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DEVELOPMENT AND EVALUATION OF ORAL FAST DISINTEGRATION TABLET OF ONDANSETRON HYDROCHLORIDE

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ABSTRACT
Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop FDTs with improved patient compliance and convenience. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. FDTs or orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. This review describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity. In particular, this review describes in detail FDT technologies based on lyophilization, molding, sublimation, and compaction, as well as approaches to enhancing the FDT properties, such as spray drying and use of disintegrants. In addition, taste-masking technologies, experimental measurements of disintegration times, and dissolution are also discussed.

KEYWORDS: Fast dissolving tablets, freeze drying, spray drying, taste masking.

INTRODUCTION

Fast Disintegrating Tablets

United States Food and drug administration defined fast disintegrating tablet as "a solid dosage form containing medicinal substance or active ingredient which disintegrate fast usually within a few seconds when placed upon the tongue." FDTs differ from traditional tablets as they are designed to be dissolved on the tongue rather than swallowed whole. Fast disintegrating tablets are also known as mouth-disintegrating tablets, melt-in mouth tablets, Orodispersible tablets, porous tablets, quick dissolving tablets, fast dissolving tablets.[1]

According to US Food and Drug Administration 2008 publications of guidance are:

1. FDTs should have an In vitro disintegrating time of approximately 30 sec or less.
2. Generally, the FDT tablet weight should not exceed 500 mg, although the combine influence of stable weight, size and component solubility all factor into the acceptability of an ODT for both patients and regulators.

Recent advances in novel drug delivery system aim to enhance safety and toxicity of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach led to development of fast dissolving tablets. Fast dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for paediatric and geriatric patient. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients who experience difficulties in swallowing traditional oral solid-dosage forms. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds.[2]

Fast dissolving tablets are a perfect fit for all of these patients. The FDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet. All FDTs approved by the Food and Drug Administration are classified as orally disintegrating tablets.

Recently the European Pharmacopoeia adopted the term "Orodispersible Tablet" as a tablet that is to be placed in oral cavity where it disperse rapidly before swallowing.

The major advantage of FDT formulation is that it combines the advantage of both liquid and conventional tablet formulation cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets Drug delivery systems are a strategic tool for expanding markets, extending product life cycles and generating opportunities.[3]

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipment choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors.[4]

Sensitivity to environmental conditions FDTs should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in FDTs are meant to dissolve in minimum quantity of water.[4]

Effectiveness factor Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Furthermore, safety profiles may be improves for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pre gastric segments of GIT.[5]

Mouth feel FDTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the FDTs should be as small as possible. Moreover addition of flavors and cooling agents like menthol improve the mouth feel. Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and oesophagus.[6]

Mechanism Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The solubility of a drug mainly depends on physiochemical properties of the drug. The rate of drug dissolution is greatly influenced by disintegration of the tablet Disintegrates are important excipients of the tablet formulation, they are always added to tablet to induce breakup of tablet when they are comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrates. The objectives behind addition of disintegrates are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together.[7-8]

Pharmacokinetics In this consideration, study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution while RDT is rapidly disintegrates in oral cavity and dissolution is rapid. Due to disintegration of RDT in mouth absorption in started from mouth, pharynx and esophagus. Some factors like age, GI pH, and blood flow through GI are taken into consideration, because elders may be considered as separate unique Medicare population. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. In geriatric patients, decrease in body mass and total body water result in decreased volume of distribution of water-soluble drugs and increased volume of distribution of lipid soluble drugs. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Super disintegrants a disintegrant is an excipient, which is added to a tablet blend to aid in the breakup of the compacted mass when it is put into a fluid environment. Recently new materials termed as superdisintegrant have been developed to improve the disintegration processes. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Now demand for faster disintegrating formulation is increased. It desires to formulate Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency. The mucilage of *Plantago ovata* is a recent innovation for its superdisintegration property when compared with Crospovidone. It shows faster disintegration time than the superdisintegrant Crosspovidone.[9]

Croscarmellose sodium is modified cellulose which described as a cross-linked polymer of carboxy methyl

cellulose (CMC). 3% w/w of this polymer is used in tablets prepared by a wet granulation process. High swelling capacity, effective at low concentration (0.5-2.0) and is used in tablets preparation by using direct compression. The dissolution rate of croscarmellose sodium is higher than that of sodium starch glycolate.[10-11]

Cyclodextrin Cyclodextrins (sometimes called cycloamyloses) are a family of compounds made up of sugar molecules bound together in a ring (cyclic oligosaccharides).

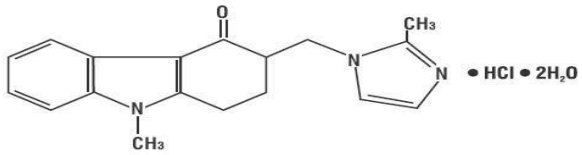
Cyclodextrins are produced from starch by means of enzymatic conversion. They are used in food, pharmaceutical, drug delivery, and chemical industries, as well as agriculture and environmental engineering.

Cyclodextrin molecules are cyclic oligosaccharides made up of six to twelve α-D-glucopyranos monomers, which are connected at 1 and 4 carbon atoms. Cyclodextrins with six to eight α-D-glucopyranose units are denoted as α-, β- and γ-Cyclodextrins respectively. Typical cyclodextrins contain a number of glucose monomers ranging from six to eight units in a ring, creating a cone shape:

- α -cyclodextrin: 6-membered sugar ring molecule
- β -cyclodextrin: 7-membered sugar ring molecule
- γ -cyclodextrin: 8-membered sugar ring molecule

ONDANSETRON HCL

Structure



Chemical name: 1,2, 3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)] -4Hcarbazol-4-one.

