Chapter 10

Preparation and evaluation of fast dissolving tablets

10.1 INTRODUCTION

Fast dissolving drug delivery systems (FDDS) have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. The difficulty of swallowing conventional tablets is also experienced by pediatric and geriatric patients. Such problems can be resolved by means of rapidly disintegrating tablets. When put on tongue, these tablets disintegrate instantaneously, releasing the drug, which dissolves or disperses in the saliva. Here, drug is absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach which result in elimination of first pass metabolism of drug. Hence, bioavailability of drug is also significantly greater than those observed from conventional tablet dosage form[1].

Some useful techniques to prepare fast dissolving tablets such as freeze drying, spray drying and sublimation[2-4] have been reported. But all these techniques are expensive. Some researchers have developed rapidly disintegrating tablets using freeze dried amorphous sucrose[5] or lactose with various particle sizes[6]. Other compressed, rapidly disintegrating tablets include one with treated agar[7] and another with camphor as a subliming material[8]. However, the manufacturing methods of all these tablets are more or less complicated.

Directly compressible rapidly disintegrating tablets using microcrystalline cellulose (MCC) and low-substituted hydroxypropylcellulose have been reported[9], but taste was unsatisfactory, as expected. Rapidly disintegrating tablets with pleasant taste containing erythritol have been reported[10] but cost of these tablets increased due to costly erythritol. In this study, approach was made to prepare the rapidly disintegrating tablets with a pleasant taste using mannitol which has a negative heat of solution, pleasant taste and low cost.

Moore and Flanner[13] recently proposed a "similarity factor, f_2" for comparison of dissolution profiles that has been adopted in SUPAC IR guidelines[14]. This similarity factor f_2 has been used to compare dissolution profile of the optimized batch in distilled

water and simulated saliva. Pillay and Fassihi[15] concluded that the results derived from the application of the similarity factor f_2 are superior to the individual time points (e.g. $t_{x\%}$) and mean dissolution time (MDT) values in differentiating between overall release pattern or the borderline release profile differences. Gohel and Panchal[16] has recently proposed a "similarity factor S_d" for the comparison of dissolution profile which is more simple and flexible than f_2 because data can be expressed either as the amount of drug dissolved or as the percentage drug dissolved. Another advantage is that, unlike the similarity factor f_2, linear interpolation can be used to accurately express the results[17]. The dissolution profiles of optimized batch in distilled water and simulated saliva (pH 6.8) were compared using "similarity factor f_2" and "similarity factor S_d".

The aim of the present study was to develop and evaluate the rapidly disintegrating tablets using MCC, lactose anhydrous and mannitol with a pleasant taste and texture acceptable to patients and with sufficient structural integrity by a low-cost direct compression method. These formulations can be useful for patients suffering from post operative or chemotherapy induced sever nausea and vomiting, ashtamatic attack or epileptic attack where quick onset of drug action is desirable and swallowing of conventional tablet dosage form is difficult.

10.2 PREPARATION AND EVALUATION OF FAST DISSOLVING TABLETS OF ONDANSETRON HYDROCHLORIDE

10.2.1 Experimentals

10.2.1.1 *Materials*

Ondansetron hydrochloride and aspartame were received as gift samples from Relax Pharmaceutical Ltd., Baroda, India. Microcrystalline cellulose (MCC), lactose anhydrous (β form) and mannitol were purchased from S. D. Chem. Ltd., Bombay, India. Magnesium stearate (Vikas Pharmaceutical Ltd., Ahmedabad, India) and croscarmellose sodium (Skymax Laboratories, Rajkot, India) were of I. P. grade. All the other

ingredients used were of analytical grade and were used without further purification. Deionized double distilled water was through the study.

10.2.1.2 *Physical properties of excipients*

The particle density was measured in benzene using gravity bottle method. Particle size was measured using laser diffraction particle size analyzer (Hydro2000SM, Malvern Instruments Ltd., UK). Water solubility was measured in distilled water at 37 °C. Data are listed in table 10.1.

Table 10.1. Physical properties of excipients.

	Ondansetron hydrochloride	**MCC**	**Lactose**	**Mannitol**	**Croscar-mellose**
Particle size (μm)[a]	229.1	121.4	63.1	137.6	48.8
Particle density (g/cc)	1.42	1.56	1.51	1.44	1.6
Solubility (w/w %)	2.7	--	20	36	6.23

a. Particle size is X_{50} in cumulative volume distribution.

10.2.1.3 *Preliminary batches*

Flat-faced tablets containing 25 mg microcrystalline cellulose, 25 mg lactose anhydrous, 10 mg mannitol, 8 mg ondansetron hydrochloride, 0.5 mg aspartame and varying amount of croscarmellose were compressed on an instrumented 36 station rotary tablet machine (Model Rimek-20PC, Karanavati Machinery Pvt. Ltd, Ahmedabad, India) using 6-mm round, flat faced tooling at different compression load at a speed of 20 rpm using direct compression. The minimum distance between the upper and lower punch was between 2.4 mm and 2.6 mm during preparation of tablets. The upper punch holder was instrumented with strain gauges (Model 5960, Senssymake, Italy) and the lower punch with a piezoelectric transducer (Model NIPCI_6024E, National Instruments Corporation, USA). The signals were transduced via a dc amplifier with two channels (Model SCC_SG04, National Instruments Corporation, USA). Data were acquired using a Lab

View Basic-1 and Lab View Basic-2 system (National Instruments Corporation, USA) and Lab View Professional software (National Instruments Corporation, USA). Preliminary batches were prepared by using two-factor spherical central composite design. The compression force (X_1) and % croscarmellose (X_2) were selected as independent variables. Two response variables, tablet tensile strength and disintegration time were measured. The tablet formulation is given in table 10.2.

Table 10.2. Design layout of central composite design and summary of experimental results. Each value is mean of three replicates.

Batch	Variables		Tensile strength kg/cm^2)	Disintegration time (sec)	Overall desirability
	X_1	X_2			
V_1	-1	-1	2.6	11	0.027
V_2	-1	1	2.1	9	0.005
V_3	1	-1	4.7	23	0.022
V_4	1	1	4.2	18	0.076
V_5	-1.7	0	1.8	8	0.000
V_6	1.7	0	5.9	27	0.000
V_7	0	-1.7	3.6	20	0.026
V_8	0	1.7	4.7	14	0.234
V_9	0	0	3.8	16	0.080
V_{10}	0	0	3.8	16	0.080
V_{11}	0	0	3.9	15	0.105

Independent variables	Level				
	-1.7	-1	0	1	1.7
X_1 = Compression force (kN)	1.3	2	3	4	4.7
X_2 = % Croscarmellose	1.6	3	5	7	8.4

The desirability function was used for the optimization of preliminary batches. During optimization of formulations, the responses have to be combined in order to produce a

product of desired characteristics. The application of the desirability function combines all the responses in one measurement[18] and gives the possibility to predict the optimum levels for the independent variables. The combination of the responses in one desirability function requires the calculation of the individual functions. The individual desirability for each response was calculated using the following methods[18,19]

The tensile strength value was maximized in the optimization procedure, as rapidly disintegrating tablets should have good hardness. The desirability functions of these responses were calculated using the following equation:

$$d_i = \frac{Y_i - Y_{min}}{Y_{max} - Y_{min}} \qquad (1)$$

Where, d_1 is the individual desirability of tensile strength of tablet. The values of Y_{max} and Y_{min} are 5.9 and 1.8 and Y_i is the experimental result.

