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Formulation and *In-vitro* Evaluation Fast Dissolving Tablets Ramosetran Hydrochloride using Co-Processed Super Disintegrating Technology

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A B S T R A C T

In the present work, an attempt has been made to develop fast disintegrating tablets of Ramosetron hydrochloride. Novel method of co processed super disintegrates technology was employed to formulate the tablets. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations, F14 formulation showed maximum drug release i.e., 99.3% in 4 min hence it is considered as optimized formulation. The F14 formulation contains CP5 as super disintegrate in the concentration of 30 mg. (CP 5 contains Vivasole and polyplasdone XL in 3:1 ratio).

Keywords: Ramosetron hydrochloride, Co processed super disintegrates, Vivasole and polyplasdone XL.

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1. Introduction

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as

pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in NDDS aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Mouth Dissolving Tablet (MDT) is one among such approaches.

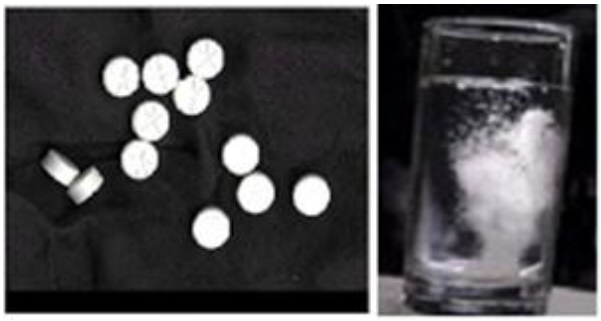

Figure 1: Mechanism of fast dissolving tablets

Improved patient compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects.But one important drawback of such dosage forms is Dysphasia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of pathological conditions including stroke, Parkinson's disease, neurological disorders, AIDS etc.

1. Parkinsonism
2. Motion sickness
3. Unconsciousness
4. Elderly patients
5. Children
6. Mentally disabled persons
7. Unavailability of water

To solve the above-mentioned problems, pharmaceutical technologists have put in their best efforts to develop a Fast dissolving drug delivery, i.e. Mouth Dissolving Tablet that disintegrates and dissolves rapidly in the saliva, within a few sec without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 10 sec to 3 min. Most of the MDTs include certain super disintegrants and taste masking agents.

Ideal properties of a mouth-dissolving tablet:

Though nothing or nobody is ideal or perfect in this world, yet there are certain limits or characteristics that judge the nearness to perfection. A mouth-dissolving tablet should:

1. Not require water or other liquid to swallow.
2. Easily dissolve or disintegrate in saliva within a few seconds.
3. Have a pleasing taste.
4. Leave negligible or no residue in the mouth when administered.
5. Be portable and able to tolerate the transportation stress. Be able to be manufactured in a simple conventional manner within low cost.
6. Be less sensitive to environmental conditions like temperature, humidity etc.

Advantages of Mouth dissolving tablet:

- No need of water to swallow the tablet.
- Can be easily administered to pediatric, elderly and mentally disabled patients.
- Accurate dosingas compared to liquids.
- Dissolution and absorption of drug is fast, offering rapid onset of action.
- Bioavailability of drugs is increasedas some drugs are absorbed from mouth, pharynx and esophagus through saliva, passing down into the stomach.
- Advantageous over liquid medication in terms of administration as well as transportation.
- First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
- Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.

Criteria for Fast dissolving Drug Delivery System:

The tablets should

1. Not require water to swallow but it should dissolve or disintegrate in the mouth in matter of seconds.
2. Be compatible with taste masking.
3. Be portable without fragility concern.
4. Have a pleasant mouth feel.
5. Leave minimum or no residue in the mouth after oral administration.
6. Exhibit low sensitive to environmental condition as temperature and humidity.
7. Allow the manufacture of the tablet using conventional processing &packaging equipments at low cost.

Salient Feature of Fast Dissolving Drug Delivery System

1. Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2. No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water. Rapid dissolution and absorption of the drug, which will produce quick onset of action.
3. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased. Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
4. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.

5. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety. New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
6. Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action required.
7. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
8. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form I n terms of stability and liquid dosage form in terms of bioavailability.

2. Materials and Methods

Materials: Ramosetron hydrochloride, Cross caramellose sodium, Cross povidone, Talc, Magnesium Sterate.

Methodology

Pre-formulation studies:

The goals of the pre-formulation study are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish its compatibility with different excipients.

Hence, pre-formulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.

Determination of absorption maximum (λmax):

Absorption maximum is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance. Ramosetron hydrochloride was weighed accurately 10 mg and transferred to 100 ml volumetric flask, dissolved in 0.1N HCL and the final volume was made up to 100 ml with 0.1N HCL to get a stock solution (100 µg/ml). From the stock solution, 1 ml was pipette out in 10 ml volumetric flask and the final volume was made up to 10 ml with 0.1N HCL to get 10 µg/ml. Then this solution was scanned at 200-400 nm in UV-Visible double beam spectrophotometer (UV-3200, Labindia, India) to get the absorption maximum (λ_{max}).

