International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 335-342 www.ijprajournal.com ISSN: 2249-7781

Mouth –Dissolving Oral Fims of Ramosetron Hydrochloride for Cancer and Ponv

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Submitted: 13-03-2024 Accepted: 23-03-2024

ABSTRACT:
Mouth-dissolving films of Ramosetron Hydrochloride were prepared by solvent casting method using hydrophilic polymers using water and ethanol as solvents. The drug excipient compatibility was studied using FTIR spectroscopy. The films were subjected to various tests to determine the organoleptic properties, thickness, weight variation, percent elongation, folding endurance,content uniformity, disintegration time, surface pH etc.The buccal film of Ramosetron hydrochloride that would provide ease of administration to cancer patients and patients experiencing PONV of any age group was successfully developed. The formulation F5 was found to be the best-optimized patch with a disintegration time of 9 minutes and drug release of 103.77 % drug at the end of 21 minutes.

I. INTRODUCTION

Vomiting refers to the expulsion of the gastric contents forcefully through the mouth and sometimes the nose.

Nausea refers to the feeling that one is about to vomit. Nausea usually proceeds but does not always lead to vomiting.

The term PONV is used to describe nausea and vomiting post-anesthesia or the immediate 24 postoperative hours.

Antiemetics are sometimes necessary to suppress nausea and vomiting. In severe cases where dehydration develops, intravenous fluid is required.

The different types of vomiting are motion sickness, morning sickness (vomiting during pregnancy), chemotherapy or radiation-induced nausea and vomiting, postoperative vomiting.

The most common gastrointestinal side effects of anesthesia are nausea and vomiting in postoperative patients and in cancer patients undergoing chemotherapy. The dosage form, like a tablet, needs to be swallowed with the help of water, and these patients sometimes are restricted to having water and food, so mucoadhesive buccal patches are convenient.

Ramosetron, a new member in the class of selective 5HT3 receptor antagonists, is a tetrahydrobenzimidazole derivative structurally independent of the previously developed 5-HT3 receptor antagonists such as ondansetron, granisetron, and tropisetron.

It is more potent and has longer-lasting effects than the older agents because of a slower dissociation rate from the target receptor and higher binding affinity.

The following project aims to develop a fast-dissolving mucoadhesive buccal film used to prevent nausea and vomiting in patients undergoing anesthesia and cancer patients undergoing chemotherapy.

II. LITERATURE REVIEW

Mouth dissolving films (MDFs) are the most sophisticated kind of solid dosage form due to various variables, including their flexibility, higher active pharmaceutical component effectiveness, and the speed with which they dissolve and disintegrate—within a minute—compared to dissolving tablets. (Zankahana et al. 2020). Ramosetron's long-term success in treating IBS has helped achieve relief from stomach pain or discomfort as well as improvements in irregular bowel movements. Finally, ischemic colitis is unlikely to be brought on by Ramosetron because it is associated with a low incidence of side effects such as abdominal distension, constipation, and firm stools. Therefore, Ramosetron would be the first option for treating IBS-D.(Toshimi et al., 2013).

Ramosetron hydrochloride was developed as a 5-HT3 receptor antagonist-style antiemetic. It has a tetrahydrobenzimidazol radical and an indole ring, the mother nucleus of serotonin (5-HT). A carbonyl radical connects these parts. According to

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non-clinical investigations, Ramosetron hydrochloride had a more robust and long-lasting antagonistic action against 5-HT3 receptors than other antiemetics of the 5-HT3 receptor antagonist type. Ramosetron hydrochloride effectively and consistently prevented vomiting caused by anticancer medications (Shilan et al. 2014).

After orthopedic surgery, between 20 and 81% of patients experience postoperative nausea and vomiting (PONV) due to the widespread use of anesthetic and analgesic medicines for pain management. Numerous studies document varying reactions to particular antiemetic medications. The most often used antiemetics to stop PONV are Serotonin receptor antagonists such as Ondansetron, Granisetron, and Dolasetron. They do not, however, have an anti-nausea action and only have a minimal impact on postoperative vomiting during the initial postoperative period. According to several studies, Ramosetron, a 5-HT3 receptor antagonist for serotonin, is more effective and has a longer half-life than other serotonin receptor antagonists in treating PONV.

However, there needs to be more information on how well Ramosetron works to prevent PONV in orthopedic patients (Sang-Uk Lee et al., 2020).

Ramosetron significantly lessens the stress-related feces and diarrhea that corticotropin-releasing hormone causes in rats. Ramosetron also raises the threshold for rats experiencing stomach pain brought on by colonic distension.

