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FORMULATION AND EVALUATION OF FAST DISSOLVING FILM OF PANTAPRAZOLE SODIUM

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ABSTRACT

New drug delivery system for the oral delivery of drug, was developed based on the technology of the transdermal patch. It consists of a very thin oral strip which releases the active ingredient immediately after uptake into the oral cavity. The technique involved in the preparation of mouth dissolving film was solvent casting method in which aqueous solution I (Pantaprazole Sodium, Sodium Starch Glycolate, Ascorbic acid, Vanilla flavour and Saccharin) and aqueous solution II (HPMC E15 and Glycerine) was prepared in specific proportion in distilled water. Both solution I & II were mixed & stir for 1 hour & kept for 1 hour to remove all air bubbles. Then the mixture solution was poured into petridish & it was dried in oven at 40-50 0C for 7- 8 hours then film was removed from petridish and cut according to Size (square film: 2cm length, 2cm width). Pantaprazole is a highly potent proton pump inhibitor, chemically a weak base, it concentrates under the acidic conditions of parietal cell secretory canaliculi where it is converted to a cationic cyclic sulfonamide by rearrangement. This activated molecule binds to two site of hydrogen/potassium ATPase (proton pump) in the gastric parietal cells, inactivating the system, which in turn blocks the final step of secretion of hydrochloric acid by these cells, producing a long lasting effect.

KEYWORDS: Mouth Dissolving Film; Oraly dissolving Film; Oral Strip; Pantaprazole Sodium.

INTRODUCTION

Various bio-adhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as oral thin films. (Jawahar N *et al*., 2012; Reddy N *et al*., 2012). A new oral fast dissolving dosage form such as the fast dissolving film has been developed which offers the combined advantages of ease of dosing and convenience of dosing in the absence of water.—Oral fast dissolving film is relatively a new dosage form in which thin film is prepared using hydrophilic polymers, which rapidly dissolves on tongue or buccal cavity. Oral Fast dissolving film (FDF) is also known as mouth dissolving films (MDF), oral strips, oro dispersible films (ODF)(Dhere P *et al*., 2011). On placing mouth dissolving films in the mouth, saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach & it may produce rapid onset of action. In such cases bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. (Satoskar R Bhandarkar *et al*., 2013; Sumitha C *et al*., 2009; Thakur S *et al*., 2013).

Ideal Characterisitcs of Fast Dissolving Drug Delivery System

- Require no water for administration
- Cost effective production methods
- Leave minimal or no residue in mouth
- Dissolve within a fraction of seconds
- Have a pleasant mouth feel (Saini S *et al*., 2011; Arun A *et al*., 2010).

Formulation

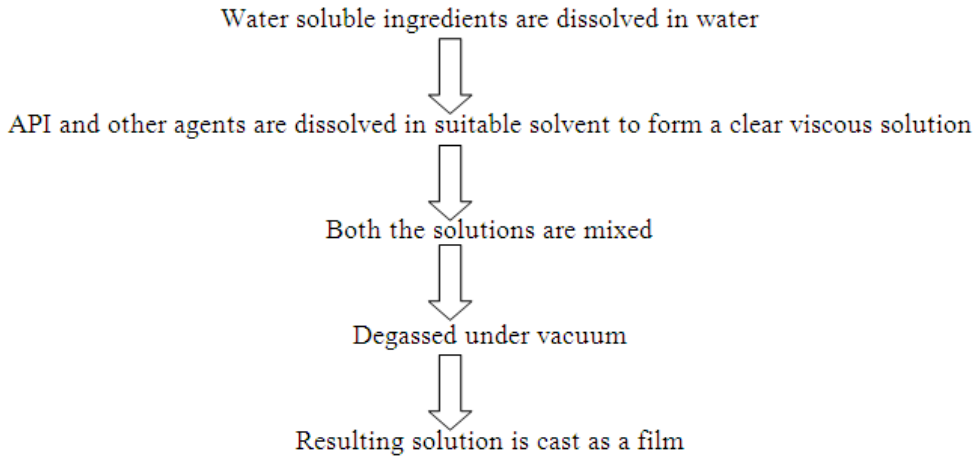
ODFs are fast disintegrating thin films having an area ranging from 5 to 20 cm2 in which drug is incorporated in the form of matrix using hydrophilic polymer. Active pharmaceutical ingredient can be incorporated up to 15 mg along with other excipients i.e., plasticizers, colorants, sweeteners, taste masking agents, etc. Plasticizer increases workability, spreadability and flexibility of films thereby reducing the glass transition temperature of polymers. (Arya A *et al*., 2010)

A typical composition contains the following excipients

- Drug : 1 - 25 %
- water-soluble polymers : 40 - 50 %
- Plasticizers : 0 - 20 %
- Fillers, colors, flavors etc : 0 - 40 %

