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Formulation and Optimization of Taste Masked Rapimelt Dolasteron Mesylate Tablets

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Abstract: *In the present work, Rapimelt tablet of Dolasetron Mesylate were designed to enhance the patient compliance and provide a quick onset of action. Hence the main objective of the study was to formulate rapimelt tablets of Dolasetron Mesylate to achieve a better dissolution rate and further improving the bioavailability of the drug. Rapimelt tablets were prepared by direct compression using super disintegrants like Polyplasdone XL 10, SSG, Ac-di-sol in different concentration and using Mannitol and Pearlitol as the diluents. Drug – resin complex were optimized by considering parameters such as optimization of resin concentration, optimization of swelling time, optimization of stirring time, optimization of temperature, and optimization of pH on maximum drug loading. The effects of variables were observed on maximum amount of drug loading. The various pre-compression parameters such as bulk density, tapped density, compressibility were evaluated. The formulated tablets were evaluated for hardness, weight variation, friability, disintegration time and in-vitro dissolution profile, taste masking. Among all the formulation S13 containing high concentration of polyplasdone XL 10 and pearlitol as the diluent was considered as the best formulation. In-vitro drug release study of S13 showed more than 90 % of the drug release within 10 minutes and was considered as the best formulation.*

Keywords: *DolasetronMesylate, Rapimelt Tablets, ion exchange resin, Kyron T 134, Polyplasdone XL 10.*

1. INTRODUCTION

The term ‘orodispersible’ tablet as in European pharmacopoeia is defined as uncovered tablet for buccal cavity, where it disperses before ingestion. They obviate the problem associated with conventional dosage forms; it has benefits like desired hardness, dosage uniformity extremely easy administration. Orodispersible tablets are also known as mouth dissolving tablets. ‘Melt in mouth’, ‘Rapimelts tablet’, Porous tablets etc [1]. ODT have started gaining popularity and acceptance as new drug delivery systems because they are easy to administer and lead to better patient compliance especially in elderly and children.

These tablets display a fast and spontaneous de-aggregation in the mouth, soon after it comes in contact with saliva, dissolving the active ingredient and allowing absorption through all possible membrane it comes in contact during deglutition [3]. Rapimelt tablets can be prepared by various conventional methods like direct compression, wet granulation, molding, spray drying. Freeze drying and sublimation [2] mass extrusion etc.

These techniques are based on the principle of increasing porosity or on addition of super disintegration and water soluble excipients in the tablets.[4] The formulations prepared from these technique differ on the basis of factors such as mechanical strength, drug and dosage form stability, taste, rate of dissolution and absorption from saliva and overall drug bio-availability.[5] Taste masking of the drug employing ion exchange resins has proved to be safe and effective method for formulation of various dosage forms. Ion exchange resins are cross linked, water insoluble polymer-carrying, ionizable functional groups. Drugs can be loaded onto the resins by an exchanging reaction and hence a drug resin complex is formed [6].Drugs are attached to the oppositely changed resin substrate or resonate through weak ionic bounding so that dissociation occur under salivary pH conditions. This masks the unpleasant taste and odour of drugs [8]. The drug is released from the resinates by exchanging with ions in the gastro intestinal fluid, followed by drugs diffusion [7]. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are inert.

Rapimelt tablet of Dolasetron mesylate was developed in present study to get rapid onset of action, to increase bioavailability and to increase patient compliance, Dolasetron is very bitter in taste and if it is incorporated directly into a Rapimelt, the of the dosage will definitely get futile. Therefore to mask

the taste of Dolasetron and to formulate Rapimelt with good Mouth feel, so as to prepare and patient friendly dosage form taste masking by ion exchange resins i.e. kyron-T134 was employed because of its better drug loading and taste masking. Ion exchange resins have been increasing used for the taste masking of better taste drug and help to prepare Rapimelt tablet. [9]

2. MATERIALS AND METHODS

Dolasetron Mesylate (Procured from Aurobindo Pharma, Kyron-T134(Procured from AurobindoPharma) as Taste masking agent, Polyplasdone XL10, SSG, &Ac- di- Sol were used as a Super disintegrates, Aspartame, Mannitol, Magnesium Stearate, Orange Flavor, Peppermint Flavor used as Flavoring agents . All materials used in the present research were commercial sample.

