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Original Article

Formulation and Evaluation of Ranolazine loaded Mouth Dissolving Film

Sakshi Patil, Sandip Tadvi, Sunil Pawar

Department of Pharmaceutics, P. S. G. V. P. Mandal's College of Pharmacy, Shahada, Nandurbar, India-425409

ABSTRACT

The development of ranolazine mouth dissolving films (MDFs), which are used to treat angina pectoris in cardiovascular illnesses, is the primary goal of the current study. Using the solvent casting method, eight formulations (F1, F2, F3, F4, F5, F6, F7, F8) were made using HPMC E15 and PVA as polymers, PEG 400 as a plasticizer, sugar as a sweetener, citric acid as a saliva-stimulating agent, and mint as a flavoring ingredient. The produced films are taken without the use of water, have a rapid onset of action, and boost bioavailability by avoiding hepatic first pass metabolism. Formulation F3 was determined to be stable under appropriate stability conditions, with a drug release rate of 94.34% in just 5 minutes. The assessment criteria of the films indicate that the use of mouth-dispersing Ranolazine films can be a noteworthy and inventive therapy option for cardiovascular conditions such as myocardial infarction, angina pectoris, and heart attacks.

Keywords: Mouth dispersing films, Ranolazine, polymers, plasticizer, solvent casting method.

INTRODUCTION

The majority of pharmaceutical researchers are mostly focused on the oral dosage form since it provides a rapid drug release and has a quick onset of action. Mouth Dissolving Films (MDFs) are a unique and state-of-the-art medicine delivery system that increases patient compliance. MDFs systematically administer the medication by the buccal or sublingual routes in addition to providing local action. MDFs are a thin film that, when placed on the tongue, quickly becomes moistened from saliva. The film subsequently dissolves and disintegrates in a matter of seconds, allowing the medicine to be absorbed. MDFs have an advantage over capsules and other dosage forms since the film dissolves quickly and exhibits an immediate commencement of action. Owing to increased blood flow and the oral mucosa's 4-1000-fold higher permeability than skin, MDFs boost bioavailability. minimizes first pass metabolism and shortens the onset time. Since it enhances drug efficacy, flexibility, disintegration, and dissolution, fast dissolving drug delivery is the most sophisticated form[1].Fear of choking on dosage forms is a common reason why many elderly and pediatric patients are reluctant to receive solid preparations. 26% of patients reported having trouble swallowing medications, according to one study. After taste and surface form, the most common complaints were over tablet size [2].

A compound of acetanilide and piperazine with anti-ischemic qualities is ranolazine. The USFDA approved it for the treatment of angina pectoris in 2006. It reduces intracellular calcium levels by blocking sodium channels, which in turn causes the heart muscle's (myocardium) tension to decrease.

Researchers refer to the quickly dissolving dosage forms by a number of names, including melt-in-the-mouth, quick-disintegrating, oral-disintegrating, and mouth dissolve [3].

Materials

Ranolazine was obtained as a gift sample from Ajanta pharmaceuticals, bharuch, Gujrat, India. HPMC E15, PVA, PEG-400, Sodium Starch glycolate. Citric acid, mint was obtained from Research lab.

Methods

Preparation of Mouth Dissolving Films (MDFs)

Using the solvent casting approach, MDFs were created[4]. This technique involves immersing polymers, including PVA and HPMC E15, for an entire night. After adding sodium starch glycolate and all additional excipients—like aspartame, PEG 400, citrus flavor, and citric acid—to the polymer solution, it was agitated for an hour at 1000 rpm. After dissolving in a little amount of methanol, ranolazine

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

was added to the polymer solution and swirled for 30 minutes at 100 rpm. After that, the obtained solution is set aside for a few minutes in order to release the trapped air bubbles. The solution was placed in a glass Petriplate (with a 10 cm diameter). and allowed to dry at 45°C for four to five hours. After carefully removing the film from the petriplate, it was inspected for any defects and sliced into the appropriate dimensions to provide each film with the equivalent dosage of 2 x 2 cm². The produced films were placed in aluminum foil bags and kept between 30 and 35 percent relative humidity in a desiccator[4].

