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FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISINTEGRATING TABLET OF ROXITHROMYCIN

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Abstract

Fast disintegrating tablets are becoming popular as one of the user friendly dosage forms. Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients and the underdeveloped muscular and nervous systems in young individuals and case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance. To overcome these drawbacks, fast disintegrating tablets (FDT) or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/ disperse in saliva within few seconds and release drug immediately. In this project DSC analysis of drug was carried out for the identification of drug. The DSC thermogram of Roxithromycin was at 121.383°C which was identical with the pure Roxithromycin DSC thermogram. The calibration curve of Roxithromycin was prepared in phosphate buffer pH 6.0 follow the beer lamberts law between the different concentration ranges at λmax 205 nm. Different pre-formulation parameters like solubility study, melting point determination, water content, drug excipients interaction study at different temperature were carried out.

Data obtained from above pre-formulation study concluded that there is no interaction between drug and involved excipients in this project study. The tablets were evaluated for thickness, hardness, friability, weight variation, wetting time, water absorption, drug content, disintegration time and *in vitro* dissolution studies. The disintegration time of all formulation showed less than 98 seconds. Formulation containing optimum amount of Crosscarmellose sodium and Sodium starch glycolate showed fastest disintegration than other formulations.

INTRODUCTION

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. A large number of patients may have difficulty in swallowing the conventional pharmaceutical dosage forms, particularly pediatric and geriatric. Such problems can be overcome by means of fast disintegrating tablets. Fast disintegrating tablets are suitable for these patients since they immediately release the active drug when they are placed on the tongue. The main criterion for fast disintegrating tablets is the capacity to disintegrate rapidly in oral cavity with assessment of saliva within a minute without need of water. Roxithromycin, a macrolide antibiotic drug, was selected as model drug because it is widely used in treatment of respiratory and urinary tract infection. To protect bitter taste of Roxithromycin, taste masking ion exchange resin Doshion P544 (R) and natural sweetening agent such as monoammonium glycyrrhizinate were used.[1-5]

MATERIALS & METHODS

Material

Roxithromycin was received as a gift sample from cadila pharmaceutical Pvt. Ltd., Dhodka Ahmedabad. Doshion P544 (R) was obtained from Doshion Limited, Vatva, Ahmedabad. Croscarmallose sodium and Sodium starch glcolate was received as a gift sample from Ethicare Pharmaceutical (P) Ltd., Por, Vadodara. Monoammonium glycyrrhizinate was purchased from Amsar Private Limited, Indore. All other

ingredients used were of pharmaceutical grade.

Method

***Preparation of Drug -Resin Complex*:** First of all distilled water was added in beaker and then slowly Dushion P544(R) added under continuous stirring into the vortex taking precaution to avoid lump formation, and allowed it to swell for 2 hour. Roxithromycin was added slowly under continuous stirring to above resin solution. Stirring was continued for 3.0 hours and allowed it for 24 hours. The solution was filtered by using whatman filter paper no 41. Residue/slurry was taken out and put it for drying at 60'C for 3-4 hour in oven. The dry powder is the Drug-Resin complex (DRC).

Preparation of Roxithromycin tablets: Accurate quantity of Roxithromycin, diluent (Mannitol) and half quantity of disintegrates (both Sodium Starch Glycollate, Croscarmellose Sodium) were weighed and sifted, through 40# sieve for uniform mixing. All above ingredients were blend in poly beg for 5 minutes. Accurate quantity of the binder (PVP K-30) was weighed and Dissolved into distilled water. Above binder solution was slowly added into the powder blend in Rapid Mixer Granulator. Obtained granules were allowed to dry into a tray dryer for around 1 hour at 60˚C. Dried granules were passed through 18# sieve to form uniform size granules. Microcrystalline cellulose, colloidal silicon dioxide, sweetener, flavor, lubricant and remaining half quantity super disintegrates were weighed accurately and sifted through 60# sieve. All ingredients were blend in poly beg for 5 minutes. Lubricated granules were compressed into tablets using 10mm FFBE (Flat Face Bevel Edge) punch set using a 23 station tablet press.

