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Formulation and development of mouth dissolving film containing Ramosetron

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Abstract
The present work was aim to develop a mouth dissolving film of Ramosetron HCl using hydrophilic polymers HPMC E5, HPMC E15 and HPMC 50 cps. Mouth dissolving films were prepared by solvent casting method. Formulation batches were prepared by varying the quantity of polymers and plasticizer and evaluated for physical properties, thickness, mechanical properties, surface pH, disintegration time, and *in vitro* dissolution studies. Fast dissolving film are having smooth surface and they are elegant. The thickness of the fast dissolving films was found 0.18-0.21 mm. Surface pH was found 6.61-7.14. The drug was dispersed in the range of 2.36-2.57. Film of 2 x 2 cm 2 size taken and disintegration time checked visually was found 58-81 sec. *In vitro* Dissolution studies shows drug release in range of 90.26±0.43-99.81±0.09 in 15 min. from formulation batch F6 selected as optimized Batch for further accelerated stability studies.
There were no considerable changes in physical parameters of film such as Appearance, Disintegration time (sec) Cumulative% releases of formulation F6 after accelerated study.

Keywords: Ramosetron HCl, oral film, folding endurance, solvent casting method

Introduction
Mouth dissolving film or orally disintegrating films when placed on tongue, immediately hydrates by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form. Odfs are kind of formulations which are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. Oral disintegrating tablets (odfs) and oral disintegrating films (odfs) are the typical examples of orally disintegrating drug delivery systems. These systems were developed in late 1970 to serve as an alternative to conventional dosage forms, for instance, fast disintegrating tablets and capsules for geriatrics and pediatric patients having difficulty in swallowing conventional dosage forms [1-3].
A thin film that readily dissolves in the oral cavity is commonly referred as or dispersible film by the European Medicines Agency (EMA) or simply soluble film by the FDA. Although, oral films initially appeared as innovative breath freshening formulations, it rapidly evolved to give response to different market needs, namely an easy-to-carry and easy-to-swallow drug delivery system. The Oral films are essentially complex polymeric matrices that may be used efficiently as drug release platforms. These polymeric matrices may be composed by several components in order to achieve well-designed drug delivery platforms, but usually hydrophilic polymers are its main core [4-6].
Ramosetron hydrochloride, an antiemetic drug, is prescribed for the treatment of diarrhea predominant irritable bowel syndrome in adult men. Ramosetron hydrochloride is also prescribed for the treatment and management of iatrogenic gastrointestinal symptoms such nausea and/or vomiting. Ramosetron hydrochloride selectively blocks serotonin receptors (5HT3). Serotonin plays a vital role in vomiting serotonin induced bradycardiac reflex and peristalsis. The pharmacological action of Ramosetron hydrochloride is sustained and potent. After oral or intravenous administration, Ramosetron hydrochloride achieves Cmax after 2 hours with a plasma half-life of 5 hours. The Cmax and AUC are linear activity in nature and dose dependent. The oral bioavailability of Ramosetron hydrochloride is about 50%. The drug is widely distributed in the body fluids including breast milk. Ramosetron hydrochloride is excreted as unchanged drug via the urine as drug metabolites and as unaltered drug [7, 8]. Ramosetron Hydrochloride is found to be more potent and having a longer duration of action with the least side effects, but the major drawback is it undergoes hepatic first-pass

metabolism so our aim is to prepare mouth dissolving film (MDF) of Ramosetron hydrochloride for rapid relief in emesis.

Materials and Methods

Materials

Ramosetron hydrochloride was obtained as gift sample from Cadila pharmaceuticals, Goa All grades of HPMC obtained from Loba Chem Laboratory Chemicals Ltd, Mumbai, and Glycerol, and Poly ethylene glycol 400, Citric acid purchased from Thomas baker, Mumbai. All the reagents and materials were of analytical or pharmacopoeia grade.