Therefore, the studies suggest that 2.5 g/day of Ramosetron is a successful treatment for IBS-D in female patients. For male patients with IBS-D, the ideal dose of Ramosetron is five g/day (Shin et al. 2016). Newer medications like Fosaprepitant, Aprepitant, and Ramosetron deserve to be recommended in addition to the traditional antiemetics (Ondansetron, Dexamethasone, Droperidol, And Granisetron). According to systematic reviews and recommendations, they should replace older, less efficient medicines like metoclopramide and scopolamine. Combinations of medications were typically superior to the corresponding single medications in ranking therapies for preventing vomiting (Weibel et al. 2021).

Preliminary trials

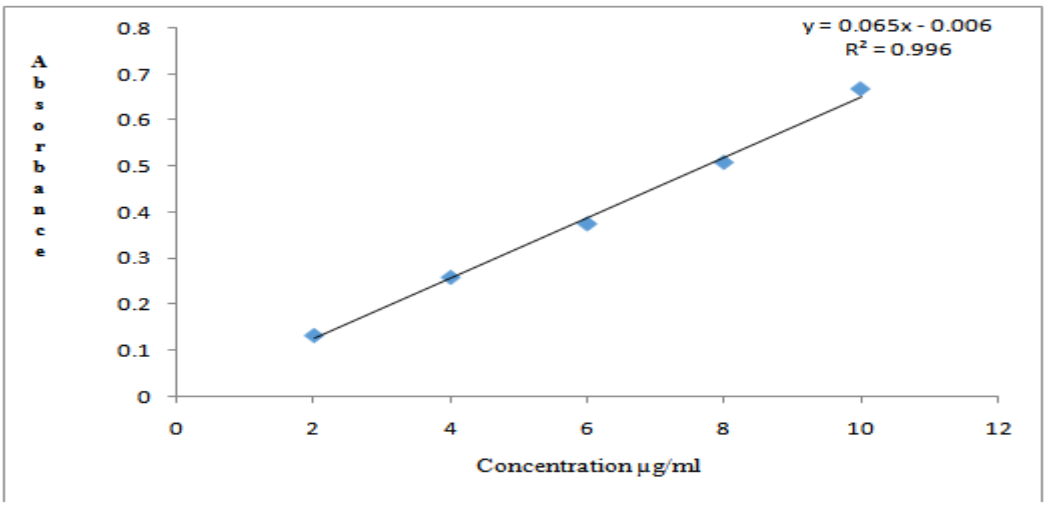
Various film-forming polymers, such as hydroxypropylMethylcellulose (HPMC), HPMC E50, and HPMC K100 were screened for film-forming capacity, of which HPMC E50 was found to be the best polymer for forming the transparent and stiff films and hence was selected.

Buccal films were prepared by using the solvent casting method.HPMC E50 is used for controlled delivery of medicament, transparent films & good elasticity.

HPMC – Type E (E50) has a higher level of hydrophobic groups and hence contributes more to crystallization inhibition as compared to HPMC – Type K (K100). Sodium saccharin was used as a sweetener.Ramosetron hydrochloride has good solubility in ethanol and was used as a Solvent.

PEG 400 was used as a Plasticizer. Propylene glycol was used as a Plasticizer as well as a penetration enhancer.Citric acid was used as a saliva-stimulating agent.

STANDARD CURVE FOR RAMOSETRON



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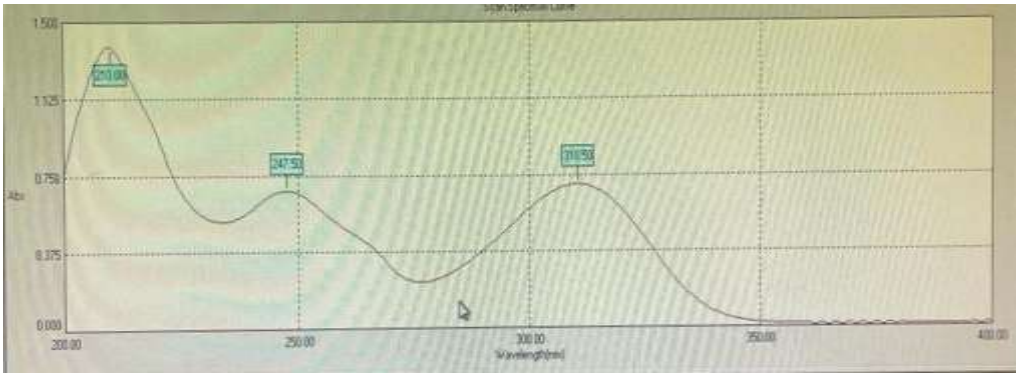
Absorption maxima of Ramosetron hydrochloride



Drug-excipient compatibility studies:

Drug-excipient compatibility studies are essential to know the interaction between drugs and excipients. The interaction may later affect the stability of the formulation or interfere with the drug's pharmacological action.