EVALUATION OF TABLETS:

Prepared tablets were evaluated for, thickness, hardness, friability, weight variation, wetting time, water absorption, disintegration time and *in vitro* dissolution studies.[6]

Hardness and Thickness: The thickness was measured using vernier calipers. Hardness was measured using Pfizer tablet hardness tester.

Friability: Friability of the tablets was determined using Roche friabilator. This

device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of 20 tablets were placed in the friabilator and subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) was given by the formula

$F = (1- W_0 / W) \times 100$

Where, W_0 was the weight of the tablets before the test and W was the weight of the tablet after the test.

Weight variation test: Twenty tablets were selected at random and average weight was determined using Dhona 200D weighing balance. The individual tablet was compared with average weight.

Determination of drug content: 5 tablets were powdered and powder equivalent to 50mg of drug was weighed and taken in a 50ml volumetric flask volume was made with Phosphate Buffer pH 6.0. The solution in the volumetric flask was then sonicated for 20 min and stirred further for 2 hours on magnetic stirrer then filtered using 0.2 µ membrane filter. From filtrate, 10 ml of solution was pipetted out and diluted up to 100 ml with the phosphate buffer pH 6.0, and absorbance was measured at 205 nm using UV double beam spectrophotometer.

Wetting time and Water absorption ratio: The wetting time of the tablet was measured by placing five circular tissue papers (10 cm in diameter) in a petri dish of 10 cm diameter. Distilled water (10 ml) containing methylene blue (0.1% w/v) was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper and the time required for the dye to reach the upper surface of the tablet was recorded as wetting time. Water absorption ratio was calculated using equation

Water absorption ratio = (Wa –Wb)/ Wb

Where Wb = weight of tablet before absorption of water, and Wa = weight of tablet after absorption of water.

***In vitro* disintegration test:** *In vitro* disintegration time was determined in phosphate buffer pH 6.0 in disintegration apparatus at 37^0 C and the time required for the tablet to disintegrate was noted down.

***In vitro* dissolution test:** *In-vitro* dissolution studies were carried out using USP

apparatus type II at 50 rpm. The dissolution medium used was a phosphate buffer pH 6.0 maintained at 37^0 C. 5 mL of sample was withdrawn and replaced with fresh dissolution medium at different time intervals and the concentration of Roxithromycin was measured by determining absorbance at 205 nm using UV spectrophotometer.

ACCELERATED STABILITY STUDIES OF BATCH F8:

Stability studies were carried out as per ICH stability testing guidelines (ICH guidelines). The optimized formulation FF8 was stored in aluminum capped clear glass vials and were subjected to a storage condition of 40°C±2**/**75% ± 5% RH for 2 months. The samples were withdrawn at time intervals of 0, 1 and 2 months and evaluated for percentage drug content using UV-visible spectrophotometer at 205 nm, crushing strength and in vitro disintegration time.

RESULTS AND DISCUSSION

From the results of flow properties of the granules, it was concluded that granules had good flow properties and compressibility property. The bulk density and taped density of powder mixtures were found to be in the range of 0.148-0.168 g/cm^3 and 0.182-0.221 g/cm^3 respectively. The value Carr's index was in the range of 12.58-25.34 and Hausner's ratio was in the range of 1.14-1.33 were suggesting good flow properties. The table (3) shows blend of the all batches by wet granulation method shows good flowability but F8 batch having good flow properties compare to other batches. The average weight of the prepared tablets was in between 349.4 and 253.3 mg. The average thickness of tablets was found to be 3.94 mm to 3.98 mm. The hardness of prepared tablets was between 2.57 to 4.16 kg/cm^2. The friability of all the formulations was less than 1% indicating the ability of tablet to withstand abrasion in handling packaging and shipment. The weight variation of prepared tablets was within limits. The wetting time of formulations was between 21 to 38 seconds. The water absorption ratio was found in between 0.621 to 0.854. The disintegration time of the tablets varied from 24 to 97 seconds. The tablet containing optimum proportion of Sodium starch glycolate and crosscarmellose sodium (4:5) disintegrates faster than tablets prepared with other formulations as

