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Aishwarya Katkar
Research Scholar,
P.E.S's Rajaram and Tarabai Bandekar College of Pharmacy
Farmagudi Ponda, Goa, India

Shilpa Bhilegaonkar
Associate Professor,
P.ES's Rajaram and Tarabai Bandekar College of Pharmacy
Farmagudi Ponda, Goa, India

Punita Naik
Research Scholar,
P.E.S's Rajaram and Tarabai Bandekar College of Pharmacy
Farmagudi Ponda, Goa, India

Corresponding Author:
Aishwarya Katkar
Research scholar
P.E.S's Rajaram and Tarabai Bandekar College of Pharmacy
Farmagudi Ponda, Goa, India

Development of floating drug delivery system of ondansetron hydrochloride using natural carriers

Aishwarya Katkar, Shilpa Bhilegaonkar and Punita Naik

Abstract
The aim of the present research work was to formulate and evaluate gastro-retentive floating dosage form of Ondansetron hydrochloride using a natural carrier system to improve its residence time in the stomach for better absorption of drug for the treatment of nausea and vomiting caused by chemotherapy drugs, radiation therapy and surgery. The natural carriers were used as an alternative to the synthetic polymers to avoid its unnecessary introduction in the body. Ondansetron hydrochloride is a competitive serotonin type 3 receptor antagonist. It is effective and widely used in the treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs, radiation therapy and post-surgery. The current marketed formulations are injectable solutions, tablets, oral solutions, films and orally disintegrating tablets. Ondansetron hydrochloride when administered orally is absorbed rapidly and possesses a bioavability of 67% and short biological half-life of about 3 hours. Hence to prolong the gastric residence time and to get a controlled release of drug and reduce dosing frequency, it was proposed to develop floating drug delivery system of Ondansetron hydrochloride.
In this study, banana based carriers were tested for its floating ability and utilized in the development of the novel floating drug delivery system. Two different banana based carriers were developed, banana stem carriers and banana leaf carriers. The carriers were coated using two polymers i.e. Ethyl cellulose and hydroxy propyl methylcellulose. The carriers were further evaluated for following parameters: dimensions, appearance, drug content, bulk density, tapped density, *in-vitro* drug release studies in 0.1 N HCl, floating time and floating lag time. The carriers were found to show excellent buoyancy for more than 12 hours. The carriers were further subjected to accelerated stability testing according to ICH guidelines and were found to be stable hence could be used as floating carriers for delivery of Ondansetron hydrochloride.

Keywords: Ondansetron, hydrochloide, banana stem, vomiting

Introduction
[1-3] Nausea is a diffuse sensation of unease and discomfort, often perceived as an urge to vomit. While not painful, it can be a debilitating symptom if prolonged, and has been described as placing discomfort on the chest, upper abdomen, or back of the throat. Vomiting (also known as puking, throwing up, barfing, emesis, among other names) is the involuntary, forceful expulsion of the contents of one's stomach through the mouth and sometimes the nose. The medical definition of Vomiting, an act or instance of disgorging the contents of the stomach through the mouth called also *emesis.* Vomiting can be caused by many conditions; it may be present as a specific response to ailments like gastritis or poisoning, or as a non-specific sequel ranging from brain tumors and elevated intracranial pressure to over exposure to ionizing radiation.

Nausea and Vomiting in Cancer patients
[4-7] Nausea and vomiting (N&V) are common side effects cancer patients might suffer from. This side effect induced by chemotherapy, radiotherapy and some medications as opioids. N&V prevention is still underestimated. Chemotherapy induced nausea and vomiting are classified as acute and delayed. Acute N&V occur within 24 hours after chemotherapy and delayed N&V occur 24 hours after treatment. Guidelines for prevention of N&V have been developed by National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and the Multinational Association for Supportive Care in Cancer (MASCC)/ European Society of Medical Oncology (ESMO). These guidelines are classified according to the risk of emesis into high emetic risk, moderate, low and minimal risk.

[8-10] Complications of Vomiting

Aspiration

Vomiting is dangerous if gastric content enters the respiratory tract. Under normal circumstances the gag reflex and coughing prevent this from occurring; however, these protective reflexes are compromised in persons who are under the influence of certain substances (including alcohol) or even mildly anesthetized. The individual may choke and asphyxiate or suffer aspiration pneumonia.

Dehydration and electrolyte imbalance

Prolonged and excessive vomiting depletes the water (dehydration), and may alter the electrolyte status. Gastric vomiting leads to the loss of acid (protons) and chloride directly. Combined with the resulting alkaline tide, this leads to hypochloremic metabolic alkalosis (low chloride levels together with high HCO^{-}_{3} and CO_2 and increased blood pH) and often hypokalemia (potassium depletion).

Mallory–Weiss tear

Repeated or profuse vomiting may cause erosions to the esophagus or small tears in the esophageal mucosa (Mallory–Weiss tear). This may become apparent if fresh red blood is mixed with vomit after several episodes.

Dentistry

Recurrent vomiting, such as observed in bulimia nervosa, may lead to the destruction of the tooth enamel due to the acidity of the vomit. Digestive enzymes can also have a negative effect on oral health, by degrading the tissue of the gums

Preventing Vomiting

Treatment plan are best course of action for related medical conditions. Vomiting trigger can vary between patients. These may include excessive alcohol consumption, eating too much food, migraines, exercising after eating, stress, hot or spicy food, lack of sleep etc. Adopting better lifestyle habits can prevent vomiting episodes. It's difficult to entirely avoid viruses that cause vomiting, but you can reduce your chances of getting exposed to a virus by maintaining good hygiene, like regular hand washing. Knowing how to treat recurrent vomiting can help you avoid further complications**.**

Antiemetic Drugs

[11-13] Some of the best known antiemetic drugs are:

- **Droperidol**

Low doses; administered usually IV – prevents post-operative nausea and vomiting

Some reports claim that Droperidol is better than metoclopromide or domperidone.

Droperidol reported useful as antiemetic for patients having caesarean section using spinal anesthesia.

Low doses not always effective – higher doses (at the end of surgery) may cause excessive recovery room sedation.

- **Metoclopromide**

Inconsistent, controversial for preoperative use.

- **Ondansetron**

5-HT3 receptor antagonist (serotonin antagonist)

Administration; IV 4-8 mg (adult) before induction: highly efficacious in preventing post operative nausea and vomiting.

Should be used selectively.

Very effective in preventing nausea and vomiting caused by chemotherapy and surgery, major role in management of nausea and vomiting due to anticancer drugs.

- **Tropisetron**

5HT3 receptor blocker

Effective in managing symptoms induced by carcinoid syndrome – also some gastro kinetic characteristics.

Effective in preventing chemotherapy and radio therapy induced emesis.

Effective in preventing postoperative nausea and vomiting when administered before general anesthesia induction.

- **Granisetron**

More selective 5-HT3 receptor blocker compared to Ondansetron

Clinical use: Effective in chemotherapy induced emesis

Effective in preventing postoperative nausea and vomiting

Elimination half-life: Nine hours, compared to about three hours of Ondansetron, suggesting less frequent dosing with granisetron.

Significantly higher cost, limiting the clinical use.

Choice of Ondansetron

[14] An antiemetic is a drug that is effective against vomiting and nausea. Antiemetics are typically used to treat motion-sickness and the side effects of opioid analgesics, general anesthesia and chemotherapy directed against cancer. They may be sued for severe cases of gastroenteritis, especially if the patient is dehydrated.

Ondansetron was patented in 1984 and approved for medicinal use in 1990. It is on the World Health Organization's list of essential medicines. It is considered to be amongst the most effective and safe medicines needed in health system. It is available as a generic medication. The wholesale cost of injectable form in the developing world is about US$0.10 to US$0.76 per dose making it cheap yet effective drug.