Construction of Ramosetron hydrochloride calibration curve with phosphate buffer PH 6.8:

100mg of Ramosetron hydrochloride was dissolved in 100ml of 0.1N HCL to give a concentration of 1mg/ml (1000µgm/ml). From the above standard solution (1000µgm/ml) 1ml was taken and diluted to 100ml with).1N HCL to give a concentration of 0.01mg/ml (10µgm/ml). From this stock solution aliquots of 0.5, 1, 1.5,2 and 2.5ml were pipette out in 10ml volumetric flask and the volume was made up to the mark with).1N HCLto produce concentration of 5, 10,1,20 and 25µgm/ml respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 290 nm.

Flow properties:

Angle of Repose:

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel, which is fixed from height of 2cm of the plane surface.

Loose bulk Density (LBD):

Loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of about 50 cm3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch.

Tapped bulk density (TBD):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus).

Hausner's ratio:

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material.

Formulation of Oro dispersible tablets of Sildenafil citrate:

Preparation of co processed super disintegrates:

Co processed super disintegrates were prepared by using sodium Vivasole and polyplasdone XL. The super disintegrates were mixed in different concentrations and labeled as CP1,CP2,CP3.The blend of super disintegrates was mixed thoroughly for a period of 15 min, collected and used for preparing formulations in different concentrations.

Table 1: Composition of co processed super disintegrates

Ingredients	CP1	CP2	CP3	CP4	CP5
Vivasole (mg)	500	500	500	1500	1000
Polyplasdone XL (mg)	500	1000	1500	500	500

CP = Coprocessed super disintegrate

Preparation of tablets:

Composition of Ramosetron hydrochloride Dispersible Tablet by direct compression is shown in table 6.4. All the ingredients were weighed. Required quantity of drug and excipients mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-10 station with 6mm flat punch, B tooling. Each tablet contains 10 mg Ramosetron hydrochloride and other pharmaceutical ingredients.

Post Compression Parameters:

Evaluation of uncoated tablets:

Shape and colour: The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Hardness test:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [W(initial)] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions.

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

***In -vitro* dissolution studies:**

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 500ml of 0.1N HCL at a speed of 50rpm at a temperature of 37^0C were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Ramosetron hydrochloride by measuring absorbance at 290 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of 0.1N HCL. Details:

Apparatus used : USP II Lab India DS 800
Dissolution Medium : 0.1N HCL
Dissolution Medium volume : 500ml
Temperature : 370C
Speed of paddle : 50rpm
Sampling Intervals : 2, 4, 6, 8, 10, 15, 20,25 and 30 min
Sample withdrawn : 5ml
Absorbance measured : 290 nm.

3. Results and Discussion

Standard Calibration curve of Ramosetron hydrochloride:

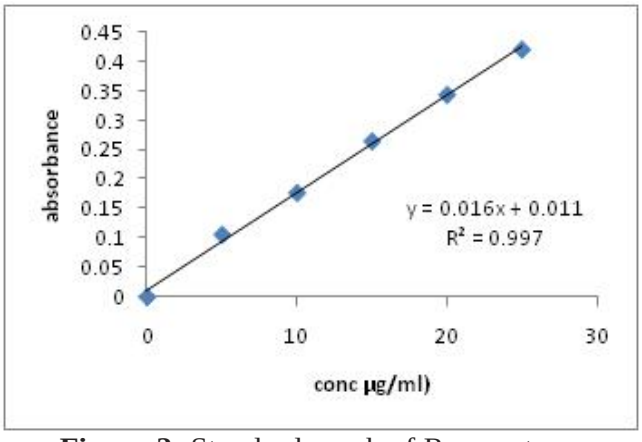

Figure 2: Standard graph of Ramosetron hydrochloride 0.1N HCL

It was found that the estimation of Ramosetron hydrochloride by UV spectrophotometric method at λ_{max} 290.0 nm in 0.1N HCL had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1.

Table 2: Concentration and absorbance obtained for calibration curve of Ramosetron hydrochloride in 0.1N HCL

S. No.	Concentration (µg/ml)	Absorbance* (at 278 nm)
1	0	0
2	5	0.106
3	10	0.177
4	15	0.265
5	20	0.344
6	25	0.431

Evaluation Parameters for Fast Dissolving Tablets of Ramosetron hydrochloride:

Pre-compression parameters: The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends was fall in the range of 13.06% to 18.18%. The Hausner ration was fall in range of 1.14 to 1.22. From the result, it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Post compression Parameters:

Weight variation test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7.3. The average weight of the tablet is approximately in range of 307 to 298.5, so the permissible limit is ±5% (>250mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 7.3. The results showed that the hardness of the tablets is in range of 2.0 to 2.5 kg/cm2, which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-7.3 .The result showed that thickness of the tablet is raging from 4.56 to 5.34.