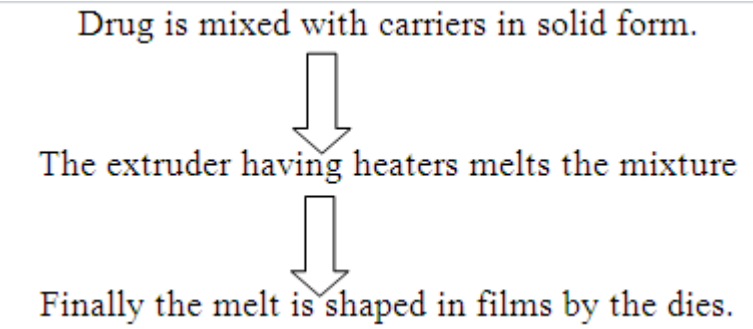
Methods of Preparation of Fast Dissolving Film

1. Solvent Casting Method



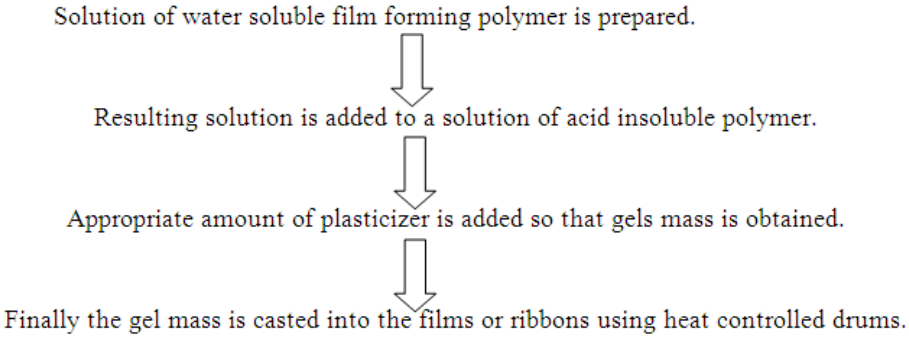
Flow Chart No1: Solvent Casting Method.

2. Hot Melt Extrusion Method



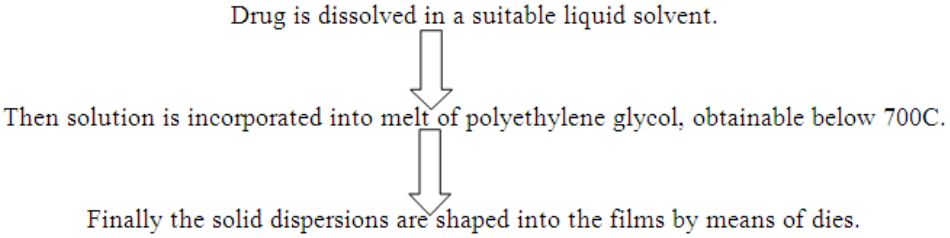
Flow Chart No 2: Hot Melt Extrusion Method.

3. Semisolid Casting Method



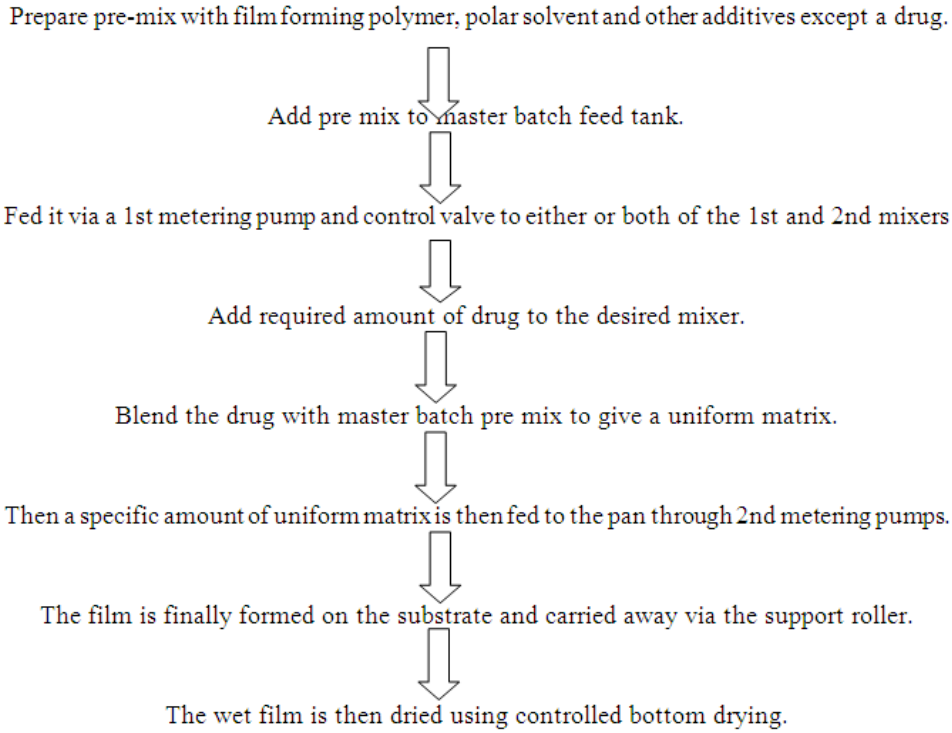
Flow Chart No 3: Semisolid Casting Method.