Advantage of using Natural carriers in formulation of antiemetic dosage forms

[15] Excipients are important partners in formulation that decide dosage form as well as pharmacokinetic and pharmacodynamics of medicament. In contemporary era, excipients are used from synthetic resources, causes unwanted effects in pharmaceutics and therapeutics. So, industries are looking towards natural resources as it delivers safe, cost effective, biodegradable, biocompatible and inert excipients to pharmaceutical industries. Leading organizations like WHO (World Health Organization), ICH (International Conference on Harmonization), IPEC (International Pharmaceutical Excipient Council) are working together to sort of complications which arise due o synthetic excipients and thus they are showing their faith inside traditional wisdom. Also in the market, consumers look for natural ingredients for food, drugs and cosmetics as they believe that anything natural will be more safe and devoid from side effects.

Hence it was decided to formulate novel dosage form of Ondansetron hydrochloride using natural carriers to explore

suitability of natural substances to deliver Ondansetron hydrochloride.

Floating drug delivery system

[16-19] Floating systems or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The bulk density of these systems is more than the gastric fluids and therefore, without affecting gastric emptying rate they remain buoyant in the stomach for a long time period. When the system is floating on the gastric fluid, the drug releases occurs slowly. The residual system is emptied from the stomach when drug is released. This results in an increased gastric residence time and a good control of the rise and fall in plasma drug concentration. The aim for designing controlled floating delivery system to increase effectiveness of drug by localization at the site of action and/ or to reduce the frequency of dosing or reducing the dose required or providing uniform drug delivery with high bioavailability of buoyant drugs.

[20] Natural Carriers: Banana Stem and Banana Leaf:

The banana plant is the largest herbaceous flowering plant. All the above-ground parts of a banana plant grow from a structure usually called a corm. Plants are normally tall and fairly sturdy, and are often mistaken for trees, but what appears to be a trunk is actually a "false stem" or pseudostem. Bananas grow in a wide variety of soils, as long as the soil is at least 60 centimeters (2.0 ft) deep, has good drainage and is not compacted. The leaves of banana plants are composed of a "stalk" (petiole) and a blade (lamina). Cultivated banana plants vary in height depending on the variety and growing conditions. Most are around 5 m (16 ft) tall, with a range from 'Dwarf Cavendish' plants at around 3 m (10 ft) to 'Gros Michel' at 7 m (23 ft) or more. Leaves are spirally arranged and may grow 2.7 meters (8.9 ft) long and 60 cm (2.0 ft) wide.

Banana stems are botanically a part of the Musa genus and are actually a flower stalk of a large, herbaceous plant belonging to the Musaceae family. All parts of the banana plant are edible, and though the fruits are the most commonly consumed portion of the plant, the leaves and stalks are also used for a variety of culinary applications in Asia. Banana stems are predominately utilized in South Indian cuisine, favored for its mild flavor, ability to complement many different spices, crisp texture, and high nutritional properties. Banana stems vary in size, averaging at least five centimeters in diameter when sold in markets, and are cylindrical to elongated in shape. The outer layer of the stem is a fibrous, green sheath that is inedible and tough to remove. Underneath this layer, the core is the edible portion of the stem and is white to pale green-yellow with a firm, dense consistency. Banana stems are crisp with a texture similar to jicama and have a mild, sweet-tart, vegetal flavor.

[21-22] Banana stems are high in fiber and can aid in the treatment of ulcers or an acidic stomach. Like the fruit, Banana stems are also very high in potassium and vitamin B6, which together benefit the muscles and the body's production of hemoglobin and insulin. Its high fibre content creates a feeling of satiation and hence, reduces the intake of food. It also helps ease constipation. Banana stem is rich in potassium and vitamin B6 just like the fruit. Potassium helps in the proper functioning of muscles, including the cardiac muscles. It also helps prevent high blood pressure, and maintain fluid balance within the body. Banana stem is said to be a diuretic and helps detoxify the body. It is used prevent and treat kidney stones.

The leaves are used for dressing wounds & blistered skin and also used to treat asthma & wheezing. These leaves were found to have phenolics and tannic acid from ethanol, methanol, acetone and petroleum ether extracts & alkaloids, steroidal lactones, cinnamic acid and ferulic acid from them powdered methanol extract. The idea behind using Banana leaf while eating food is it has dominant fire element in it the food placed in it before intake of the food will highly get energized and further will easily assist for us to digest the food easily. Eating your food in banana leaf have many health benefits are they Stimulate the appetite, good remedy for Inflammation, kills the germs in the food, cures kidney & Bladder problems, purifies the blood, soothes the mucous lining and cures ulcers.

Future Potential

The fluctuations in the plasma level of drug are reduced and results in delayed gastric emptying. Many drugs due to their limited absorption to the upper gastrointestinal tract have poor bioavailability; can be delivered efficiently in this type of dosage form and thereby maximizing their absorption and improving their absolute bioavailability. For the treatment of gastric and duodenal cancers buoyant delivery system considered as a beneficial strategy. In study banana stem and leaf is used to increase the residence time of the Ondansetron in the stomach inorder to prevent nausea and vomiting.

Fig 1: Banana stem

Fig 2: Banana leaf

Materials and Methods

Chemicals	Manufacturer
Ondansetron Hydrochloride	Zydus Cadila Healthcare Limited, Kundaim Industrial Estate, Kundaim Ponda, Goa.
Banana stem	Local Plantation, Goa
0.1 N Hydrochloric Acid	S.D. Fine Chemical Ltd, Mumbai
Hydroxy propyl methyl cellulose K 100 M	Kemphasol, Mumbai
Ethanol	S.D. Fine Chemical ltd, Mumbai

Development and evaluation of novel floating carriers

Development and Evaluation of Banana based carriers

Many polymers of natural origin could be suspected to have floating ability. The research was conducted to find out the realistic potential of these carriers as floating carriers and also to understand its suitability, for use in drug delivery systems.

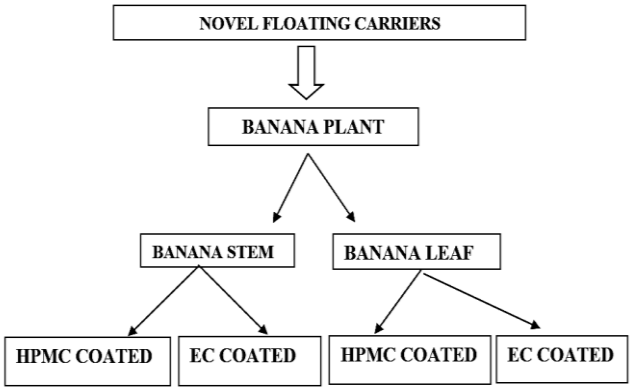

Fig 3: Flowchart of the Research conducted

Separation of Banana stem from plant

The Banana stem was procured from a nearby local plantation. The stem was then cleaned; the outer layers were carefully removed and cut into small pieces. The small pieces were then washed gently with water and stored for drying step.

Evaluation of Floating ability of Fresh Banana stems

The fresh Banana stem pieces were placed in a beaker containing 50 ml of water to determine its floatability. The time taken for the stem pieces to remain buoyant was recorded.

Drying of Banana stem pieces

The moisture from the banana stem pieces was removed by drying in a hot air oven. The separated banana stems were placed in a petri dish and subjected to drying in a hot air oven, maintained at a temperature of 60 ºC for a period of 1-2 hours with intermittent visual observation over the changes in the colour of the stem pieces during drying period.

Evaluation of Floating ability of Dried Banana stem carriers

Dried banana stem pieces were placed in USP apparatus II Dissolution flask set to 50 rpm. The time it takes to remain in a state on buoyancy was recorded.

Drug Loading of Banana stems carriers

A concentrated aqueous solution of Ondansetron Hydrochloride was prepared by dissolving 8 mg of drug in 2ml of distilled water. The dried Banana stem pieces were soaked in concentrated drug solution for a period of 24 hours. After 24 hours, the soaked stem pieces were then allowed to air dry.

