Development and Optimisation of Ondansetron Dispersible Tablet Formulation

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ABSTRACT

Recent advances in technology have presented viable dosage alternative for patients who may have difficulty in swallowing tablets or capsules. An Oral Dispersible tablets is one such approach. Oral Dispersible tablets are an innovative technology, which disperse rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Oral Dispersible tablets offer many advantages like rapid onset of action, useful for pediatric, geriatric and psychiatric patients, good chemical stability, as well as improved taste.

A Oral Dispersible tablets is one such approach. Ondansetron hydrochloride is novel antiemetic, serotonin receptor (5-HT_3) antagonist used in the prevention of chemotherapy induced nausea and vomiting. It is also beneficial in case such as motion sickness Patients who are traveling with scarcity of water. Oral Dispersible tablet of R-Ondasetron was developed in present study to get rapid onset of action, to increase bioavailability and to increase patient compliance. R-Ondasetron is very bitter in taste.

The bitter taste of the drug was masked by incorporating in the resin, Kyron T-134 (A weak acid cationic resin) by adding drug to the slurry of Kyron T- 134 in distilled water and optimizing pH, stirring time, soaking time of resin in water. The formulations were prepared by direct compression method using drug-resin complex, Polyplasdone X_L 10, pearlitol, aspartame, peppermint, bitter taste mask and magnesium Sterate.

The tablets were evaluated for taste, wetting time, disintegration time, hardness, friability, in-vitro dissolution time. The optimized formulations had pleasant taste with a hardness of 3.0 to 3.5 kg/cm^2 and disintegration time of 15 seconds and more than 90 % of drug was released in 10 minutes.

Keywords: Taste Masking, OndansetronHCl, Fast Dissolving Tablet, Mouth Dissolving Tablet, ODT, Rapid Disintegrating Tablets.

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INTRODUCTION:

INTRODUCTION TO ORAL DISPERSIBLE TABLETS

Oral dispersible tablets (ODT) are an innovative technology, which disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Conventional tablets and capsules pose difficulty for swallowing in patient groups, such as elderly, children and mentally retarded and uncooperative patients. To fulfill the above needs, formulators have devoted considerable efforts for developing ODT. Researchers have formulated ODT for various categories of drugs, which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic and drugs for erectile dysfunction. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. [1]

ODT are convenient dosage form for many application but they are challenging to formulate, if active substance has an unpleasant taste. So use of various techniques necessary for the taste masking, such as use of flavor, sweetener and amino acid, by polymer coating, by complexation with ion-exchange resin and inclusion complex with cyclodextrin.

The performance of an ODT depends on the technology used in its manufacture. The disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipinents in the formulation. ODT can be achieved by various techniques like direct compression, wet granulation, freeze-drying, tablet moulding, spray drying, sublimation, cotton candy process and mass-extrusion. ODT are also known as fast dissolving, rapid–dissolve, rapimelt, fast melts, porous tablets and orodisperse. The European Pharmacopoeia defines a term orodisperse as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. [2]

Advantage of Oral dispersible tablets: [3]

1. Improved patient compliance, patient having difficulty in swallowing tablet can easily administer this type of dosage form Rapid onset of action and may offer an improved bioavailability
2. Useful for pediatric, geriatric and psychiatric patients
3. Suitable during traveling where water is may not be available
4. Good chemical stability
5. Insensitive to environmental conditions such as humidity and temperature.
6. Improved taste without any residue in the mouth after disintegration

Characteristic of Oral dispersible tablets:[3]

1. Ease of administration for patients who are mentally ill, disabled and uncooperative.
2. Requires no water
3. Quick disintegration and dissolution of the dosage form
4. Improve taste and does not leave any residue in the mouth after disintegration. Ability to provide advantages of liquid medication in the form of solid preparation
5. Adaptable and amenable to existing processing and packaging machinery
6. Beneficial in cases such as motion sickness, suede episodes of allergic attack or coughing, where an ultra rapid onset of action require.
7. Pleasant mouth feel.
8. Durable and sufficient strength to withstand the regions of the manufacturing process and manufacturing handling.

EXPERIMENTAL WORK [4]

PREFORMULATOION STUDY OF THE PURE DRUG:

Bulk density:

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (method -1)

Method-1 (measurement Procedure - Passed a quantity of material sufficient to complete the test through a 1.00mm (no.18) screen to break the agglomerates that may have form during storage into a dry 250ml cylinder introduce without compacting approximately 100gm of test sample weight with 0.1% accuracy. If it is not possible to use 100gm, the amount of the test sample and the volume of the cylinder may be modified and the test condition volume of 150 to

250ml, and read the unsettled apparent volume, $V_{O,}$ to the nearest graduated unit. Calculate the bulk density in gm/ml by the formula

$$(M) / (V_f)$$

Generally replicate determinations are desirable for the determination of the property.2

Tapped Density:

Tapped Density was achieved by mechanically taping the measuring cylinder containing a powder sample, after observing the initial volume. The cylinder was mechanically tapped and the volume reading was taken until little further volume change was observed. The cylinder achieved the mechanically tapped and the volume reading was taken until the further volume change was observed. The cylinder achieved the mechanical tapping and allows it to drop under its own weight a specified distance by either of two methods described below devices that rotate the cylinder during tapping down.