4. Solid Dispersion Extrusion Method



Flow Chart No 4: Solid Dispersion Extrusion Method.

5. Rolling Method



Flow Chart No 5: Rolling Method (Ghorwade V *et al.*, 2011).

MATERIAL AND METHODS

The technique involved in the preparation of mouth dissolving film was solvent casting method in which aqueous solution I (Pantaprazole Sodium, Sodium Starch Glycolate, Ascorbic acid, Vanilla flavour and Saccharin) and aqueous solution II (HPMC E15 and Glycerine) was prepared in specific proportion in distilled water. Both solution I & II were mixed & stir for 1 hour & kept for 1 hour to remove all air bubbles. Then the mixture solution was poured into petridish & it was dried in oven at 40-50 $_0^C$ for 7- 8 hours then film was removed from petridish and csssssssut according to Size (square film: 2cm length, 2cm width). (Mashru R.C *et al.*, 2008).

Ingredients Used In Mouth Dissolving Film Preparations:

Pantaprazole Sodium, HPMC E15, Glycerine, Sodium Starch Glycolate, Ascorbic acid, Vanilla flavour and Saccharin.

Preformulation study

Almost all new drugs are marketed in the form of tablets, capsules or both. Prior to the development of these dosage forms, it is essential that certain fundamental physical and chemical properties of the drug molecule and derived properties of the drug powder should be determined. This information read out many of the subsequent events and approaches in formulation development. The first learning phase is known as preformulation.

Identification test for drug

1. Organoleptic Property

Drug sample was evaluated for color, odour, and taste was been evaluated.

2. Solubility

The solubility of Pantaprazole Sodium was checked in different solvents like methanol, water.

3. Melting point determination
Melting point of Pantaprazole Sodium was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate.

4. Infrared spectroscopy
A FTIR spectrum of Pantaprazole Sodium was obtained in the range of 400-4000 cm-1 and the peaks mentioned in standards were compared with those obtained.

5. UV spectrophotometer
Drug solution was scanned at 200-400 nm to observe the maxima.

Analytical Study
1. Preparation of standard calibration curve for Pantaprazole sodium in Water
The stock solution was prepared by accurately weighing 100 mg of Pantoprazole Sodium and dissolved in 100 ml of water in volumetric flask. From the stock solution 0.1, 0.5, 1, 1.5, 2.0, 2.5, ml was pipette out and made up to 10ml with water to prepare the concentrations in µg/mL. The prepared concentrations were analyzed at 295 nm by spectrophotometer. Absorbance mean of five determinations was taken to check the reproducibility. The observed absorbance was subjected to regression analysis, to study the linearity and other optical characteristics.

2. Preparation of standard calibration curve for Pantaprazole sodium in Phosphate Buffer pH 7.4:
The stock solution was prepared by accurately weighing 100 mg of Pantoprazole Sodium and dissolved in Phosphate Buffer pH 7.4 in volumetric flask. From the stock solution 0.1, 0.5, 1, 1.5, 2.0, 2.5, ml was pipette out and made up to 10ml with phosphate buffer (7.4 pH) to prepare the concentrations in µg/mL. The prepared concentrations were analyzed at 295 nm by spectrophotometer. Absorbance mean of five determinations was taken to check the reproducibility. The observed absorbance was subjected to regression analysis, to study the linearity and other optical characteristics.(Siddiqui N *et al.*,2011; Gowri R *et al.*, 2013)

Compatibility Study
1. FTIR Spectroscopy
The interaction between the drug and excipients was determined by using the FTIR spectroscopy. The scanning range was 450 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. I.R. spectral analyses of following samples were carried out to investigate any changes in chemical composition of the drug after combining it with the excipient

Table 1: Formulation Of Pantaprazole Film.

Name Of Ingredients	Quantity (in mg)					
	F1	F2	F3	F4	F5	F6
Drug	80	80	80	80	80	80
HPMC	150	200	250	300	350	400
Glycerine	30	40	45	50	55	60
Ascorbic acid	50	50	50	50	50	50
SSG	25	25	25	25	25	25
Flavour	qs	qs	qs	qs	qs	qs
Saccharine	60	60	60	60	60	60

Evaluation Parameters of Formulation
1. Physical appearance
Physical appearance by includes visual inspection of films.

2. Surface texture
Surface texture can evaluate by touching the film.

3. Thickness Uniformity
The thickness was measured using Digital Vernier Caliper. The thickness was measured at three different spot of the film and average was taken.

