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Original Article

DEVELOPMENT AND EVALUATION OF RAMOSETRON HYDROCHLORIDE MOUTH DISSOLVING THIN FILM FOR ENHANCED THERAPEUTIC EFFICACY AND PALATABILITY

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ABSTRACT

Objective: Many people have difficulties in swallowing traditional dosage forms such as tablets and capsules. The goal of this study was to develop the mouth-dissolving thin film of Ramosetron HCl (RH) for quick onset of action in the treatment of vomiting and irritable bowel syndrome, with the added benefit of disguising the bitter taste of RH.

Methods: The solvent-casting approach was employed to formulate mouth dissolving thin film. The effect of variable concentrations and different grades of hydrophilic polymer HPMC (E5, E15 and E50), and plasticizers like glycerol and PEG 400 on disintegration time, drug release, thickness, tensile strength, percent elongation, folding endurance, and on appearance were studied. The optimized batch was kept for stability study at40±2 °C/75±5% RH for 30 d.

Results: The formed films were transparent with a smooth surface texture. The thickness, weight variation, drug content and pH of the surface were within acceptable limits. Tensile strength and folding endurance values demonstrated adequate mechanical strength. In 45 seconds, the formulation F6 comprising HPMC E5 (150 mg) and HPMC E15 (150 mg) with PEG 400 (0.4 ml) disintegrated. The F6 formulation released 98.78±0.96 %drug in 8 min and considered as optimal formulation. The taste masking of drug was evaluated by a taste perception study using volunteers. The optimized batch was found to be stable at 40±2 °C/75±5% RH for 30 d.

Conclusion: The concentration of hydrophilic polymers and plasticizers had a significant effect on the formulation and assessment characteristics of thin film. Mannitol assisted in masking the bitter taste of RH.

Keywords: Mouth dissolving thin film, Ramosetron HCl, Folding endurance, HPMC, Vomiting, Irritable bowel syndrome

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INTRODUCTION

There are several routes available for the efficient delivery of desired medications. The approach used is determined by the severity of the disease and the condition of the patients. The oral route is the most favored route for drug administration due to its numerous benefits [1, 2]. Many individuals avoid taking recommended drugs out of fear. The main source of concern is the administration route. The proportion of elderly patients is growing due to a rise in life expectancy. Hand tremors and dysphagia make it difficult for this group of individuals to swallow traditional oral dose forms. Pediatric patients are unable to swallow solid dose forms because of their underdeveloped neurological and muscular systems [3]. Other populations who have trouble taking traditional oral dose forms include pregnant women, obstinate mentally ill people, and peoples having vomiting and nausea during travelling. Due to their size, shape, flavor, and odor, more than 25% of out-patients had difficulty administering solid dose forms such as tablets or capsules [4].

Vomiting and nausea are never pleasant for the sufferer. In a condition, like motion sickness, during travelling or pregnancy, unavailability of water or fear of choking of conventional solid dosage forms is common [5-7]. Emesis not only affects the quality of life but can also lead to loss of many essential electrolytes from body. To overcome these difficulties, fast-dissolving film-type drug delivery system emerged as alternative way to deliver the drug [8]. The swallowing problem related to sold oral dosage forms can be elevated by formulating oral fast dissolving thin film, which disintegrates and dissolves rapidly after placing in the mouth without the need of drinking water. The oral fast-dissolving thin film offers various advantages over conventional oral dosage forms. The foremost advantage is patient compliance due to rapid disintegration and alleviating difficulty in swallowing. Due to ease of taking without water, bedridden, pediatrics, geriatric patients and travelers etc. are benefited. Another value-added advantages are pleasant taste, ease of handling, accurate dosing and suitable for all age groups [7, 8].