The disintegration time value was minimized in the optimization procedure, as tablets should rapidly disintegrate in the mouth.

$$d_2 = \frac{Y_{max} - Y_i}{Y_{max} - Y_{min}} \qquad (2)$$

Where d_2 is the individual desirability of disintegration time. The Y_{max} and Y_{min} values are 27 and 8 and Y_i is the experimental result.

The overall desirability values were calculated from the individual values by using the following equation:

$$D = (d_1 d_2)^{1/2} \qquad (3)$$

10.2.1.4 *Preparation of tablets*

Batch V_8 was selected as a best batch having good tensile strength with an acceptable disintegration time as it showed highest overall desirability value (0.234). So, 8.4% croscarmellose as a disintegrant level and 3 kN as a compression load level were selected and fixed for the preparation of further batches. Simplex lattice design was utilized for the preparation of rapidly disintegrating tablets of ondansetron hydrochloride. Different batches of the tablets with 6 mm diameter containing 8 mg ondansetron hydrochloride, 8.4 % croscarmellose, 0.5 mg magnesium stearate, 0.5 mg aspartame and varying amount of microcrystalline cellulose, lactose anhydrous and mannitol as per table 3 were prepared using same rotary tablet machine as used for preparation of preliminary batches using direct compression at compression load of 3 kN at a speed of 20 rpm. The minimum distance between the upper and lower punch was between 2.6 mm and 2.8 mm during preparation of tablets. The actual and transformed values of ten different formulations as per simplex lattice design is given in table 10.3.

Table 10.3. Actual and transformed values of ten different formulations as per simplex lattice design.

	Formulation components (mg)			Transformed proportion		
Batch	X_1	X_2	X_3	X_1	X_2	X_3
M_1	40	10	10	1	0	0
M_2	10	40	10	0	1	0
M_3	10	10	40	0	0	1
M_4	25	25	10	0.5	0.5	0
M_5	25	10	25	0.5	0	0.5
M_6	10	25	25	0	0.5	0.5
M_7	20	20	20	0.33	0.33	0.33
M_8	25	17.5	17.5	0.5	0.25	0.25
M_9	17.5	17.5	25	0.25	0.25	0.5
M_{10}	17.5	25	17.5	0.25	0.5	0.25
M_{11}[a]	22	25	12	0.4	0.5	0.1

[a]Batch M_{11}, is a extra design check point.

Amount of microcrystalline cellulose (X_1), amount of lactose anhydrous (X_2), amount of mannitol (X_3) were selected as independent variables in a simplex lattice design. Two dependent variables, disintegration time (second) and tablet tensile strength (kg/cm^2) were measured. In order to apply the simplex equation to be derived from this experiment in a convenient manner, the actual concentration (10 mg) corresponds to 0% and the highest concentration (40 mg) corresponds to 100%. The actual amount of the factor was transferred using the following equation:

$$\text{Transformed proportion} = \frac{\text{Amount used} - \text{Minimum}}{\text{Maximum} - \text{Minimum}} \quad (4)$$

10.2.1.5 *Measurement of tablet tensile strength*

The dimensions of tablets were measured by using a micrometer. The tablet crushing load, which is the force required to break a tablet by direct compression in the radial direction, was measured using a tablet hardness tester (Model T-SHT-17, Tab Machine, Mumbai, India). The plunger was driven down at a speed of 25 mm/min. Tablet crushing strength T was calculated using the following equation 5[5,20].

$$T = 2F/\pi dt \qquad (5)$$

Where F is the crushing load, and d and t denotes the diameter and thickness of the tablet respectively.

10.2.1.6 *Measurement of wetting time*

A conventional method was used to measure wetting time and capillarity of the rapidly disintegrating tablets. The tablet was placed in a petridish of 7 cm diameter, containing 10 ml of distilled water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out four times and the mean value was calculated[21].

10.2.1.7 *Measurement of disintegration time*

The time required for disintegration of six tablets, placed in each of tube of USP disintegration test apparatus (Model ED2L, Electrolab, Mumbai, India) was measured at 37 $\pm$0.5 °C using 900 ml distilled water.

10.2.1.8 *Measurement of friability*

Friability was evaluated from percentage weight loss of 20 tablets tumbled in a friabilator (Model EF2L, Elactrolab, Mumbai, India) at 25 rpm for 4 minutes. The tablets were than

dedusted, and the loss in weight caused by fracture or abrasion was recorded as percentage weight loss.

10.2.1.9 *In vitro dissolution study*

A dissolution study was carried out in accordance with USP 25 Paddle apparatus (Model TDT-06P, Electrolab, Mumbai, India) at 37± 0.5 °C using 300 ml of deaerated distilled water or simulated saliva (pH 6.8) as a dissolution medium with stirring speed of 50 rpm. Samples (5 ml) were withdrawn at 0.0, 0.5, 1, 2, 3, 5, 10, 20 minutes time intervals and were filtered through 0.45μ whatman filter paper, diluted suitably and analysed spectrophotometrically at 249 nm (Model UV-1601, UV Visible spectrophotometer, Shimadzu, Japan). An equal volume of fresh dissolution medium maintained at the same temperature was added after withdrawing sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally ($r^2 > 0.997$). The dissolution test was performed in triplicate for each batch.

10.2.1.10 *Similarity and dissimilarity factors*

The similarity factor f_2 as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum square) difference of drug percent dissolved between the test and reference products[14]. It is given by following equation:

$$f_2 = 50 \times \mathrm{Log}\left\{\left[1 + \frac{1}{n}\sum_{n=1}^{n} W_t (R_t - T_t)^2\right]^{-0.5} \times 100\right\} \qquad (6)$$

where n is the number of pull points, W_t is an optional weight factor, R_t is the profile at time point t and T_t is the reference profile at the same time point. For a dissolution profile to be considered similar, the value of f_2 should be between 50 and 100[14,15]. An f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases.

The similarity factor S_d is defined as

$$S_d = \frac{\sum_{t=1}^{n-1} \left| \text{Log}\left((AUC_{R_t})/(AUC_{T_t})\right) \right|}{n-1} \qquad (7)$$

Where n is the number of data points collected during the in-vitro dissolution test and AUC_{Rt} and AUC_{Tt} are the areas under curves of the reference and test formulation, respectively, at time t. For the test and reference formulations to be identical, the S_d value should be zero[16,17].

10.2.2 Results and Discussion

By employing multivariable regression, interactive statistical second order polynomial equations composed of combination of casual factor X_1, X_2 and tablet properties could be obtained. The fitted equation relating the response (tensile strength) to the transformed factors is shown in the following equation:

$$\text{Tensile strength} = 3.736 + 1.142X_1$$
$$(R^2 = 0.9371; DF = 1,8; F = 64.94; P < 0.05) \qquad (8)$$

From the equation 7 it can be concluded that compression force has a synergistic effect on the tensile strength of the tablet while % croscarmellose has no significant influence on it.