Friability: Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 7.3. The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

***In-vitro* disintegration time:**

Tablets of each batch were evaluated for in vitro disintegration time. The results showed that the disintegration time of prepared tablets were in the range of 17 to 25.33 seconds. It concluded that all the formulations were showing the % drug content values within 97.23- -100.26 %.

In-vitro* drug release of the formulationIn-vitro* dissolution studies were carried out by using 500ml of 0.1N HCL in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min.

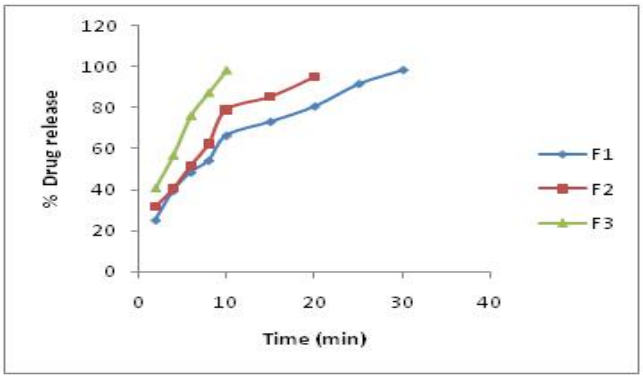

Figure 3: Dissolution profile of formulations prepared with CP1 as super disintegrate

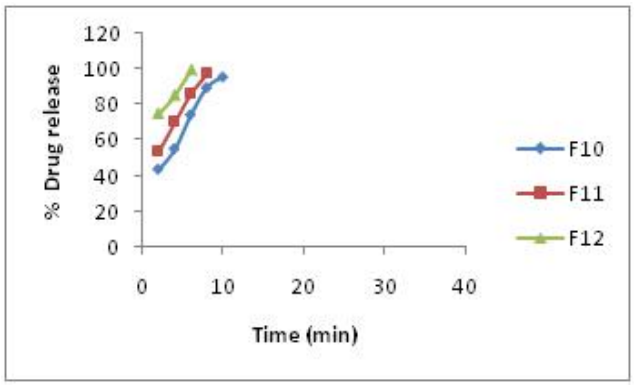

Figure 6: Dissolution profile of formulations prepared with CP4 as super disintegrate

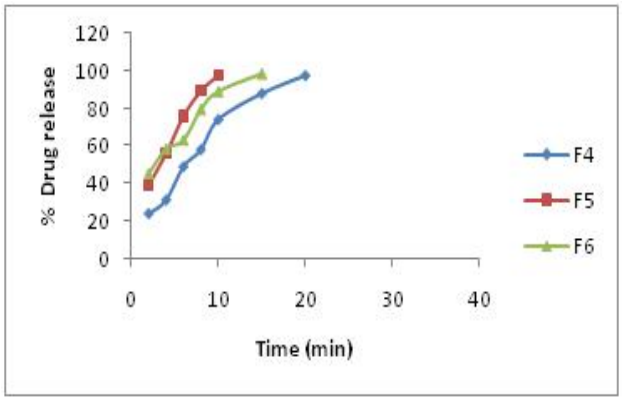

Figure 4: Dissolution profile of formulations prepared with CP2 as super disintegrate

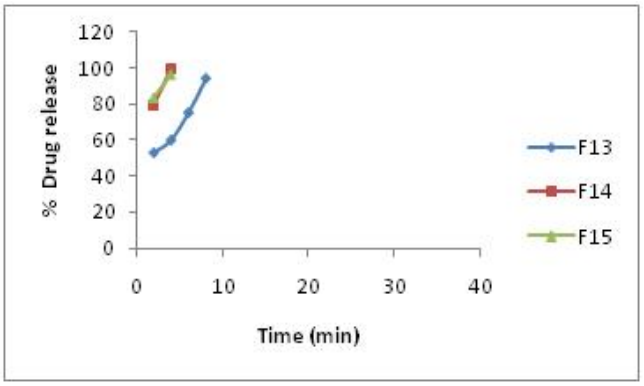

Figure7: Dissolution profiles of formulations prepared with CP5 as super disintegrate.