Apart from active pharmaceutical ingredients, the other components of mouth-dissolving thin film are hydrophilic polymers, plasticizers, sweeteners, flavours, colours, saliva-stimulating agents, preservatives, surfactants etc. Hydrophilic polymers help in giving rigidity to film [9]. The routinely used film formers are HPMC, Methylcellulose, Pullulan, carboxymethylcellulose, Polyvinylpyrrolidone, pectin, gelatin, sodium alginate, hydroxypropyl cellulose, polyvinyl alcohol, maltodextrins, eudragit and rosin [10, 11]. Plasticizer imparts flexibility and reduces the brittleness of film. The routinely used plasticizers are glycerol, propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil [12, 13]. Mouth-dissolving films are prepared by using solvent casting, hot melt extrusion or compression moulding method. Solvent casting is the most common and traditional method [14].

RH is approved by FDA for the treatment of nausea, anxiety and irritable bowel syndrome [15]. RH selectively blocks 5HT3-serotonin receptors. The pharmacological action of RH is sustained and potent in a very low dose in the treatment of nausea and vomiting [16]. The RH currently available in tablets, syrups and in injectable forms. The present work was aim to develop a mouth-dissolving thin film of RH for the rapid onset of action and to mask its bitter taste. In the presented study, various grades of HPMC in variable concentration were taken to check their impact over *in vitro* disintegration, dissolution and mechanical properties of thin film.

MATERIALS AND METHODS

Materials

RH was received as a gift sample from Cadila Pharmaceuticals, Goa, India. Various grades of HPMC, PEG-400, glycerol, sodium lauryl sulphate and aspartame were purchased from Loba Chem. Lab. Ltd., Mumbai. Citric acid procured from SD fine Chem. Ltd., Mumbai. All chemicals used were of analytical reagent grade.

Methods

Formulation of RH mouth dissolving thin film

Solvent casting method was used to formulate RH mouth dissolving thin film. Various grades of HPMC viz. HPMC E5, HPMC E15 and HPMC E50 were used alone or in combination as a film-forming polymer. Polyethylene glycol 400 (PEG 400) and glycerol were used as plasticizer. Film forming polymer was accurately weighed and dissolved in a sufficient quantity of water. It was then stirred over magnetic stirrer until polymer gets completely solubilized. Other ingredients like RH, PEG 400, glycerol, sodium lauryl sulphate (solubilizing agent), citric acid (saliva stimulating agent) and aspartame (sweetening agent) were dissolved in remaining quantity of water. Both the solutions were mixed with the help of magnetic stirrer until they get completely homogenized and the volume was made up to10 ml with water. This solution was poured into a glass petriplate and dried at room temperature for 24 h. After drying, the film was removed with the help of sharp blade and cut in to 1.5 cm ×1.5 cm size (Area of single film =2.25 cm^2). The obtained film was then wrapped in aluminum foil and kept in desiccator till further use (table 1) [17].

Table 1: Composition of RH mouth dissolving thin film

Ingredients*	F1	F2	F3	F4	F5	F6	F7	F8
RH (mg)	1.711	1.711	1.711	1.711	1.711	1.711	1.711	1.711
HPMC E5 (mg)	250	-	-	-	100	150	-	-
HPMC E15 (mg)	-	200	225	225	100	150	-	-
HPMC E 50 (mg)	-	-	-	-	-	-	150	150
Glycerol (ml)	0.4	0.4	0.4	-	-	-	0.4	-
PEG 400 (ml)	-	-	-	0.4	0.4	0.4	-	0.4
Citric acid (mg)	10	10	10	10	10	10	10	10
Sodium lauryl sulphate (mg)	1	1	1	1	1	1	1	1
Aspartame (mg)	10	10	10	10	10	10	10	10
Water (ml)	10	10	10	10	10	10	10	10

*For 10 film each size 2.25 cm^2

Calculation of drug dose

Diameter of petridish= 7 cm

Radius of Petridish= 7/2= 3.5

Area of circle A = πr^2

=22/7 × 3.5 × 3.5 = 38.5 cm sq

Film to be formulated= length=1.5 width=1.5

Area of single film = 1.5×1.5

= 2.25 cm^2

No. of films caste= 38.5÷2.25

=17.11 films

Amount of drug required=17.11× 0.1 mg

=1.711 mg

Evaluation parameters

Drug-excipients interaction study

Interaction between the mixtures of drug and excipients was studied by using a Shimadzu FT-IR 8300 Spectrophotometer (Shimadzu, Kyoto, Japan). The spectrum was recorded in the wavelength region of 4000-400 cm^{-1}. The procedure involved dispersing the sample/s in KBr and compressing into discs by using a hydraulic press. Initially a baseline correction was carried out using dry potassium bromide pellet. The pellet containing sample/s was then placed in the light path, and the spectrum was recorded [18].

