavailability for the nasal formulation [2].

Recent developments in technology have presented viable dosage alternatives for paediatric, geriatric, bedridden, nauseous or non-compliant patients, who face difficulty in swallowing or chewing solid dosage forms and are unwilling to take solid preparations due to a fear of choking [3]. Hence, mouth dissolving/disintegrating tablets are a perfect fit for them. Superdisintegrants added in the formulation increase

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the drug release, thus increasing the bioavailability of drug [4]. Mouth disintegrating tablets when placed in the mouth, disintegrate instantaneously, releasing the drug, which dissolves or disperses in the saliva and can be swallowed as a liquid, without the aid of water [5]. Also, this dosage form offers an advantage of convenience of administration while travelling where there may not be an access to water [6]. Moreover, this dosage form combines the advantages of both liquid and tablet formulation. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than that observed from conventional tablet dosage form. This system of drug delivery allows children, elderly, and the general population to take their medications discretely wherever and whenever needed, much eliminating the factor of patient non-compliance. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market [7, 8].

2. Materials and Methods

2.1 Materials

Zolmitriptan, Sodium Starch Glycolate, Croscarmellose Sodium, and Crosspovidone were obtained as gift samples from Alembic Ltd. (Vadodara, India). Kyron T - 314 was obtained as a gift sample from Corel Pharma Chem. (Ahmedabad, India). Pearlitol SD 200 was obtained as a gift sample from Piramal Healthcare Ltd. (Ahmedabad, India). Sucralose was obtained from Oxford Laboratory. Pineapple flavour was obtained as a gift sample from Pentagoan Trading Co. (Ahmedabad, India). All other chemicals in the investigation were of analytical reagent grade.

2.2 Methods

2.2.1 Drug

Excipients Compatibility Study: Drug: Excipients compatibility study was carried out for any interference of drug and excipients used for the formulation of mouth dissolving tablet of Zolmitriptan. The interference study was carried out using FTIR and DSC analysis. The infrared absorption spectra of pure drug, pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 cm-1to 400 cm-1. The DSC analyses of pure drug and physical mixture of polymer and drug were carried polymer drug interaction studies out between 50-250℃. [9]

2.2.2 Formulation and optimization of excipient

The direct compression technique was used for tablet preparation. All the raw materials were passed through a #60 sieve prior to mixing. Zolmitriptan and the superdisintegrants (Sodium Starch Glycolate/Croscarmellose Sodium/ Crosspovidone/Kyron T-314) (4%), sucralose (3%), pineapple flavour (3%) and Pearlitol SD 200 (as much as required) were blended. The powder blend was lubricated with 2.5% talc and 5% Aerosil. The powder blend was compressed using a 6-mm tooling punch on a single rotary tablet machine, (Hardik Eng. work, Ahmedabad, India). The formulation of preliminary batches using the various superdisintegrants employed in the study is shown in Table 1. In vacuum-drying the preliminary batches, the subliming agent (camphor) was mixed with the excipients of the powder blend and lubricated with anti-adherents and glident, and the tablets were compressed in the manner mentioned above. The tablets were subjected to vacuum drying using a vacuum oven (Lab fine, Ahmedabad, India) for 1 to 8 h at temperatures ranging from 40 - 60℃ and at pressures ranging from 100 -300 mm Hg. The formulation of preliminary batches using Kyron T-314 along with camphor is shown in Table 2.

2.2.3 Statistical Design Batches

The preparation of tablets for factorial design batches was performed in the manner described above. Zolmitriptan, Kyron T-314, Camphor, Sucralose, pineapple flavour and Pearlitol SD 200 were blended. The powder blend was lubricated with 2.5% talc, 5% Aerosil. The powder blend was compressed using a 6-mm tooling punch on a single rotary tablet machine. The tablets were dried in a vacuum oven for 1 to 8 h at a temperature of 60℃ and at a pressure of 100-300 mm Hg. The formulation of statistical design batches F1 through F9 is shown in Table 3.