The equation for disintegration time is as follow:

$$\text{Disintegration time} = 16.090 + 5.444X_1 - 1.750X_2$$
$$(R^2 = 0.9634; DF = 2,7; F = 105.32; P < 0.05) \qquad (9)$$

The negative sign of the coefficient suggest the antagonist effect of compression force on the disintegration time of the tablet which is understandable. The individual desirability of each response was calculated and the overall desirability calculated from individual

desirability of both responses was employed for the selection of the proper batch. The batch having the highest desirability (batch V_8) was considered as a best batch and further batches were prepared after keeping % croscarmellose and compression load level according to the batch V_8.

Simplex lattice design was used for the preparation of rapidly disintegrating tablets. This design was used to determine the relative proportion of ingredients that optimize a formulation with respect to a specified variables or outcome. The simplex design is arranged so that the experimental space is well covered in a symmetrical fashion. In, symmetrical spacing of the points allows for an easy computation of the response equation coefficients[22-27]. The general equation for the response based on a simplex design contains terms for components and all mixtures of components as follows:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 \quad (10)$$

Where, X_1, X_2, and X_3 are the proportions of components X_1, X_2, and X_3, and $X_1 + X_2 + X_3$ is equal to 1.0. Y represents the experimental response, b_0 is the intercept and b_1.. b_{123} are the estimates of the original unknown regression parameters.

In present work, three components of formulation are varied-microcrystalline cellulose (X_1), lactose anhydrous (X_2) and mannitol (X_3) with the restriction that the sum of their total weight must equal to 60 mg. The amounts of other ingredients were kept constant in each formulation.

Microcrystalline cellulose and lactose anhydrous were used as direct compressible diluents. Mannitol was used to enhance palatability of the tablet. Different croscarmellose concentrations showed no significant influence on the tensile strength of tablet. A formulation containing 8.4 % croscarmellose shows an acceptable mechanical strength of 5.8 kg/cm^2 at a compression load of 3 kN, with an optimum disintegration time.

Tensile strength greater than 5 kg/cm^2 was selected as arbitrary criteria for the selection of an appropriate batch. Batches M_1, M_3, M_5, and M_8 failed to meet the criteria. The following interactive, statistical, first order polynomial equation for the tensile strength was resulted:

$$\text{Tensilestrength} = 3.6X_1 + 6.9X_2 + 4.1X_3 + 2.2X_1X_2 + 3.4X_1X_3 + 4.8X_2X_3 - 16.8X_1X_2X_3 \quad (10)$$

From the equation 10, it can be seen that factor X_2 (amount of lactose anhydrous) has more influence on the tensile strength of the tablets. It was supposed that as high concentration of lactose anhydrous, its granules break into small crystals during the compression process, which generates many fresh contact surfaces, and tablet integrity is accordingly improved[28]. Contour plot of tensile strength is given in figure 10.1.

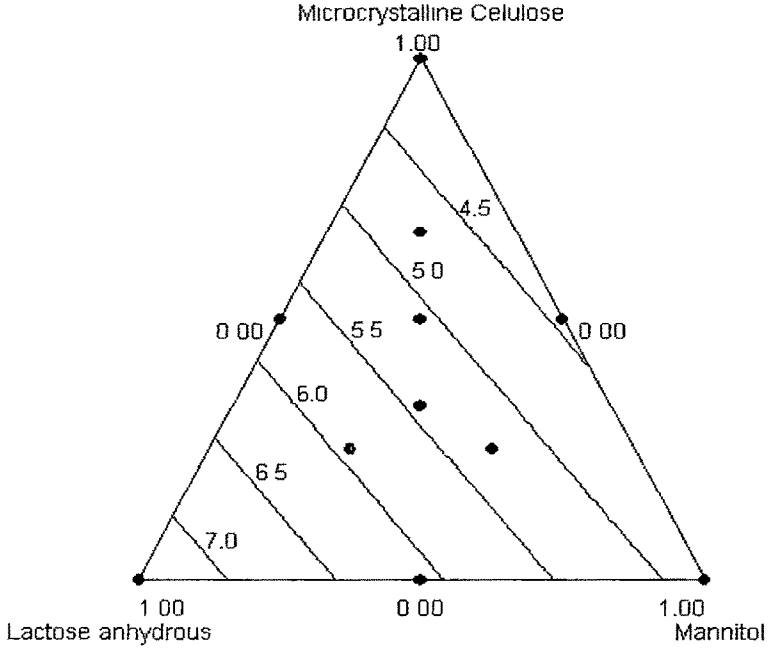


Figure 10.1. Contour plot of tensile strength obtained from simplex lattice design.

The two primary parameters on which the mechanical strength of tablet depends are the dominating bond mechanism and the surface over which these bonds are active[29]. Lactose is a sugar and mannitol is a sugar alcohol, and their main intermolecular force is the same (i.e. the hydrogen bonds between hydroxyl groups). MCC has less influence on the

tensile strength than other as it produces tablets with lesser integrity due to its fibrous characteristic. Equation 10 can be used to calculate predicted value for the other batches in the design space (e.g. checkpoint batch $_{11}$). The observed (5.6) and predicted (5.8) value of the tensile strength is in good agreement with each other. Equation 11 is the polynomial equation of disintegration time of the tablets, and it was obtained in the same was as equation 10.

$$\text{Disintegration time} = 10X_1 + 27X_2 + 20X_3 - 2X_1X_2 - 4X_1X_3 + 22X_2X_3 - 60X_1X_2X_3 \quad (11)$$

Equation 11 can be used to calculate predicted values for the other batches in the design space (checkpoint A_{11}). The observed (19) and predicted (18.8) values of tensile strength are in good agreement with each other, indicating good predictive power of equation 11. Disintegration time less than 20 second was selected as the maximum expected disintegration time. The contour plot of disintegration time is given in figure 10.2.

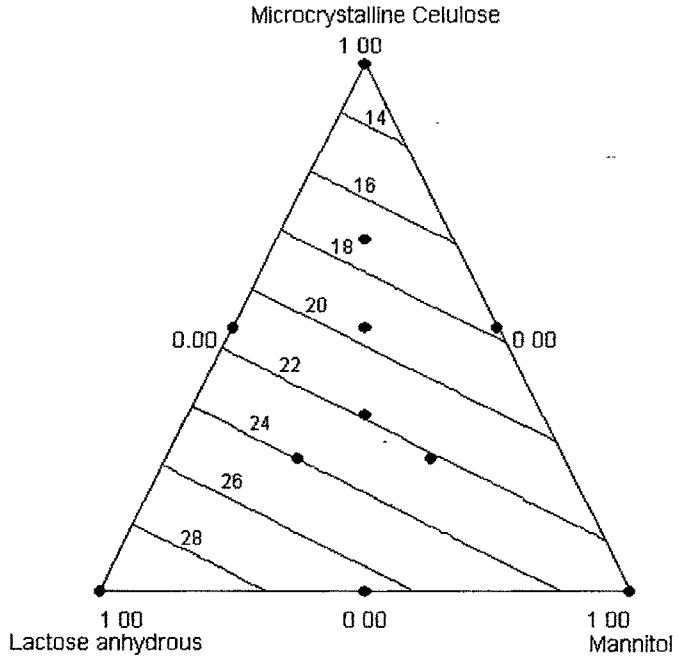


Figure 10.2. Contour plot of disintegration time obtained from simplex lattice design.