Morphological study

All prepared films were observed with necked eye for their appearance, transparency, color and Surface texture.

Thickness

Digital Vernier Calliper was used to measure the thickness of film. The pointer of Digital Vernier Calliper was set to zero, film was placed between the anvils of the Vernier Calliper, thickness was measured from three different spots of film and average was taken. Study was carried out in triplicate.

Tensile strength and percent elongation

Tensile strength is the maximum stress applied to break the film. It was calculated by measuring the weight required to break the film divided by the cross-sectional area of the film. The one end of the film was fixed over the assembly and on the other end provision was made to place the weights. The weight required to break the film was noted. Simultaneously, film elongation was measured with the help of measuring scale attached to assembly. The film should have moderate tensile strength and high percent elongation. The higher tensile strength represents brittleness of the film. The tensile strength and percent elongation was calculated by following equations 1 and 2 respectively [14]. Study was carried out in triplicate.

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Film Thickness} \times \text{Film width}} \times 100 \ldots\ldots\ldots 1$$

$$\text{Percent elongation} = \frac{\text{Increase in length}}{\text{Original length}} \times 100 \ldots\ldots\ldots 2$$

Folding endurance

A mechanical property of film was measured by folding endurance test. Folding endurance was determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value. Study was carried out in triplicate [19].

Variation of weight

About 10 Films (1.5 cm ×1.5 cm) from different batches were taken and measured over electronic balance and weight was noted. Study was carried out in triplicate [20].

Drug content

About 2.25 cm^2film was placed in a 10 ml volumetric flask and 5 ml of ethanol was added to dissolve the film. The final volume was made using ethanol. Samples were suitably diluted with artificial saliva and the absorbance was measured at 311 nm. Study was carried out in triplicate [21].

Surface pH

Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation. The pH value of a film was determined by putting the prepared film in petri plate and subsequently made wet by using distilled water and pH was measured by touching the film surface with a pH meter electrode [21].

Preparation of artificial saliva

Sodium chloride (0.844 g), potassium chloride (1.2 g), calcium chloride dehydrate (0.193 g), magnesium chloride hexahydrate (0.111 g) and potassium phosphate dibasic (0.342 g) were weighed

accurately and dissolved in sufficient quantity of distilled water. Final volume was made up to 1000 ml in a volumetric flask using distilled water [22].

Disintegration test

Petri plate method was used to determine the disintegration time of film. The film (1.5 cmx1.5 cm) was placed in a glass dish containing 10 ml phosphate buffer pH 6.8 and subjected to occasional swirling. Time required to break the film into small pieces was noted as *in vitro* disintegration time (table 2) [23].

***In vitro* dissolution test**

In vitro drug release was carried out by using a modified type-V USP dissolution apparatus (Model No. TDT-08L, Electrolab Pvt. Ltd). Artificial saliva was taken as a dissolution medium. The volume of the dissolution medium was 300 ml, temperature was 37±0.5 °C and the rotation speed was 50 rpm. Aliquots of 4 ml were withdrawn at specific time intervals and the original volume was maintained by adding fresh dissolution medium. The amount of RH released in the dissolution medium was determined spectrophotometrically at 311 nm using a UV-spectrophotometer (Shimadzu UV 1800). Study was carried out in triplicate (table 3) [24].

Statistic evaluation

The data were shown as mean±SD, n=3. One-way ANOVA was used in the statistical analysis, which was conducted using the Graph Pad Prism 8 software (Graph Pad Software Inc., San Diego CA). Differences were deemed statistically significant at $p<0.05$.