2.1. Preliminary Trials

Two gm of resin was dispersed in a beaker containing 30 ml of deionized water and allowed to swell for 30 minutes. The pH of resin solution was adjusted to 7 by using 1 M KOH. Accurately weighed Dolasetron Mesylate (as per Table 1) was added and stirred for 4 hr. The drug resin complex (DRC) was separated from dispersion by sequential filtration and washing with three portions of 75 ml of deionized water. Complex was dried and drug-loading efficiency (Table 1) was calculated.

Table1. *Preliminary trials of drug loading at different ratio of drug and resin*

Drug: resin Ratio	pH	% Drug Loading	Taste*
1:1	7	67.55 ± 0.86	-
1:2	7	87.21 ± 0.83	+
1:3	7	91.13 ± 0.92	++
* Bitterness graded from non-bitter (++), less bitter (+) and bitter (-).			

2.2. Drug Loading Efficiency Determination

Drug resin complex equivalent to 100 mg of pure drug was dissolved in 0.1 N HCl in 100 ml volumetric flask. The mixture was sonicated for 30 min, filtered and DolasetronMesylate content was estimated using UV spectrophotometer [Systronics double beam UV-visible spectrophotometer – 2101] at 284nm.

2.3. Effect of Kyron 134 Ph on Drug Loading

Seven batches each containing of 3 gm of resin, dispersed in 30 ml deionized water for 30 min. pH of all batches were adjusted up to 4, 5, 5.5, 6, 6.5, 7 and 8 respectively by using 1 M KOH maintained at room temp. One gram drug was added to each mixture, and the drug-loading efficiency was found to be in the range of 52.17 ± 1.67 at the pH of 4 to 90.21 ± 0.96 at the pH of 7 (Fig 1). The complexation was enhanced with increasing pH from 4 to 7. A maximum of 90.21% wt/wt drug loading was obtained at pH 7 (near to pKa of Dolasetron Mesylate) as pH increased above 7, the percentage drug loading decreased. The pH of the solution affects both solubility and the degree of ionization of drug and resin. The results can be attributed to the fact that Dolasetron Mesylate has a pKa between 6.08 and 8.73 and hence will have maximum solubility and complete ionization in this range.

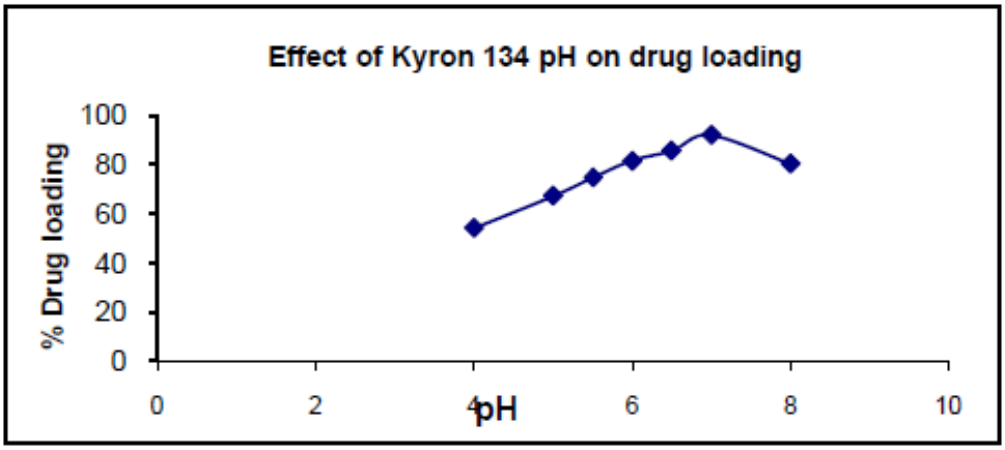


Figure1. *Effect of Kyron 134 pH on drug loading*

2.4. Effect of Temperature on Drug Loading

Dispersion of resin (three gm) in 30 ml of deionized water, stirred for 30 min. The pH of resin solution was adjusted to 7 and one gm drug was added and stirred for 4 hr at room temperature. The same process was performed at 20, 40, 50, 60, 70 and 80°C using Temperature-controlled magnetic stirring for 4 hr. The drug loading efficiency was estimated spectrophotometrically at 284 nm and was found to be in the range of 86.66 ± 1.63at the temperature of 80°C and 91.84 ± 1.23 at the temperature of 20°C (Fig 2) .Efficient drug loading on Kyron T-134 occurred uniformly in the experimental temperature range of 27ºC to 80ºC as shown in Fig 2 .Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. The continuous stirring in process does not allow the development of thick exchange zones so temperature may not show any effect on Dolasetron MesylateKyron T-104 complexation

