



Design, Characterization and Evaluation of Quick Dissolving Matrix BARETab® ODT Tablet In Ondansetron Formulation

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ABSTRACT

The oral dissolving tablets is defined as one, which has drug in it and when placed on tongue dissolves completely within a limited span of time, without additional requirement of water. Drug is released, dispersed in the saliva and swallowed and subsequently absorbed in the gastrointestinal tract (GIT). To achieve quick disintegration in oral solid dosage forms, it's important to have high porosity in the tablets. This allows faster penetration of water and thus accelerates the disintegration. Oral dissolving tablets are the preferred means for patients with oral disorders and patients with dysphagia. It could also be friendly, with geriatric, pediatric and mentally challenged people. Oral dissolving tablet formulation are made by many techniques but in this study, we have made BARETab® ODT quick dissolving matrix using spray drier, characterized by Fourier-transform infrared spectroscopy and melting point, morphology studied by scanning electron microscope, evaluation done with physicochemical test such as bulk density, flowability, average particle size distribution, compressibility index, water content and residue on ignition. Ondansetron oral dissolving tablet was thereafter made using with BARETab® ODT quick dissolving matrix. Ondansetron oral dissolving tablet was evaluated by *in-vitro* testing such as physical evaluation, weight uniformity, hardness, friability, disintegration and drug released profile. BARETab® ODT quick dissolving matrix have very good morphology, every particle contains binder, filler, glidant, sweetener and super disintegrant. It has outstanding physiochemical properties which helped to deliver good quality Ondansetron tablet. It has less friability, satisfactory hardness and quick disintegration time.

Keywords: Orally Disintegrating Tablets, Fourier-transform infrared spectroscopy, melting point, Scanning electron microscopic characteristics, *In-Vitro* Disintegration Time

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INTRODUCTION

The oral route of administration is most widely and favourable route of drug delivery system because of its convenience of self-administration, compactness¹. Oral dosage forms are easy to manufacture and convenient in handling. However, the most evident drawback of the oral dosage forms like tablets and capsules is difficulty in swallowing². It is an estimation, approximately 50% of the population is affected by this problem worldwide, leading to patient's incompliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water³. The problem can be resolved by the creation of Orally Disintegrating Tablets (ODTs). It is also known as quick dissolving tablet, fast dissolving tablet⁴. ODTs rapidly disintegrate in the mouth without chewing upon oral administration and without the need for water, unlike other drug delivery systems and conventional oral solid immediate-release dosage form. It has significant impact on the patient compliance⁵. Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty in swallowing⁶. It has been reported common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients, psychiatric patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population⁷.

Formulation scientist and tablet manufacturers faced some critical problems during ODT manufacturing such as

Dispersed in mouth within seconds:

This is one among the most critical points in an ODT formulation. It directly co-relates to the Tablet strength and is a function of the tableting force. What is essential is a delicate balance between the Tablet hardness and its disintegrating time^{8,9}.

Be portable, without concern for any friability:

This is a factor of the tablet hardness and is critical in ensuring that the dosage quantity remains intact^{10,11}.

Cost Effective, both at production level and at administration level:

ODT should be formulated with technologies, which are acceptable in terms of cost and scalability. No use of having a superior technology, which cannot be put to good patient use, due to higher costs¹².

Good mouth feel and taste masking:

Most drugs are bitter in taste. Taste masking and good mouth feel become essential traits in an ODT to be easily accepted among the kids and elders alike. Many techniques are used in taste masking like formulation of pellets by extrusion, mass extrusion or spheronization, polymer used in coating of drug, spray drying the drug in a dispersion of polymer and microencapsulation of drug etc¹³.

No leftover residue in mouth after administration:

The ODT should generate small to very small particles in the mouth and these small particles flow into the GI Tract, thus leaving no residue in the mouth. The good mouth feel is enhanced by flavour and small particles. Many orally disintegrating tablet formulations are available in the market¹⁴.