Among these various types of cyclodextrins, α-cyclodextrin is not suitable for many drugs and γ-cyclodextrin is expensive. B-cyclodextrin is widely used because it is readily available, and its cavity size is suitable for a wide range of guest molecules. In general, the special characteristic of cyclodextrins is the ability to form an inclusion complex with various organic molecules through host-guest interaction with the interior cavity that provides hydrophobic environment to trap a polar pollutant. The inclusion complex of these host–guest systems occurs through various interactions, such as hydrogen bonding, Vander Waals interaction, hydrophobic interactions and also electrostatic attraction, where the described types of bonding would alter the photochemical and photophysical properties of the guest molecules. Thus, the physical, chemical and biochemical properties of guest molecules will be modified and the application criteria of those guest molecules also can be improved.[12-14]

MATERIALS

Ondansetron Was received as gift sample from Shri swami Samarth Ayurvedic Pharmacy Jalgaon, Crospovidone Research Lab Fine Chem Industries, Mumbai, Crosscarmellose sodium Research Lab Fine Chem Industries, Mumbai, Xanthan gum SD Fine Chem. Ltd, Mumbai, Microcrystalline cellulose Research Lab Fine Chem Industries, Mumbai, Beta cyclodextrin Research Lab Fine Chem Industries, Mumbai, Magnesium stearate Research Lab Fine Chem Industries, Mumbai, Talc Research Lab Fine Chem Industries, Mumai, Mannitol Research Lab Fine Chem Industries, Mumbai, Pot. Hydrogenpthalate Research Lab Fine Chem Industries, Mumbai, Pot. dihydrogen phosphate Research Lab Fine Chem Industries, Mumbai, Sodium hydroxide Research Lab Fine Chem Industries, Mumbai, Flavor Research Lab Fine Chem Industries, Mumbai.All other chemicals and reagents that were of analytical grade were used.

METHOD

Experimental work was divided into three parts i.e.

1. Preformulation study.
2. Formulation of fast dissolving tablet of Ondansetron HCl
3. Evaluation of fast dissolving tablets.

PREFORMULATION STUDY

Identification and characterization of Ondansetron HCl

Determination of Melting point: The melting point of the drug was determined using capillary tube. One end of the capillary tube was sealed. The sample was filled and placed in the melting point apparatus. The melting point of the drug was noted and the obtained observed value was compared with the literaturevalue.[15]

Calibration Curve in 6.8 Phosphate Buffer: Standard calibration curve for the pure drug, Ondansetron was constructed in 6.8 Buffer. The standard solution was prepared by adding 100 mg drug in 100 ml buffer. From this, withdraw 10 ml in 100 ml buffer to prepare stock solution. From this stock solution, serial dilutions were performed to prepare 2- 10 µg/ml of drug concentration using same buffer solution. All the samples were analysed by UV spectrophotometer by measuring the absorbance at 310nm. A calibration plot was obtained by linear regression.

Preparation of 6.8 Phosphate Buffer: Place 50.0 ml of 0.2 M potassium dihydrogen phosphate in a 200-ml volumetric flask, add the 22.4 ml of 0.2 M sodium hydroxide and then add water to volume.

Preparation of Potassium Di hydrogen Phosphate, 0.2 M: Dissolve 27.218g of potassium di hydrogen phosphate in water & dilute with water to 1000ml.

Preparation of Sodium Hydroxide, 0.2 M: Dissolve 8 gm Sodium Hydroxide in water to 1000 ml.[16]

Compatibility Study of Drug and Excipients

It is very important parameter to study compatibility of drug and polymers under the experimental condition before the formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental condition and affected the shelf life of product. This is confirmed by Infrared light absorption scanning spectroscopy, Drug Content and Solubility Study.

FTIR spectrum: In FTIR absorption spectrum sample was prepared by mixing the drug with KBr uniformly by dispersion technique and filled in to the die cavity of sample holder and an IR spectrum was recorded using FTIR spectrometer over the range of 400 to 4000 cm^{-1} at a resolution of 2 cm^{-1}[17-20]

D.S.C: The DSC, test involves heating up a milligram-sized sample of the material under investigation, and by detecting and measuring heat evolution or heat consumption by the sample, examining and quantifying the exothermic or endothermic reactions that occur while that sample is slowly heated up.[21]

Preparation of Drug and BCD Complex by Kneading Method: A mixture of Ondansetron HCl and Betacyclodextrin was ground in a glass container and a minimum amount of water was added. The mixture was kneading for 5 min and dried at 60°C in the vacuum oven. After drying inclusion complex of Ondansetron HCl and β-cyclodextrin was obtained.[22-25]

Characterization of Inclusion Complex and Reference Mixture

FTIR studies: FTIR absorption spectrum of Drug and BCD complex was recorded by KBr dispersion technique. Dry sample of drug and Potassium Bromide was mixed uniformly and filled in to the die cavity of sample holder and an IR spectrum was recorded using IR spectrometer over the range of 400 to 4000 cm^{-1} at a resolution of 2 cm^{-1}.[22-26]

UV spectroscopic study: Complex formation between Ondansetron and CD was studied by the UV spectroscopic method. 4 mg amounts of Ondansetron was weighed accurately and dissolved in 100 ml of distilled water, diluted suitably and spectra of drug recorded at 310 nm. The same method was used only Ondansetron - CD complex equivalent to 12 mg of Ondansetron was weighed accurately and dissolved in 100 ml of distilled water, diluted suitably and spectra of complexes recorded at 310 nm. The change in the absorbance of drug in the complexes was recorded.[22-26]

Drug Content: Inclusion complex equivalent to 4 mg of Ondansetron was weighed accurately and dissolved in a suitable quantity of phosphate buffer pH 6.8. The solutions were filtered and drug content was determined at 310 nm by UV spectrophotometer after suitable dilution.[26]

In-vitro dissolution studies: Drug release studies were performed in triplicate at 37 ± 0.5 ^{0}C employing USP apparatus II at 75 rpm. The dissolution study was carried out in two dissolution media (Phosphate buffer of pH 6.8 and double distilled water). Dissolution studies were performed on pure drug (4mg) and the complexes containing an equivalent amount of the drug. Aliquots of the periodically withdrawn samples (1ml) were analyzed spectrophotometrically at 310 nm, and replaced.