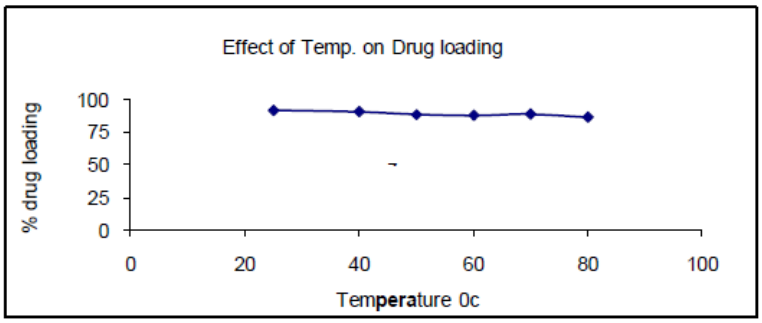


Figure2. *Effect of temperature on drug loading*

2.5. Effect of Resin Soaking Time on Drug Loading

Separate batches of Kyron T-134 (3 gm) were soaked in 30 ml of deionized water for 0, 10, 20, 30, 60, 90 and 120 minutes, respectively. Adjust pH 7 of all batches, add one gm drug to each and stirred for 4 hr. Drug loading efficiency with resin swollen for different times was determined and was found to be in the range of 70.36 ± 0.96 to 91.86 ± 1.51.Results of effect of soaking time on drug loading is shown in Fig 3. The results reveal that a 30-minute swelling time of Kyron T-134 in deionized water gave the maximum Dolasetron Mesylate loading of 92.21% wt/wt. This may result of maximum swelling and hydrating properties of Kyron T-134 that affect the rate of ion exchange. Less drug-loading efficiency may be observed in unswollen resin matrix because the exchangeable groups of resin are latent and coiled toward the backbone.

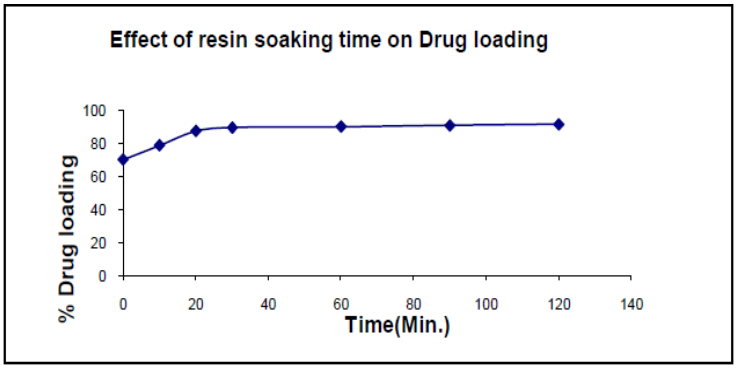


Figure3. *Effect of resin soaking time on drug loading*

2.6. Effect of Stirring Time on Drug Loading

Six gm of resin was soaked for 30 min in 250 ml beaker with stirring at 400 rpm in 90 ml of deionized water. 2gm of drug was added to resin dispersion after adjusting pH 7 and the samples were withdrawn at intervals of 30 min up to 5 hr. Each sample was analyzed spectrophotometrically for drug loading efficiency at 284 nm. The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by stirring time. The percentage drug loading (wt/wt) with a stirring time of 0.5 to 5 hr is as observed Increasing the stirring time above 4 hr did not further increase the complexation values (Fig 4). Hence, 4 hr contact time between drug and resin could be optimized to equilibrate the ion exchange process to achieve maximum drug loading. This study indicated that the optimum ion exchange could be completed in a period of 4 hr.

