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DEVELOPMENT AND CHARACTERIZATION OF ATENOLOL FAST DISSOLVING ORODISPERSIBLE FILMS

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ABSTRACT

The present research work aims at development of fast dissolving orodispersible films of sparingly water soluble atenolol with the purpose of developing rapid onset of action. Atenolol is β_1 blocker, prescribed widely in diverse cardiac abnormalities. Literature reports that faster disintegration leads to optimum drug release resulting in higher bioavailability. The present research work attempts to correlate the effect of concentration of pullulan and solubilizing agent on the disintegration time and drug release profile. Pullulan and tween 80 were used as film forming polymer and solubilizing agent respectively. The films were prepared by solvent casting method and characterized. The optimum concentration of plasticizer and solubilizing agent was developed on the basis of flexibility, tensile strength and stickiness of the film. Fast dissolving films showed optimum drug content and folding endurance. The disintegration time of formulation PUT7 film was found to be 10 sec with *in vitro* release of 100% in approximately 90 sec, which was better than other prepared formulations. Drug-excipients interaction studies performed using FTIR; showed no interaction. Surface pH was found to be neutral, indicating safety of administration. Accelerated stability studies showed no change in the physicochemical properties of all the formulated films. Thus the objective to formulate atenolol fast dissolving orodispersible films was successfully achieved.

Key Words: Fast dissolving, orodispersible films, atenolol, pullulan, solubilizing agent.

INTRODUCTION[1-3]

Constantin Hering developed the first sublingual dosage form of nitroglycerin in 1847 and reported faster absorption of nitroglycerine from the oral cavity. Since then various active pharmaceutical ingredients have been investigated for local or systemic use employing fast dissolving technologies.

The introduction of orodispersible tablets in market was accompanied by educating the mass about the proper way to administer the product like giving instructions “do not swallow” or “do not chew”; still incidence of swallowing or chewing were reported, as they are in the form of tablets.

The fast dissolving orodispersible films (FDOF) are basically an ultra-thin strip of postage stamp size with an active pharmaceutical ingredient and other excipients. However since the FDOF derived products were readily popular in the market in the form of breath-freshening strips, no further efforts were needed to re-instruct the populace about the technique of administration of this dosage form. The advantages like convenience of dosing, portability ease of swallowing and no need of water have led to better acceptability amongst pediatric, 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.

Atenolol is β_1 blocker, prescribed widely in diverse cardiac disease like hypertension, angina pectoris, arrhythmias and myocardial infarction. Atenolol is slightly soluble 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 pullulan, which is a natural film forming polymer obtained from non-animal origin and does not require any chemical modification. Literature reports suggest that films formulated are highly clear and homogenous, also has low permeability and low water content. Tween 80 was 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 sweetner respectively.

MATERIAL AND METHODS

Materials

Pullulan was a gifted sample of pharmaceutical grade obtained from DKSH Company, Mumbai. Atenolol was gift sample from Torrent pharmaceutical, Aurangabad. Tween 80, glycerin and aspartame were purchased from Durga labs, Mangalore. All the other chemicals used in the research were of analytical grade.

Methods

Formulation of atenolol fast dissolving orodispersible films without solubilizing agent[5]

Fast dissolving films of atenolol were formulated by solvent casting technique. Film forming agent i.e. pullulan was weighed and dissolved in 10 ml of distilled water. Simultaneously atenolol was weighed accurately and dissolved in 5 ml of distilled water. To the drug solution, initially polymeric solution was added followed by glycerin and aspartame with continuous stirring with magnetic stirrer. The solution was further sonicated for 20 min to remove entrapped air bubbles. The solution was transferred into fabricated glass mould with die cavity of size 2.5 × 2.5 cm, with continuous thin stream, to get uniform spread and avoid bubble entrapment during pouring. It was then kept for 12 h at 40 ^{O}C in vacuum oven for drying. After drying, the films were peeled off from the fabricated glass mould, packed in aluminum foil and stored in a desiccator for further studies. The formula is given in Table 1.

Formulation of atenolol orodispersible film with tween 80[5]

Atenolol was initially dissolved in tween 80 and then 10 ml of distilled water was added slowly with continuous stirring, till a homogenous solution was formed. To the drug solution, polymeric solution containing glycerin and aspartame were added and mixed thoroughly with the help of magnetic stirrer. The solution obtained was further sonicated for 20 min for the removal of entrapped air bubbles. The solution was transferred into glass mould with die cavity of size 2.5 × 2.5 cm, with continuous thin stream, to get uniform spread and avoid bubble entrapment during pouring. It was then kept for 12 h at 40 °C for drying in vacuum oven. After drying, these films were peeled off from the petridish, packed in aluminum foil and stored in a desiccator for further studies (Table 1).

