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CHARACTERIZATION AND EVALUATION OF MOUTH DISSOLVING FILMS OF ATENOLOL FOR HYPERTENSION

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ABSTRACT
The aim of this study was to develop a taste-masked mouth dissolving film (ODF) containing antihypertensive drug Atenolol .objective of study is to developing and characterizing the influence of agent such as tween 80 and polaxomer on the morphological and physicochemical characteristic of fast dissolving orodispersible films (FDOF)made up of film forming polymer Hydroxy propyl methyl cellulose. The embodiment of atenolol, in FDOF was achieved through solvent casting technique.Literature reports that faster disintegration leads to optimum drug release resulting in higher bioavailability. The present research work also attempts to correlate the effect of concentration of tween 80 and solubilizing agent on the disintegration time and drug release profile of the oral film. .literature reports give evidence that combination of HPMC and pectin as film forming polymer gives good film texture appearance and film properties .The atenolol FDOF were characterized for physical appearance, disintegration time, in vitro dissolution, etc. In the presence of solubilizing agent the morphological characters was found to be better than in its absence. Atenolol FDOF showed optimum drug content and folding endurance.Drug-excipients interaction studies performed using FTIR; showed no interaction. Surface pH was found to be neutral, indicating safety of administration. Atenolol FDOF formulated using tween 80 showed optimum results as compared to polaxomer and FDOF without solubilizing agent. Thus based on the results it can be concluded that the FDOF formulated using solubilizing agents can enhance the disintegration time and drug release profile.

KEYWORDS: Hypertension disease; Atenolol; oral disintegrating film; polymers, tween 80.

INTRODUCTION
Buccal delivery is considered to be an important alternative to the peroral route for the systemic administration of drugs, as it considered the most convenient, easy, safest route of administration. The fast dissolving orodispersible films (FDOF) are basically an ultra-thin strip of postage stamp size with an active pharmaceutical ingredient and other excipients. The advantages like convenience of dosing, portability ease of swallowing and no need of water have led to better acceptability amongst paediatric, geriatric population and dysphasic patients who are having difficulty in swallowing tablets or capsules. The large surface area available in the strip dosage form allows rapid wetting in the moist oral environment. Oral mucosa has rich vasculization, offers better permeability to many drugs & it act as an excellent site for the absorption of drugs . The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with a conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and paediatrics, because of physiological changes associated with these groups of patients.

Atenolol is an Adrenergic β 1-antagonists, prescribed widely in diverse cardiac disease like hypertension, angina pectoris, arrhythmias and myocardial infarction. Atenolol is freely soluble in methanol and ethanol, soluble in acetic acid and in water. It has been reported that absorption of an oral dose following conventional tablets of atenolol is rapid and consistent but incomplete that exhibits fluctuations in plasma drug concentration, resulting in manifestation of side effects or reduction in drug concentration at the receptor site. Approximately 50% of an oral dose is absorbed from GIT with peak plasma concentration reaching in 2-4 h, the reminder is excreted unchanged in feces. The elimination half-life is approximately 6 to7 h. The film forming polymer selected for the study was HPMC E15, which is a Synthetic film forming polymer. literature reports give evidence that combination of HPMC and pectin as film forming polymer gives good film texture appearance and film properties. Tween 80 and polaxomer were used as solubilizing agent, to improve the transparency of the

film and to avoid precipitation of the drug. Glycerin and aspartame were employed as plasticizer and artificial sweetener respectively.

MATERIAL AND METHODS

Materials

All materials used in the work were of analytical grade. Atenolol and HPMC-E15 was purchased from Chemdyes coporation Pvt Ltd, Rajkot, India.