The formulation's physical examination is done with the drug alone and along with the excipients. Any change in the physical appearance,shows that there is interaction.

However, some substances do not show any physical changes when combined in a formulation, so FT-IR (Fourier transform-infrared) studies are conducted.

Preparation of mouth-dissolving films:

Film-forming polymers such as Hydroxypropyl methylcellulose (HPMC E50) (HPMC K100) were screened for film-forming capacity. HPMC E50 was the best polymer to form a transparent and robust film and hence was selected. Ramosetron hydrochloride is a drug that has good solubility in ethanol and water.

An experimental design consisting of five formulations was set up; the composition of the films prepared is given in Table 1.

HPMC E50 (film-forming agent) was soaked in ethanol. The polymer solution was stirred using a magnetic stirrer. Citric acid was used as a saliva-stimulating agent, and sodium saccharin was used as a sweetening agent, dissolved in water, and added to the polymer solution. PEG 400 was used as a plasticizer, and propylene glycol was stirred until homogenous. As the drug has good solubility in water, it was dissolved in the remaining water and added to the polymer solution.

The prepared formulation was cast on a glass petri plate and was dried in the oven. The dried films were carefully peeled from the petri plates and cut into 2cm x 2cm sizes.

The films were evaluated for various parameters such as weight, thickness, folding endurance, content uniformity, percent elongation, and drug release.

Table 1: Composition of Ramosetronhydrochloride oral film formulation.

Ingredients	F1	F2	F3	F4	F5
Ramosetron Hydrochloride (mg)	4.76	4.76	4.76	4.76	4.76
HPMC E50 (mg)	750	--	250	375	500
HPMC K 100 (mg)	-	750	500	375	250
Sodium saccharin(mg)	80	80	80	80	80
Citric acid(mg)	80	80	80	80	80
PEG 400(ml)	0.7	0.7	0.7	0.7	0.7

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Propylene glycol (ml)	0.5	0.5	0.5	0.5	0.5
Water	2	2	2	2	2
Ethanol	10	10	10	10	10

Results: All the films were transparent, non-sticky, stiff, and easily peelable.

EVALUATION

1. General Appearance

The film's shape, surface texture, color, presence or absence of odor, transparency, and any recognizable marking were tested.

2. THICKNESS

Each film's thickness was measured using a digital Vernier caliper at six different film positions.
The average of the readings was determined as the mean thickness.

3. WEIGHT AND WEIGHT VARIATION OF FILMS

The weights of three films of each formulation were taken using an electronic balance, and the weight variation was calculated.

4. FOLDING ENDURANCE

Folding endurance of the film was performed by repeatedly folding one patch at the exact the same place till it broke, folded, or creased up to 300 times manually, which was considered satisfactory to reveal good film properties.
This test was done for three films.

CONTENT UNIFORMITY

A film was cut into three pieces, each of equal diameter at random places, and was taken in separate 100 ml flasks to which a phosphorus buffer pH 6.8 was added and continuously stirred for 24 hours. The resulting solutions were filtered, suitably diluted, and analyzed at 313 nm using a UV spectrometer. The average drug content of the three films was taken as the final reading.

6. Percent elongantion

A film sample stretches on applying stress, referred to as a strain. A strain is a strip's deformation divided by the sample's original dimension. Percent elongation can be helpful to find out the elasticity as well as the strength of the film.

$$\text{Percent elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

7. In vitro disintegration time

In vitro disintegration time was determined by placing the films in a petri dish containing 10 ml of pH 6.8 phosphate buffer, mimicking simulated Saliva's properties. The disintegration time is noted as the time at which film disintegrates. Three readings were taken. The mean with standard deviation was calculated.

8. Surface pH

The pH of the films was measured using an electrode pH meter. Surface contact of the electrode with the oral film, which was previously made slightly wet with water, was established. The procedure was performed in triplicate, and the mean with standard deviation was reported.