4. Weight Uniformity
Film was cut from different areas of film. The weight of each film was taken and the weight variation of six films was calculated.

5. Percentage Moisture content Test
Percentage moisture loss was determined by keeping the films in a desiccators containing anhydrous calcium chloride. and it was calculated using the following formula.

Percentage Moisture Loss = ((Initial weight – Final weight)/ Initial weight) x 100. (Yoshifumi Murata *et al.*, 2010; Sheikh S *et al*., 2013)

6. Drug Content Uniformity: (Choudhary Dhagla R *et al.*, 2012)
To check the uniformity of the drug in the film three films were taken out from each batch. Each film was then placed in volumetric flask containing 10ml of distilled water and shaken to extract the drug from film. One millilitre of above resulting solution was withdrawn, after suitable dilution with distilled water and analyzed UV-spectrophotometrically at 295 nm using distilled

water as blank. The mean and standard deviation of drug content of three randomly selected films were calculated. The same procedure was adopted for all the batches and drug content was noted from calibration curve.

7. Surface pH: (Bhupinder Bhyan *et al*., 2011)
The surface pH of the patches was determined to investigate the possibility of any irritation side, in-vivo, because an acidic or alkaline pH may cause irritation to the buccal mucosa. Therefore, the idea behind the test is to keep the surface pH as close to neutral as possible. Surface pH of the films were determined by placing the film on the surface of 1.5% w/v agar gel and allow to swell, followed by placing pH paper (pH range 1-11) on the surface of swollen film. The change in the colour of pH paper was observed and reported.

8. Folding Endurance
Folding Endurance is evaluation of films involves determining the folding capacity of the films when subjected to frequent extreme condition of folding. The number of times the film could be folded at the same place without breaking/cracking gave value of folding endurance.

9. Dissolving Time
Determined manually by dipping the film in 10 ml of water in beaker with gently shaking when film was dissolved, time was noted.

10. In Vitro Drug Release (Jawahar N *et al*., 2012)
Dissolution studies of films were performed by USP type II apparatus (paddle type) in 7.4 phosphate buffer (500ml). The temperature (37±0.5°C) and the rotation speed was 50 rpm. The samples were withdrawn at various time intervals and replaced by same volume of phosphate buffer solution and these samples analyzed spectrophotometrically. The % drug release is calculated and is given in table no 24, 25 and is graphically represented in fig no 15, 16.

11. Tensile strength (Reddy N *et al*., 2012)
The tensile strength (psi) is the property of the film that requires a load to cause load deformation failure of film.Film strips were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 0.5 mm/sec; the force and elongation were measured when the film broke. Tensile Strength is obtained by following equation.

Tensile strength (N/mm2) = breaking force (N) / cross sectional area of sample (mm2)

12. Percent elongation: (Dheerajvarma K *et al*., 2014)
The percent elongation is measured when the film snaps as sufficient force applied so as to exceed the elastic limit. Percentage elongation can be obtained by following equation:

Elongation At Break (%) = Increase In Length At Breaking Point (Mm)/Original Length (Mm) X100%.

13. Stability study
Stability study for film F3 is carried out. Films were wrapped individually in aluminium foil and maintained at oven temperature (40±0.5°C) and (75±5%) RH for 1 month as per ICH guidelines. Apart from this the films were also exposed to room condition (27 ± 20C) for 1 month. Changes in the appearance and drug content of the stored films were investigated after storage.

RESULTS AND DISCUSSION

1. Organoleptic Property
Table No 2: Organoleptic properties of Pantaprazole sodium.

Parameters	Properties
Colour	Off white
Odour	Fruit like
Taste	Metallic taste

2. Solubility
Table 3: Solubility of Pantaprazole Sodium.

Solvents	Solubility Quantity dissolved at 25°c(mg/ml)
Water	More than 1000
Methanol	More than 2000
Ethanol	More than 1000

4. Melting Point
Melting point range of Pantaprazole sodium has been reported to be 139°c to 140°c, and the substance melt with decomposition.

5. Infrared spectroscopy
As described in the methodology FT-IR studies were carried out on pure drug (Pantaprazole). The pure drug was scanned over a wave range of 4000 to 500 cm-1 in FT-IR instrument.