shown in Table 5. The *in vitro* drug release from tablets containing sodium starch glycolate and crosscarmellose sodium (4:5) was 99.246% and drug release of tablets containing only sodium starch glycolate was 80.579%. The drug release profiles of all prepared tablets were shown in Figure 1 and 2.

CONCLUSION

The result of fast disintegrating tablet revealed that the combination of disintegrants significantly affect the wetting time, disintegration time, drug release. The formulation containing sodium starch glycolate and crosscarmellose sodium in 4:5 proportion showed the fast disintegration as compared to the other formulations. It is thus concluded that by selecting proper amount and combination of disintegrants in tablets formulation, tablet with fast disintegration can be produced. Thus fast disintegrating tablet may be developed for most of the available drugs in future.

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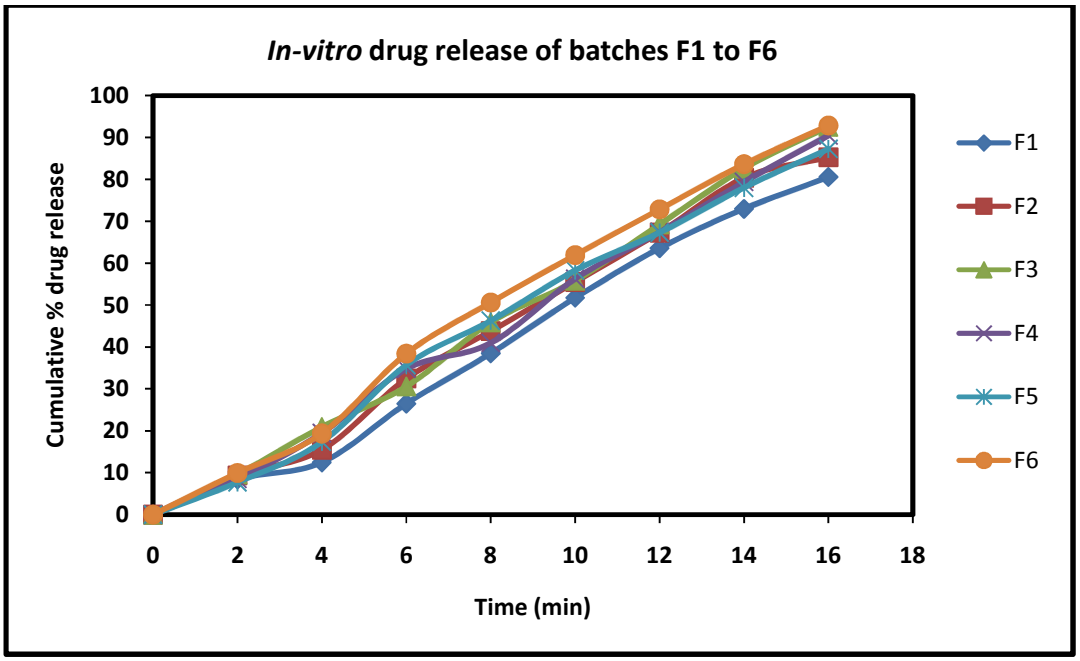