Method 1:

Procedure passed a quantity of material sufficient to complete the test through a1.00mm (no 18) screen to break the agglomerates that may have formed during the storage into a dry 250ml glass graduated cylinder weighing 220±44gm and mounted on a holder weighing 450±10gm introduce, without compacting, approximately 100gm of test sample, M, weighed with 0.1% accuracy, and read the unsettled apparent volume, V_O, to the nearest graduated unit. Mechanically taped the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ±2mm at a nominal rate of 300 drops per minute.Unless the cylinder 500 times initially and measured the tapped volume, V_O, to the nearest graduated unit. Repeat the tapping additional 750 times and measured the tapped volume, V_b, to the nearest graduated unit. If the difference between the two volumes is less than 2%, V_b is the final tapped volume,$V_{f, succeeding}$ measurement is less than 2%

Calculate the tapped density in gm per ml, by the for

$$(M) / (V_O)$$

Generally replicate determinations are desirable for the determination of this property.3

Method 2:

Same as directed under method 1 except that a suitable mechanical tapped tester that provides a fixed drop of 3mm (±10%) at a nominal rate of 250 drops per minute was used

MESUREMENT OF POWDER COMPRESSIBILITY:

The compressibility index and Hausner's ratio are measure of the flowability of powder to be compressed as such.They are measure of the relative impotence of interparticulate interaction in a free flowing powder, such interaction are generally less significant and the bulk and the tapped density will be closer in value. For poor flowing material there are frequently greater interparticulate interactions and the greater difference between the bulk and the tapped density will be observed. These differences will be reflected in the compressibility index and the Hausner's ratio.5

Table I Flow properties of Ondansetron hydrochloride.

Sr. No.	Parameter	Ondansetron Hydrochloride
1	Untapped bulk density	0.279 gm/ml
2	Tapped bulk density	0.389 gm/ml
3	Compressibility index	28.00 %
4	Hausner's ratio	1.39

Drug- Compatibility study:

The compatibility studies were carried out to study the possible interaction between the active pharmaceutical ingredients and several inactive ingredients used in the formulation. Number of some common excipients and Ondansetron hydrochloride raw materials taken in different ratio, triturated in mortar and pastel well mixed in poly bag and filled in 4 vials (5ml). For each combination.Vials Stoppard with bromobutyl stopper and initial physical observation of each combination note down. All vials are kept in stability one at 40^0 C / 75 % RH One at 25^o C /60 % RH, One at light and one at room temperature.

After one week physical nature of blend in vial should be compare with respect to vial kept at room temperature. This observation study is up-to 4 weeks.5

If there is any drastic change in flow / colour of powder comparing to room temperature sample, change should be noted.Various excipients were selected for the study was as follows:

Results have been tabulated below.

Table II Drug- Excipients studies results

No.	Drug: Excipient	Ratio	Observation Initial	Ambient Temp (A)				At 40 ^{0} C and 75% RH (B)				At 25 ^{0} C and 60% RH (C)				At light (D)			
				Week				Week				Week				Week			
				1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th
1	Drug	1:0	White Powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
2	D+Mannitol	1:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
3	D+ pearlitol	1:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
4	D+Avicel pH 200	1:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
5	D+ Polyplasdone XL10	1:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
6	D+ Acdisol	1:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
7	D+SSG	1:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
8	D+ Magnesium Sterate	5:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
9	D+ Aerosil	5:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
1	D+ Orange	5:1	OWP,F	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

0	Flavor		F	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
11	D+Peppermint Flavor	5:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
12	D+ Kyron T-134	1:1	OWP,FF	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

Abbreviation: **NC……**NO Change,**WD…....**Off white powder,D**……..**Drug Excipient,FF**…..**Free Flowing

After completion of one month physical studies of Drug-Excipients combinations, it is observed that no common excipients are creating any drastic change in the mixture with Ondansetron hydrochloride. Therefore, all these excipients can be used in the formulation of Ondansetron hydrochloride oral dispersible tablets.

TASTE MASKING OF ONDANSETRON

TASTE MASKING

ODT are convenient dosage form for many application but they are challenging to formulate if active substance has an unpleasant taste. The Ondansetron is much bitter in taste, so taste masking necessary before formulating them as ODT.

Methods Used in Taste masking

A. Complexation with ion exchange resins (Kyron T-134)

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups. Ion-exchange resins are used in drug formulations to stabilize the sensitive components, sustain release of the drug, to prepared rapid disintegrating tablets, and mask bitter taste of drug. Drug can be bound to the resin by either repeated exposure of the resin to the drug using a chromatographic column or by complexation of drug with resin. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbents or resonate through weak ionic bonding. This suitably masks the unpleasant taste. Various resins such as weak acid, strong acid and strong base are used for taste masking purpose.[6]

The purpose of this research was to formulate tasteless complexes of Ondansetron with Kyron T-134. It is a water-insoluble, high molecular weight; cross linked polyacrylic acid cation exchange

resin, which is a highly porous indigenous resin. A simple, rapid and cost-effective method was attempted for taste masking. The natural variations in pH can be used advantageously to prepare complexes that remain stable in the mouth without affecting gastric release.[6]

Procedure:

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 Ondansetron 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 was calculated.

Table III Drug Loading Efficiency Trials

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 (-)

** ± Standard deviation of triplicate

Drug loading efficiency determination:

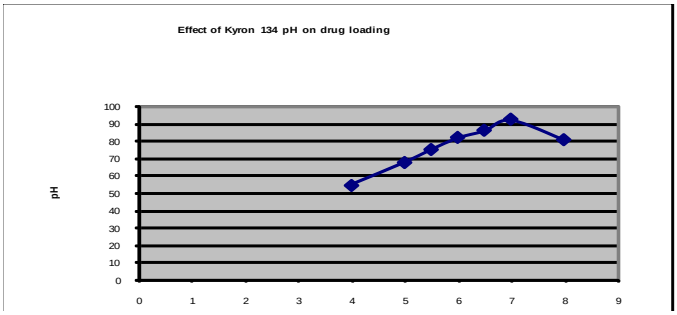
Drug resin complex equivalent to 100 mg of pure drug was dissolved in 0.1 N HCl in 100 ml volumetric flask. The mixture was sonicated for 30 min, filtered and Ondansetron content was estimated using UV spectrophotometer [Systronics double beam uv-visible spectrophotometer – 2101] at 214nm.