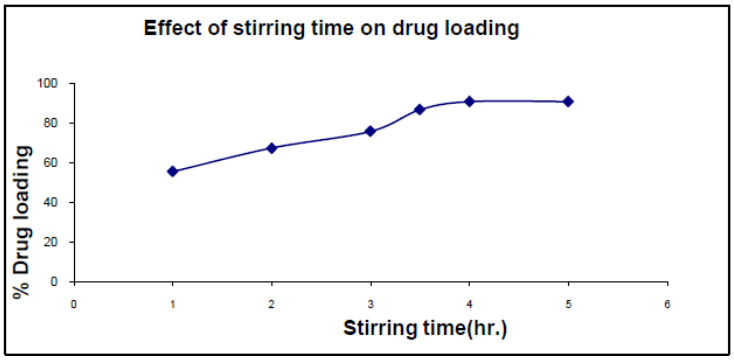


Fig4. *Effect of stirring time on drug loading*

3. Formulation of Dolasetronmesylate Rapimelt Tablets

In the present study Direct Compression technique was employed for the preparation of Rapimelt tablets. All the ingredients were weighed individually. Weighed quantity of resin was added in clean beaker containing specified quantities of water with stirring for 15 min for the Preparation of drug resin complex. Weighed quantity of Dolasetron Mesylate sifted through 40 sieves and was added to the above solution and stirred for 4 to 5 hrs continuously. Beaker was kept aside for 1 to 2 hrand mother liquor was collected and used for further formulation.Mix half of the quantity of mannitol (up to 12 batches) (Table 2) and pearlitol (from 13 to 16 batches) (Table 3) was used in the form of slurry. Dried the slurry in the tray drier for 2-3hr up-to LOD=2-3%. Sift the other excipients through 40sieves. Sift the dried powder through 20mesh, to this add above sifted excipients& mix it properly for 3 min. Mix the Magnesium Sterate through 40 sieve number & add to the mixture & lubricate for 2 min. The above powder blend was compressed using rotary tablet machine using 5.49 mm concave punches**.**

Table2. *Composition of DolasetronMesylate Rapimelt tablets*

S. No	**Ingredients**	**Formulation code**											
		S_1	**S_2**	**S_3**	**S_4**	**S_5**	**S_6**	**S_7**	**S_8**	**S_9**	**S_{10}**	**S_{11}**	**S_{12}**
1	DolasetronMesylate	50	50	50	50	50	50	50	50	50	50	50	50
2	Kyron T-134	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7
3	Purified water	20	20	20	20	20	20	20	20	20	20	20	20
4	Polyplasdone XL10	2	-	-	4	-	-	6	-	-	7.5	-	-
5	SSG	-	2	-	-	4	-	-	6	-	-	7.5	-
6	Ac- di- Sol	-	-	2	-	-	4	-	-	6	-	-	7.5
7	Aspartame	2	2	2	4	4	4	5	5	5	5	5	5
8	Mannitol	40.3	40.3	40.3	36.3	36.3	36.3	33.3	33.3	33.3	31.8	31.8	31.8
9	Orange Flavor	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
10	Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Total Wt. (mg)	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**

Table3. *Composition of DolasetronMesylate Rapimelt tablets*

S.No	**Ingredients**	**Formulation code**	
		S13	**S14**
1.	Dolasetron Mesylate	50	50
2.	Kyron T-134	04.70	04.70
3.	Purified water	20.00	20.00
4.	Polyplasdone XL10	08.00	10.00
5.	Aerosil	01.00	01.00
6.	Avicel PH 200	-	-
7.	Aspartame	05.00	05.00
8.	Paerlitol	35.3	52.8
9.	Orange Flavor	01.00	01.00
10	Magnesium Stearate	01.00	01.00
	Total Wt.	**120 mg**	**120 mg**

4. EVALUATION OF BLEND OF RAPIMELT TABLETS

4.1. Bulk Density (Db)

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by **Db = M / V0** Where, M is the mass of powder; V0 is the bulk volume of the powder

4.2. Tapped Density (Dt)

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by, **Dt = M / Vt** Where, M is the mass of powder. TVs is the tapped volume of the powder.

4.3. Compressibility Index

The Compressibility index of the blends was determined by Carr's compressibility index.