Figure 1 *In-vitro* drug release of batches F1 to F6

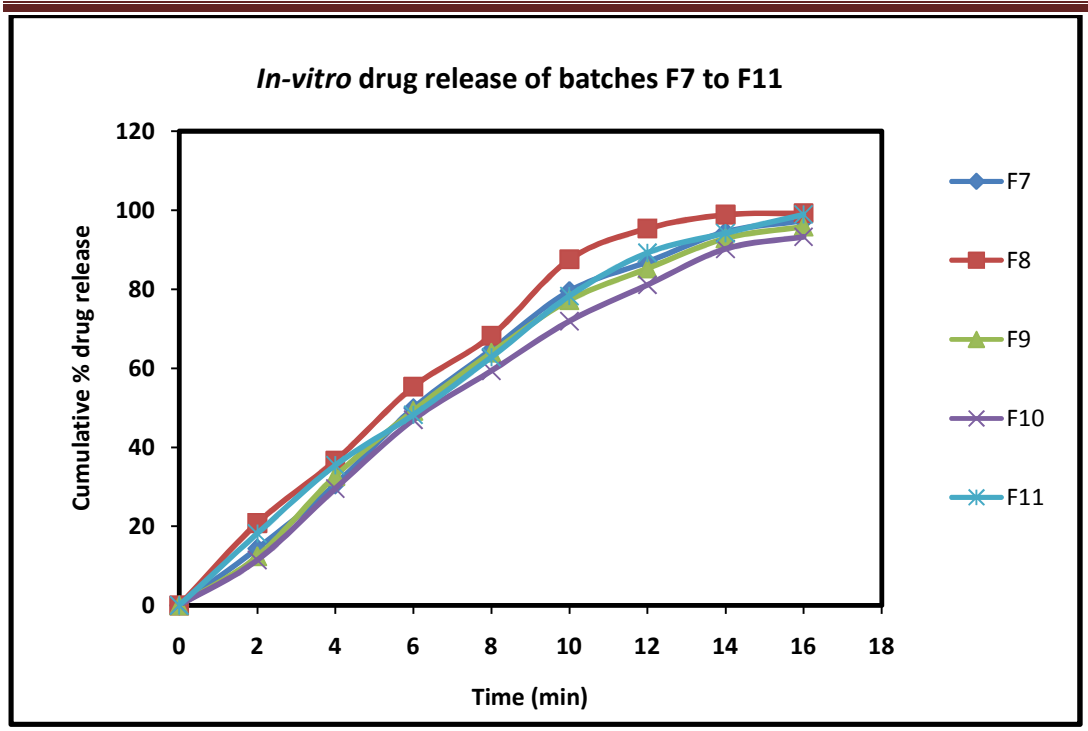

Figure 2 *In-vitro* drug release of batches F7 to F11

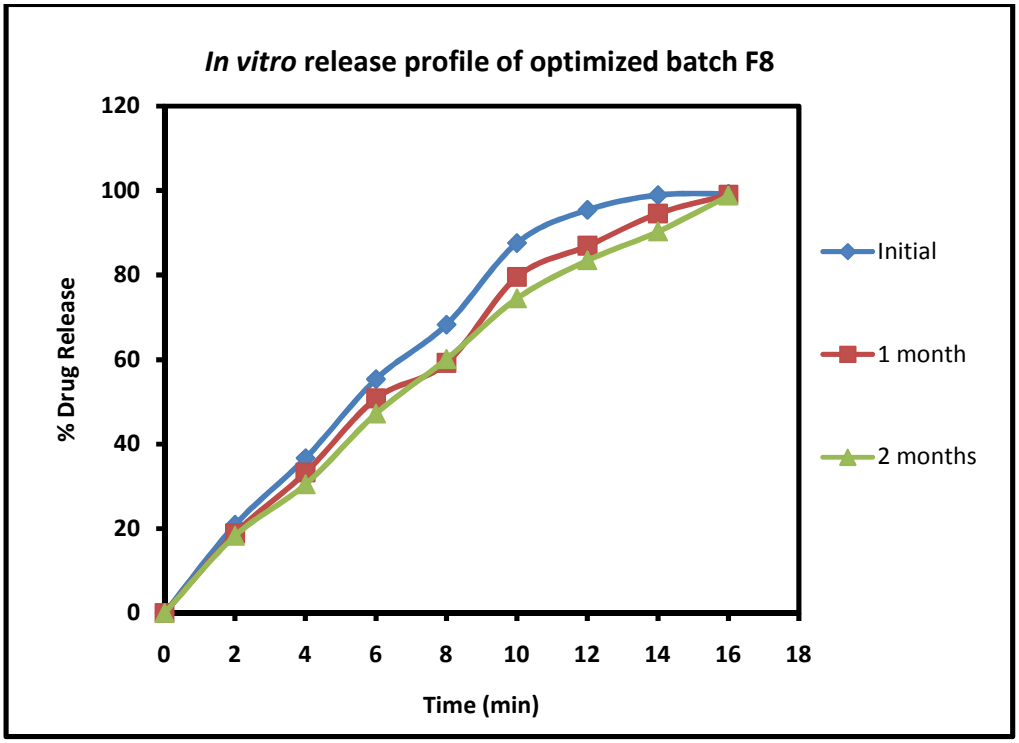

Figure 3 *In-vitro* drug release of optimized batch F8

Table 1

Formulation Composition of Batches F1-F6

Ingredients	F1 (%w/w)	F2 (%w/w)	F3 (%w/w)	F4 (%w/w)	F5 (%w/w)	F6 (%w/w)
Roxithromycin	14.29	14.29	14.29	14.29	14.29	14.29
Ion Exchange Resin	42.86	42.86	42.86	42.86	42.86	42.86
Mannitol	26.4	21.65	19.45	24.35	19.65	19.65
PVP K-30	0.15	0.20	0.20	0.20	0.20	0.20
Sodium Starch Glycolate	2	4	6	-	-	-
Croscarmellose Na	-	-	-	2	4	5
Micro Crystalline Cellulose (Avicel 102)	8	10	10	10	12	11
Magnesium Stearate	0.5	0.7	0.7	0.5	0.7	0.7
Colloidal silicone dioxide (Aerosil 200)	0.8	0.8	1	0.8	0.8	0.8
Monoammonium Glycyrrhizinate	4	4	4	4	4	4
Orange Flavor	1.0	1.5	1.5	1.0	1.5	1.5
Total	100	100	100	100	100	100

Table 2

Formulation Composition of Batches F7-F11

Ingredients	F7 (%w/w)	F8 (%w/w)	F9 (%w/w)	F10 (%w/w)	F11 (%w/w)