Numerous technologies have been developed for preparation of ODT drug delivery system like as freeze and spray drying, moulding, phase transition process, melt granulation, sublimation, mass extrusion, cotton candy process and direct compression. Among the above, spray drying and direct compression are the most common and cost-effective techniques used to make ODT¹⁵. Whereas spray drying is the fastest way to dry a solution to powder form, with very high porosity. The high porosity is developed due to rapid drying in a co-current or counter-current air flow¹⁶. Spray drying is based on particular support matrix, which is formed by co processing an aqueous solution containing the product and the medium. The ODT made by this technology disintegrate within a time frame of 20-30 seconds¹⁷. USFDA guidelines suggest 30 seconds as the disintegration time (*in-vitro*), whereas European Pharmacopoeia indicates disintegration time of less than 3 minutes. Spray drying powder is commonly used for direct compression formulation, because of its superior flowability. Direct Compression is the most common and economic form of making the ODT formulations^{18,19}.

The present study main aim is to design, characterize and evaluate ODT quick dissolving matrix. Characterization study has been done by FTIR and melting point test and evaluation study done by Morphology and physicochemical test. After that Ondansetron direct compressible ODT tablet formulation were made using BARETab[®] ODT quick dissolving matrix and evaluated *in-vitro* parameters like as tablet weight uniformity, hardness, friability, *in-vitro* disintegration time and Ondansetron released profile by dissolution test²⁰.

MATERIALS AND METHOD:

Material:

HiCel™ filler, binder, glidant and HiLose™ Super disintegrant manufactured at Sigachi Industries Ltd. in Dahej, Gujarat, Sweetener are purchased from Gujarat, India. Ondansetron purchased from Mercury Industries Ankleshwar, Gujarat (India) and magnesium stearate from Sunshine private limited, India and other chemicals used AR grades²¹.

METHOD:

Preparation of BARETab® ODT

It is a combination of binder/filler, glidant, sweetener and super disintegrant and by using co-process technology. Co-processed make product with innovative properties. BARETab® ODT quick dissolving matrix design shown in figure 1²².

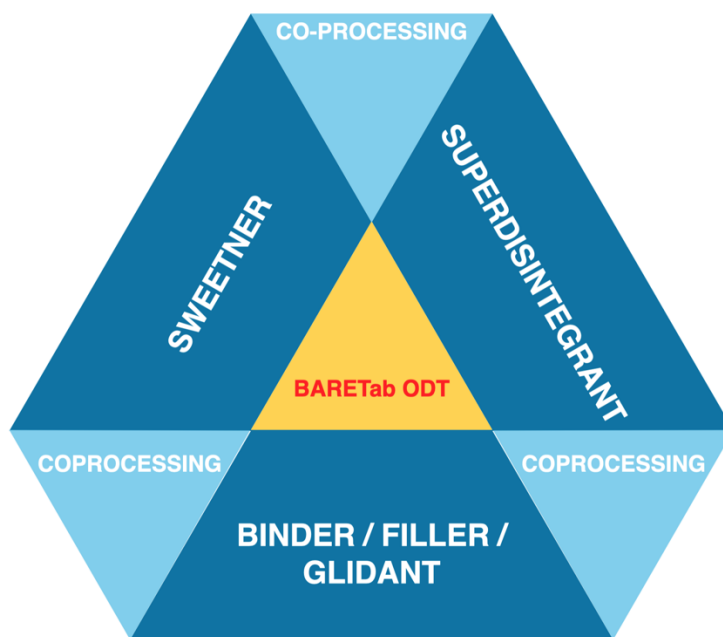


Figure 1: BARETab® ODT Design

Characterization of BARETab® ODT

Fourier-transform infrared spectroscopy

Make a mixer of BARETab® ODT and KBR in 3:1 ratio and make a homogenous mixer in mortar and pestle. Take sample in IR sample cup and placed the sample cup into sample compartment in IR, run the sample in IR;²³.

Melting Point

Take BARETab® ODT sample into a glass capillary, and place the capillary in melting point apparatus (Viggo) and observed the sample, when sample starts to melt, note the temperature²⁴.

Morphological study

Scanning electron Microscopic

Take approximate 1 to 2 milligram of sample and mounted on double sided taped on aluminum stabs. Placed stabs into sample compartment into microscope. Micrographs were taken at appropriate magnification and particles surface visualization detailed analyzed by scanning electron microscope at SICART university, Anand, Gujarat (India)²⁵.