Compressibility index (%) = (TBD-LBD) x 100/TBD

4.4. Hausner Ratio

It is the measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5. It is determined by using the following formula:

Hausner ratio = TBD / LBD

5. EVALUATION OF DOLASETRON MESYLATE TABLETS

5.1. Mechanical Strength

Tablets should possess adequate strength to withstand mechanical shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are important parameter to evaluate a tablet for its mechanical strength.

5.2. Crushing Strength (Hardness)

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of oral dispersible tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using Digital hardness testers. An average of three observations is reported.

5.3. Friability Testing

The crushing test may not be the best measure of potential behavior of tablet during handling and packaging. The resistance to surface abrasion may be a more relevant parameter. Friability of each batch was measure in "Electro lab Friabilator". Ten pre-weighed tablets were rotated at 25 rpm for 4 min that is 100 revolutions, the tablets were then re weighed and the percentage of weight loss was calculated.

5.4. Rapidly Disintegrating Property

To evaluate the tablets for their rapid disintegration properties, following tests were carried out

- *Wetting Time*: Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. 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.

5.5. Modified Disintegration Test

The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for ODT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter)

was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

5.6. Disintegration in Oral Cavity

The time required for complete disintegration of tablets in oral cavity was obtained from six healthy volunteers, who were given tablets from the optimum formulation.

5.7. In-Vitro Drug Release

In vitro dissolution studies were carried out using USP type II (Paddle apparatus) at 50 rpm. The Dissolution medium used was 0.1 N HCl (900 ml) maintained at 37 ± 0.5 ^{0}C. 10 ml of dissolution media were withdrawn at 0, 5, 10, 15, 20, 25, 30 min for a period of 10 minutes and fresh dissolution medium was replaced every time with the same quantity of the sample and content of Dolasetron Mesylate was measured by determining absorbance at 284 nm using UV Spectrophotometer (1700).The dissolution studies were carried out in triplicate. This test was carried out only for final batch.

5.8. Taste Evaluation (for Taste Masking Purpose)

Bitter taste was evaluated based on human bitter taste recognized by volunteers. The study protocol was explained and written consent was obtained from volunteers. Rapimelt tablet equivalent to 50 mg DolasetronMesylate was held in the mouth for 15seconds by each volunteer, the bitterness level was compared with formulation S1.

5.9. Stability Study

FDA and ICH specifies, the guidelines for stability testing of a new drug product, as a technical requirement for the registration of a pharmaceuticals for human use. The ICH Tripartite guidelines have established that long term stability testing should be done at 25º C/ 60% RH for 12 months. Accelerated stability testing should be done at 40º C/ 75% RH for six months. Stability testing at intermediate storage condition should do at 30º C/65% RH.

In the present work, stability study was carried out Dolasetron Mesylate Rapimelt tablet formulation S13 of 2mg label claim was found to be desirable than the other formulations. Any ideal dosage form apart from other dosage form requirement should provide consistency of drug content and release throughout its shelf life.

6. RESULTS AND DISCUSSION

6.1. Evaluation of Blend of Rapimelt Tablets

Bulk and Tapped density, Powder compressibility were performed as per procedure and the results were illustrated in Table 4

Table4. *Evaluation of Blend of Rapimelt Tablets*

Formulations	Bulk density	Tap density	Compressibility index	Hausner ratio
S1	0.61	0.712	18.6	1.186
S2	0.61	0.72	18.21	1.181
S3	0.62	0.724	16.31	1.162
S4	0.62	0.702	17.01	1.171
S5	0.62	0.717	19.52	1.195
S6	0.62	0.719	15.96	1.159
S7	0.62	0.721	15.17	1.151
S8	0.62	0.723	16.61	1.166
S9	0.61	0.723	16.8	1.168
S10	0.62	0.721	15.71	1.157
S11	0.62	0.722	16.45	1.164
S12	0.61	0.724	16.96	1.169
S13	0.63	0.727	15.39	1.153
S14	0.63	0.727	15.39	1.153

6.2. Compatibility Study

The interference of the additives used in the formulation such as resin, Superdisintegrants, Glidant, Lubricants, and Diluents etc. was verified and found that these ingredients are not interfering with the estimation of DolasetronMesylate the 0.1N HCL at 284 nm in the UV spectrophotometer.