2.2.4 Evaluation of Tablet Properties

The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). The limit for crushing strength of the tablets was kept in the range of 3-4 kg/cm2. The friability of the tablets was measured using a Roche Friabilator (Electro-lab, Ahmedabad, India). Twenty pre-weighed tablets were rotated for 4 min at rpm. The tablets were then weighed again, and the percentage of weight loss was calculated. [10]

Wetting time was measured using five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. Ten millimetres of water-containing Eosin, a water-soluble dye, is added to petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time [11].

In-vitro disintegration time was measured using USP disintegration test apparatus. Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed in 900ml distilled water at 37±0.5 ℃ temperature and at the rate of 30±2 cycles/min. the results for the evaluation of tablets are shown in table 4 [12].

2.2.5 In-vitro Drug Release

The dissolution profiles of Zolmitriptan in MDTs were

determined in a dissolution tester following the USP paddle method. All tests were conducted in 250 ml phosphate buffer pH 6.8. The dissolution medium was maintained at a temperature of 37±0.5℃ with a paddle rotation speed at 50 rpm. At definite time intervals, a 5 ml sample was withdrawn and replaced by phosphate buffer pH 6.8; these samples were assayed for Zolmitriptan content by Shimadzu UV spectrophotometer (1800, Japan) at 281.60 nm. The results of in-vitro drug release are shown in table 5 [12].

2.2.6 Statistical Design

A randomized, 32 full factorial design with two factors at three levels was adopted to systematically study the formulation of MDTs of Zolmitriptan. A total of nine experimental trials were performed at all possible combinations [13]. The independent variables, the amount of camphor (X1) and the amount of Kyron T-314 (X2), were selected on the basis of trials taken during optimization of excipient. The percent of friability and disintegration time were selected as dependent variables.

2.2.7 Release kinetic model study

The drug release data were evaluated by model dependent (curve fitting method), in the present study in-vitro drug release data were fitted to various kinetic models like zero-order, First order, Hixson-Crowell, and Weibull equation and coefficient of correlation (r) values were calculated for linear curves by regression analysis of the above plot. These models used to explain drug release mechanism along with gradual erosion of the tablet. Results of release kinetic model study are shown in table 6 [14, 15].

2.2.8 Stability Studies

Table 1

Effects of Various Superdisintegrants on the Formulation of Mouth Dissolving Tables of Zolmitriptan

Formulation Code	A1	A2	A3	A4
Sodium starch Glycolate	4 %	–	–	–
Kyron T-314	–	4 %	–	–
Croscarmellose sodium	–	–	4 %	–
Crospovidone	–	–	–	4 %
Friability (%)	0.261±0.30	0.203±0.19	0.364±0.08	0.411±0.31
Disintegration Time (sec.)	41±0.12	35±0.02	52±0.10	22±0.06
Wetting Time (Sec.)	38±0.21	40±0.07	59±0.35	31±0.15

A1-A4 contains 5 mg of Zolmitriptan, 3 mg Sucralose, 5 mg Arerosil, 2.5 mg Talc, 3 mg pineapple flavour. The final weight of the tablets was adjusted to 100mg using Pearlitol SD 200 as a diluent. The crushing strength was adjusted to 3.5 kg/cm^2.

Note: Values are mean value of 3 observations (n=3) and values in parenthesis are standard deviation (± SD).

Table 2

Effects of Sublimation Technique on Mouth Dissolving Tablets of Zolmitriptan

Formulation Code	A5	A6	A7	A8	A9
Camphor	0%	5%	8%	10%	12%
Kyron T-314	4%	4%	4%	4%	4%
Friability (%)	0.203±0.19	0.314±0.09	0.512±0.15	0.657±0.60	1.36±0.29
Disintegration Time (sec.)	35±0.02	27±0.03	22±0.14	20±0.01	12±0.31
Wetting Time (Sec.)	40±0.07	33±0.31	27±0.04	21±0.02	18±1.63

A5-A9 contains 5 mg of Zolmitriptan, 3 mg Sucralose, 5 mg Aerosil, 2.5 mg Talc, 3 mg pineapple flavour. The final weight of the tablets was adjusted to 100mg using Pearlitol SD 200 as a diluent. The crushing strength was adjusted to 3.5 kg/cm^2.