Coating of the Banana based carriers

The various polymers used for coating are Ethyl cellulose (EC), Sodium carboxy methyl cellulose (SCMC), Hydroxy propyl methyl cellulose (HPMC K4M). The coating solutions were prepared in different concentrations such as 10%, 15% and 20%. Ethyl cellulose and Hydroxy propyl methyl cellulose were selected, in concentration of 20% each. The ideal polymer in the required concentration was selected. Based on the evenness and uniformity HPMC 4KM 20% was chosen as the optimized polymer concentration and the best coated seeds were further used for evaluation.

Approaches of Coating

Four approaches of coating were used. An ideal coat was used to study the drug release. The approaches are as follows:

1) Drug loaded Uncoated substrate

Drug loading of the uncoated substrate was the first approach used in the study. In this approach the uncoated substrate was loaded with 8 mg of drug by absorption method. The uncoated stem pieces were used for comparing the efficiency of the coating polymers.

2) Load and Coat

This is the second approach where in the dried stem pieces were first loaded with drug solution containing 8 mg of Ondansetron hydrochloride by absorption method and then subsequently coated using 20% Ethyl cellulose solution and 20% HPMC solution.

3) Surface Coating (coat and load)

In the third approach, the dried stem pieces were first coated using 20% HPMC and 20% EC polymeric solution each and dried, and then the drug loading was carried out by absorption of the drug onto the coated stem pieces.

4) Simultaneous Coating

The fourth approach was Simultaneous load and coat; where in 8 mg of Ondansetron Hydrochloride was dissolved in 1ml of distilled water. To this drug solution 20% HPMC K4M was added and mixed. This mixture was then applied on the stem pieces to form a uniform coat. The same was repeated with 20% EC polymeric solution.
All the coated Banana stem pieces were further evaluated.

Evaluation of Banana stem carriers

The following are the evaluation parameters for the Banana stems.

- **Dimensions**: Dimensions of the Banana stem pieces were measured using Vernier Calliper.
- **Appearance:** The colour, odour, taste and form of the dried banana stem pieces were noted by visual observation.

- **Bulk Density**: A 10 ml measuring cylinder was filled up to the mark with the dried banana stem pieces. The cylinder was tapped three times to settle the pieces up to the mark. The mass of the stem pieces and bulk volume was recorded. Bulk density was calculated.
- **Tapped Density:** A 10 ml measuring cylinder was filled up to the mark with the dried banana stem pieces. The cylinder was tapped 50 times. The mass of the stem pieces and the tapped volume was recorded. Tapped density was calculated.
- **Drug Content:** Six drug loaded stem pieces were soaked in 10 ml 0.1 N HCL for 24 hours. The solution was then sonicated for 20 minutes and filtered. From this filtered solution 0.1 ml was pipette into a 10 ml volumetric flask and the volume was made up by using 0.1 N HCL. The solution was analyzed spectrophotometrically using UV Shimadzu 1800 at 310 nm.
- ***In-Vitro* Drug Release Studies:** *In-Vitro* drug release studies were carried out using USP Type 2 paddle apparatus, in 900 ml of 0.1 N HCL as the dissolution medium at a speed of rotation of 50 rpm and temperature maintained at 37ºC± 5ºC. Samples were withdrawn after every hour for a period of 12 hours.
- **Total Floating Time:** The Total time up to which banana stem pieces floated was recorded.
- **Floating Lag Time:** The banana stem pieces were dropped into a dissolution flask containing 900 ml of distilled water. The time taken for the seeds to sink in and travel back to the surface was noted.

Banana leaves floating carriers

Separation of Leaf Carriers

A. **Separation of Disc shaped Leaf Carriers:** The banana leaf was washed gently with water, and cut into small disc. These disc shaped carriers were then air dried.

B. **Evaluation of Floating ability:** The floating ability of the disc shaped carriers were checked in the similar way as described in section 5.2.1.B.

C. **Drying of Banana carriers**: The disc shaped carriers were in hot air oven for 15 minutes at 40ºC.

D. **Evaluation of Floating ability of Dried Disc shaped carriers**: The evaluation was done in similar way as described in above section 5.2.1.D.

E. **Drug Loading of Leaf carriers**: Since the Banana leaf is not porous in nature drug loading by absorption method was not possible, hence the drug loading and coating of the carriers were done simultaneously which is described in section G. The drug loaded leaf carriers were further evaluated for further parameters.

F. **Coating of Banana Leaf carriers**. The Banana leaf is not porous hence does not absorb any solution; therefore absorption method was not used for loading of drug. The coating of leaf disc carriers was done by 2 methods.

- Surface Coating (coat and load).
- Simultaneous Coating.

The first method used for coating of disc carriers is the Surface coating i.e. the coat and load method. Here the disc carriers were first coated with polymeric solution and was dried in hot air oven at 60 ºC for 15 minutes, the dried substrate was then loaded with drug by absorption method. The polymers used for coating of disc carriers are same as that used for stem carriers, 20% Ethyl cellulose and 20% Hydroxy propyl methyl cellulose K4M.

The second method used for drug loading for the leaf carries was Simultaneous Coating Method. In this method the drug and the polymer were dissolved in required solvent, to from a drug polymer coating. This coating was then applied to the leaf carriers to form a uniform coat. After coating the carriers were dried in a hot air oven at 60 ºC for 15 minutes. The dried coated disc shaped banana leaf carriers were further evaluated.

G. Evaluation of Banana Leaf Carriers: The Banana leaf carriers were evaluated for the same parameters as described in 5.2.1.F.

Evaluation of Coated Banana Carriers:

The film coated banana carriers were evaluated based on the same parameters described in section 5.2.1.F Evaluation of Banana stem pieces.

Development and evaluation of finished dosage form for delivery of ondansetron hydrochloride

The novel optimized drug carriers obtained by using banana i.e. the leaf and stem carriers were incorporated into a suitable pharmaceutical drug carrier, i.e. capsule, for facilitating administration of drug by patients.

The capsule size was chosen according to the number of carriers to be administered at a time is shown below:

Table 2: Size of Capsule and number of Drug loaded carriers filled

Drug Carrier	No. of Carrier for Single Dose	Size of Capsule
Banana Stem Carriers	1	0
Banana Leaf Carriers	6	0

The respective capsules were filled by hand- filled method with accurate number of carriers for delivery of drug. The capsules were further evaluated as per IP specifications for various parameters of finished dosage form for regulatory acceptance.

Evaluation Parameters for Finished Dosage form

The evaluation parameters are as follows:

i. **Dimensions:** The length of body and cap of 10 randomly selected capsules were measured by using a Vernier Calliper. The average length of body and capsule was calculated.

ii. **Appearance:** The shape, colour and visual appearance of capsule was observed.

iii. **Uniformity of Weight:** An intact capsule was weighed. The capsule was opened without losing any part of the shell and the contents were removed as completely as possible. The shell was then weighed. The difference between the weights gave the weight of the contents. The procedure was repeated with another 19 capsules. Not more than two of the individual weights must deviate from the average weight by more than the percentage shown in the table and none should deviate by more than twice the percentage.

Table 3: Percent Deviation as per IP

Dosage Form	Average Weight	Percent Deviation as per IP
Capsules	Less than 300 mg	10
	300 mg or more	7.5

i. **Drug Content:** The contents of one capsule were emptied in a beaker containing 10 ml of 0.1 N HCl. The carriers were soaked in the buffer for 24 hours. The solutions were then sonicated for 20 minutes and filtered. Subsequent dilutions were made and absorbance of the solution was determined spectrophotometrically using Shimadzu 1800 at λ_{max} 310 nm.

ii. **Disintegration Time:** One capsule was introduced into each of the six tubes of the disintegration apparatus. A disc was added to each of the tube to hold the capsule in place. The assembly was then suspended in a beaker containing water and the apparatus was operated. The time taken for the capsule to completely disintegrate was recorded.
Limit as per IP: Capsule should disintegrate within 30 minutes. If 1 or 2 capsules fail to disintegrate the test is to be repeated on 12 additional capsules; not less than 16 of the 18 capsules tested must disintegrate.

iii. **Dissolution Testing:** Each of intact capsules containing the respective carriers was evaluated for dissolution testing under the following conditions:

Media: 0.1 N HCl
Temperature: 37 ºC ± 5 ºC.
Apparatus: USP Type I Basket apparatus.
Speed of Rotation: 50 rpm.
Sampling Interval: 12 hours.