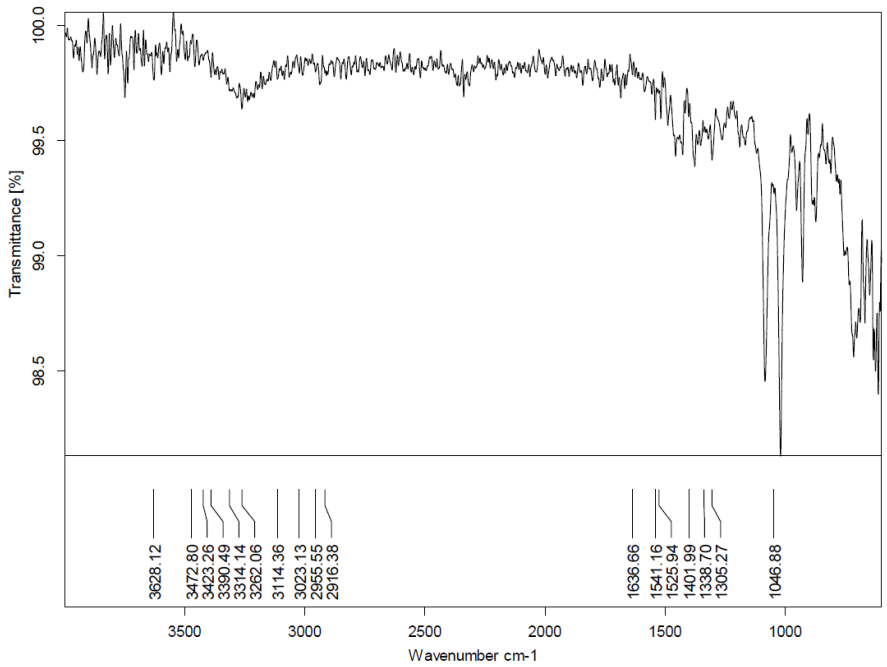


Figure 1: IR Spectra of Pantaprazole Sodium.

Table 4: IR interpretation of drug.

Sr. No	Interpretation	IR absorption band(cm^{-1})
1	N-H	3472.80
2	O-H	3314.14
3	CH_2	3114.36
4	CH_3	2955.55
5	C-O	1541.16
6	C-F	1338.70
7	S=O	1046.88

6. UV spectrophotometer

Drug solution was scanned at 200-400 nm, maxima was observed at wavelength 293 nm as shown in fig. No 11. This was confirmed with standard UV spectrum of the Pantaprazole sodium.

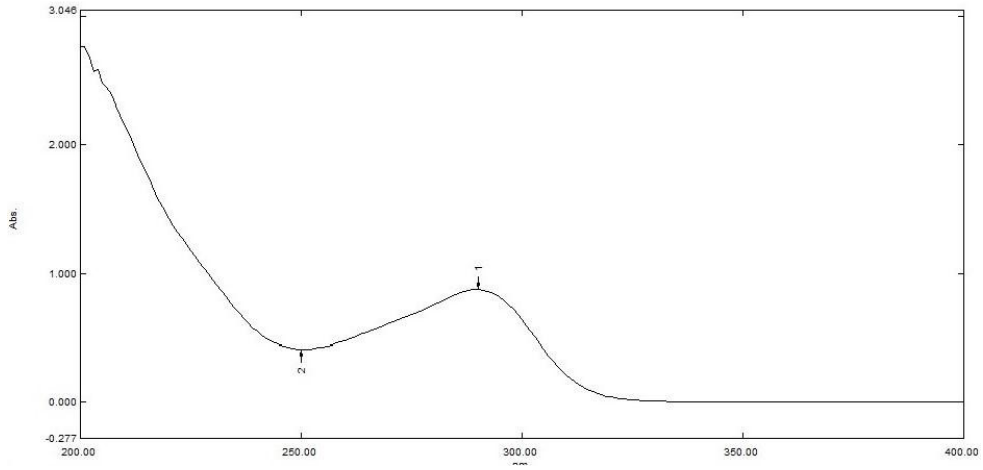


Figure 11: UV Spectrum of pantaprazole sodium in water.

7. Analytical Study

Calibration curve for Pantoprazole Sodium in water

Calibration curve of Pantaprazole sodium in water was plotted in Figure: 12 show the standard calibration curve of Pantaprazole sodium with the correlation coefficient 0.998 and regression value y = 0.0476x + 0.0217.

Table 5: Calibration curve for Pantoprazole Sodium in water.

Sr. No	Concentration(µg /ml)	Absorbance
1	0	0
2	5	0.2904
3	10	0.4858
4	15	0.7454
5	20	0.978
6	25	1.2024

Calibration curve of Pantoprazole Sodium in Phosphate Buffer pH 7.4:

Calibration curve of Pantaprazole sodium in Phosphate Buffer pH 7.4 was plotted in Figure: 13 show the standard calibration curve of Pantaprazole sodium with the correlation coefficient 0.997 and regression value y = 0.0227x + 0.0017.

Table 6: Calibration curve for Pantoprazole Sodium in Phosphate Buffer pH 7.4.