Note: Values are mean value of 3 observations (*n*=3) and values in parenthesis are standard deviation (± SD).

Table 3

32 Full Factorial Design Layout of Mouth Dissolving Tablets of Zolmitriptan

Formulation Code	Real Values		Transformed Values		Responses*	
	% Camphor	% Kyron T-314	X1	X2	% Friability	DT (Sec.)
F1	3	3	−1	−1	0.235±0.23	23±0.32
F2	3	4	−1	0	0.168±0.64	20±0.15
F3	3	5	−1	1	0.137±1.25	21±0.56
F4	5	3	0	−1	0.266±0.34	19±0.42
F5	5	4	0	0	0.213±0.47	15±0.31
F6	5	5	0	1	0.203±2.04	17±1.54
F7	7	3	1	−1	0.400±3.21	16±0.35
F8	7	4	1	0	0.257±0.12	11±1.97
F9	7	5	1	1	0.223±0.17	10±0.11

Note: Values are mean value of 3 observations (*n*=3) and values in parenthesis are standard deviation (±SD).

Stability Studies were carried out at 40℃±2℃/75 %±5 % RH for 30 days. The tablets of optimized formulation F9 were packed in amber-colored bottles tightly plugged with cotton and capped. The tablets were checked for % friability, disintegration time, hardness, % drug content and % drug release after 30 days. The results for the stability studies are shown in table 7 and 8 [16].

3. Results

3.1 Drug: Excipients Compatibility Study

Results of IR spectrum of the pure drug Zolmitriptan and powder mixture of pure drug and polymers are represented in figure 1. The Zolmitriptan has indicating presence of absorption peak due to presence of N-H of the lactam, as well as secondary amine absorption, suggesting that these functionalities are also present in the powder mixture. The aromatic and aliphatic C-H absorption are noticed from 2850 Cm-1 to 3100 Cm-1. The characteristics C=O-O of the drug exhibited a absorption peak at 1750 Cm-1, which is in cyclic form. These are the characteristics of the Zolmitriptan. Hence, it is concluded that, drug present in Free State in powder mixture not in the form of reaction product.

DSC curves obtained for pure Zolmitriptan and physical mixture of pure drug and polymers are shown in Figure 2. Pure powdered Zolmitriptan showed melting endotherm at 138.48 ℃, while physical mixture of drug and excipients showed the melting peak of the drug at 137.42℃ which indicates that all ingredients are compatible with each other.

3.2 Optimizations of formulation batches

The optimization of excipient done by direct compression technique in order to study the effect of the same concentration of superdisintegrants (Sodium Starch Glycolate, Kyron T-314, Croscarmellose Sodium, and Crosspovidone) on the disintegration time, wetting time, and percent of friability. The

Table 4

Evaluation of Post-Compression Parameters of Batch F1 to F9 of Mouth Dissolving Tablets of Zolmitriptan

Formulation code	Hardness (kg/cm^2)	Thickness(mm)	Weight Variation(mg)	% Assay	Wetting time(sec.)
F1	3.64±0.12	2.25±0.13	100.05±1.21	99.53±0.26	32±1.66
F2	3.58±0.24	2.22±0.02	100.13±0.87	98.56±0.51	31±2.31
F3	3.18±0.15	2.25±0.35	100.24±1.56	100.03± 0.24	29±0.05
F4	3.26±0.57	2.27±0.54	100.87±0.23	99.21±0.60	26±0.14
F5	3.24±0.20	2.23±0.08	99.62±0.13	98.85±0.41	24±1.11
F6	3.16±0.58	2.25±1.54	102.22±1.18	99.54±0.38	21±0.23
F7	3.09±0.19	2.29±1.14	98.37±0.08	98.78±0.43	24±0.64
F8	3.08±0.34	2.26±0.60	100.61±0.13	99.61±0.56	23±0.02
F9	3.04±0.21	2.25±0.09	100.12±0.40	99.88±0.24	19±0.08

Note: Values are mean value of 3 observations (n=3) and values in parenthesis are standard deviation (± SD).