Results and discussion

Characterization of Ranolazine

Description

Table No. 01: Description of Ranolazine.

Colour	White
Odour	Odourless
Taste	Bitter

Solubility

Ranolazine dissolved readily in both ethanol and methanol.

Melting point

Ranolazine's melting point was discovered to be 121°C. Consequently, it shows how pure the sample is.

Determination of λ max of Ranolazine

It was discovered that ranolazine's λ max was 272 nm.

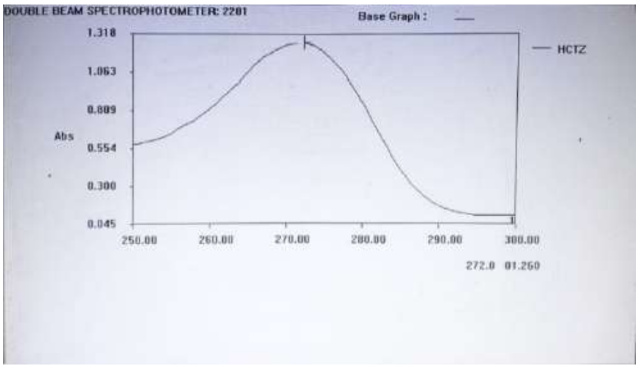

Figure No. 01: UV Spectrum of Ranolazine.

Standard calibration curve of Ranolazine

Standard calibration curve of Ranolazine in phosphate buffer

In phosphate buffer with a pH of 6.8, ranolazine exhibited maximum absorption at 272 nm. A standard curve was created by measuring the absorption of diluted stock solutions (1,2,4,6, 8, 10 µg/ml) at this wavelength[6].

Table No. 02: standard calibration curve of Ranolazine in phosphate buffer

Sr. No.	Concentration in µg/ml	Absorbance at 272 nm
1	0	0.00
2	2	0.287
3	4	0.576
4	6	0.84
5	8	1.105
6	10	1.424

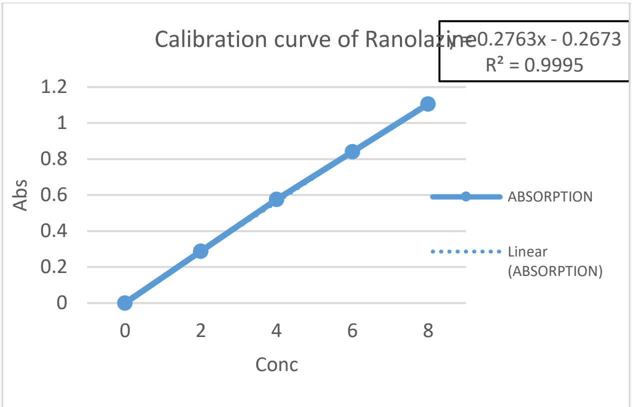

Figure No. 02: calibration curve of Ranolazine.

The standard calibration curve for ranolazine par ameters in phosphate buffer is presented.

Drug excipients compatibility studies by IR spectroscopy

Ranolazine's infrared spectrum captured on an FTIR-4100 in Jasco, Japan using a KBr pellet. The corresponding assignments for the infrared frequencies are listed below.

IR Peaks of Various Functional Groups of Ranolazine.