Preparation of films

Preparation of Polymeric films of and Hydroxy propyl methyl cellulose E15 (HPMC E15) dissolved in 10 ml distilled water, allowing to swell, keeping undisturbed for 1 hour. 50 mg Atenolol dissolved in 0.5 ml solubilising agent. Polymer solution added to drug under continuous stirring condition. glycerine, sucralose, citric acid added under constant stirring.obtained solution sonicated for 20 min, to remove entrapped air.formulation slowly poured in to glass mould. dried for 24 hour at room temperature. dried films packed in aluminium foil then stored in desicator until used for further study.

Formulation of mouth dissolving films of Atenolol

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Atenolol (mg)	50	50	50	50	50	50	50	50	50	50	50	50
HPMC E15 (mg)	100	200	300	400	100	200	300	400	100	200	300	400
Pectin(mg)	50	50	50	50	50	50	50	50	50	50	50	50
Tween 80 (ml)	-	-	-	-	0.5	0.5	0.5	0.5	-	-	-	-
Glycerine (ml)	0.2	0.4	0.6	0.8	0.2	0.4	0.6	0.8	0.2	0.4	0.6	0.8
Polaxomer (mg)	50	50	50	50	-	-	-	-	-	-	-	-
Sucralose(mg)	40	40	40	40	40	40	40	40	40	40	40	40
Citric acid(mg)	50	50	50	50	50	50	50	50	50	50	50	50
Menthol(ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Dist.water (ml)	10	10	10	10	10	10	10	10	10	10	10	10

EVALUATION

Characterization of the films

Formulated films were subjected to the preliminary evaluation tests. Films with any imperfections, entrapped air, or differing in thickness, weight or content uniformity were excluded from further studies. Physicochemical properties such as thickness, weight uniformity, folding endurance, surface pH, and drug content uniformity of the prepared films were determined.

1. Physicochemical characteristics

- Physical appearance
- Thickness uniformity
- Uniformity of weight
- Folding endurance
- Surface pH
- Drug content uniformity

2. *Invitro* drug release studies

3. Scanning Electron Microscopy

4. Stability studies

1. Physicochemical characteristics

- **Physical appearance**

All the films were visually inspected for Colour, clarity, flexibility and smoothness.

- **Thickness uniformity**

The thickness of each film was measured using screw gauge at different positions of the film and the average was calculated.

- **Uniformity of weight**

Film pieces (size of 7*2mm) were taken from different areas of film. The weight variation of each film was calculated.

- **Folding endurance studies**

The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 350 times, which is considered satisfactory to reveal good film properties. The film was folded number of times at the same place without breaking gave the value of the folding endurance. This test was done on all the films for six times.

- **Surface pH**

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH in vivo, since an acidic or alkaline pH may cause irritation to the oral mucosa. The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of pH 6.6 phosphate buffer and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1min.

Drug content uniformity

2x2 cm film was placed in 100 ml phosphate buffer of pH 6.8. Stirred for 6 hours. Filterered and absorbance was taken at 206 nm

2. *Invitro* drug release studies

Each film was placed with the help of forceps in 50 ml glass beaker containing 25 ml phosphate buffer of pH 6.8. Temperature of media was adjusted to 37±0.5°c and stirred at 50 rpm. 3ml were withdrawn at 1, 2, 3, 4, 5, 6,7, 8,9 and 10 min and replaced with fresh buffer . Absorbances were taken at 206 nm.

3. Scanning Electron Microscopy (SEM)

A Scanning electron microscope (model JFC-1100 E, Jeol, Japan) was used to study the surface characteristics of the optimized filmF7. Samples (7*2mm) were mounted on the SEM sample stab using a double sided sticking tape. The samples were coated with gold (200 A^0) under reduced pressure (0.001 torr) for 2 min using an ion sputtering device (model JFC-1100 E, Jeol, Japan). The gold coated samples were observed under the SEM at room temperature and photomicrographs of suitable magnifications were obtained.