(A) Effect of pH on complex formation

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 estimated.

- **Effect of Kyron 134 pH on drug loading**

depicts the effect of pH of resin dispersion on the % drug loading. 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 Ondansetron). The 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 ciprofloxacin hydrochloride has a pKa between 6.08 and 8.73 and hence will have maximum solubility and complete ionization in this range. The decreased complexation at lower pH is due to excess H^+ ions in the solution, which have more binding affinity to the $–COO^-$ groups of resin and compete with the drug for binding.[7]



Graph 1 Effect of Kyron T-134 pH on Drug Loading

(B)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 40, 50, 60, 70 and 80°C using temperature-controlled magnetic stirring for 4 hr. The drug loading efficiency was estimated spectrophotometrically.

- **Effect of Temperature on Drug Loading**

Efficient drug loading on Kyron T-134 occurred uniformly in the experimental temperature range of 27ºC to 80ºC as shown in Figure .Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. Ondansetron is a water-insoluble drug with a pKa of 6.08 to 8.73 that has potential at operational pH to be completely ionized. The continuous stirring in process does not allow the development of thick exchange zones so temperature may not show any effect on OndansetronKyron T-104 complexation.

Table IV Effect of Kyron T-134 pH on Drug Loading

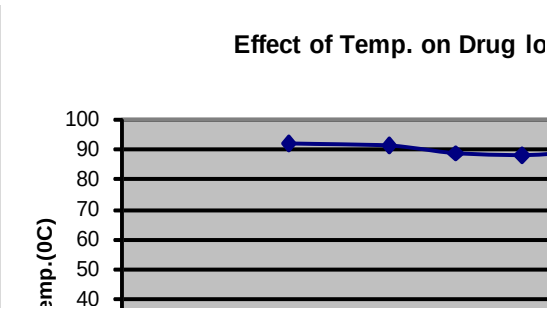
PH	% Drug loading*
4	52.17 ± 1.67
5	69.61 ± 0.99
5.5	75.32 ± 1.82
6	81.32 ± 1.36
6.5	87.17 ± 0.96
7	90.21 ± 0.96
8	80.56 ± 1.03

* ± Standard deviation of triplicate

Table V Effect of Temperature on Drug Loading

Temp (^{0}C)	% Drug loading *
27	91.84 ± 1.23
40	90.86 ± 0.86
50	88.8 ± 1.25
60	87.89 ± 1.45
70	88.87 ± 0.98
80	86.66 ± 1.63

* ± Standard deviation of triplicate



Graph 2 Effect of Temperature on Drug Loading

(C) Effect of soaking time of resin 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.

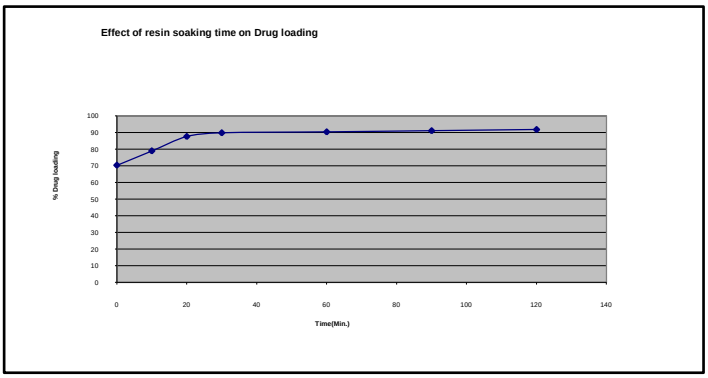
- **Effect of Resin Soaking Time on Drug Loading**

Results of effect of soaking time on drug loading are shown in Table and it is graphically presented in Figure. The results reveal that a 30-minute swelling time of Kyron T-134 in deionized water gave the maximum Ondansetron 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 un swollen resin matrix because the exchangeable groups of resin are latent and coiled toward the backbone.[8]

Table VI Effect of Resin Soaking Time on Drug Loading

Time (min)	% Drug loading *
0	70.36 ± 0.96
10	78.99 ± 1.47
20	87.67 ± 1.33
30	89.88 ± 1.11
60	90.44 ± 0.89
90	91.14 ±0.99
120	91.86 ± 1.51

* ± Standard deviation of triplicate



Graph 3 Effect of Resin Soaking Time on Drug Loading

(D) 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 214 nm.

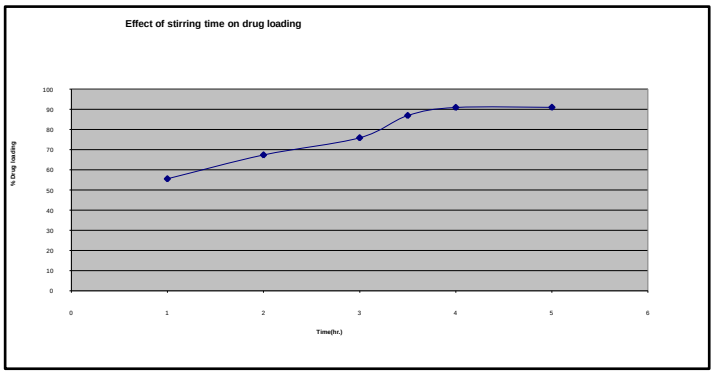
- **Effect of Stirring Time on Drug Loading**

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. 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.[9]