Table 1. Formulation of atenolol fast dissolving orodispersible films

Formulations code	Atenolol (mg)	Pullulan (mg)	Glycerin (mg)	Tween 80 (mg)	Aspartame (mg)	Distilled water (ml)
PU1	50	100	60	-	40	10
PU2	50	200	60	-	40	10
PU3	50	300	60	-	40	10
PU4	50	400	60	-	40	10
PUT1	50	100	60	40	40	10
PUT2	50	200	60	40	40	10
PUT3	50	300	60	40	40	10
PUT4	50	400	60	40	40	10

CHARACTERIZATION

1. Physical characterization and surface texture[5,6]

Physical appearance and texture parameters were verified by visual inspection of the formulated atenolol FDOF for transparency and smoothness of the formulation (Table 2).

2. Variation of mass[5,6]

The mass of 2.5 × 2.5 cm atenolol orodispersible films was determined by an analytical balance with five decimal places[5,6]. The mean weight of film as well as the deviation from the mean was calculated and recorded separately for individual atenolol FDOF of pullulan with and without solubilizing agent in Table 2.

3. Film thickness[5,6]

Film thickness was determined using the standard precalibrated micrometer screw gauge. Each 2.5 × 2.5 cm atenolol FDOF was measured at six different positions and the mean thickness was calculated and reported separately in Table 2.

4. Folding endurance[5,6]

Folding endurance was determination of folding capacity of the film when subjected to frequent extreme condition of folding. Each 2.5 × 2.5 cm atenolol FDOF was repeatedly folded at same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave value of folding endurance Table 2.

5. Measurement of Tensile Strength and Percentage Elongation[7]

The instrument which was designed in our laboratory, as per literature specification was used for the measurement of tensile strength (Fig. 1). A film of size 2.5 × 2.5 cm was clamped at

the static end and was attached to the movable rod on railing with the help of a clip. The weights were gradually added to the pan to increase the pull force until the film was cut. The elongation was determined simultaneously by noting the distance travelled by the pointer, before break of the film, on the graph paper. The weight required to break the film was noted as the break force. The tensile strength was calculated using Allen's formula (Table 2).

$$\textbf{Tensile strength} = \frac{\textbf{Break force}}{a \times b} \times \frac{1 + \Delta L}{L}$$

Where a, b, L are the width, thickness and length of the films and ΔL is the elongation at break.

$$\%\ \textbf{Elongation at break} = \frac{\textbf{Increase in length}}{\textbf{Original length}} \times 100$$

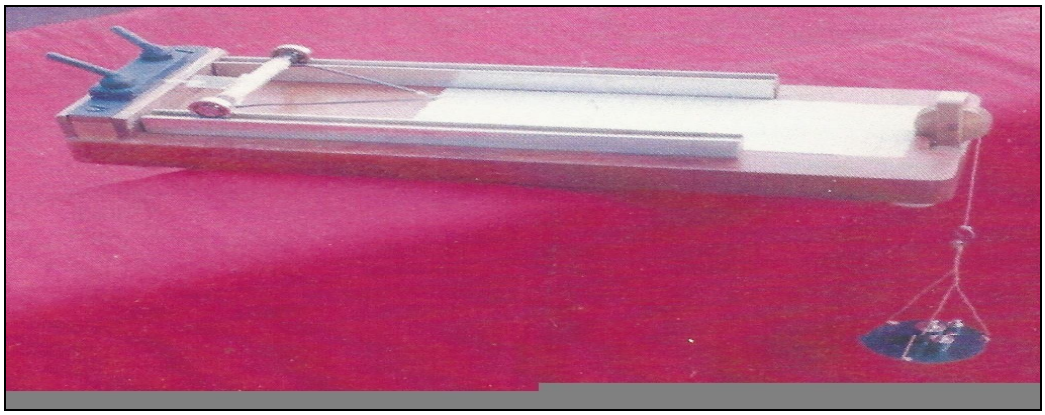

Fig. 1: Measurement of tensile strength

6. Surface pH[7]

Atenolol fast dissolving orodispersible films were moisten with distilled water. The pH was measured by bringing the combined pH electrode in contact with the surface of the oral film. The experiments were performed in triplicate, and an average values were reported in Table 2.