4. Stability studies

The stability of the entire drug loaded polymer films were studied at different temperatures using the reported procedure. Films are wrapped individually in aluminium foil and also in butter paper and placed in Petri dishes. These containers were stored at different temperatures like 27 ± 2°C, 5–8 ±2°C, 40±2^0 C for a period of 30 days. All the polymeric films were observed for any physical changes, such as color, appearance, flexibility, or texture, and the drug content was estimated at an intervals of 10 days.

Packaging

In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used packaging format. APR- Labtec has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three raid films on each side. Every dose can be taken out individually. The material selected must have the following characteristics:

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper-resistant requirement.
- They must be non-toxic.
- They must not be reactive with the product.

RESULTS AND DISCUSSION

1. Analytical Method Used in the Determination of Atenolol:

1.1 Determination of λ_{max}

The λ_{max} of the drug was found to be **276 nm**.

1.2 Standard graph for Atenolol

Preparation of standard stock solution

50mg drug dissolve it in 50ml methanol and from that 10ml was taken in a 100ml volumetric flask and made up the volume up to 100ml with phosphate buffer ph 6.8.This is stock solution of concentration 100µg/ml.

Preparation of sample solutions

From this stock solution 1ml was taken in 10ml volumetric flask and made up the volume up to 10ml with phosphate buffer of pH 6.8. (1oµg/ml).Respectively solutions of concentrations 10, 20, 30, 40, 50µg/ml was prepared. Their absorbance was measured in UV visible spectrophotometer at 275nm and a calibration curve was plotted for time versus absorbance and from that graph standard concentration was determined.

Table1: Spectrophotometric Data for the Estimation of Atenolol

CONCENTRATION (µg/ml)	ABSORBANCE
10	o.917
20	1.517
30	2.123
40	2.721
50	3.247

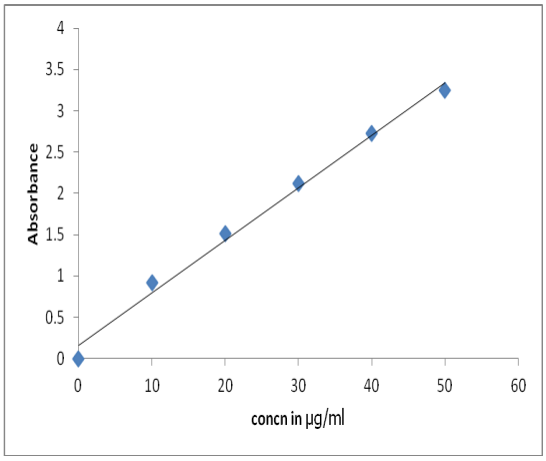

Fig1: Standard curve Atenolol

2. Preformulation Studies

2.1) Identification of pure drug

1) Determination of Melting Point

The melting point was found to be158^{0}C. This was found to be in accordance with the reference standard.

2) Physico-chemical characteristics

1) Organoleptic characters

It appears as a white amorphous substance

2.2 Solubility Study

From the solubility studies it was shown that it is freely soluble in ethanol, methanol & phosphate buffer of pH 6.6 and partially soluble in chloroform and water.

2.3 FTIR Studies

As described in the methodology section the Fourier Transform Infrared spectroscopy studies were carried out for pure drug (Atenolol) and for the Atenolol-Polymer physical mixtures. The results are summarized. There were no changes in the major peaks of Atenolol in the presence of various polymers such as, HPMC E15 and Pectin. This revealed that the drug and the polymers are compatible with each other.