Figure 2 indicates that disintegration time increases slightly with increasing lactose/mannitol ratio. The solubility of mannitol is greater than that of lactose which is thought to be the reason for the difference in disintegration time of the tablets.

When tablet porosity is not extremely high, disintegration will be influenced by the properties of the excipients used. Croscarmellose was used as a disintegrant which is one of the "superdisingetrants" and has excellent disintegrating ability. It swells to a large extent when it comes into contact with water to disintegrate tablets and has a fibrous nature that allows intraparticlulate, as well as extrapartiulate, wickening of water even at low concentration[30]. In the tablets containing large amount of water soluble lactose, the pores along the croscarmellose fiber will be enlarged by the dissolution of lactose, so the swelling of croscarmellose will have less effect on the destruction of tablet matrix compared with tablets containing more insoluble MCC. This is one reason why tablet disintegration time increased with increasing concentration of lactose. Furthermore, this may also have been due to differences in the disintegration abilities of MCC and lactose. MCC is a swellable material, and its disintegration characteristics in water have been attributed to either capillary action or swelling. Lactose is not a swellable material that undergoes so-called self-disintegration or spontaneous disintegration, the mechanism of which has been proposed to be bond (hydrogen bond) annihilation and consequent repulsion between particles. Bond annihilation is thought to be not as efficient for tablet disintegration as swelling of particles. This may also explain why tablets with a low lactose /MCC ratio disintegrate rapidly.

To find out an optimum region at which concentration all three factors produce tablet having an acceptable tensile strength (more than 5 kg/cm^2) and disintegration time less than 20 seconds was obtained by superimposing the contour plots of tensile strength and disintegration time of the simplex lattice design. Figure 3 shows a superimposed contour plot with a dark region at which rapidly disintegrating tablets with an acceptable strength can be produced.

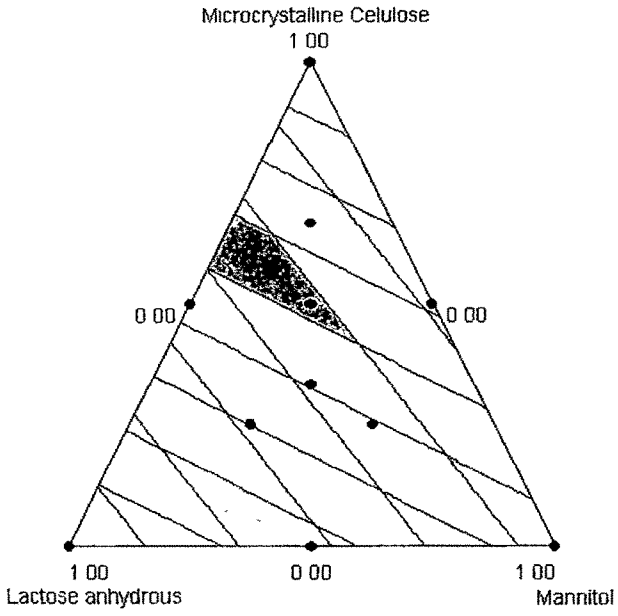


Figure 10.3. Superimposed contour plots of tensile strength and disintegration time for optimum region.

A weighted composite index was used to designate a single score utilizing both the response. Many researchers have utilized the technique of multiple responses for optimization studies. Derringer and Suich illustrated how several response variables can be transformed into desirability function[31]. The applications of one sided transformations are also demonstrated by different researchers[32,33]. The application of generalized distance function to incorporate several objectives into a single function has been reported[34]. As the relative contribution of each individual constraint to the "true" composite score was unknown, a decision was made to assign an arbitrary value of one half to each of the two response variables[35]. The empirical composite index was advised to yield a score 100 for an optimum result for each of the three variables and each test result was transformed to a value between 0 and 50. For tensile strength, highest value (6.9) was assigned a score equal to 50, and lowest value (3.6) was assigned zero score. For disintegration time, lowest value (10) was assigned to 50 and the highest value (29) was assigned to zero score. The batch M_4 showed highest composite index (61.92). So it would be considered as a batch fulfilling all the constraints favorable for the rapidly

disintegrating tablet. The optimized batch (Batch M_4) showed wetting time 6 second and % friability 0.85% which is within an acceptable limit. The Experimental values of response variables with composite index is shown in table 10.4.

Table 10.4. Experimental values of response variables with composite index.

Batch code	Tensile strength (kg/cm^2)	Disinte-gration time (sec)	Transformed value		Composite index	Rank
			Tensile strength	Disinte-gration time		
M_1	3.6	10	0.00	50.000	50.000	4
M_2	6.9	27	49.99	4.738	54.728	3
M_3	4.1	20	7.57	23.295	30.865	9
M_4	5.8	18	33.325	28.597	61.922	1
M_5	4.7	14	16.66	39.201	55.861	2
M_6	6.7	29	46.96	-0.564	46.396	5
M_7	5.4	23	27.265	15.342	42.607	8
M_8	4.6	26	15.145	7.389	22.534	10
M_9	5.8	24	33.325	12.691	46.016	6
M_{10}	6.1	26	37.87	7.389	45.259	7
M_{11}	5.6 (5.8)	20 (18.8)				

Composite index = transformed value of tensile strength + transformed value of disintegration time.

Value in bracket is a predicted value of the response calculated from the respective polynomial equation.

Table 10.5 shows the composition of the optimized tablets formulation of the ondansetron hydrochloride. pH of the tablets prepared from below formula in 5 ml distilled water was around 6.3.

Table 10.5. Composition of the optimized tablets of ondansetron hydrochloride.

Sr. No.	Name of ingredients	Quantity per tablet (mg)
1	Ondansetron hydrochloride	8.0
2	Microcrystalline cellulose	25.0
3	Lactose anhydrous (β form)	25.0
4	Mannitol	10.0
5	Croscarmellose	8.0
6	Aspartame	0.5
7	Magnesium stearate	0.5
Total weight of tablet		77.0 mg

In vitro buccal permeation through porcine buccal mucosa of ondansetron hydrochloride showed higher buccal absorption of the drug at higher pH. Therefore to increase the pH of the tablets, sodium carbonate was added to increase the pH of the tablets. The final composition of the fast dissolving tablets of ondansetron hydrochloride is shown in table 10.6.

Table 10.6. The final composition of the fast dissolving tablets of ondansetron hydrochloride.

Sr. No.	Name of ingredients	Quantity per tablet (mg)
1	Ondansetron hydrochloride	8.0
2	Microcrystalline cellulose	30.0
3	Lactose anhydrous (β form)	23.0
4	Mannitol	10.0
5	Sodium bicarbonate	20.0
6	Croscarmellose	8.0
7	Aspartame	0.5
8	Magnesium stearate	0.5
Total weight of tablet		100.0 mg

The pH of the tablets prepared from above formula in 5 ml distilled water was around 8.5. At this pH the buccal absorption of the ondansetron hydrochloride is higher than that of tablets prepared from formula of table 5. The various evaluation parameters of the tablets are given in table 10.7. The disintegrating time, wetting time and friability of the tablets were satisfactory.