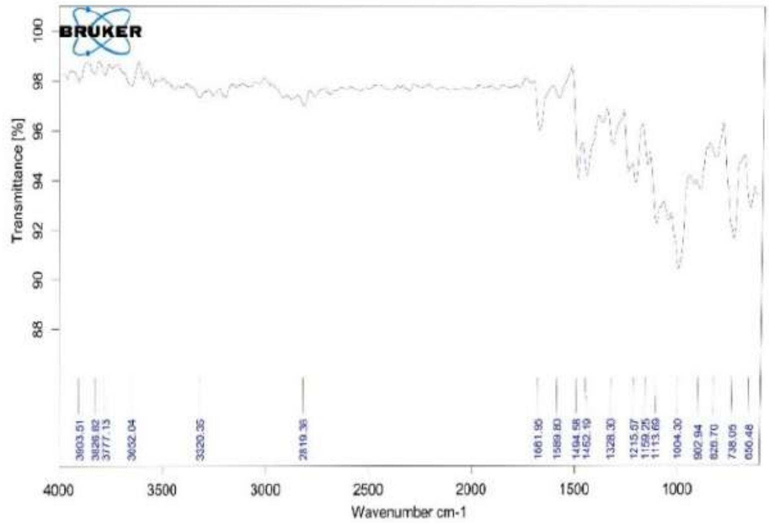

Figure no. 03: IR spectrum of Ranolazine

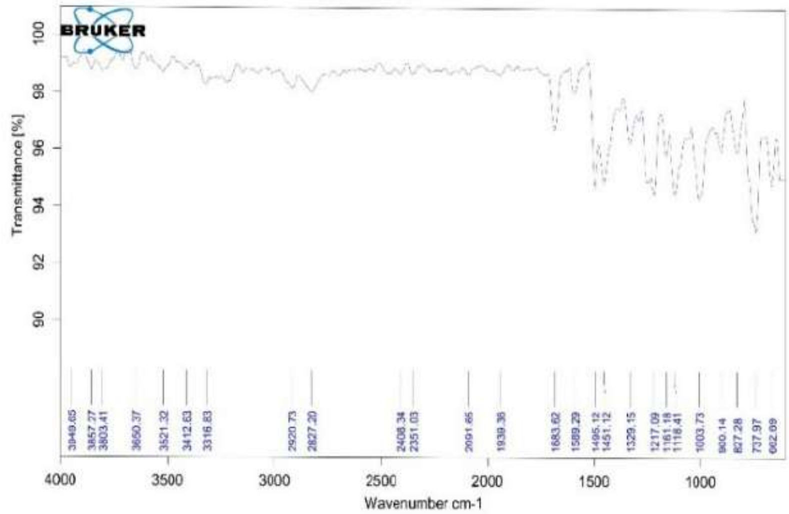

Figure No. 04: IR Spectra of Ranolazine with HPMC E15

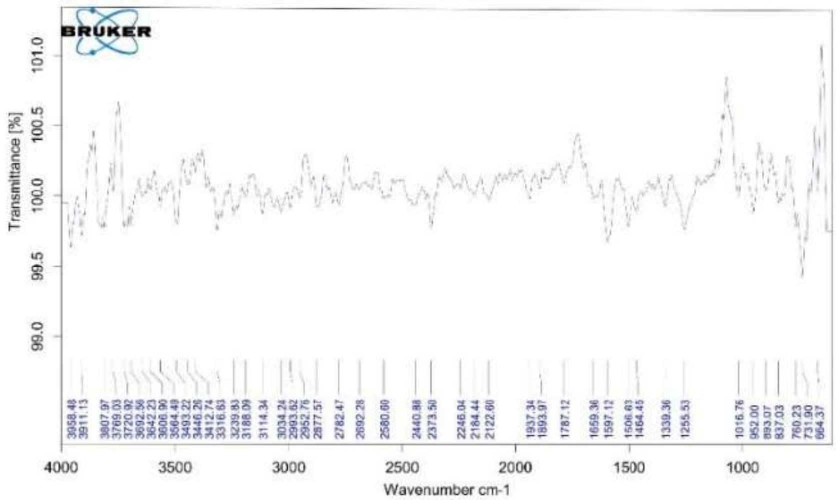

Figure No. 05: IR Spectra of Ranolazine With PVA

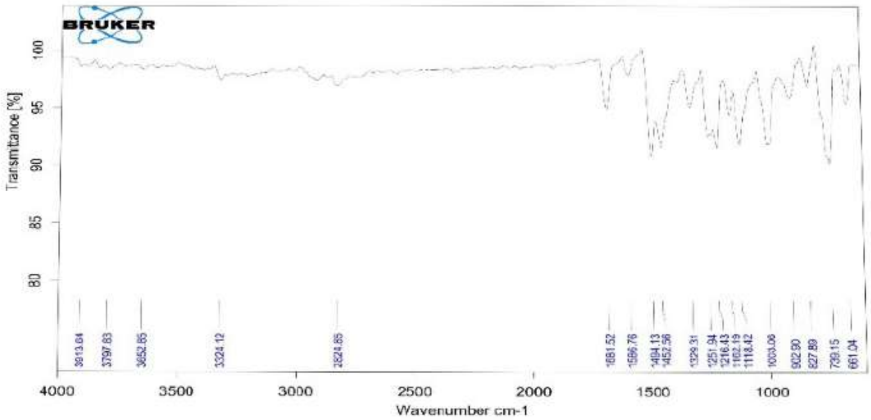

Figure No. 06: IR Spectra of Ranolazine with PEG 400

Dose calculation:

The drug dose dictated how much drug to be put into the film, and the glass plate's area dictated how much drug should be loaded into it.

The plate's diameter is 10 cm.

Plate area = πr^2 = 78.5 cm^2

Total number of 4 cm^2 films on the plate = 78.5/4 s = 19.62

The medication content of each film is 20 mg.

Each plate has to contain 19.62 x 10 = 392.4 mg of medication.

Table No. 03: Formulation of mouth dissolving film

Components (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Ranolazine	392.4	392.4	392.4	392.4	392.4	392.4	392.4	392.4
HPMC E15	100	200	250	300	350	400	450	500
PVA	50	100	125	150	175	200	225	250
PEG 400(ml)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
SSG	20	20	20	20	20	20	20	20
Aspartame	25	25	25	25	25	25	25	25
Citric acid	20	20	20	20	20	20	20	20