Stability Studies

Short-term accelerated stability testing on the selected formulations was carried out for a period of 3 months with sample interval of one month. This is done in order to evaluate the stability of dosage form during the delivery period, also to determine the effect of presence of formulation additives on stability of the drug under accelerated storage conditions. The stability testing was carried out according to the ICH guidelines. The finished dosage form in capsules were sealed in glass bottles, internally packed with cotton balls, and were kept at elevated temperature conditions of 40 ± 2 ºC and 75% ± 5% RH for 90 days. Samples were evaluated for physical appearance and drug content.

Results and Discussion

Development and evaluation of novel floating carriers

Development and Evaluation of Banana stem based carriers.

A. Separation of Banana stem from the tree:

The separated Banana stem from the tree are shown in figure 4.

Fig 4: Fresh banana stem separated from the tree.

Evaluation of Floating Ability of fresh Banana stem pieces:

The fresh banana stem pieces were found to have a good extent of buoyancy and remained floating over water about 12 hours, as shown below in figure 5.

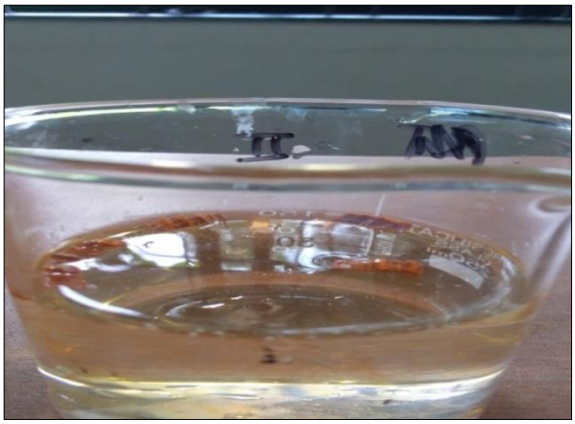

Fig 5: Fresh banana stem pieces floating in water

Drying of Banana stems

Banana stem pieces after drying in the hot air oven were found to appear darker and also did shrink in size, as shown in figure 6.

Fig 6: Dried Banana stems carriers

Evaluation of Floating ability of Dried Banana stem pieces

The floating ability of dried banana stem pieces was determined as described in sec 5.2.1.D.

Evaluation of Floating ability of Dried Banana stems.

The dried Banana stem pieces were found to have excellent floating ability and were found to remain floating for up to 12 hours, as shown in figure 6. Thus, it was decided to use dried banana stems as floating carriers for Ondansetron hydrochloride.

Fig 7: Dried Banana stem carriers floating

Drug loading of Banana stems

The dried banana stem pieces were loaded with Ondansetron hydrochloride as described in section.

Drug loading of Banana stems. It was found that the stem was sufficiently porous which would facilitate the drug to enter within the carrier by diffusion through its pores at the same time maintaining its buoyancy. Hence it is used in the study as a novel floating carrier.

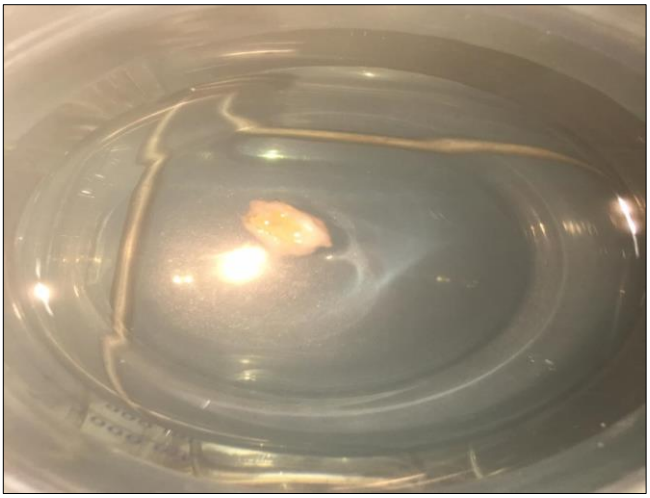

Fig 8: Drug loaded Banana stems floating in Dissolution flask.

Coating of Banana stem carries:

The drug loaded carriers were coated with two different polymers, Ethyl cellulose and Hydroxy propyl methyl cellulose. Different approaches were used for coating of Banana stem carriers i.e. Surface coating, Load and coat and Simultaneous coating. Coating was done to ensure efficiency and application of the carriers and also to get a controlled released system. The polymers were used in concentration of 10%, 15% and 20%.

The carriers coated with 20% polymer gave uniform coat as compared to the other two concentrations.

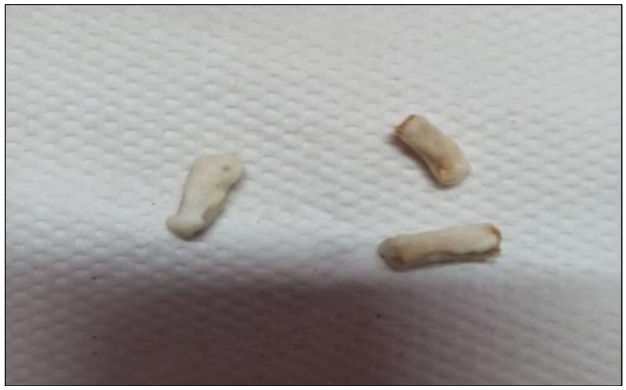

Fig 9: 20% EC coated Banana stem carriers.

Fig 10: 20% HPMC coated Banana stem Carriers.

Evaluation of Banana stems

Depending on the floating ability and physical stability of the banana stem based carriers, the dried banana stem pieces were further used for evaluation of parameters.

Evaluation of Uncoated and Coated Banana stem carriers:

The results of the evaluation parameters for uncoated, EC and HPMC coated banana stem pieces are given and discussed as follows:

- **Dimensions**

Table 4: Dimensions of Uncoated and Coated Banana stems:

Sr. No.	Uncoated Banana stem pieces		Coated Banana stem pieces	
	Length(mm)	Breadth (mm)	Length (mm)	Breadth(mm)
1	10.84	3.40	11.30	3.72
2	10.82	3.26	11.22	3.56
3	10.83	3.22	11.12	3.74
4	10.84	3.24	11.24	3.82
5	10.87	3.59	11.34	3.55
6	10.82	3.36	11.42	3.84
7	10.82	3.26	11.02	3.56
8	10.84	3.40	11.26	3.72
9	10.82	3.34	11.15	3.74
10	10.83	3.26	11.19	3.68
Average:	10.833	3.33	11.226	3.69

- **Appearance**

The colour, texture and shape of the stem are given in table 6.10.

Table 5: Appearance characteristics of Banana stem carriers.

	Uncoated Banana stem	Coated Banana stem
Colour	Light brown to pale yellow	White in color
Texture	Rough textured	Smooth textured
Shape	Slightly rectangular	Slightly cylindrical

- **Bulk Density**

Bulk Density of the banana stem carriers was found to be 0.236 gm/ml.

- **Tapped Density**

Tapped Density of the banana stem carriers was found to be 0.252 gm/ml.

- **Drug Content**

The drug content was performed as described in the above section. The drug content of uncoated and coated Banana stem pieces complied with Ondansetron hydrochloride limits of 95-105% as per IP, as given in table 6.

Table 6: Drug Content of Banana stems carriers

Banana stem carriers	Drug Content (%)
Uncoated Banana stem carriers	98.99%
EC Coated Banana stem carriers	97.11%
HPMC Coated Banana stem carriers	98.56%

- ***In-Vitro* Drug Release Studies:**

The in-vitro drug release studies of uncoated and coated banana stem strips were carried out in 0.1N HCL. The study was carried out for a period of 12 hours. The results are as given in figure 10,11, 12.

Since the Banana stem pieces were coated using different approaches, all the coated carriers were selected for dissolution studies, the results of which are given below.