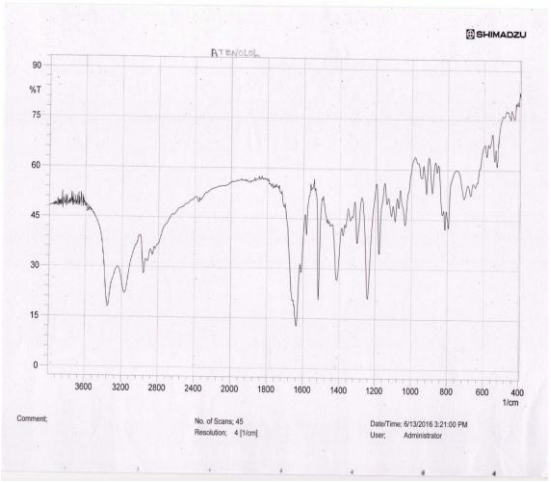

Fig 2: FTIR Spectrum of Atenolol

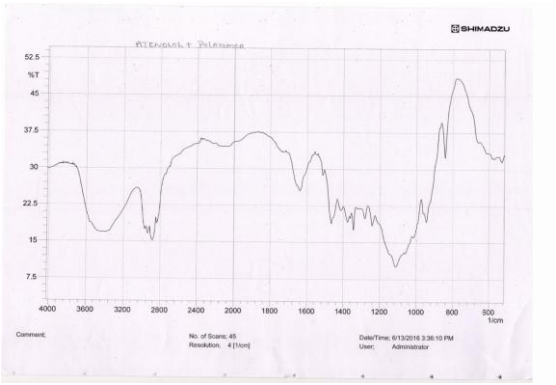

Fig3: FTIR Spectrum of Atenolol + polaxomer physical mixture

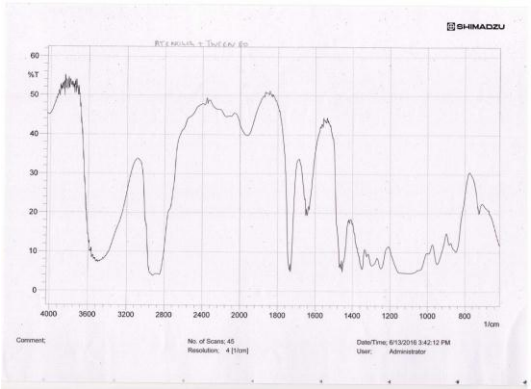

Fig4.: FTIR Spectrum of Atenolol + tween 80 physical mixture

3. Evaluation of Atenolol oral Films

3.1 Physical Appearance: All polymer combinations used for fabrication of oral films showed good film forming properties and reproducibility. The fabricated films were thin, flexible, elastic and smooth.

3.2 Physicochemical evaluation data

- **Thickness of the Films**

The thickness of each film was measured at 6 different points and the average thickness was calculated.The thickness of various films is given in table. The data of films thickness indicated that there was no much difference in the thickness within the formulations.

Table. 2: Measurement of thickness

Formulation code	Thickness(mm)
F1	0.061**.061**
F2	0.062
F3	0.068
F4	0.063
F5	0.069
F6	0.072
F7	0.063
F8	0.075
F9	0.076
F10	0.062
F11	0.067
F12	0.064

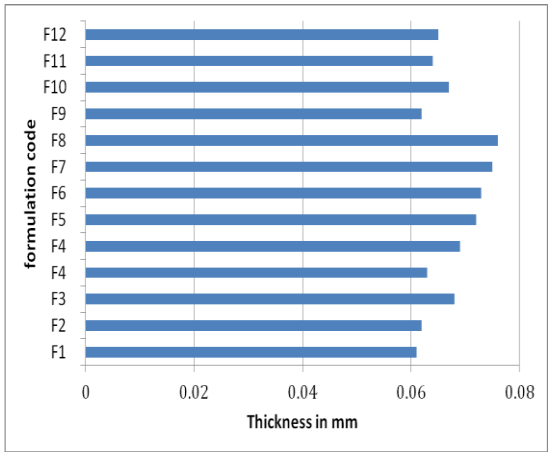

Fig.5.Thickness of formulations

Folding endurance

The folding endurance value for all films was > 200; it indicates that all formulations had ideal film properties.