Physicochemical Evaluation

Untapped density

Untapped bulk density analysed by Scott volumeter. Weight empty cup, place it under the chute and 10g of each sample is poured into funnel through volumeter, at a rate suitable to prevent clogging, until the cup overflows. Level the excess powder and weight the filled cup²⁵

$$\text{Untapped density (g/ml)} = \frac{\text{Sample Mass(g)}}{\text{Sample Volume(ml)}} \quad (\text{i})$$

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of final blend powder on a mechanical tapper apparatus (Model No. ETD 1020) which is operated at fixed number of tapped (500) until powder bed reached a minimum volume.

$$\text{Tapped density (g/ml)} = \frac{\text{Sample Mass(g)}}{\text{Sample Volume(ml)}} \quad (\text{ii})$$

Hausner's ratio

It is indirect index for ease of measuring powder flow. Lower Hausner's ratio (<1.25) indicates good flow property.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Untapped density}} \quad (\text{iii})$$

Compressibility

Compressibility known as carr's index. Based on the apparent bulk density and the tapped density. Percentage compressibility is calculated by below formula

$$\text{Compressibility (\%)} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \quad (\text{iv})$$

Angle of repose

Angle of repose is the angle obtained between freestanding surface of powder heap and the horizontal plane. It was determined by using the fixed funnel method. 20 gm of final blend powder was poured into funnel keeping the orifice of the funnel blocked by thumb. When powder was cleared from funnel then the peak height was measured²⁶.

Particle size distribution analysis

Particle size was analysed at Cubic Analytical Solution, Ankleshwar, Gujarat using lesser diffraction (Malvern instrument, Mastersizer v3.63).

Water content

Water content analysed by using Karl Fischer (Viggo). Take 0.15 gm BARETab ODT sample and transfer in to the titration vessel containing previously neutralized methanol with Karl Fischer reagent. Dissolve the sample for about one minute and titrate the sample. Calculate water content using below formula²⁷

$$\text{Percentage of water content (W/V)} = \frac{\text{Vol. of KF reagent consumed} \times \text{KF Factor} \left(\frac{\text{mg}}{\text{ml}}\right) \times 100}{\text{Sample weight (gm)} \times 1000} \quad (\text{v})$$

Residue on ignition

Heat a cleaned silica crucible to redness for 15 minutes in muffle furnace at 600 °C. ±50°C and allow to cool it in desiccators' and take the weight. Take 1 to 2 grams of sample into tarred crucible. Moisten the sample with a small amount of sulphuric acid. Heat it gently until the material is completely charred at a temperature as low as practicable, and ignite it at 600 °C. ±50°C for 3 hrs. Cool it in desiccators and weigh. Calculate the percentage of residue on ignition using below formula²⁷

$$\text{Residue on Ignition (\%)} = \frac{\text{Final weight (gm)} - \text{Tare weight (gm)}}{\text{Sample weight (gm)}} \times 100 \quad (\text{vi})$$

Ondansetron blend Preparation

Weigh accurately BARETab® ODT and Ondansetron using digital weighing balance (Mettler Toledo, ME303/A04), transfer both material into powder blender (Reva Pharma machinery, TRMIX-20) and blend the material for 5 minutes, after that added magnesium stearate for lubrication, lubricated the material for 3 minutes. Ondansetron blend is ready for tableting

Table 1: Ondansetron 4 mg tablet manufacturing details

Ingredient Name	Quantity (W/W %)
Ondansetron	16.67
BARETab® ODT	82.83
Magnesium stearate	0.50

Ondansetron Tablet compression

120 mg tablets were manufactured by using 10 station Proton Mini Press (MINI PRESS 10 "D") using D tooling dies and punches with 10 mm diameter, process of tableting shown in figure 2 .