Flavour	q.s	q. s	q.s	q.s	q. s	q. s	q. s	q. s
Water(ml)	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Methanol(ml)	5	5	5	5	5	5	5	5

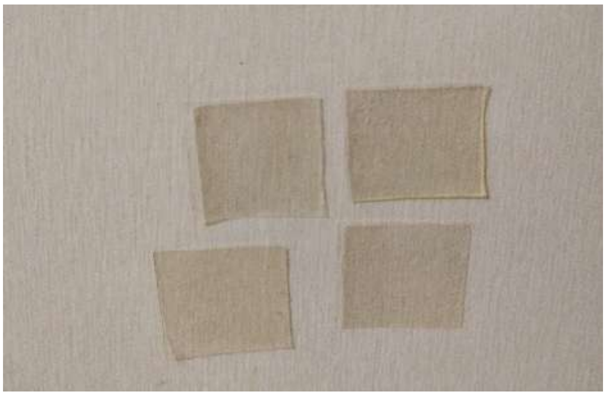

Figure No. 07: Picture of mouth dissolving film (F3)

7.5 Evaluation of formulation F3

A) Appearance & Tack test:

Analysing Films Made for Formulation Design The tack test and appearance were examined in the table that is as follows.

Table No. 04: Evaluation For Film Forming Capacity, Tack Test and Appearance of Film

Sr. no.	Formulation code	Tack test	Appearance
1	F1	Tacky	Transparent
2	F2	Non tacky	Transparent
3	F3	Non tacky	Transparent
4	F4	Tacky	Transparent
5	F5	Non tacky	Transparent
6	F6	Non tacky	Transparent
7	F7	Non tacky	Transparent
8	F8	Non tacky	Transparent

B) Thickness of mouth dissolving film:

A screw gauge with a resolution of 0.1 mm and a range of 0-10 mm was used to measure the thickness of the film. After ensuring that the pointer was set to zero, the MDF sample equal to the medicine dosage was taken, the thickness gauge's anvil was lifted, and the MDF was inserted. The MDF was placed at anvil, and the dial's reading was recorded. The mean thickness was determined by averaging the three values.