Table VII Effect of Stirring Time on Drug Loading

Time (hr)	% Drug loading *
1	55.56 ± 1.31
2	67.36 ± 0.89
3	75.86 ± 1.62
3.5	86.88 ± 1.25
4	90.98 ± 0.98
5	90.94 ± 1.43

* ± Standard deviation of triplicate



Graph 4 Effect of Stirring Time on Drug Loading

TABLET PREPARATION[10]

Materials and Methods

Table VIII Materials used

Sr. No.	**Materials**	**Application / Use**
1	Ondansetron hydrochloride	Active Drug
2	Kyron-T134	Taste Masking Agent
3	Polyplasdone XL10	Super Disintegrants
4	Ac- di- Sol	Disintrigatting agent
5	Aspartame	Sweetening Agent
6	Mannitol	Flawing Agent
7	Orange Flavor	Flavouring Agent

Preparation of Tablets

In the present study Direct Compression technique was employed for the preparation of oral dispersible tablets.

Direct compression is widely used in tableting because it requires fewer processing steps, is simpler to validate and improves drug stability when compared with the wet granulation method. Direct compression also eliminates exposure to heat and moisture during processing and is a more economical process. However, the majority of active pharmaceutical ingredients exhibit poor compressibility. Therefore the addition of directly compressible adjuvant is mandatory in such cases.

Directly compressible filler should exhibit good flowability and compactibility. Good flowability is necessary to ensure rapid and uniform die filling, where as high compactibility is necessary to produce tablets having sufficient mechanical strength.[11]

Method for tablet preparation:

Direct Compression:

- Best batch obtained by complex formulation equivalent to 2mg of Ondansetron was used for the ODT preparation using direct compression technique.

- Pearlitol was used as a diluent, Polyplasdone XL10 as a superdisintegrant, Aerosil as a Glidant, magnesium Stearate as a lubricant. All the ingredients were accurately weighed and passed through 40 # sieve and mixed with complex. The above powder blend was compressed using rotary tablet machine using 5.49 mm concave punches.[12]

Experimental method

Two types of methods were used for the preparation of Ondansetron hydrochloride Tablet.

Manufacturing procedure

*** Method 1 (For formulation of Placebo tablet)**

1. All the ingredients were weighed individually.
2. Preparation of drug resin complex
   a) Weighed quantity of resin was added in clean beaker containing specified quantities of water with stirring for 15 min.
   b) Ondansetron was not added in the formulation as it is the placebo formulation used for analysis purpose.
   c) Beaker was kept aside for 1 to 2 hr& mother liquor was collected and used for further formulation.
   d) Mix half of the quantity of mannitol (up to 12 batches) and pearlitol (from 13 to 16 batches) was used in the form of slurry.
   e) Dried the slurry in the tray drier for 2-3hr up-to LOD=2-3%
3. Sift the other excipients through # 40 sieves.
4. Sift the dried powder through # 20 mesh to this add above sifted excipients & mix it properly for 3 min.
5. Mix the Magnesium Sterate through # 40 sieve number & add to the mixture & lubricate for 2 min.
6. Compress the blend by using 7/32 SC punch.

***Note: Trial 1 was only for taste comparison hence resin was not added.

****Method 2**

1. All the ingredients were weighed individually.
2. Preparation of drug resin complex
   a) Weighed quantity of resin was added in clean beaker containing specified quantities of water with stirring for 15 min.
   b) Weighed quantity of Ondansetron, sifted through # 40 sieves and was added in step 2A and stirred for 4 to 5 hrs continuously.
   c) Beaker was kept aside for 1 to 2 hr& mother liquor was collected and used for further formulation.
   d) Mix half of the quantity of mannitol (up to 12 batches) and pearlitol (from 13 to 16 batches) was used in the form of slurry.
   e) Dried the slurry in the tray drier for 2-3hr up-to LOD=2-3%
3. Sift the other excipients through # 40 sieves.
4. Sift the dried powder through # 20 mesh to this add above sifted excipients & mix it properly for 3 min.
5. Mix the Magnesium Sterate through # 40 sieve number & add to the mixture & lubricate for 2 min.
6. ompress the blend.

Table IX Tablet formulation for S1, S2, S3, S4, S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, S15, S16 batches[13]

Name of ingredient	Units per tablet	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S-13	S-14	S-15	S-16 Placebo
Complex preparation																	
Ondansetron Hydrochloride	Mg	02.30	02.30	02.30	02.30	02.30	02.30	02.30	02.30	02.30	02.30	02.30	02.30	02.30	02.30	02.30	00.00
Kyron T-134	Mg	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90	06.90

Purified water	Ml	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
Polyplasdone XL10	Mg	02.00			04.00			06.00			07.50			08.00	10.00	08.00	08.00
SSG	Mg		02.00			04.00			06.00			07.50		01.00	01.00	01.00	01.00
Ac-di-Sol	Mg			02.00			04.00			06.00			07.50	-	-	16.44	-
Aspartame	Mg	02.00			04.00	04.00	04.00	05.00	05.00	05.00	05.00	05.00	05.00	05.00	05.00	05.00	05.00
Mannitol	Mg	60.3	60.3	60.3	56.3	56.3	56.3	53.3	53.3	53.3	51.8	51.8	51.8	55.3	72.8	38.36	57.60
Orange Flavor	Mg	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	01.00	01.00	00.75
Magnesium Sterate	Mg	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	00.75	01.00	01.00	00.75
Total Wt.	Mg	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	80.00	100.00	80.00	80.00

EVALUATION OF ONDANSETRON [14]

Evaluation of oral dispersible tablets

Evaluation parameters of tablets mentioned in the pharmacopoeia need to be assessed, but some, which require special concern or need to be modified, are discussed here.