Table 10.7. Various evaluation parameters of tablets of ondansetron hydrochloride (n=5).

Parameters	Values ± S.D.
Hardness	3-5 kg/cm^2
Disintegration time	18 ± 0.17 second
Friability	<1.5%
Wetting time	< 10 Second

The % drug release of the tablets of ondansetron hydrochloride prepared from formula of table 10.6 was conducted in distilled water and simulated saliva (pH 6.8). Table 10.8 shows the % drug release of tablets in different dissolution media. Figure 10.4 depicts the dissolution profiles of the tablets in both media.

Table 10.8. % Drug release of the tablets of ondansetron hydrochloride in different dissolution media (n=5).

Time (minute)	% Drug release in distilled water ± S.D. (reference)	% Drug release in simulated saliva ± S.D. (test)
0	0.00 ± 0.00	00.00 ± 0.00
0.5	76.43 ± 0.07	65.24 ± 0.16
1	97.24 ± 0.48	87.24 ± 0.54
2	98.75 ± 0.79	97.35 ± 1.21
3	99.64 ± 0.21	98.33 ± 0.09
5	99.75 ± 1.05	98.56 ± 0.33
10	99.65 ± 0.58	99.12 ± 0.67
20	99.88 ± 0.89	99.32 ± 1.05

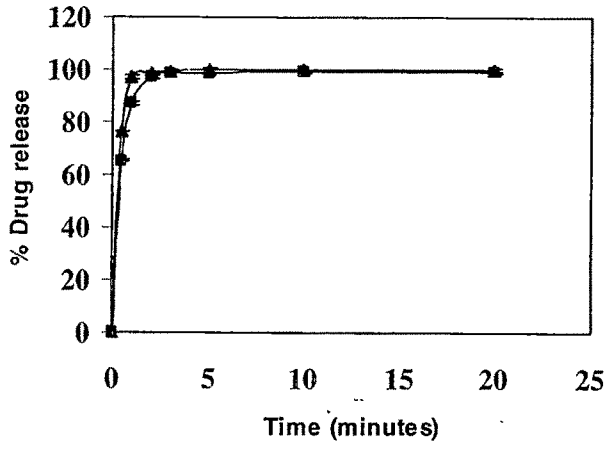
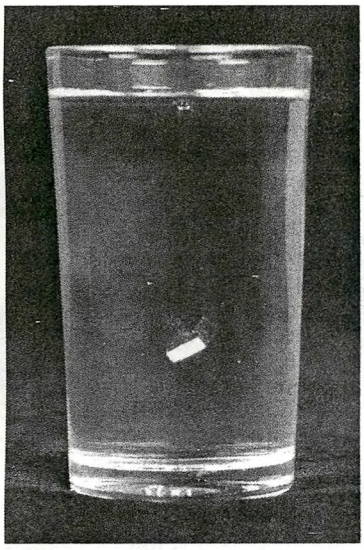
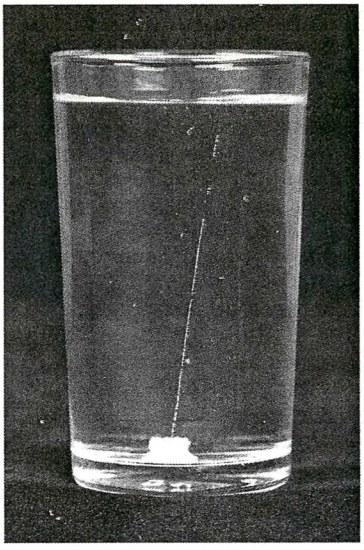


Figure 10.4. Comparative dissolution profile of tablets of ondansetron hydrochloride in distilled water (▲) and simulated saliva (pH 6.8) (■). Each value is mean ± S.D. of five experiments.

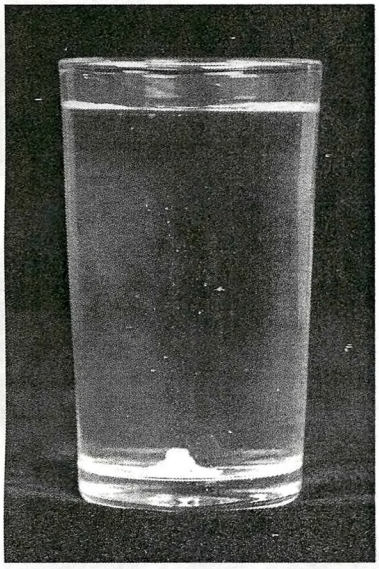
The dissolution data of the tablets in distilled water were compared with the dissolution data in simulated saliva using f_2 statistics. An f_2 of 63.12 and S_d value of 0.042 indicates that the release profile of tablets in distilled water and simulated saliva are comparable and in a good agreement with each other. Figure 10.5 showed that the fast dissolving tablet of ondansetron hydrochloride was disintegrated within the 20 seconds in distilled water.



(A)



(B)



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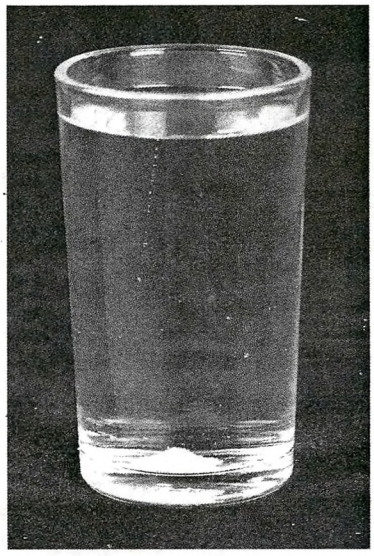

(D)

Figure 10.5. Disintegration of the fast dissolving tablet of ondansetron hydrochloride in distilled water in glass. (A) tablet put into the glass, (B) tablet at 10 seconds, (C) tablet after 15 seconds, (D) tablet after 20 seconds.

10.2.3 Conclusions

In the proposed work, microcrystalline cellulose, lactose anhydrous, croscamellose, mannitol and sodium bicarbonate were used as excipients to prepare rapidly disintegrating tablets in mouth with good taste and sufficient tensile strength. Central composite design and simplex lattice design were successfully used for the preparation of the rapidly disintegrating tablets with sufficient tensile strength and acceptable disintegration time. Two mathematical tools, desirability function and composite index were used successfully for the optimization of the formulation. The drug release pattern of the best formulation in distilled water and simulated saliva were comparable. The optimized formulation predicted 18 second disintegration time and 5.8 kg/cm^2 tensile strength when the MCC, lactose anhydrous and mannitol were 20mg, 20mg and 10mg respectively. We conclude that the described method was useful for the preparation of rapidly disintegrating tablets in the mouth with good taste and sufficient tensile strength. The proposed rapidly disintegrating tablets of ondansetron hydrochloride can be useful for patient suffering from post operative or chemotherapy induced sever nausea and vomiting where quick onset of drug action is desirable. Sodium bicarbonate was successfully applied to increase the pH of the tablets.