The Uncoated carriers showed a maximum release at the 3rd hour (87.04%). This could be due to the porous nature of the banana stem which lead to burst release. Hence to get a controlled release pattern coating of the substrate is necessary.

The 20% EC coated carriers showed maximum release at the 8th hour following which the release decreased. Hence, Dissolution studies were carried out using 20% HPMC, the 20% HPMC coated carriers were used to check the peak release within 12 hour period as the EC coated carriers were capable of providing maximum release up to 8 hours only.

In case of uncoated carriers, the maximum drug release which is 87.04% was obtained at 3rd hour. This could be due to the greater permeability of the banana stem and could also cause the drug to release in an uncontrolled manner. Hence the carriers were coated with polymers to get a controlled released system.

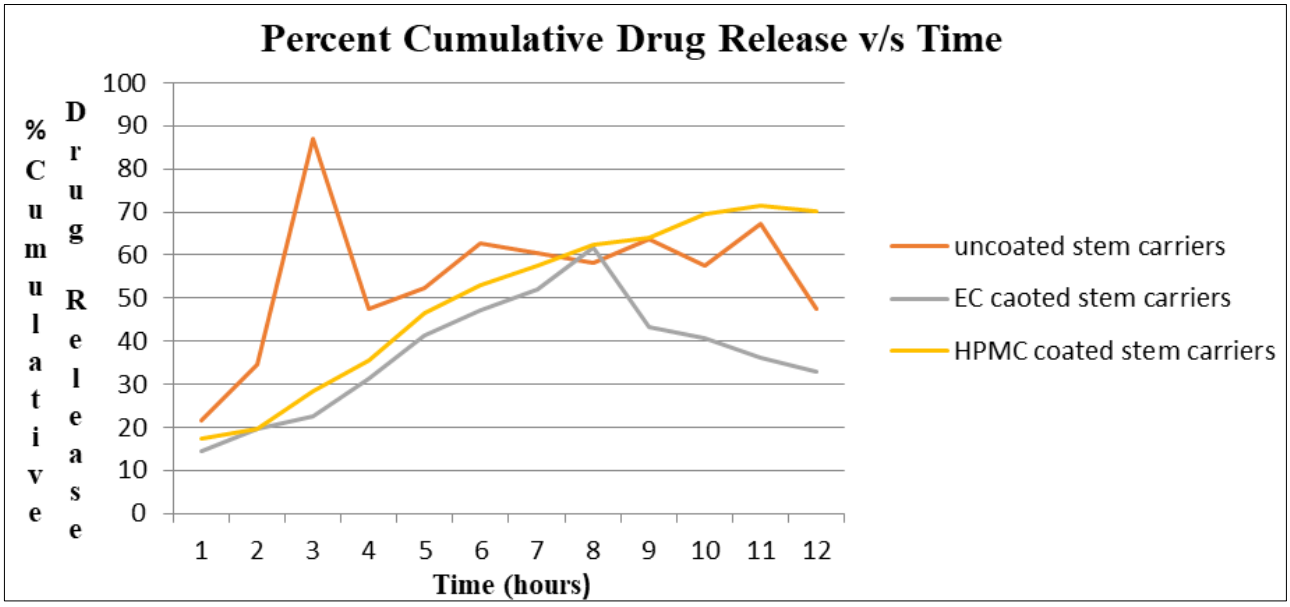

Fig 11: Percent Cumulative Drug Release of Uncoated, EC coated and HPMC coated Banana stem carriers (Load and Coat method).

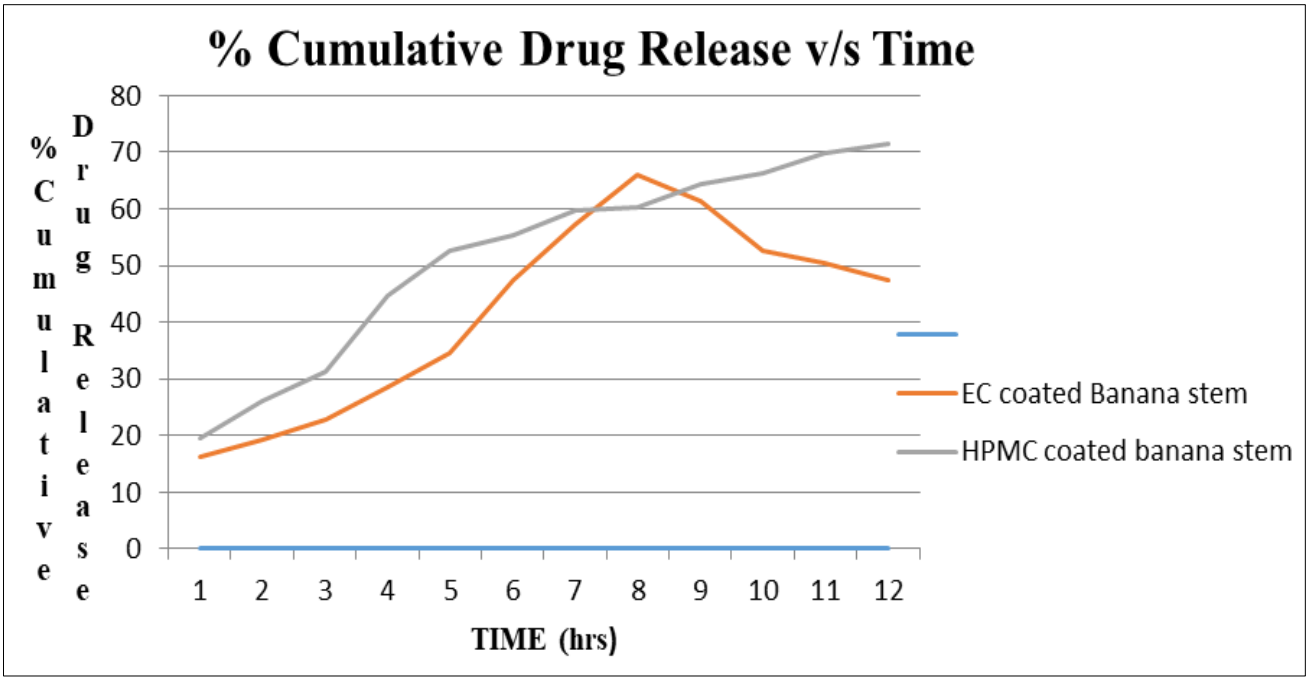

Fig 12: Percent Cumulative Drug Release of EC coated and HPMC coated Banana stem carriers (Surface coating)

The above results indicate that the stem carriers coated with 20% HPMC coat showed better release pattern, they released the drug in controlled manner. Whereas the stem carriers coated with 20% EC showed maximum release only up to the 8th hour, followed by decrease in the release of drug.