Mechanical Strength:

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

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.

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.

Rapidly Disintegrating Property

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

Wetting time[15]

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.

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.

In-Vitro drug release

Release of the drug *in vitro*, was determined by estimating the dissolution profile.

Dissolution test:

Parameter for dissolution test:

Apparatus : USP 2 (Paddle apparatus)

Revolution per minute : 50 rpm.

Dissolution medium : 0.1 N HCl (900 ml).

Temperature : 37 ± 0.5 ^{0}C.

Dissolution time : 30 min.

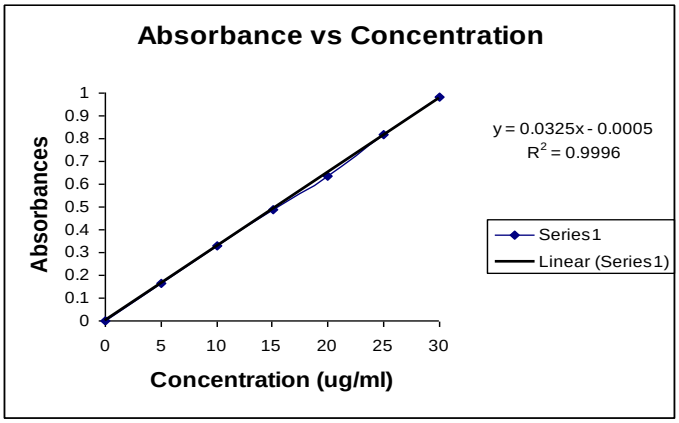
Sample quantity withdrawn : 10 ml.

Sampling interval time : 0, 5, 10, 15, 20, 25, 30 min.

Autosampler for sampling purpose the fresh dissolution medium was replaced every time with the same quantity of the sample. Determination of amount of drug dissolved form tablets was carried by Shimadzu UV Spectrophotometer (1700) at 214 nm. The cumulative percentage drug release was calculated. This test was carried out only for final batch.

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. Oral dispersible tablet equivalent to 50 mg of Ondansetron hydrochloride was held in the mouth for 15seconds by each volunteer, the bitterness level was compared with formulation S1.



RESULTS AND DISCUSSION

ANALYTICAL METHODS

Table X Data and Calibration Curve of Ondansetron hydrochloride in 0.1 N HClsolution at 214 nm

Sr. No.	Concentration (µg/ ml)	*Absorbance at 233 nm AM ± SD
1	0	0.000 ± 0.000
2	5	0.164 ± 0.005
3	10	0.328± 0.001
4	15	0.487 ± 0.002
5	20	0.634 ± 0.004
6	25	0.816 ± 0.002
7	30	0.980 ± 0.002
* Each value is an average of three determinations		

COMPATIBILITY STUDY[15]

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 Ondansetron hydrochloride the 0.1N HCL at 214 nm in the UV spectrophotometer.

Table XI Absorbencies of Solutions in 0.1 N HCL as Medium at 214 nm

Resin (Drug : Resin) (1:3)	Absorbencies of solutions			Interference Yes / No
	Suspension with drug	Placebo	Pure Drug	
Kyron-T134	0.357	0.005	0.352	No

Table XII Evaluation parameters of the Ondansetron hydrochlorideoral dispersible tablets

Sr. No	Evaluation Parameters	Trail 1			Trail 2			Trail 3			Trail 4			Trail 5		
		S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15
1	Hardness (kg/cm^2)	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	3.2
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	0.14
3	Disintegration time (sec)	45	52	50	40	48	45	30	40	35	18	32	25	15	22	18
4	Wetting time (sec)	64	70	68	55	62	58	42	52	47	30	42	35	22	32	29
5	Thickness (mm)	3.58	3.57	3.55	3.52	3.53	3.51	3.48	3.53	3.49	3.24	3.25	3.20	3.16	2.86	3.18
6	Taste	Sight bitter	Sight bitter	Sight bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter

Trail 1: 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 we can increase the concentration of sweeter Aspartame.

Also found that the friability of the tablet was more to minimize this we can increase the Hardness of the tablets.

Trail 2 & Trail 3: By comparing formulation S-4, S-5, S-6, S-7, S-8, S-9 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. Among three the rapid disintegration was seen in the formulation containing Polyplasdone XL-10.

To minimize the disintegration time we can increase the concentration of the above three superdisintegrant.

We also found that the bitterness of the drug was not observed in the above trials.

There was slight increase in the hardness as compare to previous trials but not found satisfactory results for friability test, so we have to improve the hardness in further trials.So we have to improve the hardness, so we can use pearlitol as a diluent.

Trail 4: By comparing formulation S-10, S-11, S-12 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. Among three the rapid disintegration was seen in the formulation containing Polyplasdone XL-10.

By observing the above results we conclude that the among the all three disintegrantsPolyplasdone XL-10

By using the Pearlitol as diluents there is increase in the hardness, decrease in the friability and decrease the disintegration time

The rapid disintegration was seen in the formulation containing Polyplasdone XL-10. To minimize the disintegration time we can increase the concentration of Polyplasdone Xl-10.

Trail 5: By observing the previous trials we increase the concentration of Polyplasdone XL-10 as well as total weight of the tablet, 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 Polyplasdone XL-10. And 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, So we are not suppose to increase the tablet weight.

By comparing the batch no S-13 & S-15 we conclude that by using combination of diluents in the ratio of 30 : 70 Avicel PH 200 : Pearlitol (in batch no S-15) instead of Pearlitol (In batch no S-13) other evolution parameter remains same instead of disintegration time which is slightly increased in the batch no S-15, so S-13 is optimized formulation.