Table 3: Measurement of folding endurance

Formulation code	Folding endurance
F1	231
F2	256
F3	265
F4	288
F5	271
F6	284
F7	304
F8	296
F9	275
F10	281
F11	286
F12	290

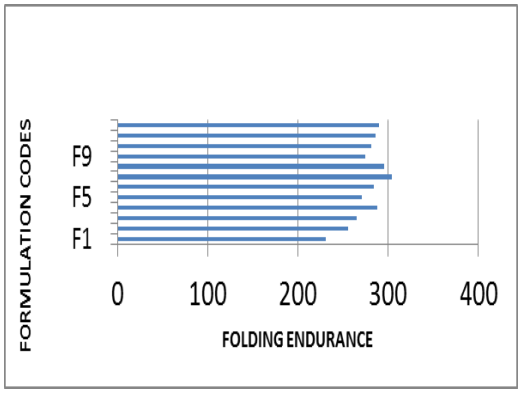

Fig6: folding endurance of various formulations

Surface pH

Surface pH of all the formulations was determined as described in the methodology chapter. All the formulations were found to have pH between 6 –7. This reveals that the prepared films would not alter the pH of the oral cavity and therefore may not cause any irritation.

Table. 4: Measurement of Surface Ph

Formulation code	Surface pH
F1	.16.1.**19**
F2	6.29
F3	6.12
F4	6.51
F5	6.48
F6	6.70
F7	6.80
F8	6.90
F9	6.45
F10	6.52
F11	6.32
F12	6.21

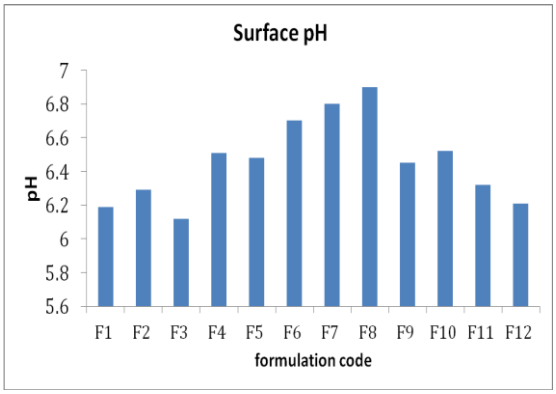

Fig7: Surface pH of various formulations

Drug content uniformity

The percentage drug content in various formulations ranged from 88.5% to 98.8%given in table. It was observed from the drug content data that there was no significant difference in the uniformity of the drug content.

Table 5.: Measurement of percentage drug content

Formulation code	% Drug content
F1	88.5%
F2	89.3%
F3	90.3%
F4	91.9%
F5	89.3%
F6	94.6%
F7	98.8%
F8	96.2%
F9	90.4%
F10	91.4%
F11	92.3%
F12	94.2%

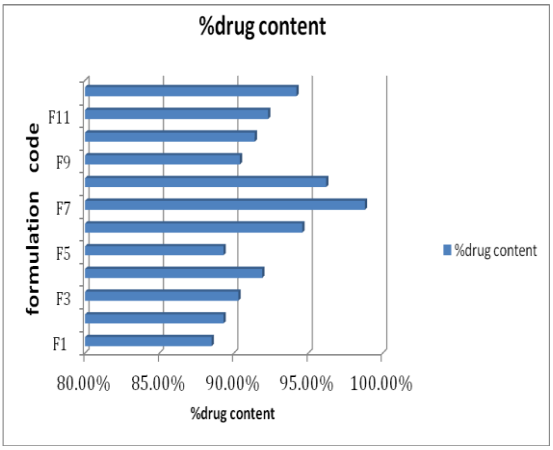

Fig7: drug content of various formulations

3. *In-vitro* drug release

The releases of Atenolol from the oral films were varied according to type & concentration of polymer. The cumulative % drug release data of all the formulation batches has been shown in Table. and graph is plotted between cumulative % drug releases versus time as shown in Figure.