Preformulation Study of Drug-Bcd Complex and Excipients

The quality of tablet, once formulated by rule, is generally detected by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested are as follows;

Angle of repose: The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. In which 4 gm powder blend was taken. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula;

tan = h/r. Where; θ = Angle of repose, h = Height of the cone, r= Radius of the cone base

Table 1: Effect of Angle of repose on Flow property.

Angle of repose (θ)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density: Density is defined as weight per unit volume. Bulk density, ρ_0, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm^3. The sample powder was 4 gm accurately weighed, previously been passed through standard sieve no. 60 is carefully introduced in to the 25 ml graduated cylinder. Bulk density of each formulation was then obtained by dividing the weight of sample in gm by the final bulk volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation;

$$\mathbf{P_0 = M / V_p.}$$

Where; ρ_0 = Bulk Density, M = Weight of sample in gm. V_p = Final volume of blend.

Tapped Density: Tapped density was obtained by dividing the mass of powder by the tapped volume in cm^3. The sample powder 4 gm was accurately weighed, previously been passed through standard sieve no.60 is carefully introduced in to the 25 ml graduated cylinder. Tapped density of each formulation was then obtained by

dividing the weight of sample in gm by the final tapped volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation;

Tapped density (ρ_t) = M / V_P,

Where, ρ_t = Tapped density, M = Weight of sample in gm., V_P= Final volume of blend in cm^3 after tapped.

Carr's Index: An indirect method of measuring powder flow from bulk density was developed by Carr's. The percent compressibility of a powder was a direct measure of the potential arch or bridge strength and stability.

% Compressibility = (Tapped density-Bulk density)/ Tapped density x 100

Hausner's Ratio: Hausner's ratio is defined as a ratio of tapped density to bulk density. It is a major of relative importance of interparticulate interaction. Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula[27-31]

Hausner's Ratio = Bulk density/ Tapped density

Table 2: Effect of Carr's Idex an d Hausner's Ratio on flow property.

Carr's Index (%)	Flow	Hausner's Ratio
5-15	Excellent	1.00-1.11
12-16	Good	1.12-1.18
18-21	Fair to passable*	1.19-1.25
23-35	Poor*	1.26-1.34
33-38	Very poor	1.35-1.45
>40	Extremely poor	1.46-1.59

Porosity: Percent relative porosity (ε) was obtained using the relationship between apparent density (ρapp) and true density (ρ true) which is calculated by following formula;

ε = (1 - ρapp / ρtrue) × 100

Void Volume: Void volume (V) was obtained by difference between bulk volume (Vb) and tapped volume (Vp). Void volume can be calculated by following formula; **V= Vb-Vp** with an equal volume of plain dissolution medium.[22]

Preparation of Co-Ground Mixture For Fdts By Using Ball Mill

Coground Mixture and FDTs Coground mixtures prepared at a 1 g size scale using a ball mill.The Coground mixtures were blended with drug, mannitol, and magnesium stearate in a glass bottle using manual shaking. After blending, the mixtures were compressed using a single tableting machine. The purpose of this study was to prepare oral fast disintegrating tablets (OFDTs) by directly compressing a mixture of mannitol and Crospovidone. When the mixture of mannitol and Crospovidone was co-processed by ball mill. To improve the compatibility and their stability during storage. The (OFDTs) without this co-processing, the powder mixture had poor compatibility, and the stability of the tablet was inferior, probably due to the high Hygroscopicity of Crospovidone. The OFDTs containing co-ground mixture of crospovidone/mannitol showed good stability for six months under humid conditions with rapid disintegration and increase hardness of the tablets Tablet stability could not be achieved using a physical mixture of crospovidone/mannitol without including the co-ground process.[32]

Formulation of oral fast disintegrating tablets

The Best batch obtained from Kneading method with 1:2 ratio of inclusion complex was prepared by direct compression method containing 12mg of Ondansetron. Drug + Beta cyclodextrin inclusion complex equivalent to 4mg of Ondansetron was taken and pass through the # 40. Diluents, superdisintegrants, sweetener and flavour were passed through # 40. All above ingredients were mixed and blended properly. Magnesium stearate was passed through # 40 and mixed properly with above blend. Powdered lubricated blend was compressed into tablet by Rimek, minipress-2nd DL 09 station Tooling machine using B9 Tolling, 7 mm round flat punches.[24]

Table no 3: Composition of Oral Fast disintegrating tablets of Ondansetron HCl.

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
OSH+BCD complex (equivalent to 4mg Drug) (1:2)	12	12	12	12	12	12	12	12	12	12	12	12
Xanthan Gum	3	6	9	-	-	-	-	-	-	-	-	-
Karaya Gum	-	-	-	3	6	9	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	3	6	9	-	-	-
Cross Carmellose Sodium	-	-	-	-	-	-	-	-	-	3	6	9
Avicel 101	55.5	55.5	55.5	55.5	55.5	55.5	55.5	55.5	55.5	55.5	55.5	55.5
Mannitol	71.5	68.5	65.5	71.5	68.5	65.5	71.5	68.5	65.5	71.5	68.5	65.5
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3
Orange flavour	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

***All the quantities mentioned above in mg**

EVALUATION OF ORAL FAST DISINTEGRATING TABLETS

Weight variation: Tablets are considered to contain a definite amount of drug in a specific amount of tablet formula; the weight of the tablet is measured to help in such a way that the tablet contains the accurate amount of drug. Average weight of 20 tablets were selected randomly from the lot and weighed individually to check for weight variation.

Table 4: Specification for uniformity of weight as per IP.

Avg. Weight of tablet (mg)	Percent deviation
80 or less	10
More than 80 but less than 250	7.5
250 or More	5

Tablet Thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using Vanier calliper. It is measured in mm.