Table 5

Results of in-vitro dissolution batch F1 to F9 of Zolmitriptan Mouth Dissolving Tablet

Time in sec.	F1	F2	F3	F4	F5	F6	F7	F8	F9
30	5.82±2.20	13.06±1.03	14.60±1.00	30.31±0.69	16.32±2.42	28.30±2.04	31.89±7.76	15.36±1.36	27.06±1.40
60	31.17±1.40	35.00±4.16	41.91±3.41	55.96±9.05	42.91±1.82	53.82±1.22	64.50±19.78	33.99±2.54	51.89±6.07
120	53.29±1.00	61.70±6.85	66.72±11.0	82.48±9.29	66.53±0.20	84.17±0.61	81.28±19.79	55.29±1.56	81.24±4.42
180	82.40±1.61	86.31±4.15	84.53±2.03	100.59±0.48	82.65±2.63	98.85±0.41	94.69±6.75	81.42±0.77	97.16±1.15
240	99.39±0.20	99.60±0.42	85.13±2.01	100.78±0.23	99.05±0.21	99.88±0.20	100.66±0.43	94.38±0.78	100.32±0.47

Note: Values are mean value of 3 observations (*n*=3) and values in parenthesis are standard deviation (± SD).

Table 6

Release kinetic model study

Formulation code	Zero order		First order		Weibull		Hixson
	R^2	Slope	R^2	Slope	R^2	Td	R^2
F1	0.977	0.437	0.824	-0.009	0.967	142.55	0.946
F2	0.971	0.409	0.837	-0.010	0.969	122.91	0.962
F3	0.871	0.328	0.944	-0.003	0.967	90.47	0.929
F4	0.967	0.56	0.999	-0.006	0.999	67.76	0.996
F5	0.952	0.371	0.85	-0.008	0.964	113.99	0.957
F6	0.864	0.337	0.965	-0.013	0.988	70.45	0.896
F7	0.878	0.381	0.981	-0.007	0.980	58.79	0.977
F8	0.981	0.376	0.952	-0.005	0.986	137.16	0.987
F9	0.955	0.457	0.963	-0.009	0.991	93.35	0.997

disintegration time of the MDTs of Zolmitriptan showed wide variation, thus indicating that the type of superdisintegrant had an effect on disintegration time. The percent of friability values ranged between 0.2% and 0.5%.

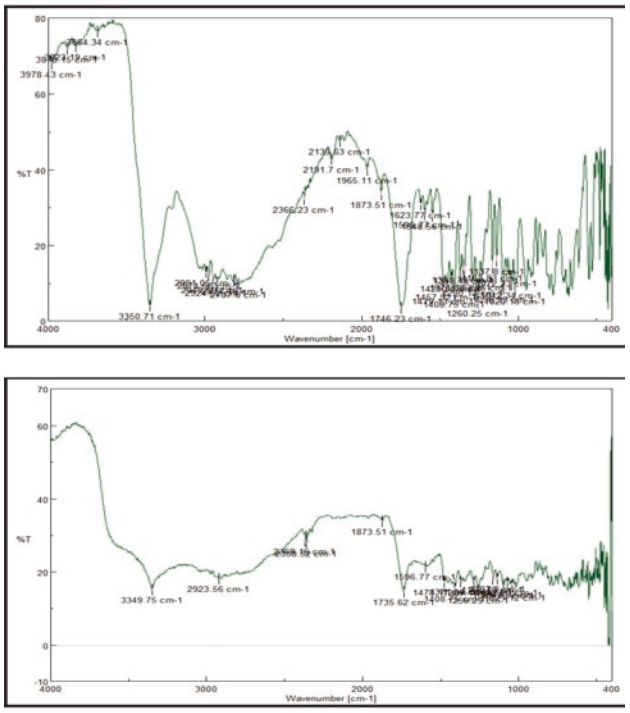

Figure 1: FT-IR Spectra of Zolmitriptan Pure drug (a) and Physical Mixture of Pure Drug and Polymers (b)