Taste perception

Taste perception study was carried to access the acceptance of the prepared formulation. Three groups of tester viz. children in age between 10-18 y, adults in age between 30-40 y and elder in an age between 60-70 y were formed. Each group has 3 volunteers.

The tester was fully apprised of the necessary information and the study's objectives. Prior to tasting the samples, each tester received, read, and signed a written consent form.

At the day of the study, the tester was not given any thing orally for one hour. After one hour of fasting, the optimized formulation was given to the tester to keep over the tongue and percept the taste. After 1 minute, the tester was asking to gargle and wait for 1 h for the next sample. The prepared film not containing the mannitol, was given to tester to keep over the tongue and percept the taste. Depending upon the taste sensation, the scoring was received from the tester [25, 26].

Table 2: Scoring of taste by the panel of tester

Panel no.	Participants	Optimized formulation	Formulation without mannitol
1.	Children	+++	+
2.	Adult	+++	++
3.	Elder	+++	++

+: Indicates very bitter; ++: Bitter; +++: Acceptable (Palatable)

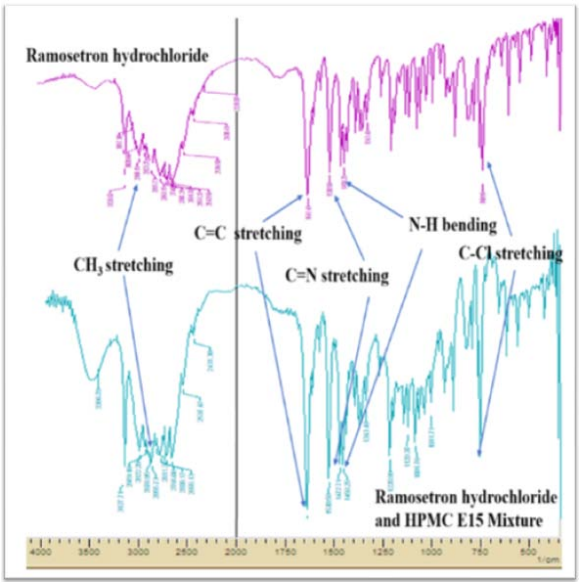

Fig. 1: FT-IR spectrum of (a) RH; (b) Mixture of RH and HPMC E15

Accelerated stability studies

The batch F6 was stored at 40±2 °C/75±5% RH for 30 d in the environmental control chamber. Samples under evaluation were wrapped in a butter paper followed by aluminum foil. The films were evaluated for appearance, disintegration time, drug content and *in vitro* drug release after storage for 30 d. At 15th and 30th day, samples were withdrawn and appearance, disintegration time, drug content and *in vitro* percent drug release was determined.

RESULTS AND DISCUSSION

Mouths dissolving thin films are the best option for the patient who found difficulties in taking medicines orally or needs medicines in some emergency cases. Mouth-dissolving films rapidly disintegrate in mouth and start releasing the drug, which leads to rapid absorption of drug. In the presented study the mouth-dissolving thin film was prepared using different film-forming agents and plasticizers in variable concentrations to analyze their effect on different film properties. The film was prepared by solvent casting method. During the analysis various tests were performed to assure the viability of the film.

Drug-excipients compatibility study

FT-IR spectrum of physical mixture of RH and HPMC E15 was compared with FTIR spectrum of RH. RH given characteristic peak at 2855 cm^{-1}(CH_3 stretching), 1641 cm^{-1}(C=C stretching), 1530 cm^{-1}(N-

H bending), 1641 cm^{-1}(C=N stretching), 760 cm^{-1}(C-Cl stretching). All these peaks of RH were also interpreted in FT-IR spectrum of RH and HPMC E15 mixture without major shift in peaks, indicating no interaction between RH and HPMC E15 (fig. 1).

Evaluation of RH mouth dissolving thin film

RH mouth dissolving thin film was prepared by solvent casting method. Effect of various grades and concentrations of film-forming polymer HPMC and other ingredients were studied by formulating 8 batches (table 3).

