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A Research Paper On Development And Evaluation Of Floating Microspheres Of Famotidine Using Different Polymers.

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Abstract

The goal of this study was to create a famotidine floating medication delivery system. The floating microspheres can be created to boost famotidine's absorption and bioavailability by keeping the system in the stomach for a prolonged period of time. Floating microspheres carrying famotidine were produced using a variety of polymers, including ethyl cellulose and hydroxy propyl methyl cellulose, using the solvent diffusion-evaporation method. The microspheres featured smooth surfaces, free-flowing behaviour, and good packing. Ethyl cellulose microspheres, with a yield of up to 73.320.14%, contained the most medication. Scanning electron microscopy confirmed their hollow structures with diameters of 331.6 nm. Extended drug release was seen in the created microspheres, and 73.250.23 percent buoyancy was found. The generated batches were examined for % entrapment efficiency, flow characteristics, and yield investigations. The formulations underwent stability testing, and information on in-vitro release and release kinetics was fed into a number of dissolving models. The oral bioavailability, effectiveness, and patient compliance of famotidine floating microspheres were found to be improved by this good and practical strategy for sustained drug release over an extended period of time.

Keywords: Famotidine, Hydroxypropyl Methyl Cellulose, Solvent Diffusion Evaporation Method, Ethyl cellulose microspheres.

Introduction:

Oral drug delivery is regarded as the finest way of administration in the pharmaceutical business. since it has numerous benefits and has higher patient compliance than many other methods, including parenteral and topical, etc. Because it is easy to eat, adaptable enough to accept a variety of drug candidates, pain-free, and most importantly, patient compliance, oral administration is the most practical form of administration. Solid doses are frequently used because they are more convenient to deliver. The patient's compliance, self-medication, exact dose, and pain avoidance are of highest significance. However, several patient populations, such as the elderly, young children, and those with cognitive impairment who are ill or on restricted liquid intake or diets, have difficulty ingesting other dose forms, such as tablets and capsules.

The main problems with oral dosage forms are the inability to swallow in the absence of water, allergic reactions, bronchitis, kinetosis, and unplanned coughing fits during a cold. For these reasons, oro-dispersible pills are made and developed.

Oral dispersible tablets are also known as melt in mouth tablets, mouth dissolving tablets, rapid disintegrating tablets, quick disintegrating tablets, repayments, and fast disintegrating pills.

Despite all of the aforementioned terminology, the United States Pharmacopoeia (USP) has recognised these dosage forms as ODTs. The European Pharmacopoeia refers to Oro dispersible pills, which swiftly dissolve in the mouth before being ingested. According to the United States Food and Drug Administration, ODTs are solid dosage forms that include a medicinal drug or active compounds that dissolve swiftly in a couple of seconds when put on the tongue. Some medications have a bioavailability that is substantially greater than that seen with standard tablet dosing when they are absorbed from the mouth, throat, and oesophagus as the saliva descends into the stomach. Tablets that dissolve instantaneously when placed on the tongue are known as oro dispersible tablets. Will ultimately see a deterioration in their bodily functions and physical abilities. It was proposed to provide patients with access to conventional ways of medicine administration through the use of fast dissolving drug delivery devices. Fast-dissolving dose forms can be suspended, dissolved, or disintegrated in saliva in the mouth. These Oro-dispersible tablets rapidly disintegrate when put on the tongue, releasing the drug for dissolution or scattering in the saliva.

Fast-dissolving tablets are advantageous for people who lead an active lifestyle and experience persistent nausea, sudden episodes of allergic attacks, or coughing. They are also advantageous for people with conditions like paediatric, geriatric, bedridden, or mental disabilities who may struggle to swallow conventional tablets or capsules, which can lead to ineffective therapy. Oro-dissolving tablets are also useful when oral action in the mouth is sought, such as for local anaesthetic for toothaches, oral ulcers, cold sores, or teething, or for persons who are unable to swallow complete continuous action.

Capsules/ Tablets

Advantages of ODT:

- Patients who are incapable of swallowing tablets or capsules, such as stroke victims, elderly patients who are bedridden, patients with esophageal difficulties, and patients who refuse to swallow, such as paediatric, geriatric, and psychiatric patients, can be administered ODTs.
- Useful for travelling in places without access to water.
- Water is not necessary.
- People's attitudes towards drugs are changing as a result of the pleasant mouthfeel of ODTs.
- Rapid medicine administration eliminates the need for chewing.
- Appropriate for tasks needing a controlled or prolonged release.
- Have a pleasant texture and an acceptable taste; the drug loading may be increased.

- New commercial prospects for the marketing, differentiation, growth of the patient base, and management of lifestyle decisions were made possible by the introduction of ODT.
- The administration is easier and the dose is more accurate as compared to liquid formulation.
- Rapid pharmaceutical absorption and dissolution may cause the effects to start acting right away.
- Leave the least residue possible.
- Effectively priced.
- Increased stability.
- Tools utilised in traditional production (Kuchekar et al., 2003).
- If specific packaging is not required, push-through blister packing is a possibility.
- The danger of choking or suffocating during oral administration of normal formulations is decreased by eliminating physical impediments, enhancing safety.