Sr. No	Concentration(µg /ml)	Absorbance
1	0	0
2	5	0.1259
3	10	0.2314
4	15	0.3318
5	20	0.4505
6	25	0.5575
7	30	0.6986

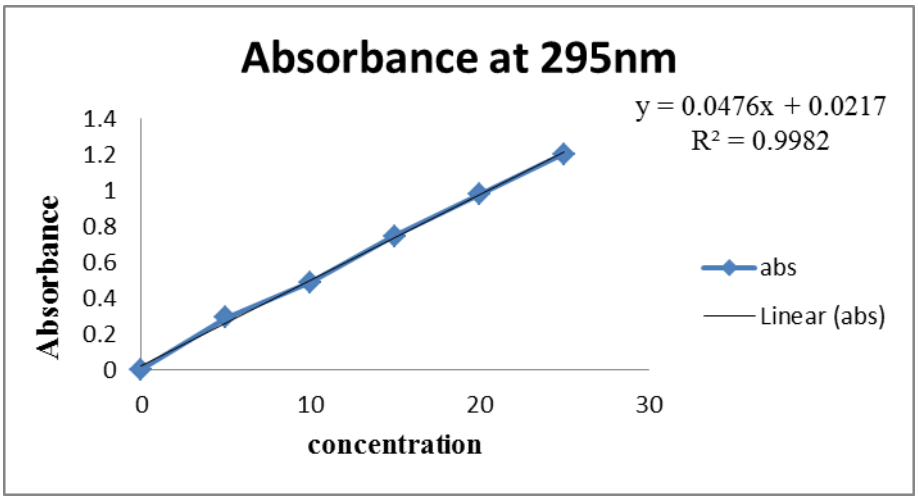


Figure 12: Calibration curve for Pantoprazole Sodium in water.

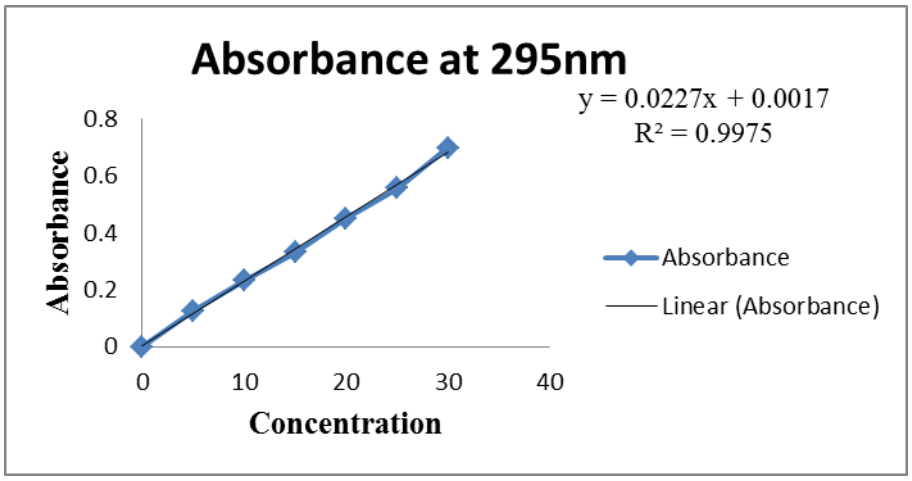


Figure 13: Calibration curve for Pantoprazole Sodium in Phosphate Buffer pH 7.4

8. Compatibility Study

Fourier Transform Infrared (FTIR) Spectroscopy

An IR spectrum of API was already shown in Fig No.10 and an IR spectrum of drug- excipient physical mixture was reported in Fig. No 14 The FT-IR studies were conducted to ensure interactions among the pantaprazole sodium and HPMC used in the formulation. The same peaks were also observed in the formulation indicating the stable nature of the drug.