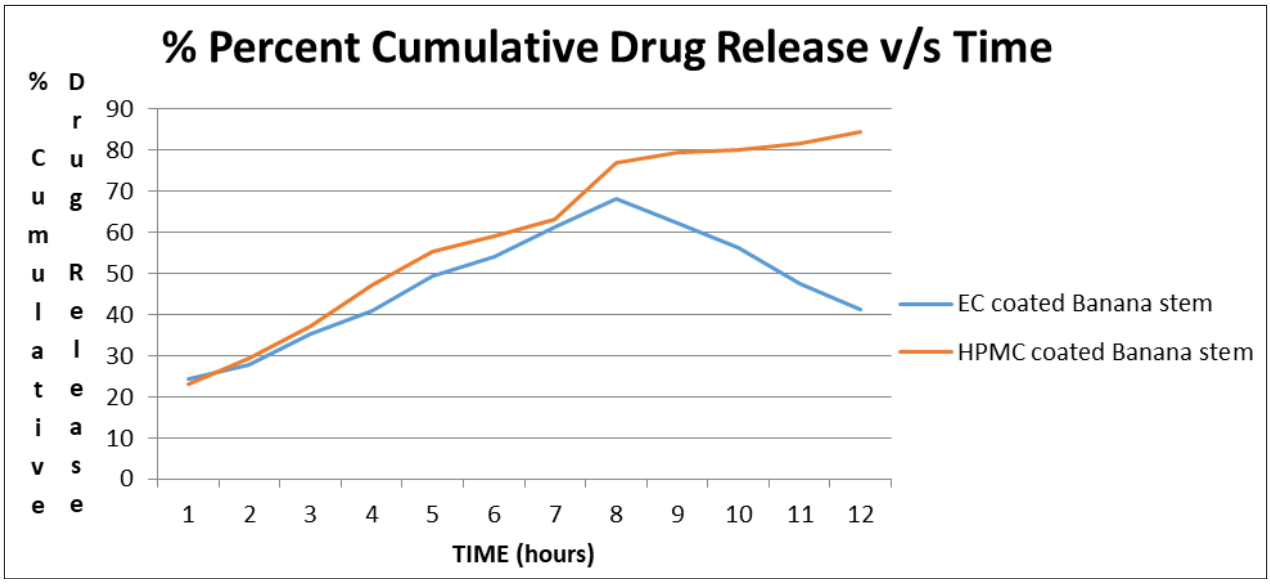

Fig 13: Percent Cumulative Drug Release of 20%EC and 20% HPMC coated Banana stem carriers (Simultaneous coating)

In case of 20% Simultaneous coat EC coated carriers; maximum drug release of 68.11% was observed at the 8th hour, following which the release decreased due to subsequent dilutions by dissolution medium.

In case of 20%HPMC Simultaneous coated stem carriers; it released the drug in a controlled manner, thus giving a maximum release of 84.23% at the 12th hour. Thus the stem carriers coated with HPMC 20% have given better results and hence are used for further evaluation of finished dosage from.

Form the above dissolution studies it can be stated that among the three approaches used for coating the carriers, the carriers coated using 20% HPMC by Simultaneous coating method showed desired drug release. The carriers coated with Surface coating and Load and Coat method have shown less release of drug as compared to the Simultaneous coat i.e. at the 12 hour the drug release was 71.63% (for surface coated carriers) and 70.32% (Load and coat method) which is less than the simultaneous coated carriers which have show a maximum release of 88.14% at the 12th hour.

Thus, proving that the carriers coated with Simultaneous coat using 20% HPMC K4M have shown desired release, and can be used further for evaluation of finished dosage form.

Development and Evaluation of Banana Leaf Carriers:

The development and Evaluation of leaf carriers is similar to that of stem carriers**.**

Separation of Banana leaf from tree: The leaf was gently washed and air dried and cut into small disc shaped carriers as given in figure 14.

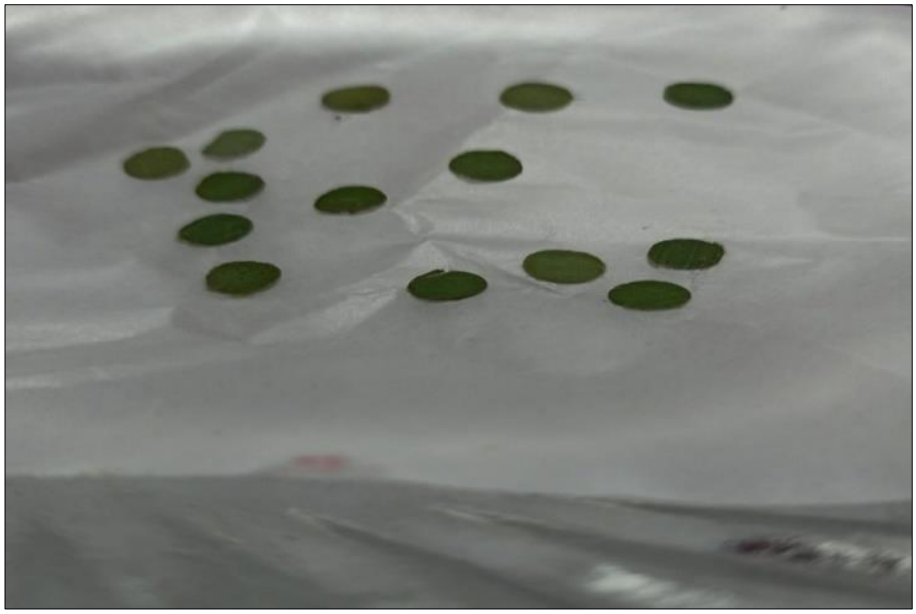

Fig 14: Fresh banana leaf carriers

Evaluation of the floating ability of fresh Banana Leaf Carriers

The fresh leaf carriers were evaluated for floating ability. The fresh leaf carriers were found to have good extent of buoyancy and remained floating over water for a period of 12 hours as shown in figure 15.

Fig 15: Floating ability of fresh Banana leaf

Evaluation of the floating ability of Dried Banana Leaf Carriers:

The banana leaf carriers after drying in hot air oven were found to appear dark in colour also did shrink in size as shown in figure 16.

Fig 16: Dried Banana Leaf carriers

Evaluation of Floating ability of Dried Banana Leaf Carriers

The dried Banana leaf carriers were found to have excellent floating ability and were found to remain floating for up to 12 hours, as shown in figure 16. Thus, it was decided to use dried banana leaf as floating carriers for Ondansetron hydrochloride.

Fig 17: Floating ability of dried Banana leaf carriers

Drug Loading of Banana Leaf Carriers:

The banana leaf being non-porous in nature, drug loading was not possible by absorption method. Hence drug loading of Banana leaf was carried out using two coating approaches i.e. Surface coating and Simultaneous coating. The polymers used were 20% EC and 20% HPMC K4M. The surface coating method involves first coating of the carrier and then allowing the coated carrier to absorb the drug solution. The simultaneous coating involves forming the drug polymer paste and then this was applied on to the carrier.

Fig 18: 20% EC coated Banana leaf carries.

Fig 19: 20% HPMC coated Banana leaf carriers.

Evaluation of Uncoated and Coated Banana leaf carriers: The Uncoated and coated leaf carriers were evaluated for different parameters; the results are given and discussed as follows:

- **Dimensions:** From the data of dimensions of leafs it indicated that there was no significant difference in dimensions. The average diameter of uncoated leaf was 0.164 mm, and that of EC coated was 3.798 mm and HPMC coated was 4.136 mm.
- **Appearance:** The appearance characteristics of uncoated and coated are discussed in table 6.17.

Table 7: Appearance characteristics of uncoated and coated banana leaf carrier

	Uncoated banana leaf carries	EC coated Banana leaf carriers	HPMC coated banana leaf carriers
Colour	Dark green in colour	White to off-white in colour	White in colour
Texture	Smooth texture	Smooth texture	Smooth texture
Shape	Disc shape	Disc shape	Disc shape

- **Bulk Density:** The bulk density of Banana leaf carriers was 0.234 gm/ml.
- **Tapped Density:** Tapped density of Banana leaf carriers was 0.246 gm/ml.
- **Drug Content:** The drug content of EC and HPMC coated leaf carriers comply with the limits given in IP, the results of which are given in table 11.

Table 8: Drug Content of Banana leaf carriers:

Banana leaf carriers	Drug Content (%)
EC coated leaf carriers	98.15%
HPMC coated leaf carriers	98.77%

- ***In-Vitro* Drug Release Studies:** In-Vitro Drug Release of EC and HPMC coated Banana leaf carriers were carried out in 0.1 N HCl. The study was carried out for a period of 12 hours. The results of which are given in figure 19 and 20.

The banana leaf carriers were coated using two types of polymers, i.e. 20% Ethyl cellulose and 20% hydroxy propyl methyl cellulose. The drug was loaded using two approaches Surface coating and Simultaneous coating. The carriers in which drug was loaded using Surface coating have shown poor drug release as compared to the carriers in which drug was loaded using Simultaneous approach. The reason for the poor drug release could be that the drug solution was not entirely absorbed by the coated carriers. Hence this proves that Surface coating is not a satisfactory method of loading the drug in banana leaf carriers, whereas the carriers in which drug was loaded by simultaneous coating have shown good drug release stating that simultaneous coating can be used for loading drugs in non-porous carriers.