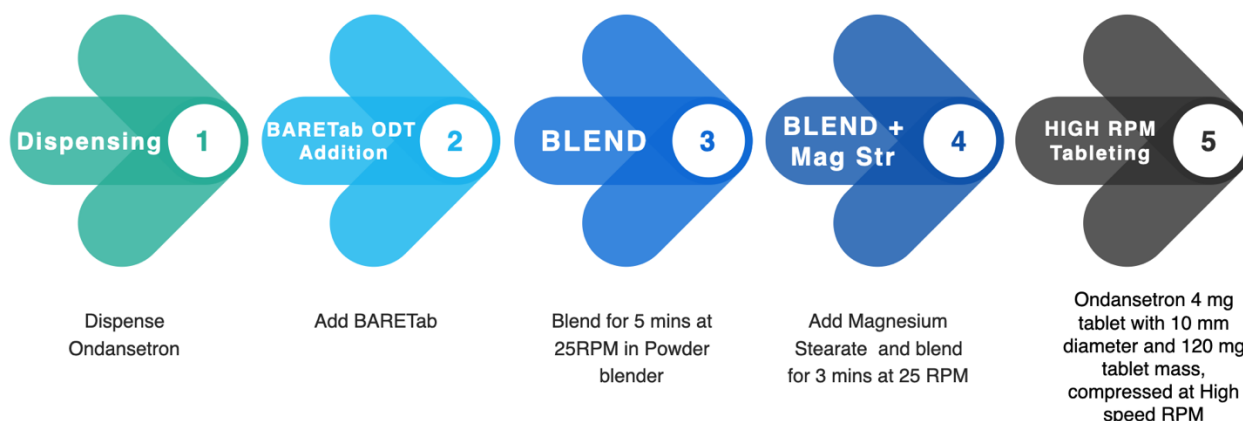


Figure 2: Ondansetron tablet preparation flow chart

Physical appearance

The general appearance Ondansetron tablet was studied visually in shape, colour, texture.

Weight variation

Weight variation test was performed by weighing 10 tablets individually using four-digit digital weighing balance (Mettler Toledo, MS304S/A01) and calculate the average weight²⁸.

Hardness

Randomly 10 tablets were selected and analysed by electronic digital hardness test machine (TH1050 M). Single tablet was placed between two anvils, force was applied to the anvils, and the tensile strength that was just required to break the tablet was recorded. Finally, the reading was noted in Newton²⁸.

Friability

10 tablets were taken and weighed by using electronic digital balance which was considered as the initial weight. All the tablets were placed in the drum of friability tester (FT1020) and allowed rotate 100 times at 25 rpm. After 100 revolutions, 10 tablets were removed and re-weighed which was considered as the final weight. The percentage friability was calculated by below mention formula. As per USP, the tablets should not lose more than 1% of their total weight²⁹.

$$\text{Percentage Friability} = \frac{\text{Initial weight}(\text{gm}) - \text{Final weight}(\text{gm})}{\text{Initial weight}(\text{gm})} \times 100 \quad (\text{vii})$$

In vitro disintegration time

Disintegration time of Ondansetron tablets were analysed by using tablet disintegration tester (Lab India, DT 1000) at $37 \pm 2^\circ\text{C}$ in 800 ml Demineralized water. Six tablets were taken and one tablet was introduced in each tube, disk was placed and basket was positioned in one litre beaker

containing $37\pm 2^\circ\text{C}$ temperature of water. Note down tablet breaking time. Note the time when the tablet broke down into smaller particles³¹.

***In vitro* dissolution profile**

Ondansetron released profile was analysed by using dissolution test apparatus (Lab India, DS 8000) and followed by USP method, apparatus type 2 (paddle), speed 50 rpm in 500 ml distilled water at $37\pm 2^\circ\text{C}$ medium temperature. Randomly select 6 tablets and one tablet introduced in each beaker of dissolution. 5 ml Sample were withdrawal from each beaker at different time intervals 5, 10, 15, 20, minutes. Samples filter with Whatman filter paper (42). Take 1 ml sample from the beaker and transfer into 10 ml of volumetric flask and make up the volume up to the mark. Repeat the same procedure for all remaining 5 tablets containing samples. Take sample and standard absorbance using UV Spectrophotometer (Shimadzu model no-1900) at $\lambda=310\text{nm}$ wavelength. Calculate ondansetron released profile with the help of below mention formula³²

Amount of ondansetron released (mg) =

$$\frac{\text{Conc. of released drug} \times \text{dilution factor} \times \text{Volume of dissolution medium}}{1000} \quad (\text{viii})$$

$$\text{Ondansetron released (\%)} = \frac{\text{Amount of ondansetron released}}{\text{Dose of ondansetron}} \times 100 \quad (\text{ix})$$

RESULTS AND DISCUSSION:

Characterization of BARETab[®] ODT

Fourier-transform infrared spectroscopy

Sweetener has properly coated on binder, filler, glidant and super-disintegrate and binder, glidant and super disintegrate peaks have shifted. BARETab ODT FT-IR graph shown in figure 3.