Limitation of Oro-Dispersible Tablets:

- These tablets may leave an unpleasant taste and/or grittiness in the mouth if they are not correctly formed.
- Since oro-dispersible tablets often lack sufficient mechanical strength, cautious handling is required.
- It is difficult to convert drugs with comparatively greater doses into ODTs, such as antibiotics like ciprofloxacin, which come as adult-use tablets containing about 50mg of the drug.
- ODTs may not be the best option for individuals who are concurrently taking anti-cholinergic medications; these tablet formulations may not be appropriate for those with Jorgen's syndrome or dry mouth caused by decreased salivation.

Disadvantages Of Oro dispersible:

- ODTs need to be carefully packed for the product's stability and safety.
- ODTs need to be maintained in a dry environment owing to their hygroscopic nature.
- Technically, dosage uniformity is challenging.
- It occasionally displays the delicate effervescence characteristic of the granules.

Ideal Properties of ODT:

The following desired qualities should be included in ODTs.

- Doesn't need to be consumed with water, but it should melt and dissolve quickly in the mouth.
- Immediately melt or scatter in saliva after a brief period of time.
- > Let drugs be loaded heavily.
- Accept taste masking with grace.

- Create a pleasant sensation in the mouth.
- There should be minimal to no aftertaste following oral use.
- Be less sensitive to environmental elements like temperature and humidity.
- Flexible and reasonably priced compatibility with conventional processing and packaging machinery.
- Permit the manufacture of tablets using conventional techniques.
- Able to be manufactured at a fair price using a simple, traditional process.

Mechanisms of ODT:

- In order to obtain the requisite rapid dissolving qualities, ODTs use a number of techniques.
- Water must quickly enter the tablet's matrix for the tablet to instantaneously dissolve and disintegrate.
- Including a suitable disintegration agent or highly water soluble excipients in the formulation of the tablet.
- Using the highlighted techniques, the tablet is broken up into tiny pieces, resulting in a solution or suspension of the drug.

The systems are:

- High swell disintegration capability
- Chemical process
- Cavernous action

OVERVIEW OF ORAL MUCOSA:

The morphological and physiological properties of the oral mucosa have been extensively reviewed by a number of authors (Shojaei et al., 1998; Gandhi et al., 1994). The oral cavity is made up of the tongue, cheeks, soft and hard palates, and the floor of the mouth. The throral mucosa, the word used to describe the lining of the oral cavity, includes the buccal, sublingual, gingival, palatal, and labial mucosa. The buccal, sublingual, and mucosal tissues close to the ventral part of the tongue make up around 60% of the oral mucosal surface area. The upper one-third to one-fourth of the oral mucosa is made up of closely packed epithelial cells (Fig. 1). The oral epithelium's main job is to shield the underlying tissue from potentially dangerous substances found in the oral environment.

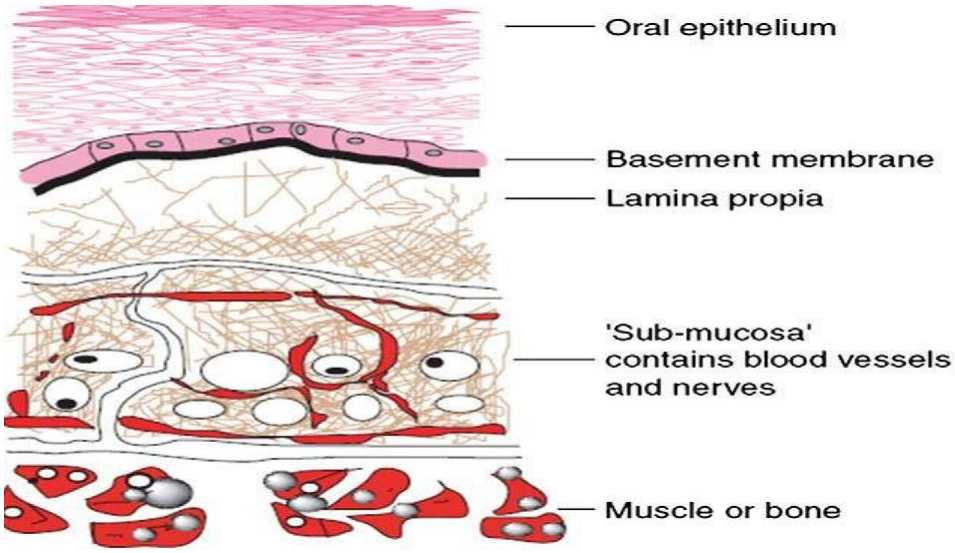


Fig 1: schematic diagram of buccal mucosa

The buccal mucosa and sublingual area (the floor of the mouth) comprise the lining mucosa, which is one of three main kinds of oral mucosa found in the oral cavity (Fig. 1). The specialist mucosa is found on the dorsal surface of the tongue, whereas the masticatory mucosa is found on the hard palate (the top surface of the mouth) and the gingival (gums) (Smart et al., 2004).