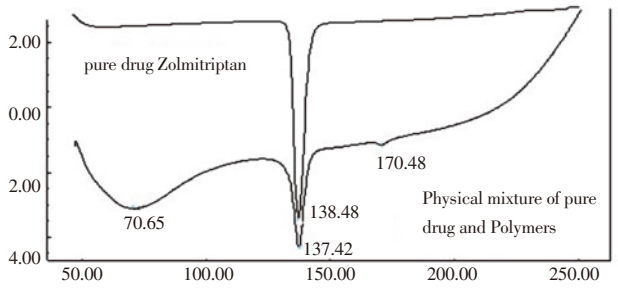

Figure 2: DSC curve of pure drug Zolmitriptan and Physical mixture of pure drug and Polymers

Subsequent batches were prepared to study the effect of different concentrations of camphor on sublimation time and disintegration time. Sublimation time (5-8 hr.) was dependent on the amount of camphor present initially (0%, 5%, 8%, 10%, and 12%). Formulation code A6 containing 5% camphor showed the shortest disintegration time with better friability. The results shown in Table 2 indicate that the disintegration time was significantly affected by the camphor concentration, by increasing the camphor concentration there is significantly decrease in disintegration time. The porous structure induced in the tablet matrix due to the sublimation of camphor was responsible for faster water uptake, thus facilitating the swelling action of KyronT-314 and allowing faster disintegration which has also been reported in the literature [17, 18]. Also as the concentration of camphor increases, the wetting time decreases, from 40 sec for batch A5 to 18 sec for batch A9.

3.3 Statistical Experimental Design: A three-level, two-factor full factorial statistical experimental design was used to optimize and evaluate the main effects, the interaction effects, and the quadratic effects of the independent variables on the response variables. The amount of subliming agent (camphor, X1) and the amount of superdisintegrant (Kyron T-314, X2) were chosen as independent variables, and percent of friability and disintegration time were chosen as the dependent variables. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses,

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b12X12 + b22X22 \ldots\ldots (1)$$

Where, Y is the measured response associated with each run, b0 is the arithmetic mean response of the total 9 runs, and bi is the regression coefficient for factor Xi computed from the observed response Y. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction term X1X2 shows how the response changes when two factors are simultaneously changed. The polynomial terms X12 and X22 represent the nonlinearity in the model. Two conclusions could be drawn from the equation: a coefficient with a negative sign increases the response when the factor level is decreased from a higher level to a lower level, and the factor with a higher absolute value of the coefficient and a lower significance value "P" has a major effect on the response variables. The dependent variables, percent of friability and disintegration time, showed a wide variation (0.13% to 0.40% and 23 seconds to 10 seconds, respectively). The data clearly indicates that the response variables are strongly dependent on the selected independent variables. The high values of the correlation coefficient for disintegration time and the percent of friability indicate a close fit. The fitted equations (full and reduced) relating the responses to the transformed factor are shown in Table 9 and 11. Analysis of variance (ANOVA) was carried out to identify the insignificant factors, which were then removed from the full model to generate the reduced model. The results are shown in Table 10 and 12.

Table 7

Stability study

Parameters	Initial	After 30 days
% Friability	0.223±0.17	0.221±0.23
Hardness (kg/cm^3)	3.04±0.21	3.04±0.25
Disintegration Time (Sec.)	10±0.11	11±0.25
% drug content	99.88±0.24	100.12±0.41

Note: Values are mean value of 3 observations (n=3) and values in parenthesis are standard deviation (± SD).