Morphological study

Batch F1 containing HPMC E5 does not get solidified at room temperature thus not studied further. Solvent casting technique was showed better film-forming property and mechanical strength. The prepared films were transparent, clear, homogeneous and smooth.

Thickness

Thickness of the films was observed uniform through. When the concentration of HPMC was increased, as well as when higher viscosity grades HPMC were used, thickness of individual film was increased. This indicated that, viscosity of HPMC plays a role in thickness of the film. The results were confirming to the finding of Maddela and Nalluri [7]. The study illustrated that, concentration of HPMC and plasticizers had a significant effect on formulation of fast dissolving films. Film prepared using HPMC E50 show ed higher thickness (90±03 to 91±04 µm) than the film prepared using HPMC E15 (73±03 to 85±03 µm).

Tensile strength and percent elongation

The tensile strength and percent elongation was increased when the concentration of HPMC E15 was increased. The films prepared with HPMC E15 have moderate tensile strength and high percent elongation compared to film prepared with HPMC E50. Plastisizer PEG 400 imparted high percent elongation and tensile strength compared to film containing glycerol (F2 and F3). This finding was confirming to the results interpreted by Watetwar *et al.* [6]. According to Watetwar *et al.*,"glycerol film shows poor flexibility due to its moisture retaining capacity". Batch F6 and F8 offered highest elongation strength.

Folding endurance

Folding endurance test helps to determine the mechanical strength of the film. It was observed that films containing PEG 400 (F4 and F8) imparted higher strength compared to films containing glycerol (F3 and F7). The concentration of film-forming agents also has mark effect over folding endurance. When the concentration of HPMC E15 and HPMC E50 was increased, folding endurance was increased.

Variation of weight, drug content and surface pH

Negligible weight variation was observed in prepared batches indicating uniformity in film. All films showed uniformity in drug content indicating uniform distribution of drug and delivery of fixed dosing. Surface pH of all the films was near to the pH of mouth and saliva.

***In vitro* disintegration test**

The prepared films showed disintegration time between45±02 sec to 60±06 sec. The concentration of HPMC E50 have great impact than HPMC E5 and HPMC E15 on disintegration time. The film took more time to disintegrate when the concentration of the HPMC was increased. This may be due to higher viscosity of film forming polymer. The results were in correlation with the findings of Roy *et al.* [19], Batch F6 showed lowest disintegration time of 45±02 sec.

***In vitro* dissolution test**

The *In vitro* dissolution profile of RH is shown in table 4. It was observed that when the concentration of HPMC E 15 was increased, the *in vitro* release of drug was decreased. The results were complying with the findings of Bobde and Tank [27]. The probable reason would be the increased concentration of HPMC tightens the matrixing in film which resulted in slow down of water penetration and ultimately decreased in drug release. Batch F6 showed faster drug release (26.21±4.19% in 1 min) compared to other studied batches and 98.78±2.03% drug was released in 8 min.

Results illustrated that Batch F6 was transparent in appearance having smooth texture, uniformity in thickness, moderate tensile strength (2.90±0.22 N/cm^2) and high percent elongation (88.26±0.96 %). Also, folding endurance, drug content and surface pH were in acceptable limit. Batch F6 disintegrated in 45±02 sec which was lowest compared to other studied batches. Batch F6 also depicted quick release and 98.78±2.03% drug was released within 8 min which was faster compared to other studied batches. Therefore batch F6 containing HPMC E5 (150 mg) and HPMC E15 (150 mg) with PEG 400 (0.4 ml) considered as optimized batch for the delivery of RH and used further for the stability study.