Tablet Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsatoo hardness tester.

Friability (F): Friability of the tablet is determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

%Friability = loss in weight / Initial weight x 100

Wetting Time: The wetting time of the tablets can be measured using a simple procedure. Twice folded circular tissue papers of 10 cm diameter were placed in a Petridis with a 10 cm diameter.10 ml of pH 6.8 phosphate buffer. A tablet is carefully placed on the surface of the tissue paper. The time required for phosphate buffer to reach upper surface of the tablet is noted as a wetting time.[33-37]

Water Absorption Ratio: A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of pH 6.8 phosphate buffer. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.[33-38]

$$R = 100 \times (Wa - Wb)/Wa$$

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

In vitro dispersion time: In vitro dispersion time was measured by dropping a tablet in a 10 ml measuring cylinder containing 6 ml of buffer solution simulating saliva fluid (pH 6.8) at 37 ± 0.5ºC and the time required for complete dispersion was determined.[39-41]

Content Uniformity: The content uniformity of the prepared formulas orodispersible tablets was performed by taking ten tablets and assayed individually. The requirement for this test is met if the amount of ingredient in each of the ten tablets lies within the range of 95%-102%.[42]

Taken five tablets were powered and the blend equivalent to 20 mg of Ondansetron was weight and dissolved in 100 ml of phosphate buffer (pH 6.8). Stock solutions are sonicted for 14 minute. Filter the sample and withdraw 1ml filtrate was taken in25 ml phosphate buffer (pH 6.8) and analysed spectrophotometrically at 310 nm. The amount of Ondansetron was estimated by using standard calibration curve of drug.[42-43]

In-vitro drug release study: The release rate of Ondansetron from rapid disintegrating tablet was determined by using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of phosphate buffer pH 6.8, at 37±0.5^{0}C and 50 rpm. A sample (1 ml) of the solution was withdrawn from the dissolution apparatus every 2 min for 14 min and the samples were replaced with fresh dissolution medium. The samples were filtered through what Mann filter paper. Absorbance of these solutions was measured at 310 nm using UV spectrophotometer. Cumulative Percent drug release was calculated by using an equation obtained from a standard curve.[42-46]

The effect of different paddle speed on drug release: The In vitro dissolution study was also performed on the optimum f_6 formulation by using different rotation speed of 50, 75 and 100 rpm to check the effect of rotation on drug release.

The effect of different concentration of SLS on drug release: The In vitro release study also performed on optimum formulation by using different concentration of sodium lauryl sulphate (SLS) respectively 0.25%, 0.5%, 1%.To check the effect of different concentration of SLS on drug release.

Parameter of in-vitro dissolution test

1. Apparatus : USP Type –II (paddle)
2. Volume of medium : 900 ml
3. Temperature : 37 ± 0.5ºC
4. Paddles Speed : 75 rpm
5. Dissolution medium used : 6.8 Buffer
6. Aliquot taken at each time interval : 1 ml

7. Time interval : 2 min.
8. Dilution factor : 10

Stability Study: The tablets of best formulation were subjected to stability studies. Stability testing of the final drug product was carried out as mentioned in the ICH guidelines for stability testing of the drug products. India being in the zone 4 of the climatic zone classification, the real time stability studies were carried out at 30±2^{0}C and 70±5% RH. The orally dispersible tablets were subjected to the accelerated stability testing at the temperature of 40^{0}C±2^{0}C and 75±5% RH for 3 months. The samples were withdrawn from the stability chambers after 1 month, 2 month and 3 months and studied for physical characteristics like any colour change, visual defects, hardness, dissolution, disintegration and assay. The data so obtained was compared with the initial data of the tablets.[47-49]

RESULTS

Identification and Characterisation of Ondansetron HCl

Melting Point

The melting point of the Ondansetron HCl was found to be 231^{0}C, which complies with BP.

Standard Calibration Curve of Ondansetron HCl

Table no 5: Standard Calibration Curve of Ondansetron HCl in phosphate buffer pH 6.8 at 310 nm.

Sr. no.	Concentration (µg/ml)	Absorbance (mean±SD)
1	0	0.000±0.000
2	2	0.142±0.003
3	4	0.289±0.004
4	6	0.461±0.003
5	8	0.621±0.005
6	10	0.788±0.001
7	12	0.923±0.002

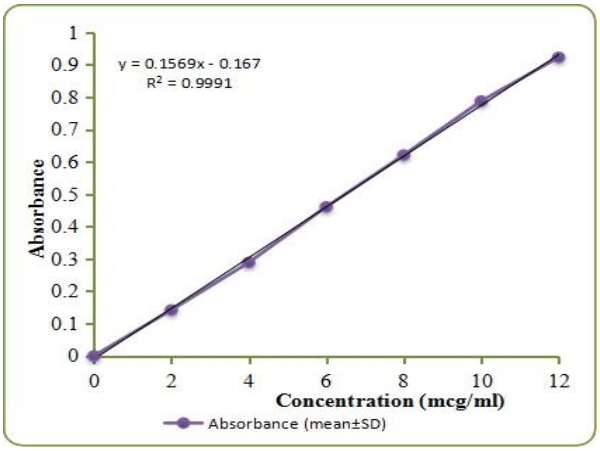


Figure no 1: standard calibration curve of Ondansetron HCl.

FTIR Analysis

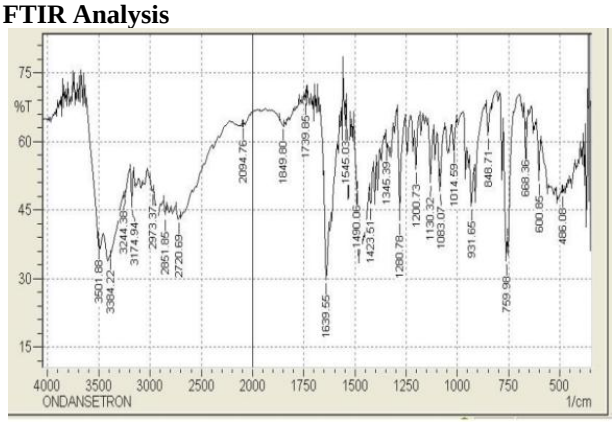


Figure no 2: FTIR spectrum of Ondansetron HCL.