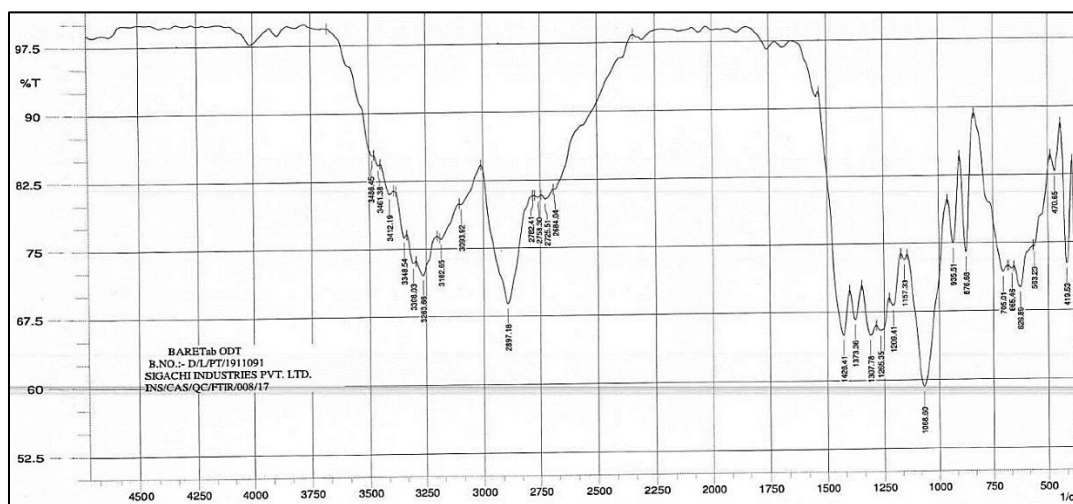


Figure 3: FTIR graph of BARETab[®] ODT

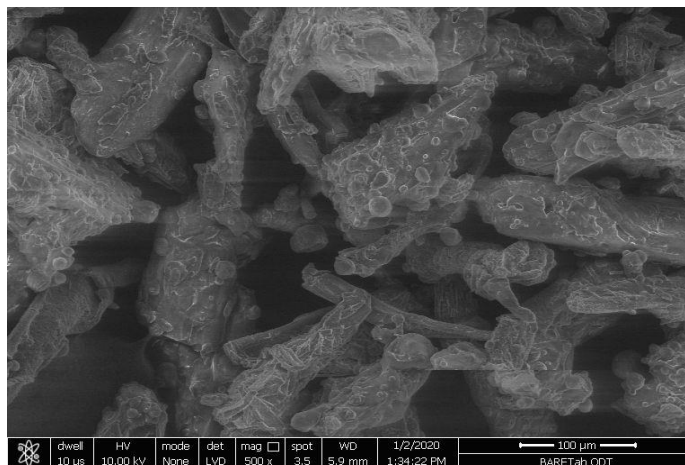
Melting point

BARETab[®] ODT started to melt between 162°C to 168°C.

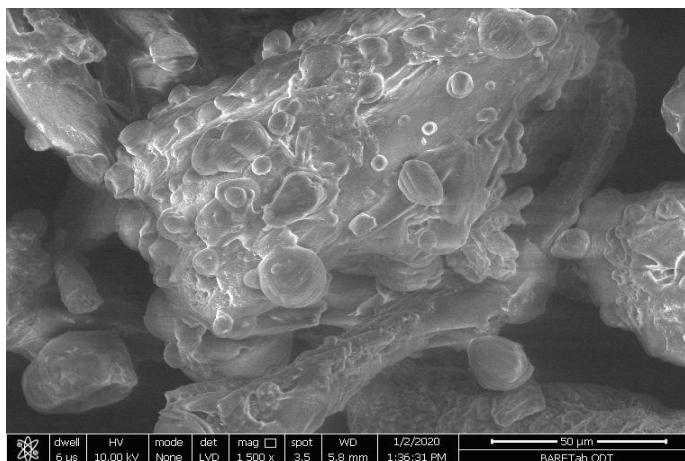
Morphological study

Scanning electron Microscopic

BARETab[®] ODT single particle contains binder, filler, glidant, sweetener and disintegrant. Which gives homogenous mixing. SEM images shown in figure 4 binder, filler, glidant and disintegrant coated on every particles of mannitol. Which helped to made powder free flowing and good compressibility.