Table 3: Evaluation parameters of RH mouth dissolving thin film

Evaluation parameters	F2	F3	F4	F5	F6	F7	F8
Appearance	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent
Surface texture	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Thickness (µm)	80±01	73±03	80±02	80±01	85±03	90±03	91±04
Tensile strength (N/cm^2)	2.23±0.15	2.46±0.21	2.62±0.85	2.33±0.25	2.90±0.22	3.10±0.21	3.26±0.19
Elongation (%)	69.16±3.18	72.06±2.73	74.53±3.60	78.06±2.73	88.26±0.96	79.90±1.35	82.63±1.95
Folding endurance	380±004	374±003	400±004	390±006	400±005	400±006	450±008
Variation of weight (mg)	3.46±0.12	3.32±0.22	3.80±0.32	3.19±0.71	3.81±0.22	3.91±0.48	4.10±0.32
Drug Content (mg/cm^2)	0.08±0.03	0.08±0.08	0.07±0.04	0.06±0.05	0.08±0.03	0.07±0.01	0.09±0.02
Surface pH	6.84±0.02	6.70±0.01	6.91±0.02	6.68±0.03	6.87±0.01	6.72±0.03	6.74±0.04
Disintegration time (sec)	52±02	54±04	57±03	56±04	45±02	58±03	60±06

Data are given as mean±SD, n=3

Table 4: *In vitro* cumulative percent drug release

Time (min)	F2	F3	F4	F5	F6	F7	F8
1	17.01±4.34	3.21±2.45	7.81±4.91	12.41±2.20	26.21±4.19	12.41±4.11	11.62±5.51
2	21.32±6.32	30.39±4.41	25.86±2.40	21.32±6.10	34.93±7.47	21.32±8.12	20.55±7.10
4	38.93±7.11	47.88±8.67	34.45±6.91	47.88±8.62	61.31±6.43	38.93±6.21	36.56±6.91
6	51.63±6.23	60.46±6.20	56.05±9.82	56.05±7.32	73.70±6.31	56.05±3.98	52.87±6.32
8	72.66±5.90	68.31±8.32	59.61±6.20	77.02±6.32	98.78±2.03	72.66±6.16	68.31±2.20
10	97.36±2.41	98.73±2.45	98.95±1.81	97.08±2.63	--	97.36±3.03	96.95±3.13

Data are given as mean±SD, n=3

Taste perception

The RH film with and without mannitol was given to 3 panels of tester. Members of all the panel confirmed the sufficient taste masking by giving+++marking to the film containing mannitol, indicating that the film is palatable. On the other side for the film prepared without mannitol, the panel given+, and++marking indicating very bitter to bitter in taste. From the results, it was confirmed that mannitol masked the bitter taste and the prepared film is palatable.

Accelerated stability studies

Storage conditions affect the stability of preparation. The long-term stability ensures the acceptability of dosage form. Batch F6 was chosen for accelerated stability study and stored at 40±2 °C/75±5% RH for 30 d in environmental control chamber. At the end of 30 d, the under observation batch showed a disintegration time 45±05 sec, drug content 0.08±0.01 mg/cm^2 and 97.45±2.19 % *in vitro* drug release after 8 min. Data illustrated that the film was stable during 30 d accelerated stability study (table 5).

Table 5: Stability study data of F6 batch

S. No.	Parameters	0 d	15 d	30 d
1.	Appearance	Transparent, uniform	Transparent, uniform	Transparent, uniform
2.	Disintegration time (sec)	45±02	45±03	45±05
3.	Drug content (mg/cm^2)	0.08±0.03	0.08±0.02	0.08±0.01
4.	*In vitro* drug release at 8 min (%)	98.78±2.03	98.63±1.51	97.45±2.19

Data are given as mean±SD, n=3

CONCLUSION

Mouth dissolving thin film of RH was successfully prepared. The study illustrated that the concentration of polymer and plasticizer had a significant effect on the formulation of oral films. The solvent casting method was found to be simple, reproducible, economical and consistent. Among all the formulations, F6 disintegrated in minimum time i.e. 45±02 sec and 98.78±2.03% drug was released within 8 min. Taste masking of RH incorporated in film was confirmed by panel of taster. Evaluation study indicated that the films have potential to deliver drug quickly and also confirmed as an innovative dosage form to improve the delivery of RH. Additionally, the excipients used for the formulation were economical and easily available. It was concluded that this type of dosage form is potentially better than other marketed conventional formulations and can be commercially processed.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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