The spectrum of Ondansetron HCl shows the following groups at their frequencies.

Cm^{-1}	Group
3174.94	: Ar-H(
2851.85	: C-H Stretching
1739.86	: C=O
1545.03	: C=C
1490.06	: C=N
1280.78	: C-N

CHARACTERISATION OFDRUG + BETACYCLODEXTRIN COMPLEX

Formulation Study of Drug + Betacyclodextrin Complex.

Table no 6: Pre Formulation Study of Drug + Betacyclodextrin Complex Pre.

Formulation	Angle of repose (^{o})	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio
Drug	33.6	0.22	0.27	18.52	1.23
Drug +BCD	31.2	0.41	0.51	19.61	1.24

Drug content of prepared complex

Table no 7: drug content of prepared complex.

Sr no.	Drug+BCD ratio	%drug content in complex
1	1:1	13.44
2	1:2	32.88
3	1:3	29.78

FTIR ANALYSIS OF ONLY BETACYCLODEXTRIN

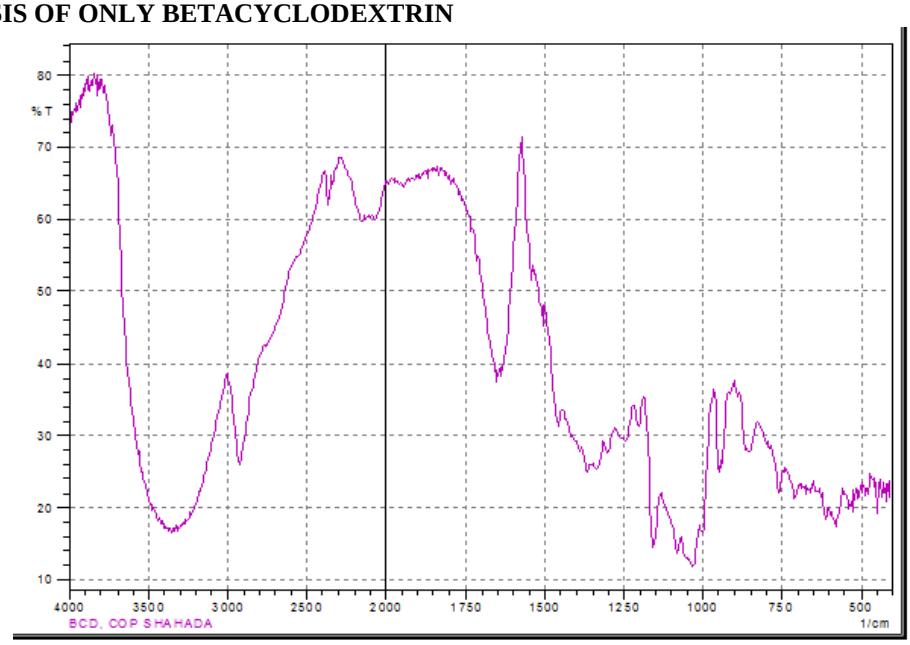


Figure no 3: FTIR Spectrum of Betacyclodextrin.

The spectrum of Betacyclodextrin shows the following groups at their frequencies;

Cm^{-1}	**Group**
2857.64	C-O Stretching
3545.28	O-H Stretching
1456.30	C-O Stretching

ANALYSIS OF DIFFERENTIAL SCANNING CALORIMETRY

Differential Scanning Calorimetry of Ondansetron HCl

The physicochemical compatibility between Ondansetron HCl and polymers used in the formulations was studied by using differential scanning calorimeter (DSC, Perkin Elmer – Pyris 6 DSC, Salem, MA).In DSC analysis, the samples were weighed (5 mg), thermetically sealed in flat-bottom aluminium pans, and heated over a temperature range of 0 to 250ºC in an atmosphere of nitrogen (20 mL/min) at a constant increasing rate of 10ºC/min. The thermograms obtained for Ondansetron HCl and mixtures of it with polymers were compared. The combined DSC physical obtained is given below.

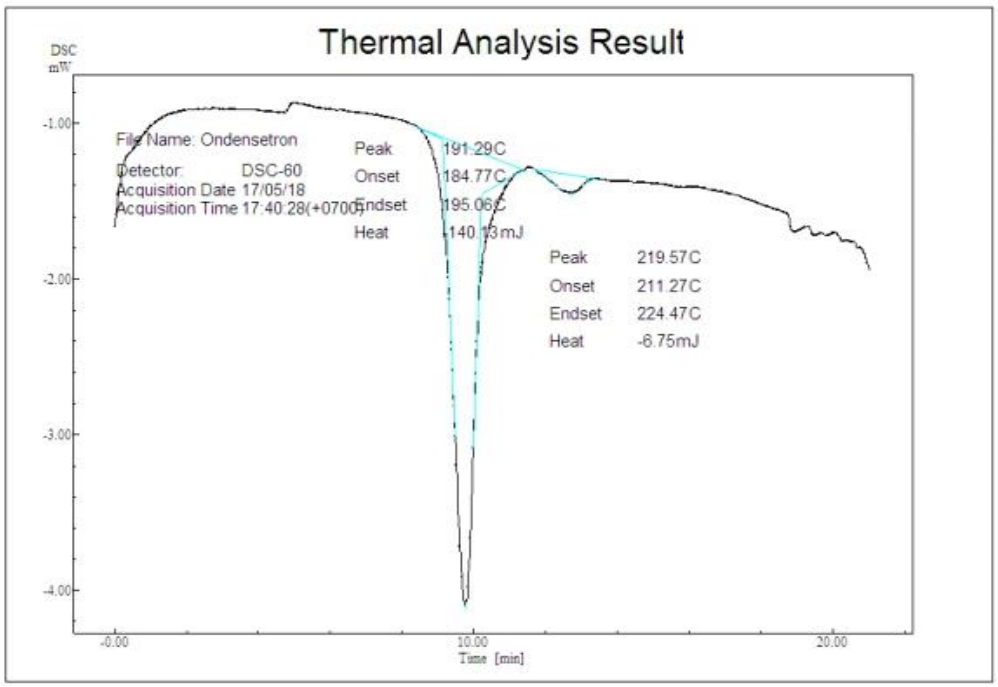


Figure no 4: Differential Scanning Calorimetry of Ondansetron HCl.