Roxithromycin	14.29	14.29	14.29	14.29	14.29
Ion Exchange Resin	42.86	42.86	42.86	42.86	42.86
Mannitol	15.65	15.65	15.65	16.65	14.63
PVP K-30	0.20	0.20	0.20	0.20	0.20
Sodium Starch Glycolate	4	4	5	4	5
Croscarmellose Na (Ac-D-Sol)	5	5	4	4	5
Micro Crystalline Cellulose (Avicel 102)	11	11	11	11	11
Magnesium Stearate	0.3	0.7	0.7	0.7	0.7
Colloidal silicone dioxide (Aerosil 200)	1.2	0.8	0.8	0.8	1
Monoammonium Glycyrrhizinate	4	4	4	4	4
Orange Flavor	1.5	1.5	1.5	1.5	1.5
Total	100	100	100	100	100

Table 3

Flow Properties of Powder Blend

Batch	Loose bulk density (g/cm^3)	Tapped bulk density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
1	0.160	0.199	19.33	1.23	29.25
2	0.159	0.199	19.86	1.24	29.77
3	0.162	0.201	18.91	1.23	28.80
4	0.149	0.187	19.87	1.25	27.55
5	0.148	0.185	19.75	1.25	28.65
6	0.151	0.188	19.49	1.24	27.90
7	0.164	0.221	25.34	1.33	27.82
8	0.163	0.193	14.96	1.17	25.68
9	0.168	0.192	12.58	1.14	26.65
10	0.161	0.186	13.42	1.15	27.39
11	0.159	0.182	12.58	1.14	26.85