The in-vitro drug release of banana leaf was compared using two different polymers, the carriers coated with 20% EC have shown maximum drug release up to the 8th hour (71.43%), followed by decrease in the drug release. At the end of 12th hour the drug release has decreased drastically i.e. 27.51%. This drug release is not desired in floating drug delivery system hence HPMC was used. HPMC is a cellulosic polymer and is used in the development of controlled released drug delivery system, the release of drug takes place at a steady state hence a constant release of drug is obtained. The Banana leaf carriers coated with 20% HPMC have shown a controlled drug release pattern, showing the maximum drug release at the 12th hour (81.64%).

Thus proving that the Banana leaf carriers coated with HPMC (20%) have better drug release then EC (20%) coated carriers.

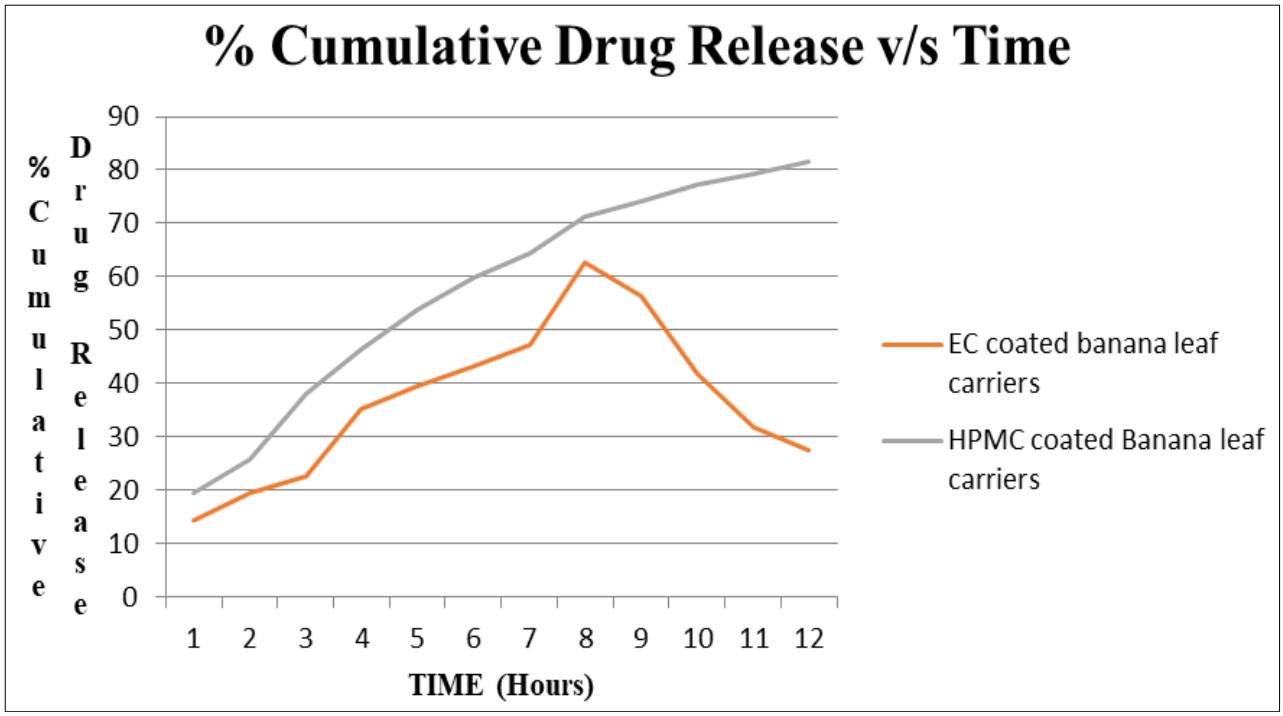

Fig 20: Percent Cumulative Drug Release of Simultaneously coated Banana leaf carriers

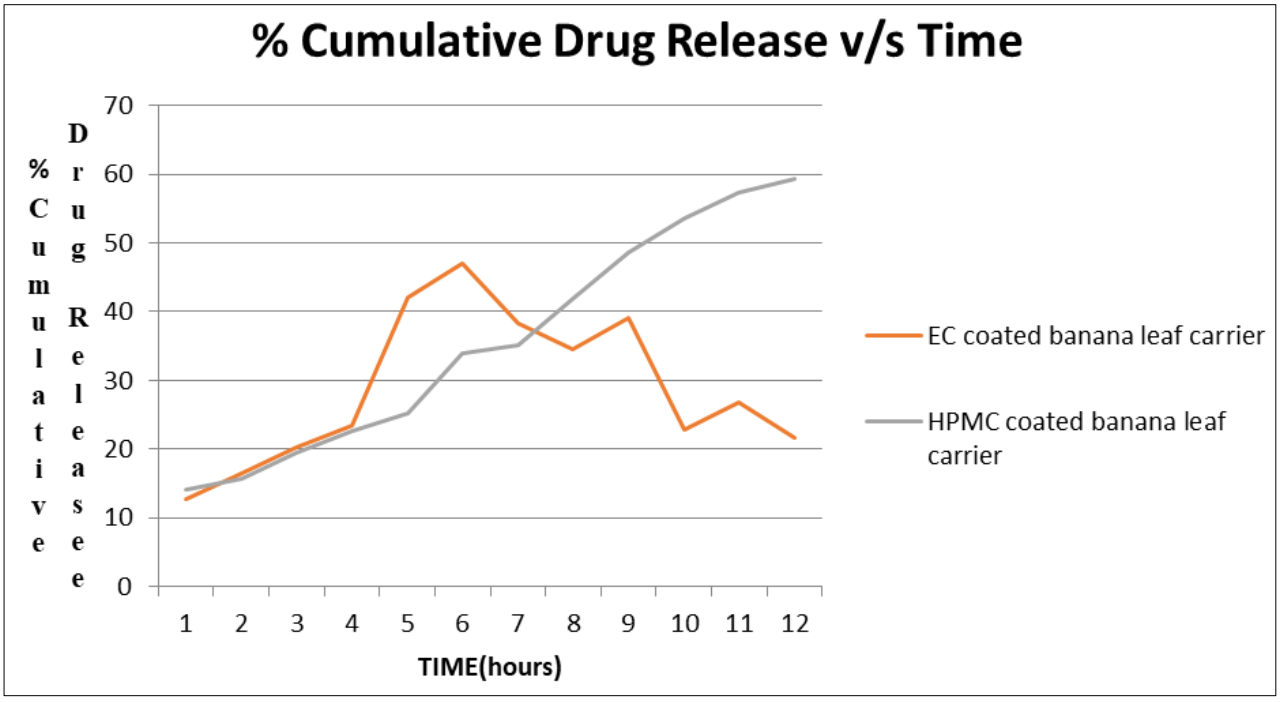

Fig 21: Percent Cumulative Drug Release of Banana leaf carriers (Surface coated)

From the above results we can state that the carriers in which drug was loaded by surface coating method have shown poor drug release as compared to the carriers in which the drug was loaded by simultaneous coating method. The poor drug release could be due to the inefficient absorption of the drug solution by the coated carriers. Whereas in simultaneous coating the drug and polymer are mixed thoroughly forming a drug-polymer coating solution, and these carriers have shown desired drug release. From the above results we can confirm that the banana leaf carriers coated with 20% HPMC by simultaneous coating method have shown desired drug release and hence are used for further evaluation of finished dosage from.

Development and evaluation of finished dosage form for the delivery of ondansetron hydrochloride

The novel optimized drug carriers obtained by using Banana i.e. the 20% HPMC K4M coated banana stem carriers and 20% HPMC K4M coated banana leaf carriers were incorporated into a suitable pharmaceutical drug carrier i.e. capsule for facilitating the administration of drug.