10.3 PREPARATION AND EVALUATION OF FAST DISSOLVING TABLETS OF SALBUTAMOL SULPHATE.

The polluted environment and the raising levels of nitrogen dioxide, sulphur dioxide, particulates in the air and fast life of the common man has increased the diseases like asthma[36]. Salbutamol sulphate, (RS)-1-(4-hydroxy-3-hydroxy-methyl phenyl)-2-(tert-butylamino) ethanol sulphate, a β-receptor agonist is most widely used as a sympathomimetic for the treatment of acute as well as chronic asthma. Generally, it is given through inhalation route but is also effective after oral administration[37].

10.3. 1 Experimentals

10.3.1.1 *Materials*

Salbutamol sulphate was received as a gift sample from Relax Pharmaceutical Ltd., Baroda, India. Microcrystalline cellulose (MCC), lactose anhydrous (β form) and mannitol were purchased from S. D. Chem. Ltd., Bombay, India. Magnesium stearate (Vikas Pharmaceutical Ltd., Ahmedabad, India) and croscarmellose sodium (Skymax Laboratories, Rajkot, India) were of I. P. grade. All the other ingredients used were of analytical grade and were used without further purification. Deionized double distilled water was through the study.

10.3.1.2 *Preparation of fast dissolving tablets of salbutamol sulphate*

Flat-faced tablets containing 25 mg microcrystalline cellulose, 25 mg lactose anhydrous, 10 mg mannitol, 4 mg salbutamol sulphate, 0.5 mg aspartame and varying amount of croscarmellose were compressed on same rotary machine used for the preparation of tablets of ondansetron hydrochloride. The optimized formulation of the tablets of salbutamol sulphate is given in table 10.9. pH of the tablets prepared from below formula in 5 ml distilled water was around 7.2.

Table 10.9. The final composition of the fast dissolving tablets of salbutamol sulphate.

Sr. No.	Name of ingredients	Quantity per tablet (mg)
1	Salbutamol sulphate	4.82
2	Microcrystalline cellulose	25.0
3	Lactose anhydrous (β form)	25.0
4	Mannitol	10.0
5	Croscarmellose	8.0
6	Magnesium stearate	0.5
Around total weight of tablet		73.0 mg

Note: 1 mg salbutamol sulfate is equivalent to 850 µg of salbutamol (Reference - I.P. 96, pg. 670). So, we have taken 4.82 mg salbutamol sulphate which is equivalent to 4 mg salbutamol.

In vitro buccal permeation through porcine buccal mucosa and Parallel artificial membrane permeation assay (PAMPA) study of salbutamol sulphate showed higher buccal absorption of the drug at higher pH. Therefore to increase the pH of the tablets, sodium carbonate was added to increase the pH of the tablets. The final composition of the fast dissolving tablets of salbutamol sulphate is shown in table 10.10.

Table 10.10. The final composition of the fast dissolving tablets of salbutamol sulphate.

Sr. No.	**Name of ingredients**	**Quantity per tablet (mg)**
1	Salbutamol sulphate	4.8
2	Microcrystalline cellulose	27.0
3	Lactose anhydrous (β form)	20.0
4	Mannitol	10.0
5	Sodium bicarbonate	15.0
6	Croscarmellose	8.0
7	Magnesium stearate	0.5
Around total weight of tablet		85.0 mg

The pH of the tablets prepared from above formula in 5 ml distilled water was around 8.62. At this pH the buccal absorption of the salbutamol sulphate is higher than that of tablets prepared from formula of table 8.

10.3.1.3 *Evaluation of tablets*

Evaluation of the tablets prepared as per the formula of table 10.10 such as tensile strength (hardness), disintegrating time, friability, wetting time were carried out similar to that of ondansetron hydrochloride tablets.

10.3.1.4 *In vitro dissolution study*

A dissolution study was as according to that of ondansetron hydrochloride tablets with analysis of the sample by spectrophotometrically at 276 nm (Model UV-1601, UV Visible spectrophotometer, Shimadzu, Japan). An equal volume of fresh dissolution medium maintained at the same temperature was added after withdrawing sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally ($r^2 > 0.993$). The dissolution test was performed in triplicate for each batch.

10.3.2 Results and Discussion

Microcrystalline cellulose and lactose anhydrous were used as direct compressible diluents. Mannitol was used to enhance palatability of the tablet. Different croscarmellose concentrations showed no significant influence on the tensile strength of tablet. A formulation containing 8.0 % croscarmellose shows an acceptable mechanical strength of 3-5 kg/cm^2 at a compression load of 3.2 kN with an satisfactory disintegration time. The various evaluation parameters of the tablets are given in table 10.11. The disintegrating time, wetting time and friability of the tablets were satisfactory.

Table 10.11. Various evaluation parameters of tablets of salbutamol sulphate (n=5).

Parameters	Values ± S.D.
Hardness	3-5 kg/cm^2
Disintegration time	19 ± 0.24 second
Friability	<1.5%
Wetting time	< 10 Second

The % drug release of the tablets prepared according to the formula of table 9 was conducted in distilled water and simulated saliva (pH 6.8). Table 10.12 shows the % drug release of tablets in different dissolution media. Figure 10.6 depicts the dissolution profiles of in both media.

Table 10.12. % Drug release of the tablets of salbutamol sulphate in different dissolution media (n=5).

Time (minute)	% Drug release in distilled water (reference)	% Drug release in simulated saliva (test)
0	00.00 ± 0.00	00.00 ± 0.00
0.5	76.43 ± 0.26	65.24 ± 0.22
1	97.24 ± 0.57	87.24 ± 0.47
2	98.75 ± 1.34	97.35 ± 0.93
3	99.64 ± 0.63	98.33 ± 0.58
5	99.75 ± 0.84	98.56 ± 1.07
10	99.65 ± 0.32	99.12 ± 0.82
20	99.88 ± 0.64	99.32 ± 0.44

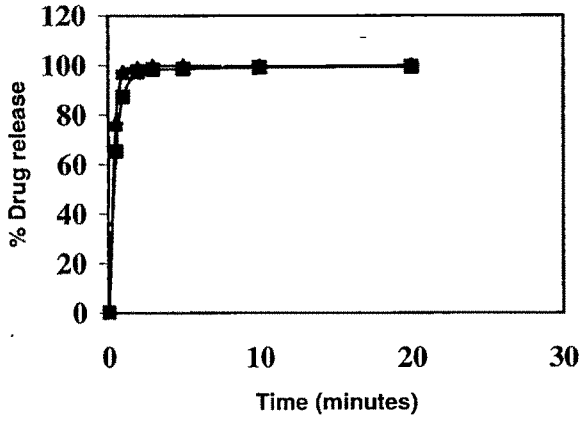

Figure 10.6. Comparative dissolution profile of tablets of salbutamol sulphate in distilled water (▲) and simulated saliva (pH 6.8) (■).Each value is mean ± S.D. of five experiments.