Table No. 05: Thickness of mouth dissolving film

Sr.no.	Formulation code	Thickness (mm) (Mean +- SD) n=3
1	F1	0.34 + 0.010
2	F2	0.42 + 0.025
3	F3	0.31 + 0.015
4	F4	0.45 + 0.030
5	F5	0.61 + 0.015
6	F6	0.54 + 0.040
7	F7	0.85 + 0.045
8	F8	0.61 + 0.070

C) Weight variation of strip:

By using the solvent casting procedure, mouth dissolving films were created. After cutting each 2 sq. cm film from the cast, the weight variation was measured, and the mean and standard deviation of the data were determined.

Table No. 06: Weight variation of mouth dissolving film

Sr. no.	Formulation code	Weight variation (mg) (Mean +- SD) n=3
1	F1	89.5 + 0.5131
2	F2	92.4 + 0.4
3	F3	96.56 + 0.5131
4	F4	90.5 + 0.4682
5	F5	95.33 + 0.4163
6	F6	91.5 + 0.5
7	F7	97.26 + 0.3055
8	F8	87.6 + 0.5291

D) Folding endurance:

The ability of three films from each batch to fold repeatedly was tested by folding a single film at the same location for 200 times, or until it broke or folded, which is deemed sufficient to demonstrate good patch qualities.

Table No. 07: Folding endurance of mouth dissolving film

Sr. no.	Formulation code	Avg. Folding endurance +- SD, n=3
1	F1	104 + 2
2	F2	92.3 + 0.577
3	F3	162 + 2.645
4	F4	155 + 1
5	F5	122.6 + 1.154
6	F6	91 + 1
7	F7	105.3 + 0.577
8	F8	106.6 + 1.154

A range of 150–200 folds was found to yield a high enough score for folding endurance. This suggests the appropriate flexibility of the required strip.

E) Surface pH:

To find the pH, dissolve one oral film in 10 milliliters of distilled water. Then, measure the pH of the resulting solution by touching the electrode of a pH meter to the film's surface and letting it acclimate for a minute. Every calculation was done three times.

Table No. 08: Surface pH of mouth dissolving film

Sr. no.	Formulation code	Surface pH (mean+- SD) n=3
1	F1	104 + 2
2	F2	92.3 + 0.577
3	F3	106.6 + 1.154
4	F4	155 + 1
5	F5	122.6 + 1.154
6	F6	91 + 1
7	F7	105.3 + 0.577
8	F8	162 + 2.645

F) Tack test:

The strength with which a strip sticks to a piece of paper or an accessory after being pressed into contact with it is known as its tack. These observations are recorded in Table No.

Table No. 09: Content uniformity of mouth dissolving film

Sr. no.	Formulation code	Drug content uniformity (mean+- SD) n=3
1	F1	95.5 ± 0.03
2	F2	98.2 ± 0.03
3	F3	94 ± 0.04
4	F4	94.8 ± 0.02
5	F5	93.3 ± 0.04
6	F6	97.6 ± 0.02
7	F7	95.2 ± 0.05
8	F8	95.4 ± 0.03

H) *in-vitro* Disintegration time:

Table No. 10: *in- vitro* Disintegration time of mouth dissolving film

Sr. no.	Formulation code	*In-vitro* Disintegration time (mean+- SD) n=3
1	F1	47.33 + 1.527
2	F2	50.33 + 1.154
3	F3	57 + 1.732
4	F4	69.66 + 0.577
5	F5	74 + 1
6	F6	82.66 + 1.154
7	F7	121 + 1
8	F8	122.33 + 2.516

Measurements of the *in-vitro* disintegration times for each batch revealed that the disintegration times increased with polymer concentration.