Table XIII Comparison of the disintegrating agent with the disintegration time. (Part I)

Batch No.	**S-1**	**S-2**	**S-3**	**S-4**	**S-5**	**S-6**	**S-7**	**S-8**	**S-9**	**S-10**	**S-11**	**S-12**	**S13**	**S14**	**S15**
Ingredients	**mg**	**Mg**	**mg**	**mg**	**mg**	**mg**	**mg**	**mg**	**mg**	**mg**	**Mg**	**mg**	**mg**	**mg**	**Mg**
Polyplasdone XL10	2			4			6			7.5			08.00	10.00	08.00
SSG		2			4			6			7.5				
Ac- di- Sol			2			4			6			7.5			
Disintegration time (sec)	45	52	50	40	48	45	30	40	35	18	32	25	15	22	18

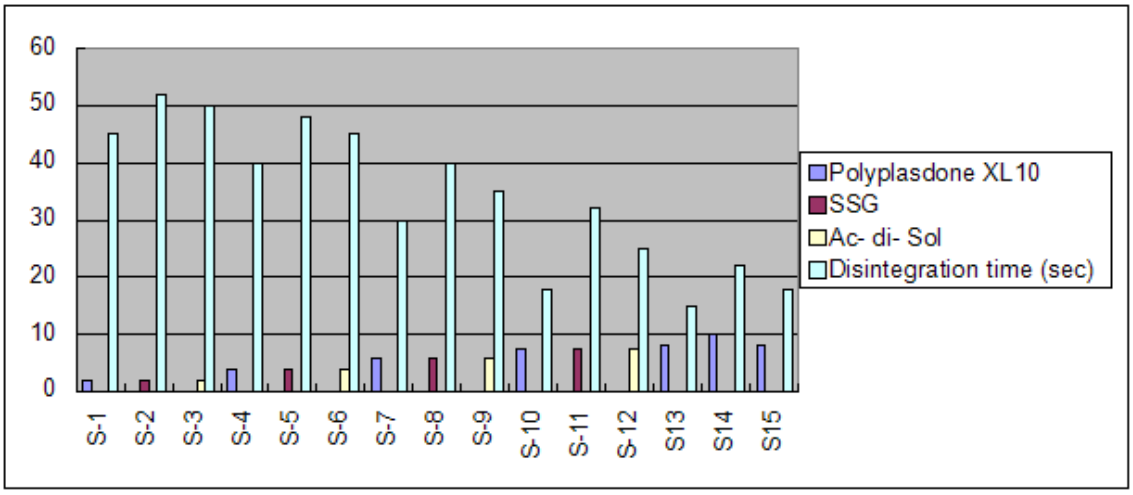


Figure : Effect of Disintegrating agent on Disintegration Time

Table XIV Comparison of concentration of Polyplasdone XL10 with the disintegration time.

Evaluation	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15
Hardness (kg/cm^2)	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	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	0.14
Disintegration time (sec)	45	52	50	40	48	45	30	40	35	18	32	25	15	22	18
Wetting time (sec)	64	70	68	55	62	58	42	52	47	30	42	35	22	32	29
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	3.18
Taste	Sight bitter	Sight bitter	Sight bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter	Not bitter

CONCLUSION

The In vitro disintegration time of all the 15 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.

Table XV Evaluation comparisons of the all batches

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	S14	10	22
7	S15	8	18

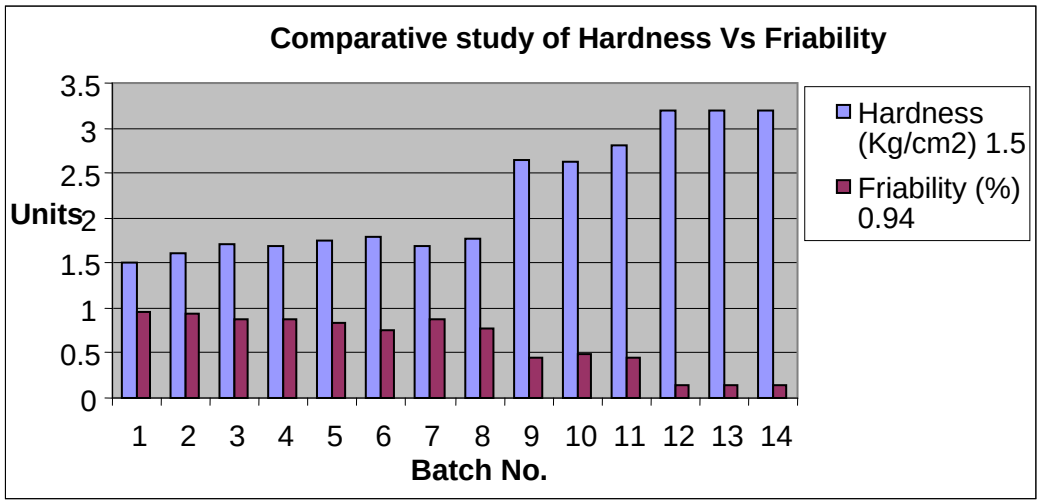


Fig. 1 Comparative study of Hardness Vs Friability

From above graph it was observed that the as there is increase in the Hardness there is decrease in the Friability of the tablet. So Hardness was increased to reduce the Friability and the concentration of the Disintegrating agent was also increases for the rapid disintegration time.

OPTIMIZED FORMULA

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 Ondansetron hydrochloride Oral dispersible tablets using ion exchange resin.

Dissolution Profile of the Prepared Oral Dispersible Tablet

After getting all the parameters satisfactory for S13 dissolution of that trial was studied. Dissolution was carried out up 30 minute using below mentioned parameters and samples were taken after 5, 10, 15, 20, and 30 min.