Table 8

Comparative dissolution profile of optimized formulation after 30 days

Time (Sec.)	% CDR
30	30.06±2.54
60	49.28±0.27
120	84.98±1.94
180	95.14±0.87
240	100.17±0.02

Note: Values are mean value of 3 observations (n=3) and values in parenthesis are standard deviation (± SD).

Table 9

Summary of Results of Regression Analysis for Percentage Friability

Response (% Friability)	b0	b1	b2	b11	b22	b12	R^2
FM	0.206	0.056	−0.056	−0.019	0.009	0.031	0.9461
RM	0.234	0.056	−0.056	–	–	–	0.8628

Table 10

Calculation for testing the models in proportions for Percentage Friability

	DF	SS	MS	F	
Regression					Fcal = 1.54
FM	5	0.042005	0.008401	10.541	Ftable = 19.33
Rm	2	0.038307	0.019154	18.874	DF = (2,6)
Residual					
FM	3	0.002391	0.000797	–	
RM	6	0.006089	0.001015	–	

Table 11

Summary of Results of Regression Analysis for Disintegration Time

Response(DT)	b0	b1	b2	b11	b22	b12	R^2
FM	16.1	−4.66	−1.72	−0.91	−0.55	2.27	0.986
RM	15.77	−4.66	−1.72	–	–	2.27	0.962

Table 12

Calculation for testing the models in proportions for Disintegration Time

	DF	SS	MS	F	
Regression					
FM	5	162.7175	32.54313	45.09678	Fcal = 2.75
Rm	3	158.7398	52.91326	43.08348	Ftable = 9.01
Residual					DF = (3,5)
FM	3	2.164886	0.721629	–	
RM	5	6.140783	1.228157	–	

3.4 Full and Reduced Model for Percent of Friability

The significance levels of coefficients b12, b22and b12 were found to be greater than *P*=0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 9. The coefficients b1 and b2 were found to be significant at P > 0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b12, b22and b12 contribute significant information for the prediction of the percent of friability. The results of testing the model in portions are shown in Table 10. The critical value of F for α = 0.05 is equal to 19.33 (df = 2, 3). Since the calculated value (F = 1.54) is less than the critical value (F = 19.33). The results are shown in the form of response surface plot (Figure 3).

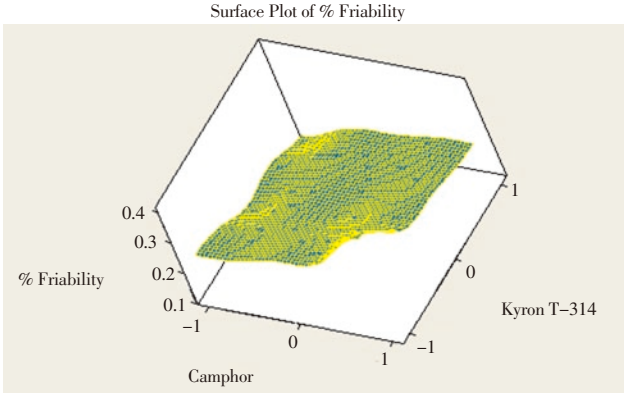

Figure 3: Response Surface Plot of % Friability of Zolmitriptan Mouth Dissolving Tablet

Polynomial equation for % friability FM: 0.206X + 0.056X1 − 0.056X2 − 0.019X11 + 0.009X22 + 0.031X12

Polynomial equation for % friability RM: 0.234X + 0.056X1 − 0.056X2

The coefficient of X1, b1 bears a positive sign, thus an increase in the concentration of camphor leads to an increase in the percent of friability. When higher percentages of camphor are used, more-porous tablets are formed, which are mechanically weak. The coefficient of X2, b2 bears a negative sign, thus an increase in the concentration of Kyron T-314 decreases friability; Kyron T-314 is known to produce mechanically strong tablets.