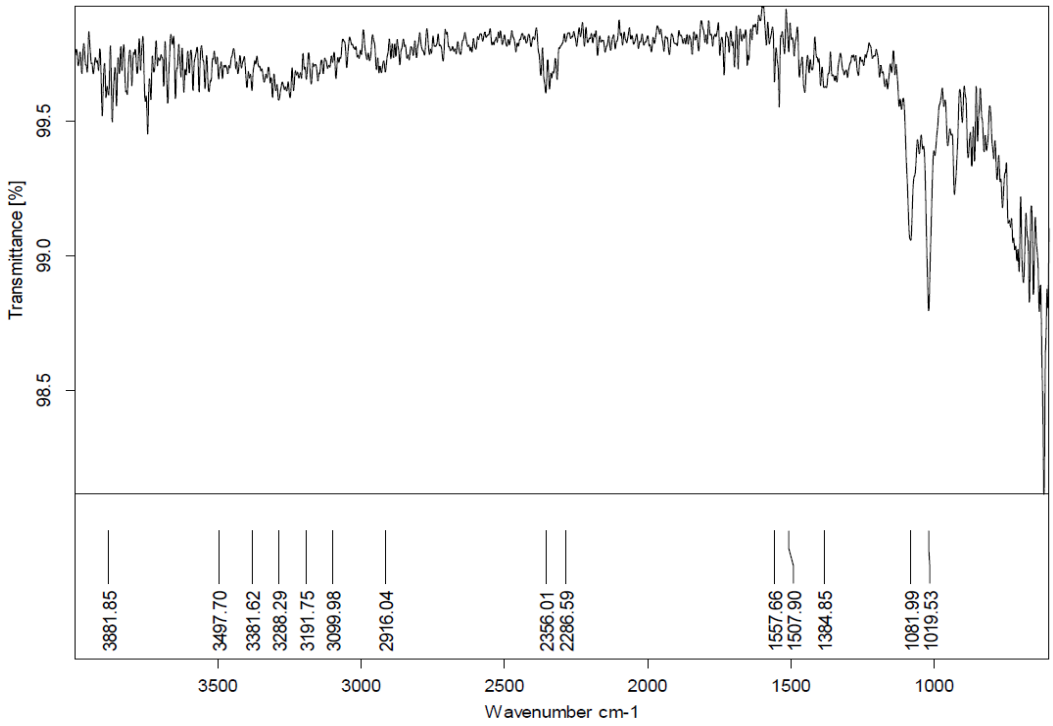


Figure 14: IR Spectrum of physical mixture of Pantaprazole-polymer.

Table 14: IR Interpretation of drug-polymer.

Sr. No	Interpretation	IR absorption band(cm^{-1})
1	N-H	3497.70
2	O-H	3381.62
3	CH_2	3191.75
4	CH_3	2916.04
5	C-O	1557.66
6	C-F	1384.85
7	S=O	1019.53

Table 15: Drug-Polymer Interaction Studies through IR Spectroscopy.

Sr. No	IR absorption band(cm^{-1})	
	API	API+HPMC
1	3472.80	3497.70
2	3314.14	3381.62
3	3114.36	3191.75
4	2955.55	2916.04
5	1541.16	1557.66
6	1338.70	1384.85
7	1046.88	1019.53

9. Evaluation Parameters of Pantaprazole Sodium Fast Dissolving Film

9.1 Physical Appearance and Surface Texture

Physical appearance and Surface texture of Films prepared using different concentration of HPMC and Glycerine.

9.2 Thickness Uniformity

Film of each batch was assessed at different points of film and film f3 has low thickness.

9.3 Weight Uniformity

The weight of all the prepared batches was found to quite uniform. Standard deviation in weight of all the film ranged between 26 to 40. The change in the concentration of polymers and plasticizer did not show the difference in the weight of film.

9.4 Percentage Moisture Content

The moisture uptake content was found to increase with increasing concentration of polymer. The low moisture content in the formulation is highly appreciable to protect formulation from microbial growth. From this study film F3 and F4 has less moisture content.

9.5 Drug Content Uniformity

All the formulations showed more than 80% of the drug loading indicating much of the drug is not lost. From the above test film F3 has highest drug content.

9.6 Surface pH

Surface pH of all films is near about neutral.

9.7 folding endurance

The highest folding endurance was observed in the case of F3 (140) and lowest in the case of F1 (92), the range of folding endurance study ensure the flexibility of these films.

9.8 Dissolving Time

From this test film F3 has very low dissolving time i.e film F3 dissolves faster than other films.

9.9 Tensile Strength and Percent Elongation

Tensile strength of film is also important parameter in selection of best batch. And film F3 has highest tensile strength. And film F3 and F4 has highest percent elongation among all films.

Table 16: Evaluation parameters of formulation.

Batch	Physical Appearance	Surface Texture	Thickness Uniformity	Weight Uniformity	Percentage Moisture Content	Drug Content Uniformity	Surface pH
F1	Smooth	Yellowish white	0.2	30	6.63	75.93	7
F2	Smooth	Yellowish white	0.2	26	7.40	82.56	7
F3	Smooth	Yellowish white	0.15	36	4.57	89.65	7
F4	Very smooth	Yellowish white	0.4	35	5.78	87.98	6
F5	slightly sticky	Light brown	0.4	40	10.74	89.09	7
F6	slightly sticky	Light brown	0.5	41	6.97	78.45	6

Table 17: Evaluation parameters of formulation.

Batch	folding endurance	Dissolving Time (sec)	Tensile strength	Percent Elongation
F1	92	71	0.94	6.63
F2	100	100	0.98	6.75
F3	140	65	0.99	6.95
F4	130	80	1.01	7.00
F5	134	150	1.02	7.1
F6	128	76	1.05	7.2

9.10 *In Vitro* Drug Release

The *in vitro* drug release profile of formulation F1- F6 was performed. Among these six formulations, F3 was found to be highest percentage drug release was shown in Table no 24, 25 and the graphical representation of % drug release is shown in Figure: 15, 16.

Table 18: In vitro drug release of film F1, F2, F3.