Differential Scanning Calorimetry of Ondansetron HCl with Excipients

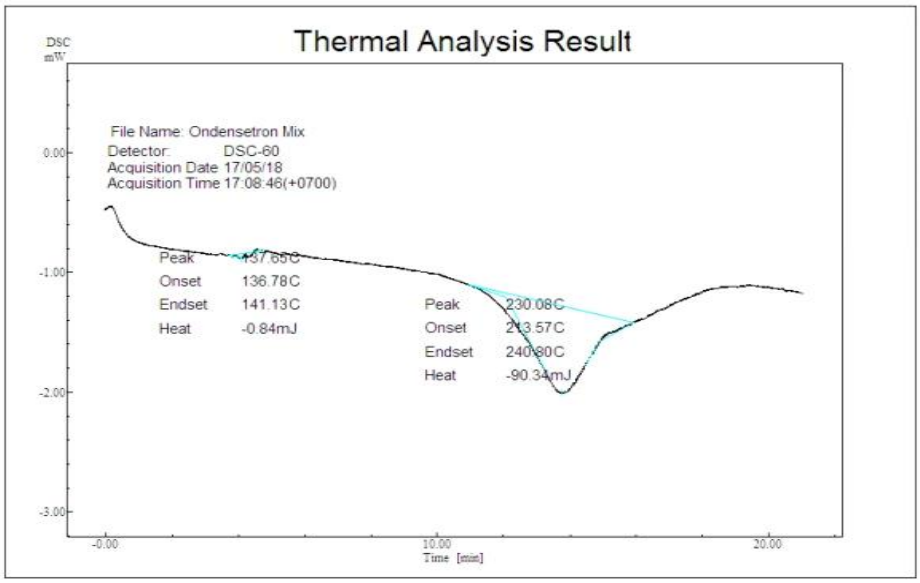


Figure no 5: Differential Scanning Calorimetry of Ondansetron HCl with Excipients.

PRE- COMPRESSION PARAMETERSOF POWDER BLEND BACHES

F_1 -F_{12},(Tablet)

Table no 8: Pre-Compressional Parameters of Tablets.

Parameter Batches	Bulk Density (gm/cm^3) (mean ± SD)	Tapped Density (gm/cm^3) (mean ± SD)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose(^{0})
F1	0.24 ± 0.04	0.28 ± 0.02	14.29	1.16	29.2
F2	0.31 ± 0.09	0.37 ± 0.01	16.22	1.19	30.8
F3	0.24 ± 0.02	0.27± 0.04	11.11	1.12	34.7
F4	0.28 ± 0.1	0.31 ± 0.03	9.68	1.10	29.1
F5	0.38 ± 0.03	0.40 ± 0.03	5	1.05	30
F6	0.41 ± 0.01	0.45 ± 0.06	8.89	1.09	34.1
F7	0.37 ± 0.06	0.41 ± 0.08	9.76	1.10	28.3
F8	0.40 ± 0.04	0.44 ± 0.01	9.09	1.1	22.1
F9	0.42 ± 0.04	0.47 ± 0.01	10.63	1.11	19.8
F10	0.33 ± 0.05	0.39 ± 0.03	2.34	1.18	20.6
F11	0.35 ± 0.06	0.40 ± 0.04	12.5	1.14	22
F12	0.31 ± 0.02	0.33 ± 0.03	6.06	1.06	21.3

POST-COMPRESSION PARAMETER of TABLET

Table no 9: Post-Compression parameters of Fast disintegrating tablets of Ondansetron HCl.

Formulation	Thickness (n=3) (mm)(SD)	Hardness (kg/cm^2) (n=3)(SD)	Friability (%) (n=10)	Weight Variation (n=20)(mg) (SD)	Diameter (n=3) (mm)(SD)
F1	2.88± 0.1	2.93 ± 0.03	0.63	148± 0.4	7.50± 0.2
F2	2.96± 0.3	2.99 ± 0.04	0.62	147± 0.3	7.50± 0.4
F3	2.62± 0.3	3.02 ± 0.06	0.67	148± 0.7	7.51± 0.6
F4	2.08± 0.2	3.00 ± 0.10	0.67	152± 0.1	7.50± 0.2
F5	2.47± 0.3	2.98 ± 0.06	0.66	151± 0.2	7.48± 0.8
F6	3.02± 0.4	3.20 ± 0.07	0.60	149± 0.5	7.49± 0.7
F7	2.97±0.3	2.90± 0.02	0.61	151± 0.2	7.51± 0.2
F8	2.76± 0.3	3.00 ± 0.02	0.66	149± 0.1	7.50± 0.2
F9	2.53± 0.2	2.99 ± 0.05	0.64	148± 0.4	7.51± 0.4
F10	2.35± 0.1	2.94 ± 0.03	0.69	152± 0.1	7.49± 0.5
F11	2.64± 0.2	2.98 ± 0.08	0.60	150± 0.4	7.50± 0.1
F12	2.59± 0.1	3.08 ± 0.06	0.63	150± 0.6	7.50± 0.3

EVALUATION OF F6 FORMULATIONS

In-Vitro Release Study Of Formulation F6 At Different Paddle Speed

Table no 10: In Vitro Release Study of Best Formulation F6at 50 rpm, 75 rpm, 100, rpm.