The lining mucosa accounts for over 60% of the oral mucosal lining's total surface area in an adult human, followed by the masticatory mucosa, which accounts for approximately 25%, and the specialised mucosa, which accounts for approximately 15%. Particularly vulnerable to stress and strain from masticatory action are the regions where the masticatory mucosa is present. Outside cells of the masticatory mucosa are keratinized, and a strong lamina propria firmly attaches it to the periosteum underneath. The lining mucosa, which is less susceptible to masticatory stresses, has a non-keratinized epithelium that is supported by a thin and elastic lamina propria and a sub mucosa. The mucosa on the dorsum of the tongue is a specialist gustatory mucosa with well-papillated surfaces that are both keratinized.

Orally disintegrating dosage forms:

Orally disintegrating dosage forms were developed with the intention of providing patients with more conventional pharmaceutical administration methods. It's noteworthy to note that the demand for ODDFs has increased dramatically over the past 10 years, particularly among elderly and paediatric patients who have difficulty swallowing standard pills and capsules. As a result, they reject the advice, which greatly increases the likelihood of ineffective therapy.

Oro-Dispersible Tablets:

Patients don't accept systems well, therefore they continue to be used. the need for non-invasive medicine administration, adherence to present distribution guidelines, a tiny market for pharmaceutical firms, constrained drug use, and high healthcare expenses. One such pharmaceutical class that is helpful for older people, especially those with dysphasia and hand tremors, is ODT. Particularly for people who have experienced prolonged, persistent nausea and are difficult to swallow.

• Paediatric patients with swallowing difficulties caused by underdeveloped internal muscles and central nervous systems.

• Travelling patients with motion sickness and diarrhoea who do not have easy access to water.

• Those with mental diseases, the elderly, and those confined to psychiatric hospitals.

Material Used in The Formulation of ODTs:

- Super breaks down.
- Agents that disguise flavours
- Binders.
- Extreme disintegrants

- **Super disintegrants,** which are more effective at low concentrations, more effective intra-granularly, and at dissolving. Super disintegrants function by swelling, and when this pressure is given in an outward or radial direction, they either cause tablets to rupture or hasten water absorption, which results in a significant increase in granule volume and promotes disintegration. The detailed disintegration mechanism is shown in Figure No. 1.

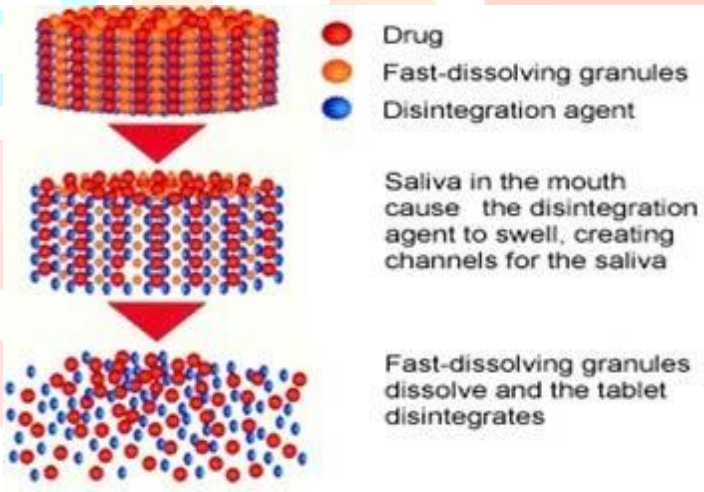


Figure: mechanisms of disintegration.

Selection of Super Disintegrants:

- The choice of super disintegrants might benefit from a variety of factors.
- The makeup of medications.
- The volume of pieces utilised during the procedure.
- Tablet scratching.
- There are substances with surface activity.
- A combination of adding and combining.
- Compact tablets, which are less fragile.

- Outstanding flowability.
- The patient gains from a nice dental experience.

Ideal Properties of super-disintegrants:

- **Poor Solubility:**

The solubility of the active component in a tablet composition can have an effect on both the rate and manner of tablet disintegration. In contrast to insoluble chemicals, which often result in tablets that dissolve fast, water-soluble substances are more likely to dissolve than disintegrate.

- **Good hydration capacity:**

Drugs and other excipients that are hydrophobic and may adsorb on disintegrate surfaces have an impact on the degree of hydration and efficacy of these disintegrates. High hydration capacities and quick disintegrates are supposed to minimise this problem and hence improve dissolve.

- **Good compressibility and flow properties:**

When the particles' compressibility is between 12 and 16 percent, they are considered to be good flow powders. Crospovidones are much more compressible than other super- disintegrants in comparison.