Methods

Infrared absorption spectrophotometry

It is important to check any kind of interaction between drug and polymer. To determine any possible interactions between the drug and polymer utilized, the FTIR spectra of drug and their physical mixtures with polymers were carried out. All samples were dried in hot air oven at 50 °C for 2 h. The samples were prepared as KBr discs compressed under pressure of 10 Ton/nm^2. The selected wave number range was from 400 to 4000 cm^{-1} and peaks belonging to major functional groups were identified. The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer [9].

Differential Scanning Calorimetry (DSC)

The thermal behavior of drug was studied using DSC thermogram. Any polymorphic change in the drug causes changes in the melting point, bioavailability and release kinetics. Melting point of drug was determined by using DSC [10].

Formulation of mouth dissolving oral film

Dose calculation

The drug to be loaded in the film was determined by the dose of the drug and the drug loading in the glass plate was determined by the area of the glass plate [11].

Exploration of polymers for preparation of films

Different polymers were used for the preparation of films. Films were prepared by the solvent casting method. They were screened for their film forming capacity, appearance and disintegration time [12].

Selection of plasticizer for optimization of films

Different plasticizers were used for the preparation of films. They were screened for their film forming capacity, appearance and disintegration time [13-14].

Formulation of mouth dissolving film of Ramosetron Hcl

Film forming polymer was weighed accurately and dissolved in sufficient water. It was rotated for 30 min on magnetic stirrer for complete solubilization of polymer. Other ingredients like Ramosetron hydrochloride, polyethylene glycol, sodium lauryl sulphate and aspartame were dissolved in remaining quantity of water. Both the solutions were mixed on magnetic stirrer until they get completely homogenized and volume made up to 10ml with water. This solution was poured into a glass petri plate and dried at room temperature for 24 h. After drying, the film was removed with the help of sharp blade. Films were subjected to different evaluation parameters [15-16].

Table 1: Formulation of mouth dissolving film of Ramosetron HCl

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Ramosetron HCl (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 50 CPS (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
SLS (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

Evaluation parameters of oral-fast dissolving film

Thickness

Digital Vernier Calliper was used to measure the thickness. Thickness was measured from three different spots of film and average was taken [17].

Folding endurance

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 [18].

Dryness test/tack test

This test is performed to find out the ability of a film to get adhered to a piece of paper pressed between strips obstinacy with which the film adheres with the piece of paper or any other accessory pressed in between the films is known as tack. Dryness or tack test can also be performed by with the help of some newly invented instruments [19].

Surface pH

The pH value of a film is usually determined by putting the prepared film in petri dish and subsequently film is made wet by using distilled water and noting pH by touching the film surface with a pH meter electrode. Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation [20].

Disintegration time

The film (1.5cmx1.5cm) 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.

In vitro dissolution Studies for Ramosetron HCl film

In vitro drug release was determined by USP Paddle dissolution apparatus-II (Model No. TDT-08L, Electrolab Pvt. Ltd). The release of Ramosetron HCl from Mouth dissolving film was performed at 37±2 °C using a standard dissolution apparatus. The rotation speed was 50 rpm and the volume of the dissolution medium was 300 ml. The pH of the medium was maintained at 6.8 up to the end of the experiment. Aliquots of 4 ml were taken at specific time intervals and the original volume was maintained by adding fresh dissolution medium. The amount of Ramosetron HCL released in the dissolution medium was determined spectrophotometrically at 311 nm using (Shimadzu UV 1800). The cumulative% drug release at different time intervals was calculated.

Stability Studies

Stability studies was carried out on optimized formulations as per ICH guidelines by keeping the formulation sample at 40 °C±2 °C/75% RH ± 5% RH for 3 months. The optimized formulation F6 was stored in stability chamber (Remi, India) at 40 °C and 75% RH for 3 months. Periodically samples were withdrawn and estimated for the Disintegration time (sec), Appearance and Cumulative% releases.

Results and Discussion

Infrared absorption spectrophotometry

When IR spectra of individuals were compared with IR spectra of mixture, no considerable change in peaks were observed, which proved that, there was no interaction between Ramosetron HCl and polymers. Drug and polymers were subjected for FT-IR study. The IR spectra did not show any significant difference from those obtained for their physical mixtures. The result obtained indicated that there was no positive evidence for the interaction between Ramosetron HCl and polymers.