Table 3: Composition of various tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Ramosetron hydrochloride (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
CP 1(mg)	10	20	30	-	-	-	-	-	-	-	-	-	-	-	-
CP 2(mg)	-	-	-	10	20	30	-	-	-	-	-	-	-	-	-
CP 3(mg)	-	-	-	-	-	-	10	20	30	-	-	-	-	-	-
CP 4 (mg)	-	-	-	-	-	-	-	-	-	10	20	30	-	-	-
CP 5(mg)	-	-	-	-	-	-	-	-	-	-	-	-	10	20	30
Mg St(mg)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc(mg)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
MCC(mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Table 4: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle of Repose (Θ)
F_1	0.45	0.55	18.18	1.22	27.91
F_2	0.47	0.55	14.54	1.17	28.23
F_3	0.50	0.58	13.79	1.16	29.34
F_4	0.46	0.55	16.36	1.19	26.71
F_5	0.50	0.58	13.79	1.16	29.34
F_6	0.47	0.55	14.54	1.17	28.23
F_7	0.50	0.58	13.79	1.16	29.34
F_8	0.41	0.50	18.34	1.21	26.78
F_9	0.41	0.50	18.02	1.21	26.78
F10	0.45	0.55	18.18	1.22	25.85

F11	0.48	0.57	15.78	1.18	27.45
F12	0.46	0.54	14.81	1.17	28.12
F13	0.49	0.58	15.51	1.18	27.02
F14	0.51	0.59	13.55	1.15	26.36
F15	0.41	0.49	16.32	1.19	28.75

Table 5: Post-Compression parameters

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F1	305.9	2.5	4.59	20.33	0.43	97.23
F2	304.4	2.3	4.64	23.66	0.34	98.55
F3	310.7	2.5	4.59	25.33	0.49	98.16
F4	309.2	2.4	4.58	19.00	0.47	99.34
F5	299.4	2.3	4.59	20.33	0.49	98.16
F6	302.4	2.6	4.64	22.66	0.34	98.55
F7	301.3	2.5	4.59	20.33	0.49	98.16
F8	307.3	2.3	4.56	17.00	0.34	99.25
F9	302.32	2.3	4.56	19.45	0.34	100.26
F10	298.36	2.5	4.98	24.36	0.43	98.45
F11	295.34	2.4	4.73	23.72	0.52	99.36
F12	300.2	2.4	4.82	20.63	0.35	100.02
F13	301.3	2.2	5.03	18.34	0.64	97.34
F14	297.6	2.3	5.13	17.47	0.53	99.36
F15	299.4	2.5	5.32	19.35	0.48	98.63

Table 6

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
2	25.4	31.7	40.8	24.3	39.5	44.9	35.2	44.2	53.2	43.7	54.2	75.2	53.2	79.3	83.1
4	39.6	40.5	56.72	31.6	56.3	58.4	50.2	52.1	66.2	55.2	70.3	85.3	60.2	99.3	96.3
6	48.6	51.9	76.16	49.3	76.2	63.1	62.1	64.9	79.3	74.2	86.3	99.3	75.3		
8	54.3	62.4	87.4	58.3	89.7	79.7	73.5	75.3	85.2	89.3	97.3		94.3		
10	66.4	79.1	98.5	74.3	97.8	89.3	80.4	87.3	98.2	95.3					
15	73.1	85.5		88.1		98.9	89.3	96.2							
20	80.6	95.2		97.6			94.2								
25	91.5						100.2								
30	97.86														

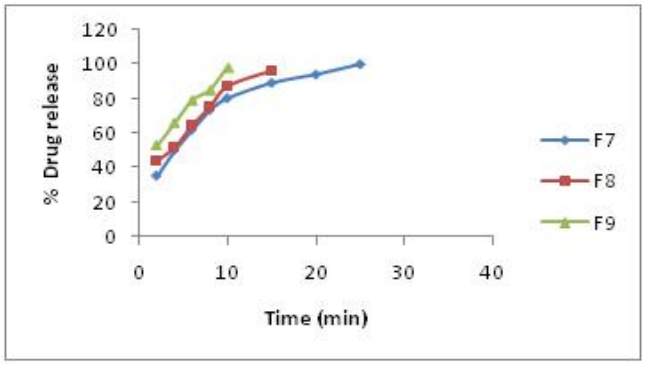

Figure 5: Dissolution profile of formulations prepared with CP3 as super disintegrate

From the tabular column it was evident that the formulations prepared with super disintegrate CP5 showed maximum % drug release in 4 min i.e.99.3%, 96.3% (F13, F14) formulations and the concentration of super disintegrate is 30mg,45 mg). So the principle of coproceesed super disintegrates was found to be useful to produce Oro dispersible tablets.F13 formulation was considered as optimized formulation as it contains less concentration of super disintegrates.

4. Conclusion

In the present work, an attempt has been made to develop fast disintegrating tablets of Ramosetron hydrochloride. Novel method of co processed super disintegrates technology was employed to formulate the tablets. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations, F14 formulation showed maximum drug

release i.e., 99.3% in 4 min hence it is considered as optimized formulation. The F14 formulation contains CP5 as super disintegrate in the concentration of 30 mg. (CP 5 contains Vivasole and polyplasdone XL in 3:1 ratio).

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