9. Diffusion studies

A modified dissolution apparatus (Dinge et al.) was used to determine the drug diffusion or release. A Phosphate buffer of 6.8 pH was prepared, and 20 was taken in a 50 ml beaker. The magnetic stirrer was fixed at 100 rpm, and the film was placed in it. The sample solution was withdrawn at 3,6,9,12,15,18,21, and 5 ml phosphate buffer was added to the beaker every time the sample solution was removed. The drug content was measured using UV spectroscopy.

III. RESULTS

General Appearance

Shape and size: Each of the film was square shaped and of 2×2 dimensions (area = 4 cm ²)
Texture: Smooth
Transparency: All the films obtained were transparent
Odour: Odorless
Recognizable marking: No physical flaws were seen.
Thickness :
The thickness of individual films is mentioned in the table given below
The thickness of all five films (F1-F5) was in the range (0.13 to 0.15) ± 0.03 mm; therefore, the

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thickness of the film is suitable for oral administration.

Weight and weight variation of films:

The weight of individual films is mentioned in the table given below.

The weight of the films was in the range of 60 to 88 mg.

Weight variation among different formulations was obtained, which may be related to the type and amount of polymer used.

Folding endurance

The folding endurance of individual films is mentioned in the table given below.

Folding endurance is in the range of 300 times.

This range of folding endurance showed all the formulations have good film properties.

Content uniformity

Drug content uniformity results of all five formulations are mentioned in the table below.

The drug content was found to be in the range of 11.15 ± 12.79 percent, which is within the acceptable limits.

Percent elongation

Values range from 5 to 15 %. It can be associated with the type and amount of polymers used.

In vitro disintegration time

The table below mentions the in vitro disintegration results of all five formulations.

In vitro disintegration time values range from ± 6 minutes to ± 9 minutes.

The disintegration time taken by the formulation varied with the type and amount of polymers.

Formulation	Disintegration time(min)
F1	6± 0.1
F2	6± 0.1
F3	6± 0.2
F4	6± 0.1
F5	9± 0.2

Surface pH

Surface pH results of all five formulations are mentioned in the table below.

The surface pH of all five formulations ranges from 6.70 to. 6.78

The pH of the film should be near the pH of the oral mucosa so there is no irritation.

Formulation	Surface pH
F1	6.78
F2	6.70
F3	6.77
F4	6.78
F5	6.76

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Table 2:Evaluation of mucoadhesive films of Ramosetron

Formulation	Thickness (mm)	Weight variation (mg)	Drug content uniformity	Folding endura	% Elongation	Disintegration time (min)	Surface pH
F1	T-0.14±0.03 C-0.14±0.03 B-0.14±0.03	T-70 C-65 B-70	11.82	>300	T- 10 C-15 B-10	6 ± 0.1	6.78
F2	T-0.14±0.03 C-0.13±0.03 B-0.13±0.03	T-80 C-88 B-80	12.79	>300	T-5 C-5 B-10	6 ± 0.1	6.70
F3	T-0.14±0.03 C-0.14± 0.03 B-0.15±0.03	T-60 C-70 B-60	11.15	>300	T-10 C-10 B-10	6 ± 0.2	6.77
F4	T-0.12±0.03 C-0.14±0.03 B-0.14±0.03	T-65 C-68 B-70	11.52	>300	T-10 C-10 B-10	6 ± 0.1	6.78
F5	T-0.14±0.03 C-0.15±0.03 B-0.15±0.03	T-70 C-72 B-65	12.41	>300	T-5 C-5 B-5	9 ± 0.2	6.76

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Diffusion studies:

Time	Abs	Concentration in µg/ml	Concentration in mg / 5ml	Concentration in mg /50 ml	Cumulative drug release	% Cumulative drug release
3	0.132	2.003034901	0.010015175	0.100151745	0.11016692	36.72
6	0.162	2.458270106	0.012291351	0.122913505	0.13292868	44.31
9	0.201	3.050075873	0.015250379	0.152503794	0.174810319	58.27
12	0.256	3.884673748	0.019423369	0.194233687	0.231790592	77.26
15	0.261	3.960546282	0.019802731	0.198027314	0.255007587	85.00
18	0.271	4.112291351	0.020561457	0.205614568	0.282397572	94.13
21	0.282	4.279210926	0.021396055	0.213960546	0.311305008	103.77

IV. CONCLUSION

The buccal film of Ramosetron hydrochloride that would provide ease of administration to cancer patients and patients experiencing PONV of any age group was successfully developed. The formulation F5 was found to be the best-optimized patch with a disintegration time of 9 minutes and drug release of 103.77 % drug at the end of 21 minutes.

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International Journal of Pharmaceutical Research and Applications
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