The dissolution data of this batch in distilled water were compared with the dissolution data in simulated saliva using f_2 statistics. An f_2 of 67.04 and S_d value of 0.038 indicates that the release profile of tablets in distilled water and simulated saliva are comparable and in a good agreement with each other.

10.3.3 Conclusions

In the proposed work, microcrystalline cellulose, lactose anhydrous, croscamellose, mannitol and sodium bicarbonate were used as excipients to prepare rapidly disintegrating tablets in mouth with good taste and sufficient tensile strength. The final formulation predicted 19 second disintegration time and 3-5 kg/cm^2 tensile strength. We conclude that the described method was useful for the preparation of rapidly disintegrating tablets in the mouth with good taste and sufficient tensile strength. The proposed rapidly disintegrating tablets of salbutamol sulphate can be useful for patient suffering from asthmatic attack where quick onset of drug action is desirable. Sodium bicarbonate was successfully applied to increase the pH of the tablets.

10.4 PREPARATION AND EVALUATION OF FAST DISSOLVING TABLETS OF LAMOTRIGINE.

10.4.1 Experimentals

10.4.1.1 *Materials*

Lamotrigine and aspartame were received as gift samples from Torrent pharmaceuticals Limited, Ahmedabad, India and Relax Pharmaceutical Ltd., Baroda, India, respectively. Microcrystalline cellulose (MCC), lactose anhydrous (β form) and mannitol were purchased from S. D. Chem. Ltd., Bombay, India. Magnesium stearate (Vikas Pharmaceutical Ltd., Ahmedabad, India) and croscarmellose sodium (Skymax Laboratories, Rajkot, India) were of I. P. grade. All the other ingredients used were of analytical grade and were used without further purification. Deionized double distilled water was through the study.

10.4.1.2 *Preparation of fast dissolving tablets of lamotrigine*

Flat-faced tablets of lamotrigine containing beta cyclodextrin, microcrystalline cellulose, lactose anhydrous, mannitol, were compressed on same rotary machine used for the preparation of tablets of ondansetron hydrochloride. The optimized formulation is table 12. pH of the tablets prepared from below formula in 5 ml distilled water was around 8.1.

10.4.1.3 *Formulation steps for fast dissolving tablets of lamotrigine*

Step 1: Screen lamotrigine, lactose anhydrous, mannitol and magnesium stearate through 40 mesh-sieves.

Step 2: Screen Ac-di-sol through 20 mesh-seive.

Step 3: Mix the lamotrigine (5 mg) and beta cyclodextrin (5 mg) powder in a suitable mixer with adding tanscutanol solution (0.001 ml) above the powder mixture in mortar with pestle. Homogenize the powder in mixer about for one hour.

Step 4: Add lactose anhydrous and blend for 5 min.

Step 5: Add mannitol and blend for 5 min.

Step 6: Add microcrystalline cellulose and Ac-di-sol and blend for 15 min.

Step 7: Add magnesium stearate and blend for 5 min.

Compress into tablets using standard concave tooling. The composition of the fast dissolving tablets of lamotrigine is given in table 10.13.

Table 10.13. The composition of the fast dissolving tablets of lamotrigine.

Sr. No.	**Name of ingredients**	**Quantity per tablet (mg)**
1	Lamotrigine	5.0
2	Beta cyclodextrin	5.0
3	Transcutanol	0.001
2	Microcrystalline cellulose	20.0
3	Lactose anhydrous (β form)	10.0
4	Mannitol	10.0
5	Croscarmellose	8.0
6	Aspartame	0.3
7	Magnesium stearate	0.5
Around total weight of tablet		63.0 mg

Buccal absorption test on human volunteers, in vitro buccal permeation through porcine buccal mucosa of lamotrigine showed higher buccal absorption of the drug at higher pH. Therefore to increase the pH of the tablets, sodium carbonate was added to increase the pH of the tablets. The final composition of the rapidly disintegrating fast dissolving tablets of lamotrigine is shown in table 10.14.

Table 10.14. The final composition of the fast dissolving tablets of lamotrigine.

Sr. No.	**Name of ingredients**	**Quantity per tablet (mg)**
1	Lamotrigine –	5.0
2	Beta cyclodextrin	5.0
3	Transcutanol	0.03
2	Microcrystalline cellulose	20.0
3	Lactose anhydrous (β form)	10.0
4	Mannitol	10.0
5	Sodium bicarbonate	7.0
6	Croscarmellose	8.0
7	Aspartame	0.3
8	Magnesium stearate	0.5
Around total weight of tablet		70.0 mg

The pH of the tablets prepared from above formula in 5 ml distilled water was around 9.2. At this pH the buccal absorption of the lamotrigine is higher than that of tablets prepared from formula of table 10.13.

10.4.1.4 *Evaluation of tablets*

Evaluation of the tablets prepared as per the formula of table 13 such as tensile strength (hardness), disintegrating time, friability, wetting time were carried out similar to that of ondansetron hydrochloride tablets.

10.4.1.5 *In vitro dissolution study*

A dissolution study was as according to that of ondansetron hydrochloride tablets with analysis of the sample by spectrophotometrically at 305 nm (Model UV-1601, UV Visible spectrophotometer, Shimadzu, Japan). An equal volume of fresh dissolution medium maintained at the same temperature was added after withdrawing sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally ($r^2 > 0.996$). The dissolution test was performed in triplicate for each batch.

10.4.2 Results and Discussion

Microcrystalline cellulose and lactose anhydrous were used as direct compressible diluents. Mannitol was used to enhance palatability of the tablet. Different croscarmellose concentrations showed no significant influence on the tensile strength of tablet. A formulation containing 8.0 % croscarmellose shows an acceptable mechanical strength of 3-5 kg/cm^2 at a compression load of 3.6 kN with an satisfactory disintegration time. The various evaluation parameters of the tablets are given in table 10.15. The disintegrating time, wetting time and friability of the tablets were satisfactory.

Table 10.15. Various evaluation parameters of tablets of lamotrigine (n=5).

Parameters	Values ± S.D.
Hardness	3-5 kg/cm^2
Disintegration time	23 ± 0.19 seconds
Friability	<1.5%
Wetting time	< 12 Second

The % drug release of the tablets prepared according to the formula of table 10.14 was conducted in distilled water and simulated saliva (pH 6.8). Table 10.16 shows the % drug release of tablets in different dissolution media. Figure 10.7 depicts the dissolution profiles of in both media.

Table 10.16. % Drug release of the tablets of lamotrigine in different dissolution media (n=5).