Materials & Methods:

LIST OF GENERAL CHEMICALS

Name, Source and Grade of Used Chemicals

Sr. No.	Drug / chemical	Company
1	Ondansetron	Sun Pharma,
2	Veegum	S.D.Fine – Chem. Limited, Mumbai
3	Kyron	S.D.Fine – Chem. Limited, Mumbai
4	Mannitol	S.D.Fine – Chem. Limited, Mumbai
5	Magnesium stearate	S.D.Fine – Chem. Limited, Mumbai
6	Talcum powder	S.D.Fine – Chem. Limited, Mumbai
7	Microcrytaline cellulose	S.D.Fine – Chem. Limited, Mumbai

LIST OF INSTRUMENTS

List of Instruments

Sr. No.	Equipments	Model/ Company
1	UV-Visible Spectrophotometer	Systronics 2202,India
2	Electronic Analytical balance	Electronic balance, Shimandzu, Japan
3	FTIR	4100 Jasco,Japan
4	USP dissolution apparatus	Jyoti scientific,India

Formulation of fast dissolving tablet

Direct compression method

By using the direct compression approach, the superdisintegrants Kyron and Veegum were employed to make the ondansetorn fast-dissolving tablet. Based on pill disintegration time and powder mix qualities, the ideal combination was determined.

Preparation of powder blends for compression

A 100 # seive was used to pass Mannitoll, Kyron, and veegum before combining. This powder mixture included ondansetron. Magnesium stearate and microcrystalline cellulose were then added and combined after that.

Compression of tablets

Using a rotating tableting machine, powder mixtures created for various batches were compacted into flat tablets weighing 150 mg.

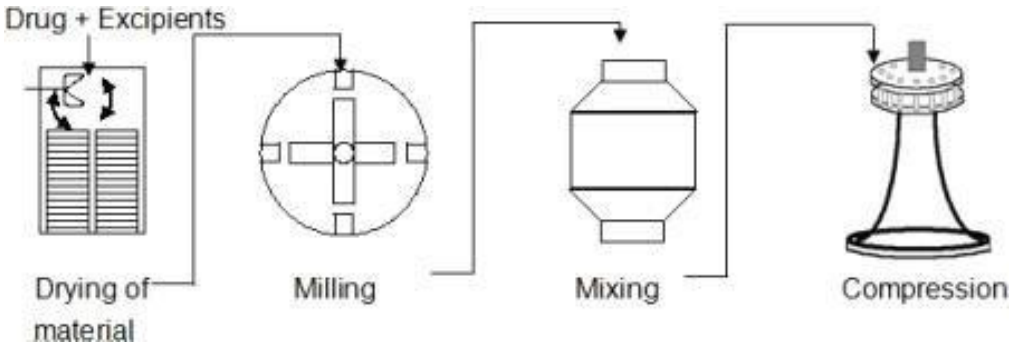
Manufacturing steps for direct compression:

Direct compression just requires a handful of steps:

• Drug and excipient milling.

• Drug and excipient mixing.

• Compression of tablets.



Manufacturing Steps For Direct Compression

List of Formulation Design of Ondansetron mouth dissolving tablets

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
X1 Variable Level In	-1	-1	-1	0	0	0	+1	+1	+1
Coded Form X2	-1	0	+1	-1	0	+1	-1	0	+1
Mannitol (x1)	25	25	25	30	30	30	35	35	35
Kyron (x2)	20	25	30	20	25	30	20	25	30
Veegum (x2)	20	25	30	20	25	30	20	25	30

Ondansetron 4 mg, Mannitol (X1), Kyron (X2), and Veegum (X3) are all contained in every batch.

Coded values of the variables

Coded value	Amount value in (mg)	
	X 1	X2
-1	25	20
0	30	25
+1	35	30

Evaluation Of Mouth Dissolving Tablets

Weight variation

From each formulation, 20 tablets were chosen at random and weighed separately using a Shimadzu digital balance (BL-220H). The weight variance was calculated by comparing the individual weights to the average weight.

Hardness

It is the amount of force needed to break a tablet by compression in the radial direction. This is a crucial consideration when formulating mouth dissolve tablets since too much crushing strength drastically shortens the time it takes for the tablet to dissolve. A tablet's hardness reveals its capacity to tolerate managing mechanical shocks. Pfizer hardness testers were used in the current investigation to determine the tablet's hardness strength. It is stated as kg/cm2.

Friability Test

The mechanical strength of tablets is measured. The following approach was done to determine the friability using the Roche friabilator. The friabilator, which consists of a plastic container that rotates at 25 rpm while dropping tablets at a distance of 6 inches with each revolution, was filled with a preweighed tablet. For at least 4 minutes, the tablets were spun in the friabilator. At the conclusion of the test, the tablets were dusted and reweighed. The percentage loss in weight is the measure of friability and is stated as