Table6. Percentage Cumulative drug release of formulations

Time (min)	% Cumulative drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	28.3	36.3	59.6	65.3	37.5	47.3	68.6	62.6	29.3	35.6	45.7	58.1
2	62.4	73.8	88.5	83.8	75.7	81.8	91.4	90.8	51.6	62	72.8	81.8
3	83.4	88.5	91.6	93.7	89.2	92.7	98.1	97.5	83	86.6	87.1	88.6
4	84.1	88.9	92	94	90.1	93.1	98.3	97.9	83.7	87.3	88.9	89.7
5	84.8	89.2	92.8	94.7	91.2	93.8	98.5	98.2	84.8	88.2	89.3	89.9
6	85.2	90.1	93.4	95.3	92.4	94.2	98.7	98.4	85.6	88.4	90.1	90.8
7	86.3	90.9	94.1	95.8	92.9	95.6	99.1	98.6	86.2	88.6	90.7	91.2
8	87.1	91.4	94.8	96.4	93.1	96.7	99.3	98.8	86.7	89.0	91.0	92.3
9	87.9	91.9	95.3	96.9	93.9	97.3	99.6	99.1	87.7	89.1	91.3	92.5
10	88.6	92.5	96.2	97.1	94.7	98.3	99.8	99.3	89.9	90.3	91.5	92.9

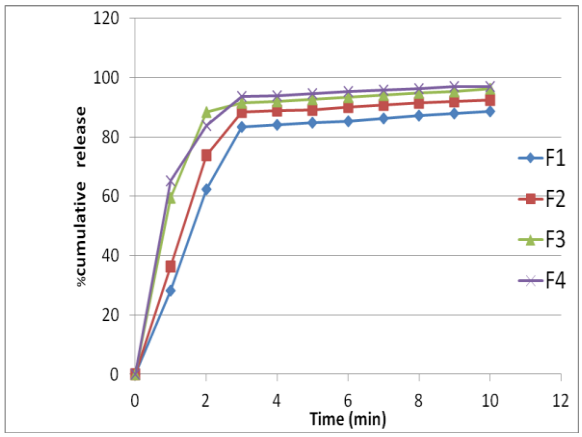

Fig 8:% cumulative release of formulations F1-F4

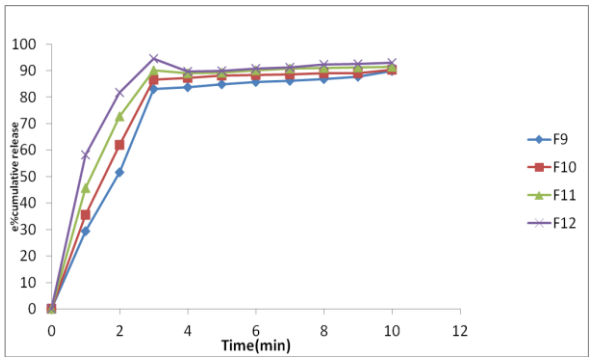

Fig10: %cumulative release of formulations of F9-F12

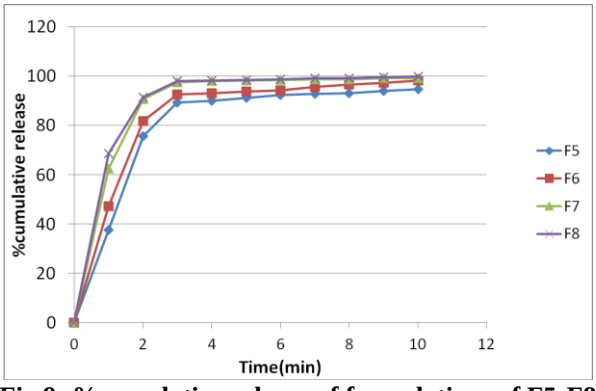

Fig 9: %cumulative release of formulations of F5-F8

Fig 11: Best formulation F7 selected

4. Scanning Electron Microscopy (SEM)

Scanning electron micrographs indicate that prior to drug release, the top surface of the films is smooth which exhibits pores as can be seen in Figure. These pores indicated that the film F7 had sufficient drug loading capacity.