I) *In-vitro* dissolution study (Drug release study):

Table No. 11: *In-vitro* dissolution study of F1 to F4

Time	F1	F2	F3	F4
30 sec	35.95 ± 0.03	34.78 ± 0.60	37.23 ± 0.20	33.21 ± 0.6
1 min	39.04 ± 0.01	40.46 ± 0.30	42.35 ± 0.03	39.19 ± 0.12
2 min	44.24 ± 0.03	45.86 ± 0.01	50.14 ± 0.12	43.34 ± 0.08
3 min	73.07 ± 0.02	62.34 ± 0.02	77.35 ± 0.03	60.61 ± 0.08
4 min	77.43 ± 0.01	79.16 ± 0.12	86.4 ± 0.20	66.68 ± 0.06
5 min	85.33 ± 0.02	92.92 ± 0.02	94.34 ± 0.02	80.20 ± 0.11

Table No. 12: *In-vitro* dissolution study of F5 to F8

Time	F5	F6	F7	F8
30 sec	33.26 ± 0.08	35.35 ± 0.04	37.22 ± 0.17	32.63 ± 0.02
1 min	37.54 ± 0.46	39.48 ± 0.07	40.18 ± 0.22	36.72 ± 0.02
2 min	38.58 ± 0.05	45.67 ± 0.10	43.72 ± 0.02	55.18 ± 0.02
3 min	43.34 ± 0.29	65.87 ± 0.10	63.82 ± 0.03	64.36 ± 0.04
4 min	68.27 ± 0.24	78.19 ± 0.09	74.54 ± 0.14	77.57 ± 0.04
5 min	79.53 ± 0.03	86.32 ± 0.08	90.51 ± 0.44	81.74 ± 0.07

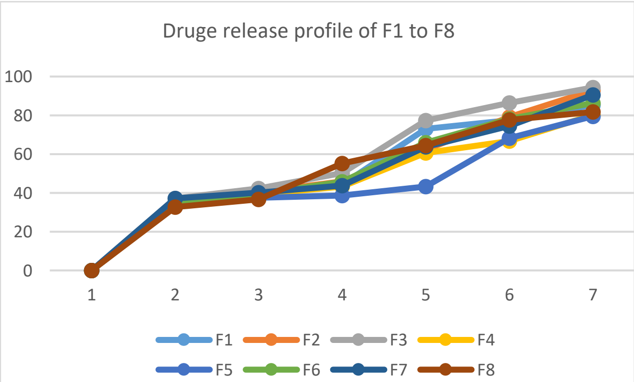

Figure No. 08: Drug release profile of batch F1 to F8

As can be seen from the preceding in-vitro dissolution analysis of Formulation batches F1–F8, of which Formulation F3 showed that 94.34% of the medication was released in 5 minutes in simulated saliva made of phosphate buffer saline solution. Due to its rapid commencement of action, it is most desirable for mouth dissolving films to dissolve quickly; hence, research reveals that these films dissolve quickly.

J) Stability study:

The stability study's findings showed that the medication product complies well with the suggested stability requirements. According to the data, there hasn't been any noticeable change in either the physical or chemical properties, meaning that the formulation will stay effective and high-quality for the duration of its suggested shelf life.

Table No. 13: Stability study of mouth dissolving film

Sr. No.	Temperature	Physical appearance	Drug content	*In- vitro* dissolution
1	Room temperature	Transparent and easily peelable	95.33 ± 0.574	97.44 ± 0.02 (For 5 min.)

CONCLUSION

By creating MDFs of ranolazine, the current study's goal has been accomplished. Solvent casting has been successfully used to create ranolazine mouth dissolving films (MDFs). In comparison to other formulations, the F3 formulation releases the medication immediately, according to the in vitro studies. As no appreciable variations in drug release, content homogeneity, or other physical attributes were noticed, the formulation F3 was determined to be stable. These current findings imply that oral thin films containing ranolazine dissolve in less than a minute, suggesting that they may be helpful in treating angina, dysphasia or aphasia patients, elderly patients who refuse to take pills, and other conditions.

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