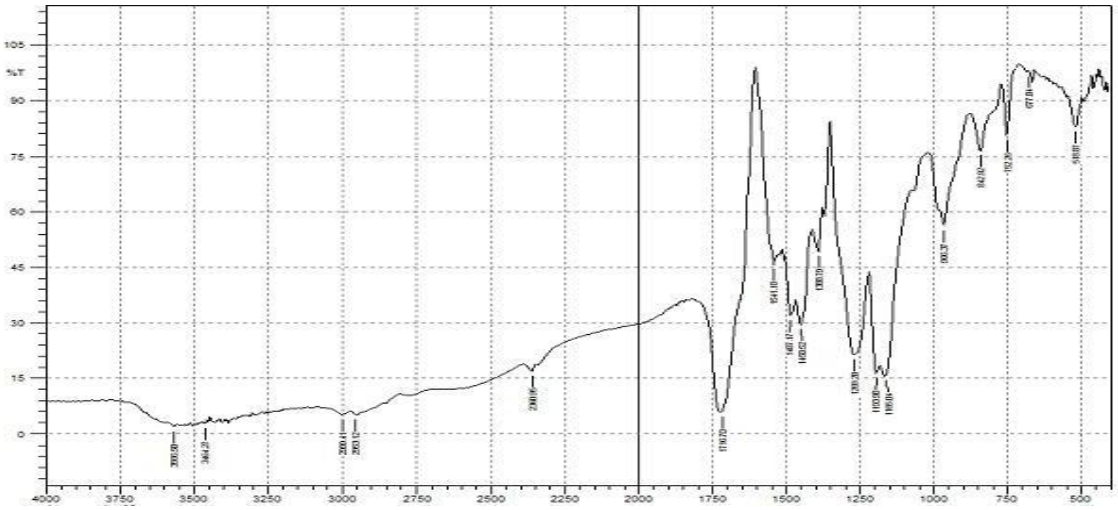
Weight reduction / starting weight multiplied by 100 percent equals reliability.

Tablets with less than 1% friability are taken into account.

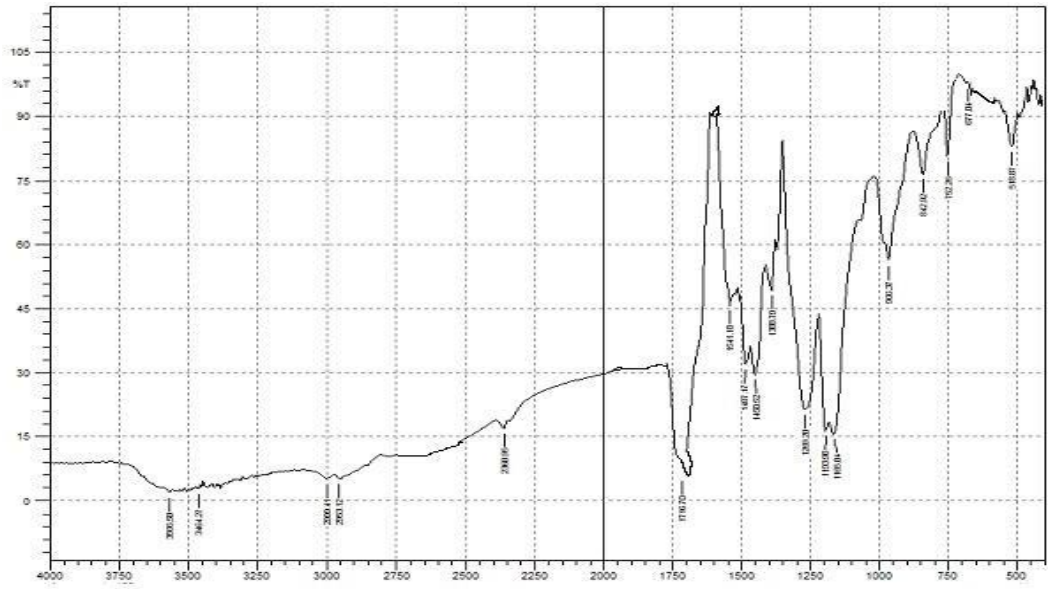
Thickness

A straightforward approach may be used to measure tablet thickness. Varnier callipers were used to gauge the thickness of 5 tablets.

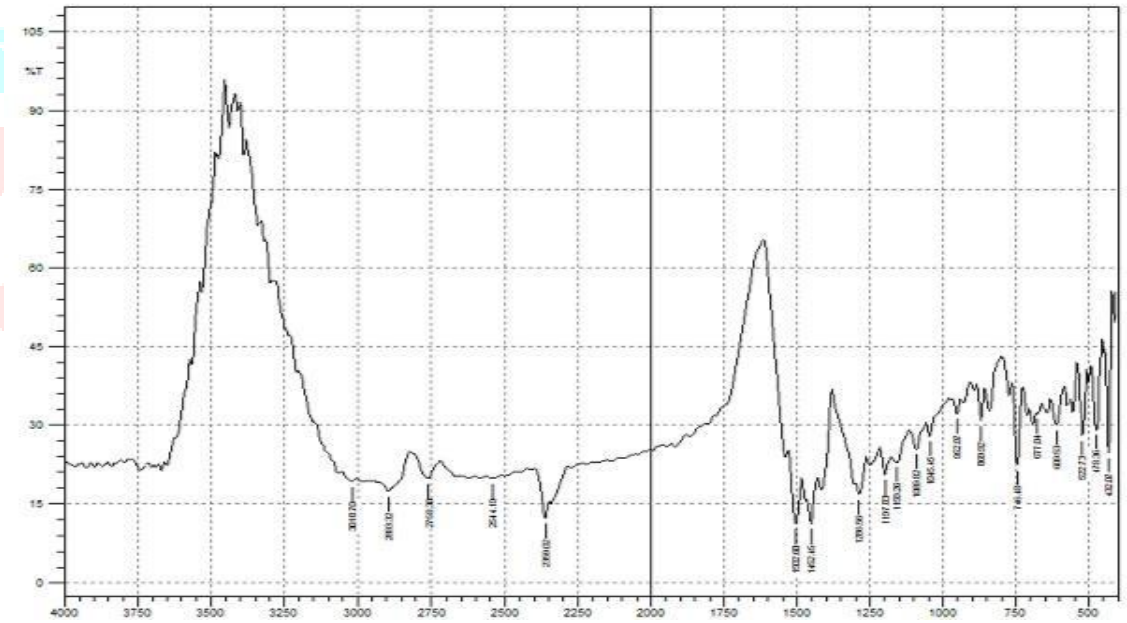
Results & Discussion:



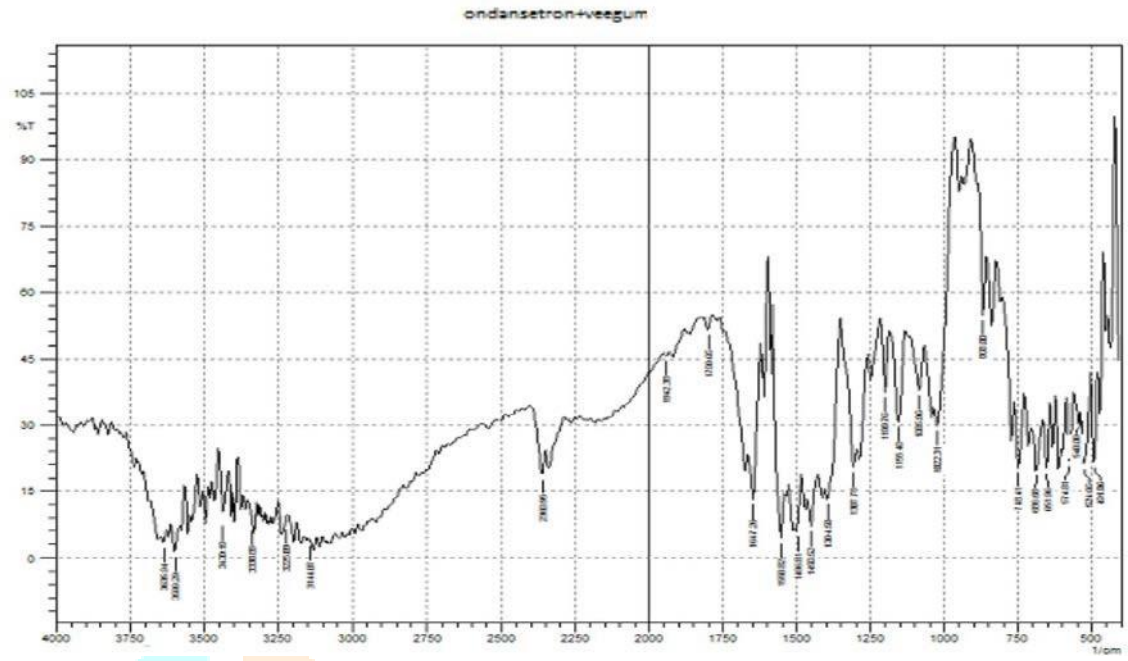
FTIR Spectra of Ondansetron (Standard)



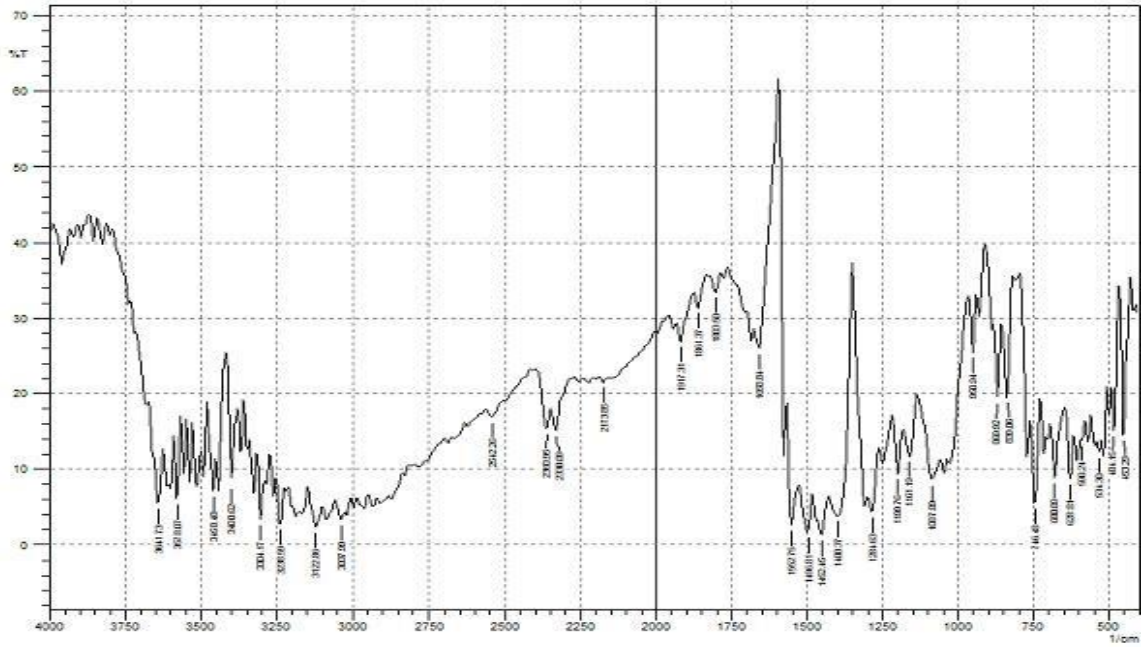
FTIR Spectra of ondansetron (Sample)