Table 4

Evaluation Parameter of Tablet

Batch	Hardness (Kg/cm^2)	Avg. weight ± SD	% Friability	Thickness (mm)	% Drug Content
F1	2.57 ± 0.135	351.0±5.34	0.70	3.95 ± 0.015	99.73
F2	2.83 ± 0.129	351.9±6.29	0.70	3.94 ± 0.013	99.83
F3	2.87 ± 0.145	349.8±5.35	0.70	3.95 ± 0.012	99.78
F4	3.03 ± 0.130	350.3±4.90	0.56	3.96 ± 0.015	99.40
F5	4.16 ± 0.159	350.6±4.91	0.43	3.97 ± 0.023	99.64
F6	3.86 ± 0.219	352.3±5.77	0.27	3.95 ± 0.020	100.07
F7	4.03 ± 0.119	350.3±4.21	0.14	3.98 ± 0.017	100.23
F8	3.99 ± 0.134	350.1±4.47	0.14	3.96 ± 0.016	100.25
F9	4.06 ± 0.211	349.7±5.02	0.28	3.95 ± 0.009	100.20
F10	3.97 ± 0.170	350.2±4.44	0.28	3.96 ± 0.111	101.78
F11	4.00 ± 0.117	349.4±5.40	0.14	3.95 ±0.116	99.10

Table 5

Evaluation Parameter of Tablet

Batch No.	Average Disintegration Time (sec)	Average Wetting Time (sec)	Water absorption ratio
F1	97	38	0.621
F2	84	33	0.634
F3	65	26	0.748
F4	88	30	0.784
F5	72	29	0.825
F6	55	30	0.841
F7	25	21	0.854
F8	24	22	0.849
F9	31	27	0.809
F10	38	28	0.840
F11	24	23	0.835

Table 6

In Vitro Dissolution Profile of Batches F1 to F6

Time (min)	Cumulative % drug release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
2	8.362	9.356	9.598	8.528	7.722	9.972
4	12.467	15.497	20.918	19.435	17.356	19.365
6	26.486	32.462	30.572	34.764	35.687	38.42
8	38.496	43.786	45.863	40.935	46.267	50.635
10	51.743	55.528	55.789	56.254	58.272	61.935
12	63.578	67.325	69.232	67.378	67.265	72.873
14	72.971	80.356	82.543	79.356	77.992	83.625
16	80.579	85.265	92.511	90.425	87.235	92.837

Table 7

In Vitro Release Profile of Batches F7 to F8

Time (min)	Cumulative % drug release				
	F7	**F8**	**F9**	**F10**	**F11**
0	0	0	0	0	0
2	14.387	20.846	12.435	11.487	18.235
4	30.625	36.645	32.735	29.576	35.472
6	49.916	55.347	49.254	46.972	48.254
8	64.675	68.256	63.98	59.356	62.837
10	79.56	87.567	77.276	71.942	78.345
12	86.927	95.4	85.267	81.111	89.254
14	94.526	98.902	92.876	90.224	94.256
16	97.356	99.246	95.876	93.263	98.974

Table 8

Stability data for optimized formulation F8

Formulation	Parameters Evaluated	Time interval (months)		
		0	**1**	**2**
F8	Disintegration time (sec)	24.00	24.28	24.85
	Hardness (kg/cm^2)	4.00	3.94	3.90
	Friability (%)	0.14	0.17	0.18
	% drug content	100.25	100.14	99.97

Table 9

Dissolution profile of optimized batch F8

Time (min)	Cumulative % drug release		
	Initial	**After 1 month**	**After 2 months**
0	0	0	0
2	20.846	18.832	18.275
4	36.645	33.249	30.476
6	55.347	50.787	47.201
8	68.256	59.209	60.111
10	87.567	79.562	74.472
12	95.4	86.929	83.48
14	98.902	94.547	90.311
16	99.246	99.011	98.792

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