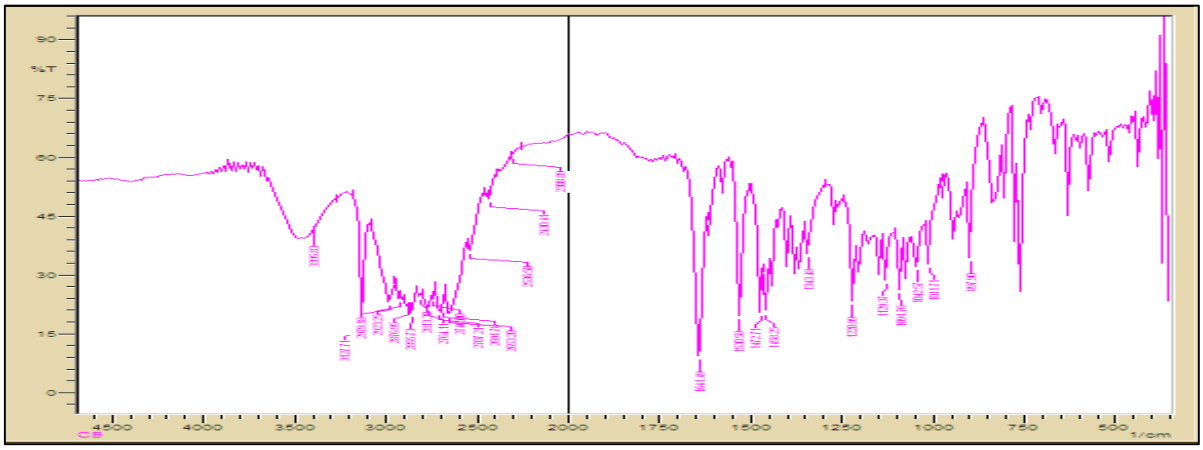

Fig 1: FTIR Spectrum of Ramosetron hydrochloride and HPMC E5

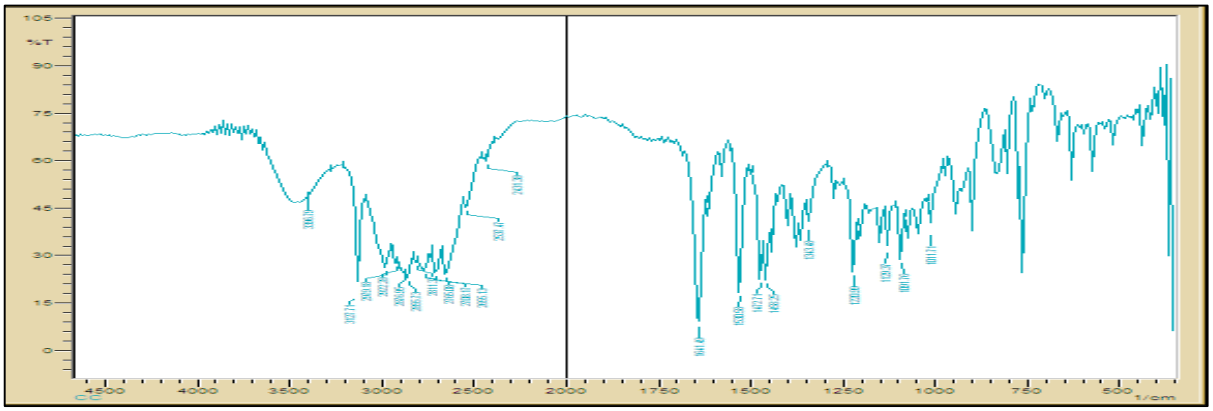

Fig 2: FTIR Spectrum of Ramosetron hydrochloride and HPMC E15

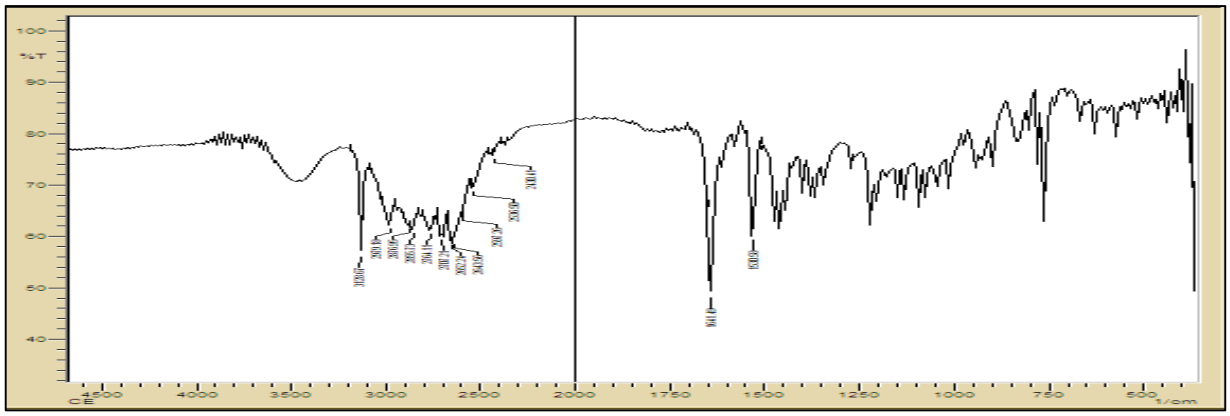

Fig 3: FTIR Spectrum of Ramosetron hydrochloride and HPMC 50 cps.

Differential Scanning Calorimetry

Thermogram for Ramosetron HCl was obtained using DSC (Mettler DSC 1 star system, Mettler-Toledo, Switzerland). The drug was hermetically sealed in perforated aluminium pans and heated at constant rate of 10 °C /min it exhibits a sharp melting endothermic peak at temperature of 247.01 ºC. The samples were put on DSC reference pan and DSC thermograms were obtained.

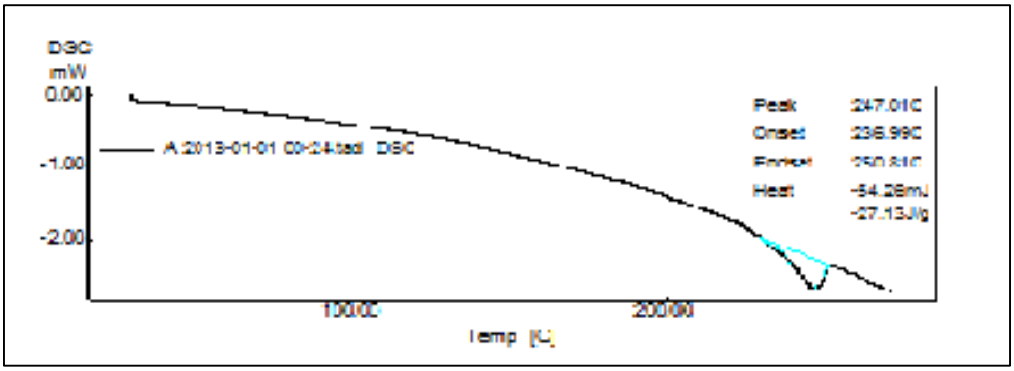

Fig 4: DSC thermograph of Ramosetron HCl.

Evaluation of mouth dissolving film of Ramosetron HCl

Films prepared with HPMC E5, HPMC E15 and HPMC 50cps. Were transparent, clear, homogeneous and smooth. From the study, it can be concluded that solvent casting technique showed better film forming property and mechanical strength. The study illustrated that concentration of polymer and plasticizer had a significant effect on formulation of fast dissolving films. Films prepared with Ramosetron HCl have low disintegration time up to45sec to 60 sec. The increase in the disintegration time may be due to increase in concentration of the polymer. As the concentration of polymer was increased thickness of the individual film was also increased. Folding endurance of the film is grater with films prepared by PEG 400 as compared to films prepared with glycerol. Surface pH of all the films is suitable for mouth and saliva pH. All prepared films are found to be dry, no presence of moisture observed.