The capsule size chosen here is size 0 for incorporating carriers, a single coated banana stem carrier and six coated banana leaf carriers were incorporated in capsules respectively.

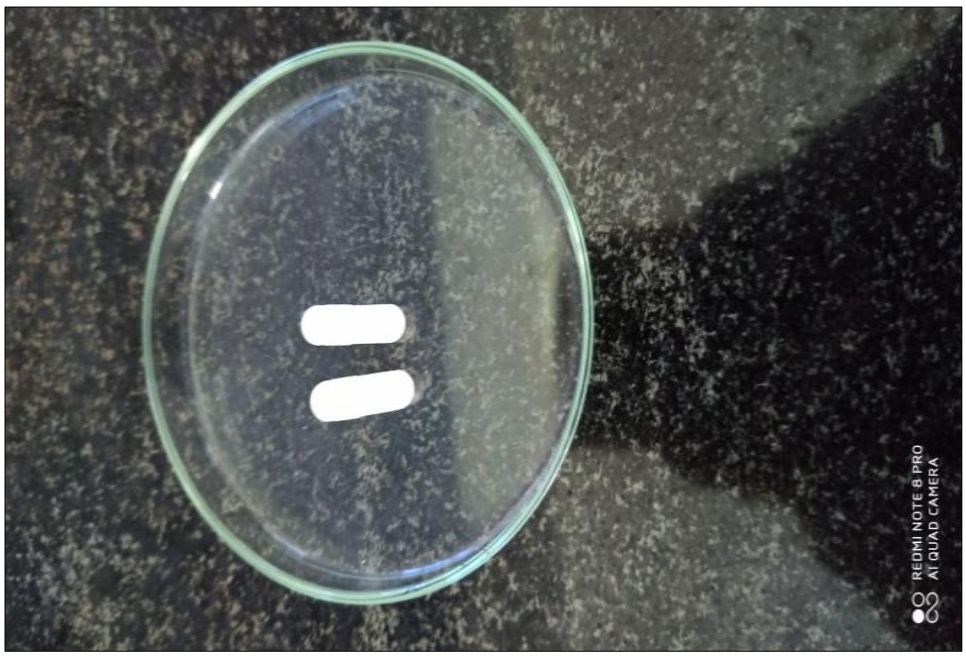

Fig 22: Filled capsules of size 0

Evaluation Parameters of Finished Dosage Form for delivery of Ondansetron hydrochloride

The results of evaluation parameters finished dosage from are discussed below

- **Dimensions**

Table 9: Dimensions of Body of Capsule

Sr. No.	Length Of Body of Capsule (mm)	Inner Diameter of Body (mm)	Outer Diameter of Body (mm)
1	18.33	7.15	7.43
2	18.53	7.2	7.76
3	18.49	7.32	7.48
4	18.62	7.4	7.71
5	18.92	7.18	7.51
Average	18.578	7.25	7.57

Table 10: Dimensions of Cap of Capsules

Sr. No.	Length of Cap of Capsules(mm)	Inner Diameter of Cap (mm)	Outer Diameter of Cap (mm)
1	10.22	7.31	7.63
2	10.26	7.34	7.72
3	10.16	7.32	7.79
4	10.28	7.45	7.66
5	10.20	7.41	7.62
Average	10.224	7.366	7.684

- **Appearance:** The capsules were white in colour; they were free from black particles and defects.
- **Uniformity of Weight:** The average weight of the capsules was than 300 mg, thus the limit for % deviation as per IP was 10%. It was found that none of the capsules deviated from the required range.

Table 11: Drug Content of Capsules

Carrier	Drug Content
20% HPMC Coated Banana stem carrier	98.37%
20% HPMC Coated Banana leaf carrier	98.13%

IV: Drug Content
The drug content of capsules complies with limit as per IP.

V: Disintegration Time
The average disintegration time of the capsule was found to be 14.64 minutes. This complies with the limit of 30 min as per IP. Thus the capsules pass the test.

VI: Dissolution Testing
The results comply with IP per specifications.

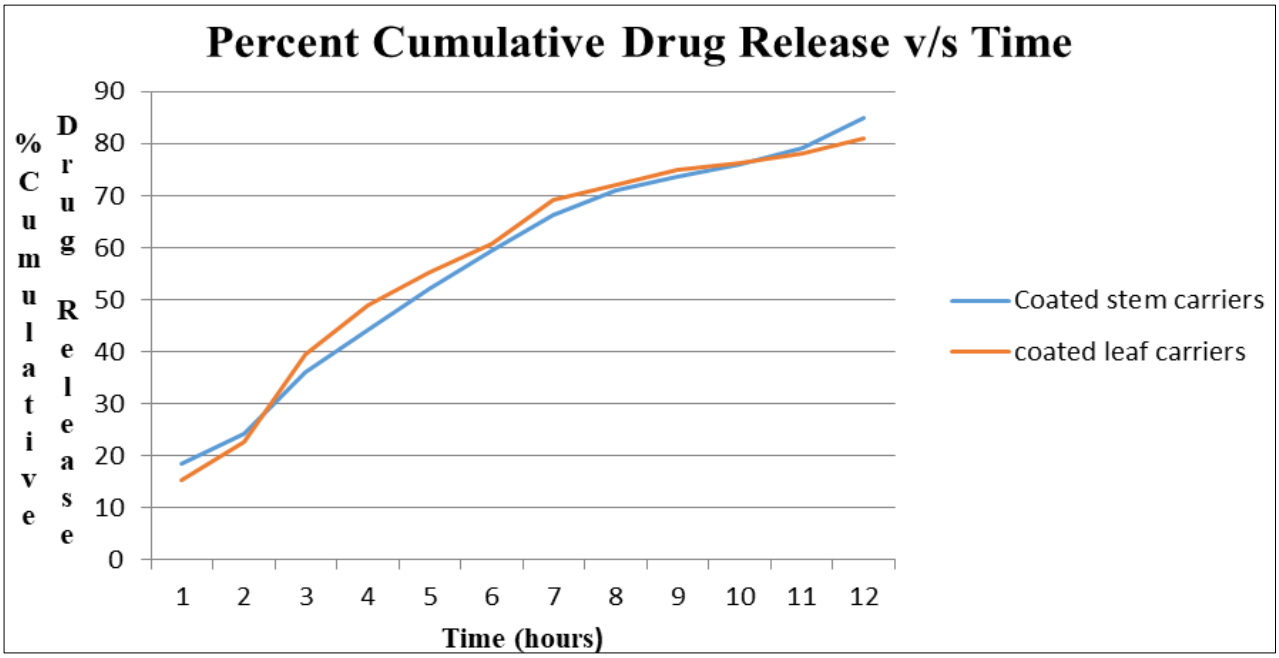

Fig 23: Percent Cumulative Drug Release of Coated Banana stem and Banana leaf carriers

Stability studies
The selected formulations were subjected to short term accelerated stability studies as per ICH guidelines. The drug loaded carriers were examined for appearance and drug content. Percent drug content in the formulations were determined spectrophotometrically. It was found that there was no significant drug loss even after storage of 90 days. There was no significant change in the texture and appearance of the carriers.

Conclusion
In the present study, the floating potential of banana based carriers for the administration of Ondansetron hydrochloride was explored. The enhanced extend of buoyancy possessed by the banana stem and leaf carriers, its drug loading ability and floating ability and the drug release proved its application as a successful novel floating drug delivery system for the treatment of nausea and vomiting.
From the results it can be concluded that the present research has successfully achieved its aim of formulating a stable novel gastro-retentive floating dosage form of Ondansetron hydrochloride to improve its residence time in the stomach for better absorption during treatment of nausea and vomiting. Also the research has successfully fulfilled its objective of formulating floating dosage form of Ondansetron hydrochloride for controlled release effect and exploring natural carrier systems for formulating of dosage forms, thereby avoiding use of synthetic polymers. The banana based carriers were found to be suitable for drug loading and were stable for a required period of time. Thus, this approach suggested use of banana based carriers as

promising floating carriers for the delivery of drugs requiring prolonged residence time.

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