3.5 Full and Reduced Model for Disintegration Time

The significance level of coefficients b12 and b22 were found to be greater than P = 0.05, thus they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 11. The coefficients b1, b2 and b12 were found to be significant at P = 0.05, thus they were retained in the reduced model. The reduced model was tested in portions to determine whether the omitted coefficients contributed significant information for the prediction of disintegration time. The results for testing the model in portions are shown in Table 12. The critical value of F for α = 0.05 is equal to 9.01(df = 3, 5). As the calculated value (F = 2.75) is less than the critical value (F = 9.01). The results are shown in the form of a response surface plot (Figure 4).

Polynomial equation for DT FM: 16.1X − 4.66X1 − 1.72X2 − 0.91X11 − 0.055X22 + 2.27X12

Polynomial equation for DT RM: 15.77X − 4.66X1 − 1.72X2 + 2.27X12

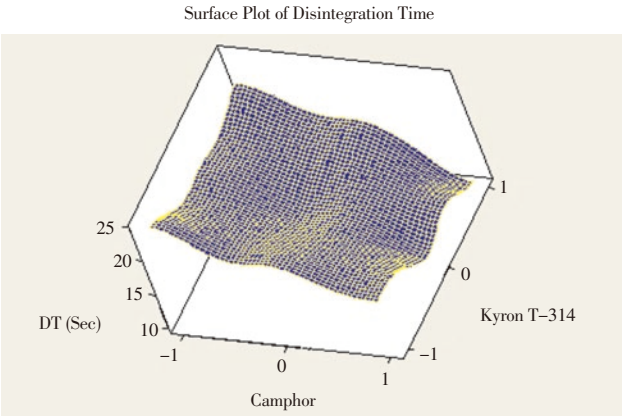

Figure 4: Response Surface Plot of Disintegration Time of Zolmitriptan Mouth Dissolving Tablet

3.6 Release kinetics model study

Results of the release kinetic models showed that all the formulations follow the zero order kinetic release. Further it was also observed that all the batches follows constant release rate as per Weibull model and furthermore it was also confirmed by Hixson-Crowell model.

3.7 Stability studies

Stability study of the optimized formulation was carried out for one month and no significant change was observed for hardness, friability, disintegration time, wetting time, percentage assay and also in drug release profile. It shows that the optimized batch composition is stable and reproducible at plant scale in scalable.

4. Discussion:

4.1 Optimizations of formulation batches

Result of disintegration time indicate that the addition of a superdisintegrant is no capable to produce the most desirable feature of an MDT, so vacuum-drying technique was then adopted to create a porous structure in the tablets using camphor as subliming agent for further optimization. It is worthwhile to note, however, that the addition of camphor also resulted in increased friability, probably due to the generation of the porous structure in the tablet matrix. So on the basis of results obtained in the optimization studies, a factorial design was employed in the present investigation to investigate the factors systematically.

4.2 Effect of formulation variables on percent of friability

It may be concluded that the omitted terms do not contribute significantly to the prediction of percent of friability. Results of regression analysis show coefficient of X1, b1 bears a positive sign, thus an increase in the concentration of camphor leads to an increase in the percent of friability. When higher percentages of camphor are used, more-porous tablets are formed, which are mechanically weak. The coefficient of X2, b2 bears a negative sign, thus an increase in the concentration Kyron T-314 of decreases friability; Kyron T-314 is known to produce mechanically strong tablets.

4.3 Effect of formulation variables on Disintegration time

It may be concluded that the omitted terms do not contribute significantly to the prediction of disintegration time. Results of regression analysis show coefficients of X1 and X2, that is, b1 and b2, respectively, bear a negative sign, thus on increasing the concentration of either camphor or Kyron T-314, a decrease in disintegration time is observed. When a higher percentage of camphor is used, porosity in the tablet matrix is greater and thus assists in water uptake and subsequent disintegration. It is obvious that in the presence of higher percentages of Kyron T-314, disintegration time is shorter. Thus, at higher levels of superdisintegrants, shorter disintegration times were obtained.