Table 2: Evaluation of mouth dissolving film of Ramosetron HCl

Evaluation parameters	F1	F2	F3	F4	F5	F6	F7	F8
Thickness	-	0.13	0.09	0.12	0.08	0.09	0.07	0.14
Folding endurance	-	440	400	374	400	400	400	450
Disintegration time(sec)	-	52	54	57	56	45	58	60
Appearance	NA	Trans.	Trans.	Trans.	Trans.	Trans.	Trans.	Trans.
Dryness test	-	Dry	Dry	Dry	Dry	Dry	Dry	Dry
Surface pH	-	6.84	6.70	6.91	6.68	6.87	6.72	6.74
Surface texture	-	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth

***In-vitro* dissolution Studies for Ramosetron HCl film**

The amount of Ramosetron HCL released in the dissolution medium was determined spectrophotometrically at 311 nm using (Shimadzu UV 1800). The cumulative% drug release at different time intervals was calculated. F6 batch showing 98.78 percent release in 8 minutes hence it is taken as optimized batch.

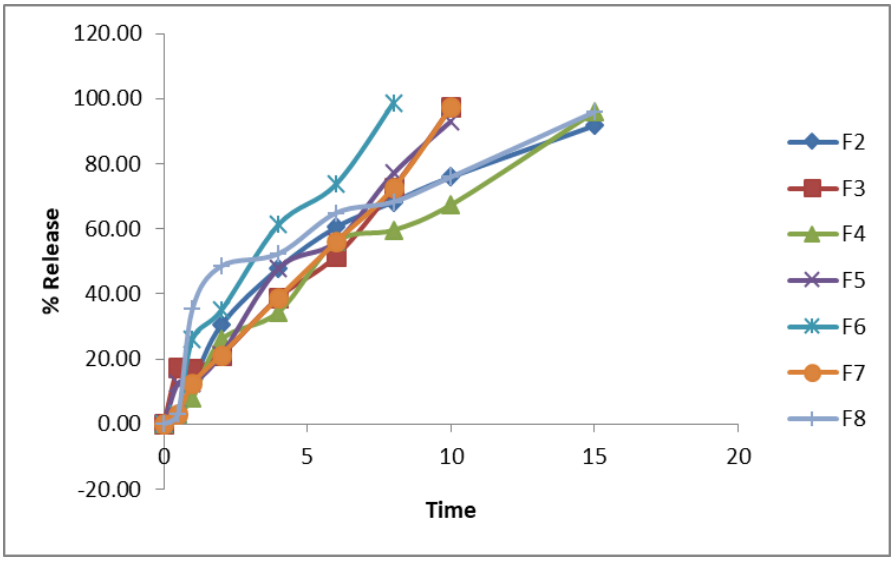

Fig 5: Cumulative% drug Release from batches F2 to F8.

Accelerated stability studies

Batch F6 kept for stability study at 40±2 °C /75±5% RH for 30 days. At the period of 30 days its physical properties, disintegration time and *in-vitro* release were determined. From the results it was revealed that, there were no significant changes observed at the end of 30 days stability study.

Table 3: Stability study of optimized F6 batch of mouth dissolving film

Sr. No.	Stability studies	0 day	15 days	30 days
1	Appearance	Transparent, uniform	Transparent, uniform	Transparent, uniform
2	Disintegration time (sec)	45	46	46
3	Cumulative% releases	98.78	98.78	98.78

Conclusion

Mouth dissolving film of Ramosetron HCl was successfully developed. The study illustrated that concentration of polymer and plasticizer had a significant effect on formulation of oral strips and it can be concluded that solvent casting technique showed better film forming property and mechanical strength. Among all the formulations F6 showed minimum disintegration time i.e. 45 sec and 98.78% drug release within 8 minutes. *In vitro* evaluation indicated that the films were potentially useful and also confirmed their potential as an innovative dosage form to improve delivery of Ramosetron HCl. The solvent casting method was found to be simple, reproducible, economical and consistent process. Additionally, the excipients used for the formulation were cheap and easily available. Other drugs which are suitable for formulation can be incorporated in mouth dissolving films. Therefore, these type dosage forms can be commercially processed easily and potentially better than other marketed formulations.

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