Dissolution medium = 0.1 N HCL

Dissolution apparatus = USP Type II (paddle)

Temperature of medium = 37.0 ± 0.5^0C

rpm = 50

For S13 dissolution parameters and results of % drug release was shown in Table 14.

Table XVI In vitro Release of Ondansetron from S13

Time of sampling in minutes	***Cumulative % drug release AM ± SD**
0	0
5	87.6
10	92.8
15	95.03
20	97.2
30	99.09
45	100.09
*Each value was an average of six determinations	

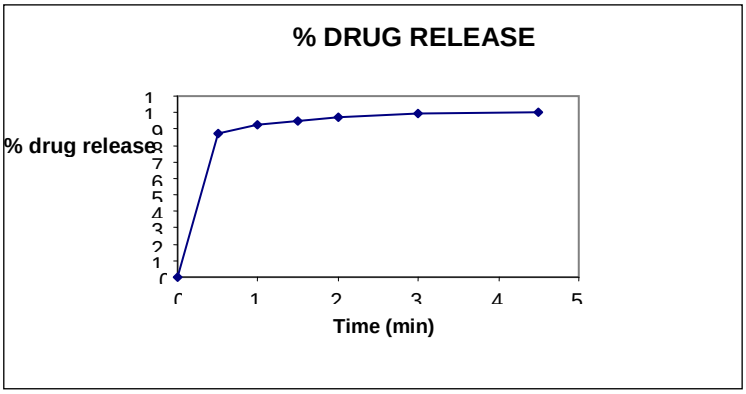


Fig. 2 Percentage Drug Release in vitro release of Ondansetron from S13

Reproducibility of optimized formula:

Batch to batch uniformity is very much essential for obtaining reproducible results. In order to verify this fact, the manufacturing procedure was confirmed by preparing one more batch of the final optimized formulations of oral dispersible tablet. The batch size was 1000 tablets. Results obtained from the Evaluation of the reproducible batch were shown in table 22

Table XVII Evaluation parameters of reproducible batch of Ondansetron hydrochloride Oral dispersible tablet

Sr. No.	Parameters	Units	S17
1	Hardness	Kg/cm2	3.2
2	Friability	% w/w	0.143
3	Disintegration time	Sec	15
4	Wetting time	Sec	22
5	Assay %	%	99.98 %
6	Taste	As per specifications	Not bitter

Accelerated Stability Study

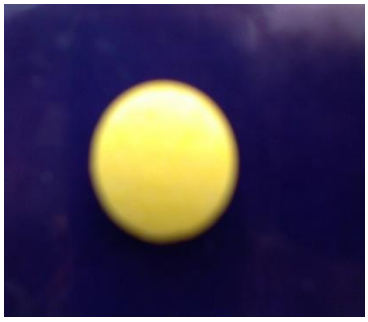
Suspension of S17, S18 were kept for accelerated stability study at 40 $\pm$ 2 ^{o}C and 75 $\pm$ 5% RH for 1 month in stability chamber. After a period of one month, the samples were observed for any change in physical parameters. It was observed that any change in color. It was also noted that suspension was free of any kind of bad odor.

Results obtained from the Evaluation after stability study are shown in table 5.14

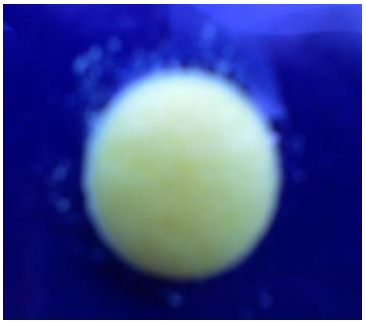
Table XVIII Evaluation parameters obtained after stability study of the Ondansetron hydrochloride Oral dispersible tablet (2 month)

Sr. No	Parameters	Units	S17
1	Hardness	Kg/cm2	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

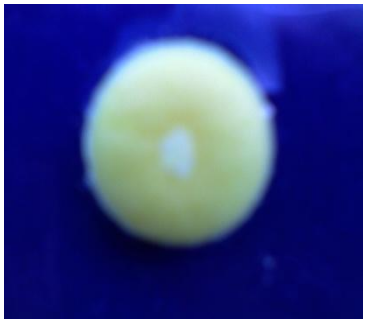
From the results and discussion, several conclusions were drawn and were given in the next chapter "Summary and conclusions".



(At initial time)



(After 4 sec)



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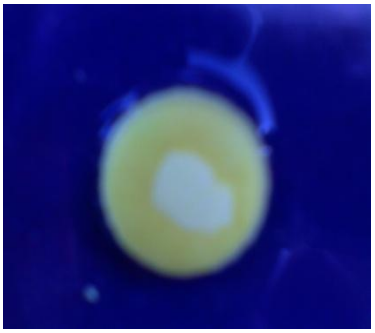

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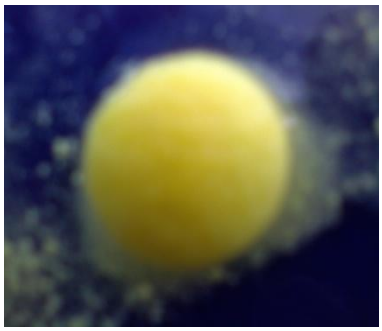

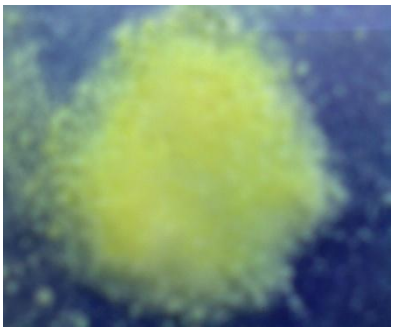

(After 12 sec) **(After 15 sec)**

Fig. 3 Tablet Disintegration photographs of batch B22

SUMMARY

The present study was carried out to prepare R-Ondansetron hydrochloride oral dispersible tablet that can be used in the motion sickness. Using various Superdisintegrants like Polyplasdone XL 10, Ac-Di Sol and SSG in 2.76-10% concentration. Tablets were prepared along with other additives. Ion exchange resin was used for taste masking & direct compression method was used for the preparation of oral dispersible tablets. A total number of 16 formulations were prepared and evaluated.