Time (minute)	% Drug release in distilled water ± S.D. (reference)	% Drug release in simulated saliva ± S.D. (test)
0	00.00 ± 0.00	00.00 ± 0.00
0.5	63.83 ± 0.43	60.03 ± 0.33
1	89.36 ± 0.61	85.27 ± 0.48
2	93.73 ± 0.98	94.82 ± 1.05
3	98.38 ± 1.07	96.19 ±0.74
5	99.26 ± 0.55	99.71 ± 1.07
10	99.62 ±0.42	99.26 ± 0.54
20	99.15 ± 0.83	99.04 ± 0.92

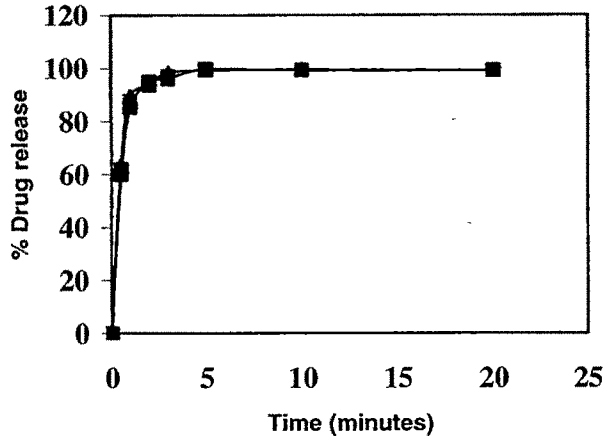

Figure 10.7. Comparative dissolution profile of lamotrigine tablets in distilled water (▲) and simulated saliva (pH 6.8) (■). Each value is mean ± S.D. of five experiments.

The dissolution data of this batch in distilled water were compared with the dissolution data in simulated saliva using f_2 statistics. An f_2 off 65.71 and S_d value of 0.042 indicates that the release profile of tablets in distilled water and simulated saliva are comparable and in a good agreement with each other.

10.4.3 Conclusions

In the proposed work, microcrystalline cellulose, lactose anhydrous, croscamellose, mannitol and sodium bicarbonate were used as excipients to prepare rapidly disintegrating tablets in mouth with good taste and sufficient tensile strength. Beta-cyclodextrin and transcutanol were used to enhance the solubility and dissolution of the lamotrigine. The final formulation predicted 23 second disintegration time and 3-5 kg/cm^2 tensile strength. We conclude that the described method was useful for the preparation of rapidly disintegrating tablets in the mouth with good taste and sufficient tensile strength. The proposed rapidly disintegrating tablets of lamotrigine can be useful for patient suffering from epileptic attack where quick onset of drug action is desirable. Sodium bicarbonate was successfully applied to increase the pH of the tablets.

10.5 STABILITY STUDIES OF THE FAST DISSOLVING TABLETS

Rapidly disintegrating tablets made by direct compression method involved the use of mannitol. Mannitol tends to absorb moister at high humidity conditions. Hence it may affect the dosage form. Therefore, it is very must important to carry out the stability studies of the fast dissolving tablets. The stability studies were done at the conditions as stated in the ICH guideline. The intermediate stability studies of the tablets were carried out at temperature of 30°C and at humidity of RH 65% RH. The accelerated stability studies were carried out at the temperature of 40°C and at humidity of RH 75% and To maintain the RH of 60% and 75 % saturated solutions of $MgCl_2$ and Mg $(NO_3)_2$ respectively were prepared. These solutions were filled in separate glass desiccators. Twenty tablets placed in a petridish were kept in each desiccator for six months. The tablets were tested at 0, 1, 2, 3, 4, 5, 6 months time intervals for friability, hardness and in vitro disintegration time in triplicate. Results of the stability studies of ondansetron hydrochloride tablets is shown in table 10.17.

Table 10.17. Results of the stability studies of ondansetron hydrochloride tablets (n=5).

Test	Time (months)												
	0	1		2		3		4		5		6	
		I	A	I	A	I	A	I	A	I	A	I	A
Hardness ± S.D. (Kg/cm^2)	3.8 ± 0.10	3.7 ± 0.09	3.6 ± 0.12	3.6 ± 0.11	399.4 ± 0.16	3.6 ± 0.08	3.2 ± 0.18	3.5 ± 0.13	3.1 ± 0.15	3.4 ± 0.14	3.0 ± 0.12	3.3 ± 0.11	2.9 ± 0.1
Friability (%)	0.58	0.61	0.69	0.67	0.74	0.72	0.89	0.85	0.95	0.92	1.2	1.1	1.4
Disintegration time ± S.D. (sec)	28 ± 1.54	27 ± 1.35	26 ± 1.24	25 ± 1.64	24 ± 1.13	23 ± 1.10	23 ± 1.07	22 ± 1.22	21 ± 1.13	20 ± 1.37	18 ± 1.45	19 ± 1.53	17 ± 1.2

I = Intermediate condition (30 °C/60%), A= Accelerated condition (45°C/75 %)

Results of the stability studies of salbutamol sulphate tablets is shown in table 10.18.

Table 10.18. Results of the stability studies of salbutamol sulphate tablets (n=5).

Test	Time (months)												
	0	1		2		3		4		5		6	
		I	A	I	A	I	A	I	A	I	A	I	A
Hardness ± S.D. (Kg/cm^2)	4.1 ± 0.14	4.0 ± 0.09	3.9 ± 0.15	3.9 ± 0.17	3.7 ± 0.16	3.8 ± 0.09	3.5 ± 0.15	3.7 ± 0.18	3.4 ± 0.16	3.6 ± 0.18	3.3 ± 0.24	3.4 ± 0.07	2.1 ± 0.11
Friability (%)	0.63	0.69	0.72	0.75	0.78	0.81	0.84	0.88	0.90	0.93	1.05	1.11	1.16
Disintegration time ± S.D. (sec)	32 ± 1.05	29 ± 1.47	28 ± 1.44	28 ± 1.54	25 ± 1.42	24 ± 1.35	24 ± 1.19	23 ± 1.26	22 ± 1.24	21 ± 1.41	20 ± 1.21	20 ± 1.44	19 ± 1.11

I = Intermediate condition (30 °C/60%), A= Accelerated condition (45°C/75 %)

Results of the stability studies of lamotrigine tablets is shown in table 10.19.

Table 10.19. Results of the stability studies of lamotrigine tablets (n=5).

Test	Time (months)												
	0	1		2		3		4		5		6	
		I	A	I	A	I	A	I	A	I	A	I	A
Hardness ± S.D. (Kg/cm^2)	4.7 ± 0.11	4.5 ± 0.08	3.6 ± 0.13	4.3 ± 0.14	3.4 ± 0.18	4.1 ± 0.11	3.2 ± 0.23	4.0 ± 0.15	3.1 ± 0.17	3.9 ± 0.16	3.0 ± 0.13	3.8 ± 0.13	3.2 ± 0.18
Friability (%)	0.46	0.60	0.64	0.68	0.72	0.72	0.84	0.78	0.89	0.93	0.99	1.2	1.3
Disintegration time ± S.D. (sec)	34 ± 1.47	33 ± 1.42	32 ± 1.31	32 ± 1.57	30 ± 1.26	31 ± 1.21	29 ± 1.16	30 ± 1.48	26 ± 1.11	28 ± 1.26	23 ± 1.42	24 ± 1.29	21 ± 1.51

I = Intermediate condition (30 °C/60%), A= Accelerated condition (45°C/75 %)

From the results of the stability studies it can be observed that at 60 % RH and 75 % RH after six months, the tablets of all the drugs showed a decrease in hardness and disintegration time while increase in friability. The tablets showed a weight gain upt to 4% and 6% at 75 % RH than 60 % RH. The moisture absorption by the tablets is the reason for this effect. This indicates that fast dissolving tablets require protection from the moisture.

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