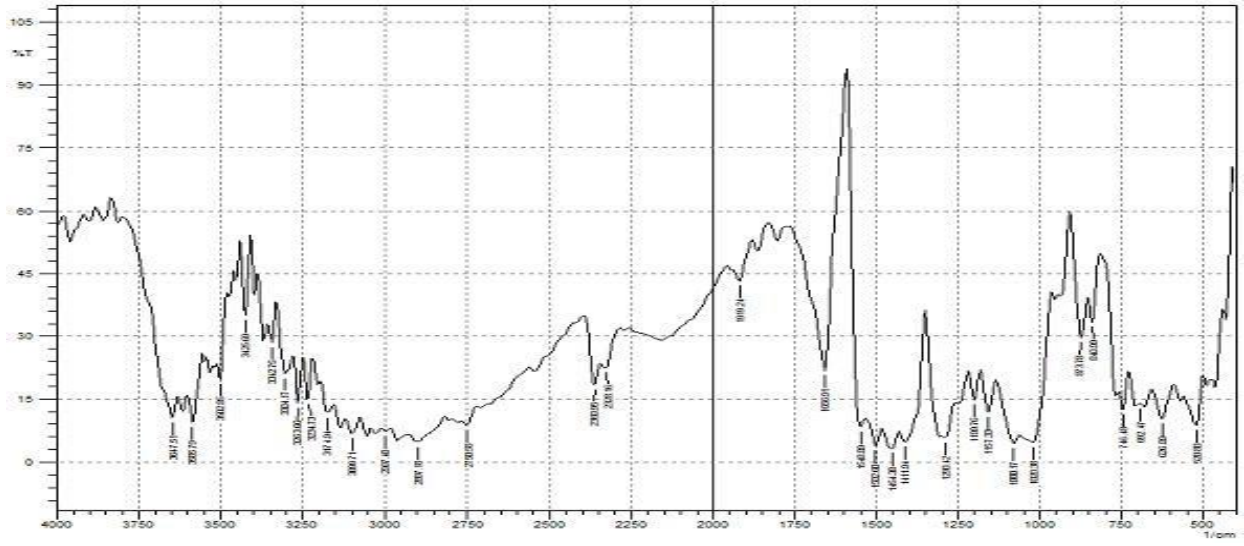
FTIR Spectra of Ondansetron and Kyron



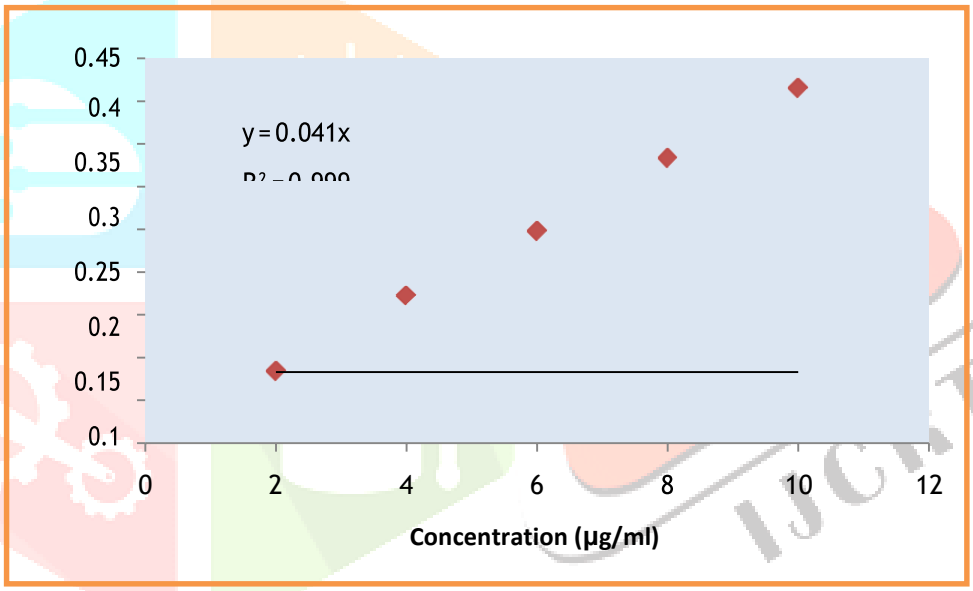
FTIR Spectra of ondansetron and Veegum



FTIR Spectra of ondansetron+mannitol+microcrystallinecellulose+kyron



FTIR Spectra of ondansetron + mannitol + microcrystallinecellulose+Veegum



Standard curve of ondansetron in methanol

Standard curve of ondansetron in methanol

Sample no.	Concentration (µg/ml)	Absorbance (nm)
1	2	0.085
2	4	0.173
3	6	0.248
4	8	0.334
5	10	0.416

Partition coefficient value of ondansetron

S.No.	Solvent System	Partition Coefficient
1.	Water	2.12

Solubility profile of ondansetron in different solvents

S.No.	Solvent (s)	Solubility indicator
1.	Methanol	++++
2.	Water	++++
	++++ Very Soluble less than 1 part	

Ondansetron was provided as a gift sample by Sun Pharmaceuticals Ltd. in Vadodara, India, and was the subject of preformulation research. The drug's melting point was discovered to be 2300C, which perfectly matched the figure given in the literature.