Time (minute)	50 rpm	75 rpm	100 rpm
2	81.5	84.51	89.65
4	85.08	91.65	97.43
6	94.61	96.7	99.01
8	98.23	98.45	

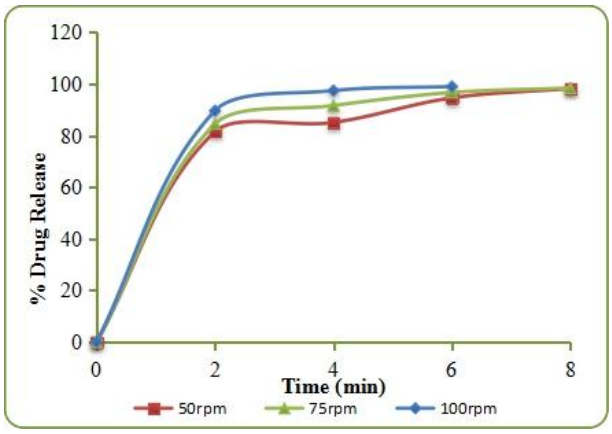


Figure no 6: Comparative in vitro drug release of F6 batch fast disintegrant Tablet of Ondansetron HCl at 50, rpm, 75, rpm and 100, rpm.

DISCUSSION

The objective of the present study was to formulate and evaluate novel fast disintegrating drug delivery system for bitter pharmaceutical. In this study, novel fast disintegrating taste masked formulations of Ondansetron HCl. Fast disintegrating tablets with one or more superdisintegrants were prepare and evaluated for various in-*vitro* parameters.

The melting point of the Ondansetron HCl was found to be 231^0C. FTIR spectrum of Ondansetron HCl shows characteristic peak at3174.94cm^{-1}, 2851.85cm^{-1}, 1739.86 cm^1, 1545.03cm^{-1}, 1490.06cm^{-1} and 1280.78 cm^{-1} due to the presence of functional group, C-H(Ar-H),C-H,C=O,C=C,C=N and C-N

The standard calibration curve of Ondansetron HCl was obtained by plotting absorbance v/s. Concentration.. The standard calibration curve shows the slope of 0.156 and correlation coefficient of 0.999. The curve was found to be linear in concentration in range of 2- 14 µg/ml (beer's range) at 310 nm.

Inclusion complex of Ondansetron HCl with Betacyclodextrin were prepared by kneading method. The prepared inclusion complexes were evaluated. Drug content of inclusion complexes shows almost 35 %.

FTIR spectra of inclusion complex of Ondansetron HCl with Beta cyclodextrin The IR spectrum which indicating no significance evidence of chemical interaction between drug and carrier, which confirmed the stability of drug with inclusion complex.

Fast disintegrating tablet of Ondansetron HCl were prepared using direct compassion method and using different superdisintegrant such as Xanthan Gum karaya Gum, Crospovidone & cross carmellose sodium, in varying concentration 2%, 4%, 6%. Before compression, the powder blend subjected to precompression evaluation to determine the drug and polymer compatibility, flow properties and compressibility. FTIR spectra of physical mixtures of Drug+ BCD complex with selected superdisintegrant samples were recorded to investigate any possible interactions. It was found that there was no interaction of the excipients with the drug at normal conditions with minor differences in the wave no. Thus the compatibility between Ondansetron HCl and superdisintegrants was established. The differential scanning calorimetry there is not interactions' of drug with polymers. The safe compatibility and stability of drug with polymers.

The results of the pre compression evaluation are given in the values were found to be in the range of 19.8° to 34.7°respectively. All the formulation shows the angle of repose within 34°.

The Bulk density and Tapped density for all the formulations varied from 0.24 gm/cm^3 to 0.42 gm/cm^3 and 0.27 gm/cm^3 to 0.47 gm/cm^3 respectively. The values lies within the acceptable range and not large difference found between Bulk density and Tapped density. This result helps in calculating the % compressibility of the powder.

The values were found to be in the range of 1.05 - 1.19. All formulations show the Hausners ratio within the range, which indicates a good flow property of the granules. The percent compressibility for all the twelth formulation lies within the range of 2.35 % to 16.22%. All formulations are showing good compressibility.

After that tablet was compressed into tablet by Rimek, minipress-2^{nd} DL 09 station Tooling machine using 7 mm round flat punches. All the tablet formulations were subjected for evaluation according to various official specifications and other parameter. Thickness, hardness, friability, weight variation, in vitro disintegration time, wetting time, water absorption ratio, drug content, in vitro dissolution time and stability studies were carried out.

The thickness of the tablets was measured by using digital caliper by picking the tablets randomly. The mean values are almost uniform in all formulations. Thickness was found in the range of 2.08±0.2 mm to 3.02±0.4 mm respectively.

Hardness test was performed by pfizer hardness tester. Hardness was found to be within 2.98±0.02 kg/cm2 to 3.20±0.07 kg/cm2, as these tablets are rapidly disintegrating. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness.

The friability was found well within the approved range (<1%) in all the formulations. Formulation F1toF12 possess good mechanical strength. The percentage weight variation for all the formulation passed weight variation test as the % weight variation was within pharmacopoeial limits of ± 10 %. It was found to be from 147± 0.3 mg to 152 ± 0.1 mg. The weight of all tablets was found to be uniform.

The content uniformity was performed for all the twelth formulations and results. Formulation analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 91.2±0.2% to 99.0±0.4 % of Ondansetron HCl. The results indicated that in all the formulations the drug content was uniform.

Wetting time is closely related to the inner structure of tablets. . All formulation showed quick wetting. This may be due to ability of swelling and also capacity of absorption of water. All superdisintegrants have high water absorption capacity and cause swelling.