(a)



(b)

Figure 4 (a) & (b): Scanning electron microscopic images of BARETab[®] ODT

Physicochemical evaluation

Physicochemical parameters are very important for final products, physical parameters help during tablet manufacturing, it controlled tablet rejection and helps to tablet machine run smoothly with high speed. Whereas chemical properties should be in limit, it controlled final

product impurities. BARETab[®] ODT untapped density 0.41.g/cc and tapped density 0.57 g/cc. higher bulk density improved flowability. Hausner's ratio and compressibility index are considered as indirect measurements of powder flowability, The Hausner's ratio is indicative of inter particle friction, while the Compressibility index shows the aptitude of a material to diminish in volume. As the values of these indices increase, the flow of the powder decrease. BARETab[®] ODT has 1.3 Hausner's ratio and 28.4 compr4essibility index. The flow properties of powders are essential in determining the suitability of a material as a direct compression excipient. Increasing value is an indication of decreasing flowability. It has excellent flowability which is represented by angle of repose and it has 33° angle of repose. Particle size play a very important role in direct compression formulation, it helps to carry equal API quantity in to the all tablets. BARETab[®] ODT average particle size is 98 µm. Water content analysed by Karl Fischer and found 1.0%. Less water content prevents micro and helps to maintain stability. Residue on ignition analysed by muffle furnace and found 0.90%.

Tablet compression

Ondansetron tablet punched at 320 KN released pressured at high speed rpm, with Ondansetron machine run smoothly and gave more output.

Ondansetron Tablet Evaluation

Tablets are elongated shape and white color, odourless, sweet in taste and good mouth feel with smooth surface and free from all defects like capping, sticking, lamination and weight variation. All tablets have weight uniformity and tablet hardness has 320 N. There is no loss have observed during friability test and found very less disintegration time 6.5 seconds whereas ODT disintegration time limit is below 30 seconds. Ondansetron released profile mentioned in figure: 5, wherein more than 80% drug released in 15 minutes.

Table 2: Orally disintegrating Ondansetron Tablet evaluation

Characteristics	Result
Tablet appearance	Elongated, white color tablet
Taste	Sweet in taste with good mouth feel
Average tablet weight (mg)	120.0 mg
Average hardness (N)	320.0 N
Friability (%)	00.0%
Average disintegration time (Sec)	6.5 seconds

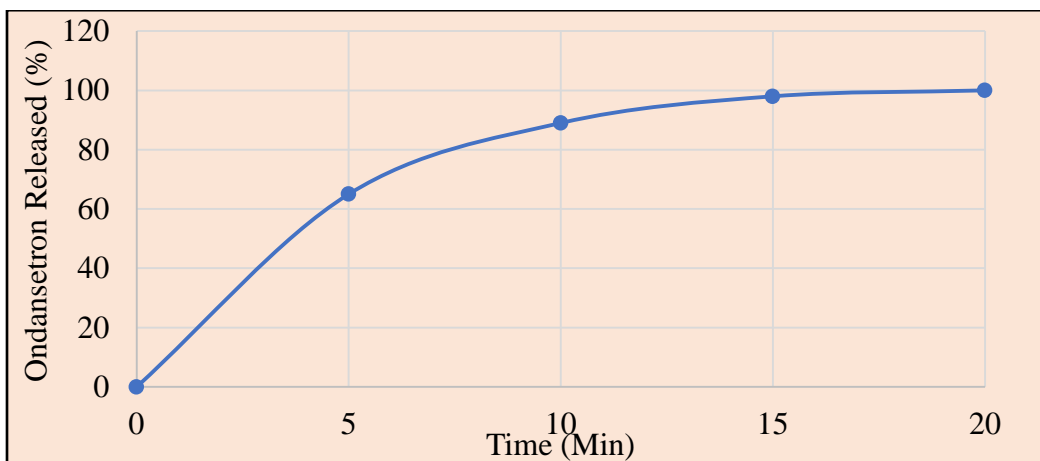


Figure 5: Ondansetron released profile

CONCLUSION:

This study concluded that BARETab[®] ODT quick dissolving matrix has multifunctional premix for ODT tablet, its each and every particle contains binder, filler, glidant, sweetener and super-disintegrant, which is proved by SEM and FTIR test, Super-disintegrant, binder, filler and glidant peaks have shifted due to coating. All material is coated to each other. It has outstanding flowability which helped during tablet manufacturing. Ondansetron tablets have good tablet taste with excellent mouth feel and have good tablet hardness and very less disintegration time. Its tablet disintegrated in 6.5 seconds and ondansetron amount more than 80% released in 10 minutes.

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CONFLICTS OF INTERESTS:

The authors state and confirm no conflict of interests. No direct funding was received for this study.

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