6.3. Evaluation Parameters of Different Formulations of Dolasetron Mesylate Rapimelt Tablets

By comparing formulation S-1, S-2, S-3 we conclude that all the physical property of all the tablet formulations was not found satisfactory. To minimize the disintegration time we can increase the concentration of the above three superdisintegrant. Among three the rapid disintegration was seen in the formulation containing Polyplasdone XL-10. The taste of the drug was slight bitter to mask the bitter taste of drug and was increased by the concentration of sweeter Aspartame. The friability of the tablet was more and to minimize this Hardness of the tablets was increased.

By comparing formulation S-4, S-5, S-6 we conclude that there was slight decrease in the disintegration time of the tablets formulation due to increase in the concentration of the super disintegrating agents. The bitterness of the drug was not observed. There was slight increase in the hardness as compare to previous trials but not found satisfactory results for friability test. By comparing formulation S-7, S-8, S-9, S-10, S-11, S-12 there was slight increase in the hardness as compare to previous trials but not found satisfactory results for friability test, so the hardness was improved by using pearlitol as a diluent. When there is increase in the concentration of Polyplas done XL-10 total weight of the tablet was increased, resulting into decrease in disintegration time of the tablets. Although there is increase in the hardness of the tablet disintegration time remains 15 sec due to the increase in the concentration of Polyplas done XL-10 where friability also decreased due to increase in the hardness. By comparing the batch no S-13 & S-14 we conclude that if there is increase in the tablet weight by increasing the concentration of diluents the disintegration time was increased.

6.4. Effect of disintegrating agent on disintegration time

Table5. *Comparison of concentration of Polyplas done XL10 with the disintegration time.*

Sr. No.	Batch No.	Polyplasdone XL10 (mg)	Disintegration Time (sec)
1	S-1	2	45
2	S-4	4	40
3	S-7	6	30
4	S-10	7.5	18
5	S-13	8	15

6.5. Effect of Concentration of Polyplasdone XL 10 With Disintegration Time

In increasing concentration Polyplasdone XL10 decrease the disintegration time that has been shown in Table no32. The In vitro disintegration time of all the 14 formulation varied from 50 ± 2.00 to 15 ± 1.16 seconds. The rapid disintegration was seen in the formulation containing Polyplasdone XL-10 and Ac-Di-Sol. This is due to rapid up take of water from the medium, swelling and bursting effect it was also notice that as the disintegrant concentration was increased from 2.67 to 10 %, the time taken for the disintegration was reduced. The in vitro disintegration time was rapid in Polyplasdone XL-10 followed by Ac-Di-Sol and then sodium starch glycolate.

Table6. *Comparison of the evaluation test for all the formulations from S1 to S14*

Evaluation	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14
Hardness(kg/cm2)	1.5	1.5	1.6	1.7	1.68	1.75	1.8	1.69	1.77	2.65	2.62	2.8	3.2	3.2
Friability%	0.94	0.96	0.94	0.88	0.88	0.84	0.75	0.88	0.78	0.44	0.48	0.44	0.14	0.15
Disintegration time (sec)	45	52	50	40	48	45	30	40	35	18	32	25	15	22
Wetting time(sec)	64	70	68	55	62	58	42	52	47	30	42	35	22	32
Thickness(mm)	3.58	3.57	3.55	3.52	3.53	3.51	3.48	3.53	3.49	3.24	3.25	3.2	3.16	2.86
Taste	+	+	+	++	++	++	++	++	++	++	++	++	++	++

+ slight bitter,++ non bitter

From all 16 batches of formulations prepared with Kyron T-134 resin, Batch **S13** showed good taste masking. The physical parameter of S13 was found satisfactorily & complies with official specification. Hence, **S13** was considered as optimized formula for preparation of taste masked Dolasetron Mesylate Rapimelt tablets using ion exchange resin.