IR and UV spectroscopy were also used to identify ondasentron. Ondansetron's identification was supported by distinctive peaks that corresponded to functional groups found in the drug's molecule. Using a JASCO Japan UV visible spectrophotometer, the ondansetron solution in methanol was scanned in the 400-200nm region. Methnol's max was discovered to be 266 nm. Ondansetron's standard curve was created in methol at 266nm. For concentration ranges of 2–10 g/ml, the estimation method was shown to be reasonably repeatable and tolerably sensitive; standard curve values are provided in table 4.1. Ondansetron was determined to be extremely soluble in both methol and water for equilibrium solubility. The outcome was displayed in table 4.3. It was discovered that the partition coefficient between water and n-octanol was 2.12, which is quite comparable to the number listed in the literature. The outcome was displayed in table 4.2. Based on how well they worked together, the medication and polymer were chosen. Infrared spectra of the drug's absorption with various polymers were displayed. Fast dissolving tablet preparation polymers were discovered to be drug-compatible.Fourier Transform Infrared Spectroscopy (FTIR) analysis of the pure medication (odansetron) alone and in combination with the polymers (kyron and veegum) under examination was done as part of the preformulation study. Figure presents IR spectra. In the presence of polymers, the major frequencies of the functional groups of pure drugs remained unaltered. Therefore, there is no significant interaction between the medicine and the study's polymers.

Future Prospective:

Famotidine's absorption and bioavailability can be increased by the floating microspheres by maintaining the system in the stomach for a long time. The solvent diffusion-evaporation technique was used to create floating microspheres containing famotidine from a range of polymers, including ethyl cellulose and hydroxy propyl methyl cellulose. The microspheres had excellent packing, free-flowing characteristics, and smooth surfaces. The highest concentration of medicine was found in ethyl cellulose microspheres, with a yield of up to 73.320.14%. With diameters of 331.6 nm, scanning electron microscopy verified their hollow architectures. Many dissolving models were given data on in-vitro release and release kinetics. This effective and efficient method for continuous drug release over an extended period of time was shown to increase the oral bioavailability, efficacy, and patient compliance with famotidine floating microspheres.

Discussion:

In the pharmaceutical industry, oral medication delivery is recognised as the best method of administration. because it is more patient-compliant than many other approaches, such as parenteral and topical, and offers a number of advantages. Oral administration is the most practical route of administration since it is simple to consume, flexible enough to accept a variety of drug candidates, pain-free, and most significantly, patient compliance. The Oro dispersible tablets, which quickly dissolve in the tongue before being consumed, are mentioned in the European Pharmacopoeia. ODTs are solid dosage forms that include a medication or active ingredients that dissolve quickly in a few seconds when placed on the tongue, according to the US Food and Drug Administration. When drugs are absorbed through the mouth, throat, and oesophagus as the saliva descends into the stomach, their bioavailability can be significantly higher than with conventional tablet dosage.

Conclusion:

The concentration vs. absorption graph for the drug sample complies with Beer's law and is almost perfectly straight, it is obvious that the sample was pure. The output of microballoon manufacture was good. The microspheres floated well for more than 12 hours. SEM verified their spherical form, smooth surface with perforations, and hollow interior. In vitro drug testing was done in pH 1.2 Simulated Gastric Fluid. Various drug release kinetics models were applied to select batches. Hugichi was found to be the ideal match model for kinetic drug release. The hollow floating microspheres were made using the solvent evaporation diffusion method. The floating microspheres are made of free-flowing powder with a particle size of less than 100 m. Different batches have been made, and the result. The effects of numerous factors have been studied on a number of produced batches. The average particle size of the microspheres was determined by optical microscopy. It was found that the mean particle size of the microspheres rose when the drug polymer ratio was raised in the batches. When the volume of the internal phase was decreased, the mean particle size of the microspheres dramatically grew. Additionally, we deduced that the formulation's higher stirring rate had

resulted in smaller particle sizes. The bulk density of the powder after a certain compaction method is referred to as "tapped density". It is based on tapped density since bulk density is a property that can vary depending on how a material is processed. This strategy may be useful in creating a formulation with ideal pharmacokinetic patterns since it is well known that the physical characteristics of the dosage form have an impact on the pharmacokinetic characteristics of the medication. We can optimise the processing settings to develop the necessary properties in our formulation after analysing the effects of such factors on the physical characteristics of the microspheres.

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