Water absorption ratio, which is an important criterion for understanding the capacity of disintegrants to swell in presence of little amount of water, was calculated. It was found to be in the range of 51±0.3 to 69±0.5. The water absorption ratio increased with increase in the correlation of superdisintegrant from 2%, 4% and 6%. There existed a direct relationship for each Fast disintegrating tablet formulation of Ondansetron HCl. This increase was due to the water up taking ability of the superdisintegrants. More the superdisintegrant concentration greater was the water uptake and thereby increases in water absorption.

Internal structure of the tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. All formulations show disintegration time less than 60 seconds. Among the four superdisintegrants used, Karaya gum showed less disintegrating time followed by Crospovidone, Crosscarmellose sodium and Xanthan gum. The co processing of D-mannitol & crospovidone by using ball mill because the D-mannitol is sticks in dies & punches to create the problem directly compression of tablet & so increase the compatibility & stability of FDTs.

All the twelth formulations were subjected for the in vitro dissolution studies using tablet dissolution tester USP XXIII. The sample were withdrawn at different time intervals and analyzed at 310 nm. Cumulative drug releases were calculated on the basis of mean amount of Ondansetron HCl present in respective tablet. The results obtained in the in vitro drug release for the formulations F1, F2, F3 are tabulated in, Formulations F4, F5, F6 are tabulated in Formulations F7, F8, F9 are tabulated in, Formulations F10, F11, F12, are tabulated in the plots of cumulative % drug release v/s. time.

The dissolution rate was found to increase linearly with increasing Concentration of superdisintegrants. Formulation F1, F2 and F3 which contained Increasing concentration of Xanthan Gum from 2%w/w, 4%w/w and 6%w/w, Have recorded drug release and respectively, at the end of 14 minutes.

Formulation F4, F5 and F6 which contained increasing concentration of Karaya Gum from 2%w/w, 4%w/w and 6%w/w, have recorded drug release and respectively, at the end of 8-14 minutes.

Formulation F7, F8 and F9 which contained increasing concentration of Crospovidone from 2%w/w, 4%w/w and 6%w/w, have recorded drug Release and respectively, at the end of 14 minutes.

Formulation F10, F11 and F12 Which contained increasing concentration of crosscarmellose sodium from 2%w/w, 4%w/w and 6%w/w, have recorded drug release and respectively, at the end of 12- 14 minutes.

In all the formulations the drug releases were near to 100% within the 14 minutes. The relative efficiency of different superdisintegrants and natural Superdisintegrant to improve the dissolution rate of tablets was in order, Karaya Gum > Crosscarmellose sodium > crospovidone > Xanthan gum.
From the outcome of above results, it was clear that the formulation F6 was the best formulation having comparable disintegration time and in vitro drug release.This formulation contain 6% concentration of Karaya Gum.

The dissolution rate was found to increase linearly with increasing the rotation speed .The effect of rotation speed on drug release of F6 formulation. The drug release at the rotation speed of 75 rpm and 100 rpm are 98.45%, 99.01% the end of 6 to 8 minute.

The dissolution rate of best F6 formulation was found to increase linearly with increasing the concentration of SLS. The effect of different concentration of SLS on drug release. The drug release of the optimized batch F6 formulation was found to be 101 %, 99% and 101% at the end of 6 to 8 minute.

The tablets were stored at 40 ± 2 ^{o}C / 75 ± 5% RH for duration of three month. The tablets were withdrawn after the interval of each month and analyzed for

disintegration time, drug content, wetting time and *in-vitro* drug release study.

The co-processing of superdisintegrant and excipient like that sugar alcohol content mannitol this is use as diluent and sweetener but mannitol is sticky material to stick a dies & punches after that to create the problem of tablet punching. They were prepared by co-ground mixture of mannitol with crospovidone by the use of ball mill.

CONCLUSIONS

- Preformulation studies of Ondansetron HCl with Betacyclodextrin and Excipients were performed. The FTIR analysis revealed that the Betacyclodextrin and polymer used were compatible with Ondansetron HCl.
- The DSC analysis that the BCD polymer was used, compatible with OSH.
- A complex of Betacyclodextrin and Ondansetron HCl was successfully formed in 1:2 ratios which are confirmed by solubility determination, using FTIR.
- The Fast disintegrating tablets of Ondansetron HCl were prepared by direct compression method using different synthetic superdisintegrant such as Crospovidone, crosscarmellose sodium and natural superdisintegrant such as Karaya gum and Xanthan gum in different concentration.
- Disintegration time decrease with increase in the concentration of superdisintegrant from 2%, 4% and 6%.
- Among all formulation, containing Karaya Gum as superdisintegrants is fulfilling all the parameters satisfactorily. It has shown excellent in vitro disintegration, in vitro dissolution time, compared to other superdisintegrants.
- The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rates of tablets was in order,
- Karaya Gum> crosscarmellose sodium > Crosprovidone >Xanthan gum.
- In vitro release studies that almost 98% of drug was release from all the formulation were within 14 minute. Formulation F6 showed faster drug release within 8min in comparison to other formulation.
- Drug release rate of best formulation F6 was increase with increasing the rotation speed (50 rpm, 75 rpm, 100 rpm) and also increasing the SLS concentration in dissolution media(0.25%, 0.5 %,1%).
- Stability studies were conducted for the F6 formulation at 40^0C/75%RH for 3 months. Various parameters like disintegration time, wetting time, drug content and dissolution rate were analyzed at a time interval of 1 month till the period of 3 months. Not much variation or change was observes in any parameters throughout the study period. Best formulation batch F6 found to be stable. To prepared fast disintegrating tablets to disintegrate in second without need of water and enhance the absorption; this leads to increase in the bioavailability of Ondansetron HCl.
- Because the mannitol was stick to dies and punch therefore ball mill is use to prepare coground mixtures of crospovidone and mannitol to improve the compatibility and stability of product

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