In all the formulation thickness varies between 3.16 to 3.26mm and hardness of the optimized batch was found to be 3.2 kg/cm^2. No variation in the hardness was found in the optimized batch which clearly indicates that the blending was uniform.

The prepared tablet in the optimized formulation possessed good mechanical strength with sufficient hardness. Friability was less than 1% in the entire batches. The entire tablet from each formulation passed weight variation test, as the % weight variation was within the pharmacopeial limit of ± 7.5 % of the weight. The weight variation in all the formulations was found to be 80 - 83.5 mg which was in the pharmacopeial limits. The percentage drug content of all the formulation was found to be between 99-102.5% of R-Ondansetron hydrochloride.

The in-vitro disintegration time for all the formulations varied from 15-52.5 sec. The rapid disintegration was seen in the formulation containing Polyplasdone XL10 (S13- 15sec). This is due to rapid uptake of the water from the medium, swelling and burst effect. It was also noticed that as the disintegrant concentration was increased from 2.76 % to 10 % the time taken for disintegration was reduced. It was found that the wetting time was rapid in Polyplasdone XL 10

followed by Ac-Di sol. The drug release was found to be more than 90 % after 10 min. stability studies were conducted for the optimized formulation; the tablets were analyzed for the hardness, uniformity of drug content and in-vitro disintegration time at the interval of 10 days till a period of 30 days. The Stability batches showed no significant variations in all the parameters and were stable for a period of 30 days.

In conclusion overall results suggest that Kyron T-134 is suitable for taste masking and Polyplasdone XL 10 showed least disintegration time in the formulation of oral dispersible tablet.

REFERENCES

1. Fast Dissolving Drug Delivery System; www.pharmapedia.com, December 2006
2. Biradar S. S., Bhagavati S. T., Kuppasad I. J.; Fast Dissolving Drug Delivery Systems: A Brief Overview. The Int. J of P'cology.2006; Volume 4 (2).
3. OohmGmbh, Cokg; A new co-polymer coating masking the taste of fast – disintegrating tablets: Innovation in pharmaceutical technology, Drug Delivery and Formulation, 109-111.
4. Amin A. F., Shah T. J., Bhadani M. N. and Patel M. M.; Emerging Trends in the Development of Orally Disintegrating Tablet Technology, www.pharminfo.net, 2005.
5. Kuchekar B.S., Bandan A.C., Mahajan H.S; Fast Dissolving Drug Delivery Systems: An Update, Pharmatimes, 2003, Volume 35: 7-9.
6. Reddy L.H., Ghosh B., Rajneesh; Fast dissolving drug delivery systems: a review of the literature. Ind J Pharm Sci, 1997; Volume: 59 (4):331-336.
7. Glidert R. Banker and Christopher T. Rhodes; Modern Pharmaceutics and the pharmaceutical sciences, 4th addition, Volume 121:329-330.
8. Washington Neena, Washington Clive and Wilson Clive G.; Physiological pharmaceutics, Barrier to Drug Absorption, 2nd Edition by Taylor and Francis 2001, 50-51.
9. Bagul U. S., Bagul N. S., Kulkarni M. S., Dr. Sawant S. D., Gujar K. N., and Bidkar A. A.; Current Status of Tablet Disintegrants: A Review Pharmainfonet, July 2006.
10. Masharu R.C., Sutariya V.B., Sankalia M.G. and Parikh P.P.; Development and Evaluation of Fast-Dissoling Film of Salbutamol Sulfate, Drug Dev and Ind Pharm, 2005; Volume1:25-34.
11. Dandagi P.M., Sreeenivas S.A., Manvi F.V., Patil M.B., Mastiholimath V.S. and Gadad A.P. ; Taste masked ofloxacin mouth disintegrating tablets, Indian Drugs, 2005; Volume 42(1): 52-55.
12. Ishikawa T., Watanabe Y., Utoguchi N., Matsumoto M.; Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter-taste-masked granules by the compression method. ChemPharma Bull (Tokyo); 1999; Volume 47(10):1451-1454.
13. Shimizu T., Sugaya A., Nakano Y., Izutsu D., Mizukami Y.; Formulation study for Lansoprazole fast – disintegrating tablet. III. Design of rapidly disintegrating tablets. Chem. Pharm. Bull, 2003; Volume 51(10): 1121-1127.
14. Gohel, M., Patel, M., Amin, A., Agrwal, R., Dave, R., Bariya, N.; Formulation design and optimization of mouth dissolve tablets of nimesulide using vaccum drying technique, AAPS Pharm. Sci. Tech., 2004; Volume 5(3): 1-6.
15. Desai S.A., Kharede S.V., Petkar K.C., Kuchekar B.S.; Orodispersible tablets of promithazine hydrochloride, Indian. J Pharm. Edu.and Research, 2006; Volume 40(3):172-174. 44. Vijay K.S.G, Mishra D.N.; Rapidly disintegrating oral tablets of meloxicam, Indian Drugs, 2006; Volume 43(2): 117-121.