6.6. Dissolution Profile of the Prepared Rapimelt Tablet

After getting all the parameters satisfactory for S13 dissolution of that trial was studied Dissolution was carried out up 30 minute and samples were taken after 5, 10, 15, 20, and 30 min.(Table 7) and the in-vitro release graph was drawn (Fig 5)

Table7. *Dissolution Profile of the prepared Rapimelt Tablets*

Time(min)	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	66.5	70	67	70.6	69.4	69.8	75.2	72.4	72.6	86	81.4	85.2	87.6	86
10	72.8	75	74	79.8	78	70.6	89.5	74	79.8	91	89	87.5	92.8	89
15	81.3	83.3	84	89	82	87	93	85	87	94	91	90	95.3	91.
20	87.2	89.2	89	93	87	93	94	92.4	91	96.4	93.5	94	97.2	95
30	94	92	93	95.2	92.4	95	98	93	95	99	96	98	100.9	98

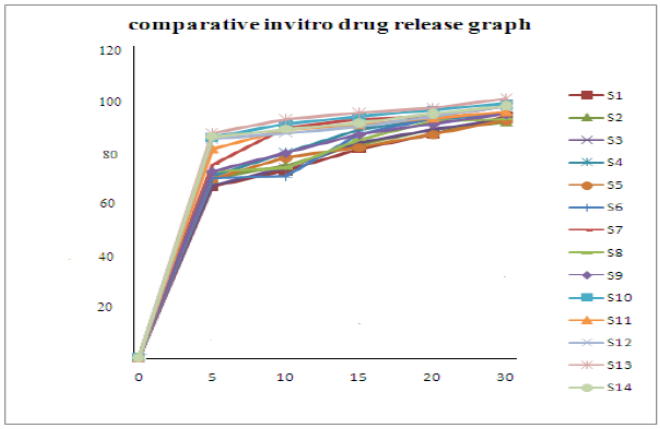


Figure5. *Invitro Release of all the Formulations*

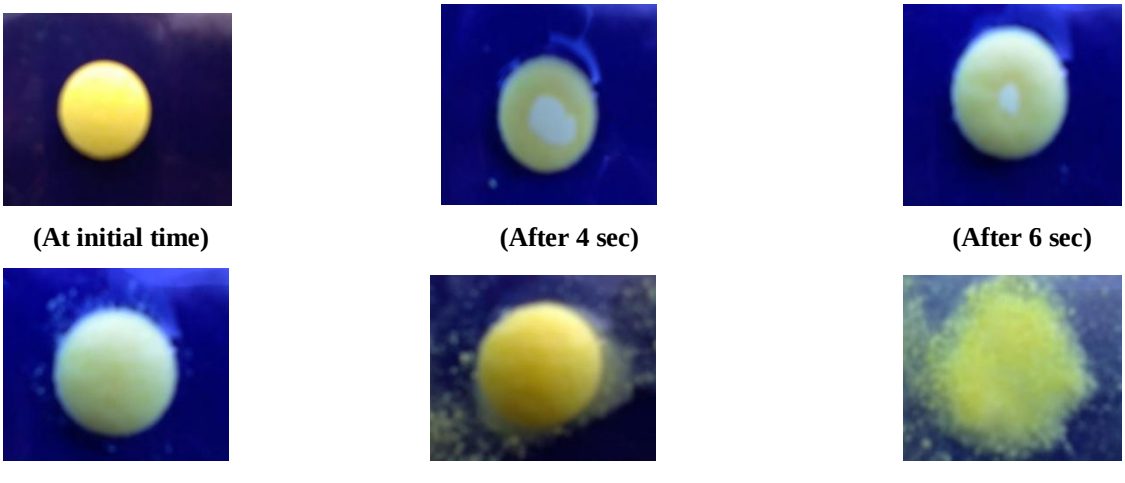
6.7. Accelerated Stability Study

The optimized formulation S13 was kept for accelerated stability study at 40 ± 2 ^{o}C and 75 ± 5% RH for 1 month in stability chamber. After a period of one month, the samples were observed for any change in physical parameters. It was observed that any change in color. It was also noted that suspension was free of any kind of bad odour.

Table8. *Stability Study of the optimized formulation S13*

Sr. No	Parameters	S13
1	**Hardness(** Kg/cm^2)	3.21
2	**Friability (**% w/w)	0.140
3	**Disintegration time (**Sec)	17
4	**Wetting time (**Sec)	25
5	**Assay %**	98.99 %
6	**Taste (**As per specifications)	Not bitter

Tablet disintegration study was carried out for the Formulation S13 and is shown in the Fig 6



(At initial time) **(After 4 sec)** **(After 6 sec)**

(After 9 sec) **(After 12 sec)** **(After 15 sec)**

Figure6. *Tablet Disintegration photographs of batch S13*

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