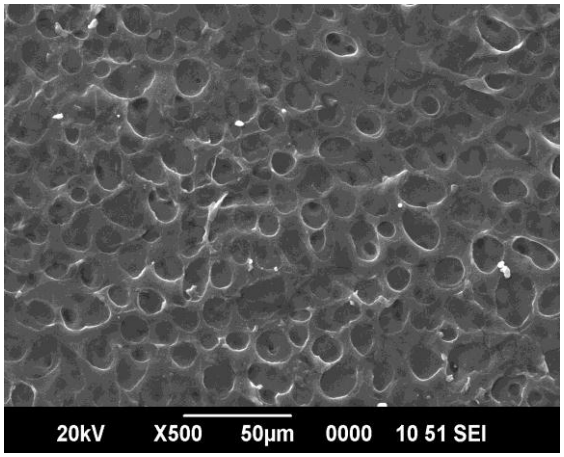

Fig 13: Scanning Electron Microscopy (SEM) Images of oral film F7

CONCLUSION

The present investigation deals with the development of Atenolol mouth dissolving films with different co-polymers in different ratios along with HPMC E15 as the main Film forming polymer. The film can be used for the treatment of Hypertension and to conduct various evaluation studies for selecting the best formulation. Materials were subjected to different preformulation studies. All characters of the pure drug complied with the standards. FTIR studies showed that there was no interaction between drug and polymers. Atenolol oral films were formulated with HPMC E15 as the main film forming polymer and different co-polymers in different ratios and subjected to various physicochemical studies. Measurement of thickness indicated that there was no much difference in thickness within formulations.some formulations showed brittleness due to low amount of film forming polymer & plastisizer. Almost all formulations showed low disintegration time & good drug release due to action of film solubilizing agents like polaxomer &Tween80. Folding endurance studies ensures that all the formulations had good film properties that is all givesfolding endurance value above 200. The pH of all the formulations was in the range of 6.0 to 6.9, which lies in the normal pH range of the oral mucosa and would not produce any mucosal irritation.The formulation F7 showed comparatively high Percentage drug content than the others. This indicates the homogenous distribution of drug throughout the film which may be due to high entrapment of drug in the HPMC E15 - pectin matrix. *Invitro* release studies showed a good cumulative release of 99.8% within 10 minute time period for the F7 formulation.Formulation F7 gives a good drug content value of 98.8%. The formulation F7 was selected as the optimised formulation based on invitro release studies, drug content and other physico chemical evaluation data. SEM analysis before drug release studies of this optimized film showed that the film have sufficient drug loading. Stability studies indicated that the formulation F7 is stable in different temperatures. The above results confirm the benefits of using Atenolol oral film for the treatment of Hypertension in the form of films made up of HPMC E15 and Pectin as the main film forming polymers and Tween 80 and polaxomer as the copolymers in optimized concentrations for obtaining the fast release. Atenolol fast dissolving films gives immediate relief for hypertensive patients.

SUMMARY

In the present study an attempt was made to develop and evaluate oral films with HPMC E15 as the main film forming polymer and various co-polymers in different ratios for the treatment of Hypertension and to select the best formulation among them. The main objective of the work is to formulate the oral film which can release the drug within seconds and provide therapeutic action & immediate relief. Before the formulations were made, the parameters were evaluated. The compatibility of drug with the polymers was determined by performing FTIR studies.

Oral films were prepared with HPMC E15 as the main film forming polymer and various co-polymers in different ratios. From various evaluation parameters like folding endurance, percentage drug content and *in-vitro* release studies, the formulation F7 was selected as the best formulation among them.

The best formulation F7 selected was subjected to SEM analysis & stability studies. It was concluded that the prepared formulation have sufficient drug carrying capacity. The prepared film has sufficient stability.

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