4.4 Selection of optimized batch

The optimized batch was selected on the basis of percent friability $\leqslant$ 0.5% and disintegration time $\leqslant$ 40 seconds. In-vitro dissolution release profile (figure 5) shows that F4, F6 and F9 releases the drug more than 80% within 120 second, further on the basis of disintegration time F9 was selected as optimized formulation. The images of wetting time and disintegration time for optimized batch F9 are shown in figure 6 and figure 7.

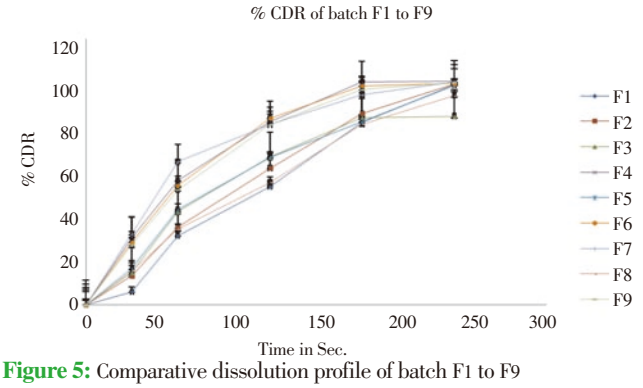

Figure 5: Comparative dissolution profile of batch F1 to F9

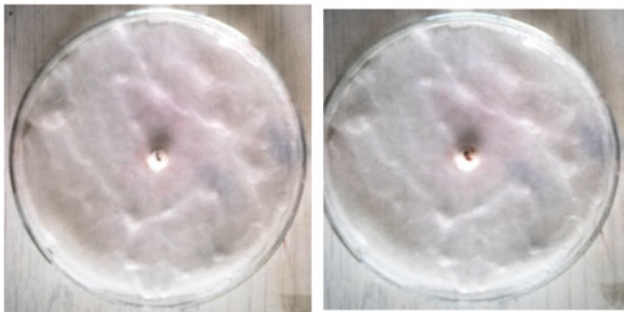

Figure 6: Wetting Time of Optimized Formulation F9

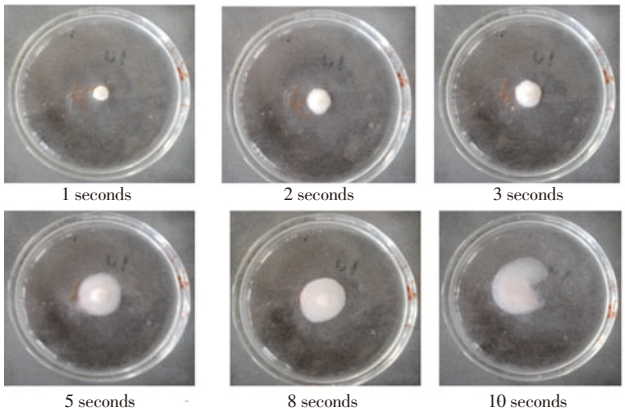

Figure 7: Disintegration Time of Optimized Formulation F9

5. Conclusion

The results of preliminary trial batches revealed that Kyron T-314 was the most effective superdisintegrant among those employed in the study, but the use of superdisintegrant alone was not able to fulfil the requirements of an MDT, and so it was accompanied by a vacuum-drying technique using camphor as a subliming agent. Camphor was able to generate porous structures in the tablet matrix, decreasing the disintegration time to below 30 sec. by acting synergistically with Kyron T-314. The results of factorial design batches showed that the percentage friability and disintegration time are strongly dependent on the amount of camphor and the amount of Kyron T-314. Thus, it is concluded that by adopting a systematic formulation approach, Zolmitriptan Mouth dissolving tablet could be formulated using superdisintegrants in combination with a vacuum-drying technique.

Conflict of interest

We declare that we have no conflict of interest.

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