Sr. No	Time (Min)	%Drug Release		
		F1	F2	F3
1	0	0	0	0
2	1	18.23	18.62	19.68
3	2	30.35	36.71	38.72
4	3	54.43	57.89	59.09
5	4	69.99	75.17	77.85
6	5	81.91	81.47	88.71
7	6	83.04	84.55	95.78

Table 19: In vitro drug release of film F4, F5, F6.

Sr. No	Time (Min)	%Drug Release		
		F4	F5	F6
1	0	0	0	0
2	1	17.28	19.62	17.34
3	2	35.10	30.71	30.09
4	3	56.76	41.89	50.09

5	4	76.89	75.23	67.78
6	5	79.91	80.43	83.56
7	6	82.45	82.34	92.04

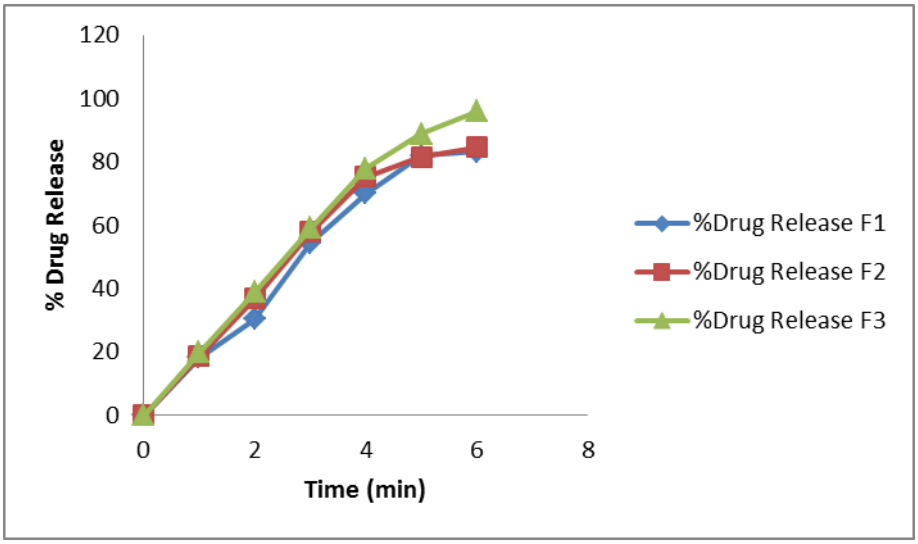


Figure 15: In vitro drug release of film F1, F2, F3

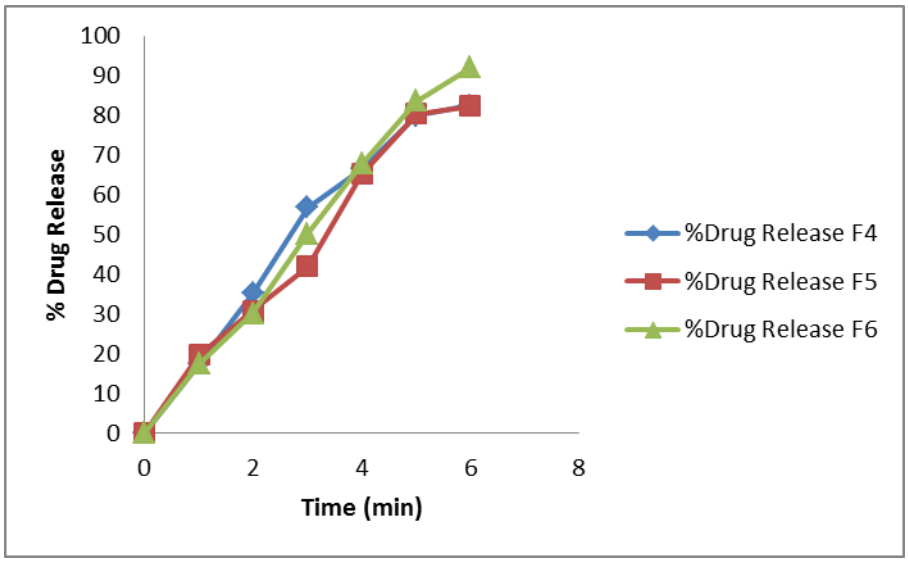


Figure 16: % Drug Release of F4, F5, F6.

Table 20: Stability Study of Film.

Stability data Time(days)	Physical Appearance	Folding Endurance	%Drug content
0	No change	120	89.65%
30	No change	118	88.78%

9.11 Stability Studies

The selected formulations (F3) were subjected to short term stability testing. Films packed in bottles and kept in a stability chamber maintained at 40 ± 2 0C and 75 ± 5% RH for 1 month as per ICH guidelines. Changes in the appearance, surface pH, folding endurance, and drug content of the stored films were investigated after 1 month. There is very less change in the folding endurance and drug content of the formulation reported in the table no: 27. Percentage drug present in the films was determined by UV spectrophotometer.

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