7. *In vitro* disintegration studies using petridish method[8,9]

In a clean dry petridish, 2 ml of simulated saliva was placed. One film was added at the surface of the simulated saliva and the time taken by the orodispersible film to completely dissolve was measured and reported in Table 2.

8. Compatibility studies by IR spectral analysis[8,9]

FTIR spectra matching approach was used for detection of any possible chemical interaction between the drug and polymers. The individual sample of drug and drug with polymer films

were prepared and mixed with suitable quantity of potassium bromide. About 50 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 15 tons pressure, in KBr Press model M-15. It was scanned from 4000 - 600 cm^{-1} in a Bruker Alpha-T FTIR spectrophotometer. The IR spectrums of the formulations were compared with those of pure drugs and matching was done to detect any changes in peak. The IR spectra are shown in Fig. 2.

9. Drug content estimation[8,9]

The film of 2.5 × 2.5 cm size was transferred into a graduated flask containing 100 ml of simulated salivary fluid (pH 6.8) followed by sonication using probsonicator to ensure the complete solubility of the film for time period of 10 min. The solution was then filtered using membrane filters. The filtered solution was appropriately diluted and analyzed using UV spectrophotometer at 224.6 nm. The data is represented in Table 3.

10. *In vitro* dissolution studies[8,9]

The dissolution study was performed in 100 ml of simulated salivary fluid of pH 6.8 as a dissolution medium in a 250 ml glass beaker. The solution was continuously stirred with magnetic bead at 100 rpm and temperature was maintained at 37 ± 2 °C. The fast dissolving atenolol FDOF placed in glass beaker and at a predetermined time interval of every 15 sec, 5 ml of sample was withdrawn and replaced with same quantity of fresh medium. Further, 1 ml of sample was adjusted to 10 ml with simulated salivary fluid in a volumetric flask. The dilutions were analyzed using Shimadzu UV-1600/1700 series spectrophotometer at 224.6 nm. The cumulative percentage drug release was calculated. Graph of cumulative percentage of drug release vs time (sec) was plotted (Fig.3).

11. Stability studies[9]

Stability study was conducted as per ICH guidelines at three different conditions of temperature and percentage relative humidity, and accordingly the oral films were stored under controlled conditions of 40 °C/ 75 % RH ± 5, 25 °C/ 60 % RH ± 5 and 2 °C/ 45 % RH ± 5 over a period of 6 months. During storage the FDOF were checked for their physical appearance surface pH, folding endurance, drug content and maximum drug release.

RESULTS

Physical characterization and surface texture

Atenolol FDOF formulated with tween 80 and coded as PUT5, PUT6, PUT7 and PUT8 had smooth upper and lower surface and the films were completely transparent. Whereas the FDOF formulated without solubilizing agent were blurred with lower surface smooth than its upper surface. The results are given in Table 2.

Variation of mass

The films had uniform weight within the same formulation. It was seen that formulation coded as PUT1 had a mass of 0.71 mg and PUT7 had a mass of 0.77 mg, rest of the formulation were in the same range. The results are reported in Table 2.

Film thickness

The thickness was found to be in the range of 0.71 mm to 0.77 mm of all the formulations as shown in Table 2.

Folding endurance

All the formulations of atenolol FDOF displayed optimum folding endurance above 200 folds, which indicate the formulation prepared can withstand sufficient rough handling during transportation and handling of the formulation (Table 2).

Measurement of tensile strength

Formulation PUT3 and PUT2 had lowest tensile strength of 0.90 and 1.05 Kg/mm^2 respectively whereas highest tensile strength was 1.58 Kg/mm^2 seen with PUT7 formulation, followed by PUT6, PUT5 and PUT8 with 1.48, 1.45 and 1.35 Kg/mm^2 respectively. Formulation PUT1 and PUT4 had approximately same tensile strength of 1.2 Kg/mm^2 (Table 2).

Percentage elongation

Atenolol FDOF coded as PUT7 showed highest percentage elongation of 60.5 followed by PUT6 with 51.8. PUT8 and PUT5 had similar percentage elongation with 45.8 and 45.1%. Lowest percentage elongation was observed with formulation PUT3 and PUT2 with 5.3 and 10.5% respectively (Table 2).

Surface pH

All the formulation of atenolol FDOF showed pH in the range of 6.75 to 6.78, indicating suitability of the formulation in the oral cavity, without causing any irritation to the oral cavity (Table 2)

***In vitro* disintegration studies**

The disintegration test performed using petridish method reviled that PUT7 disintegrated faster in 10 sec whereas PUT4 disintegrated in 18 sec. The formulation PUT5, PUT6 and PUT8 disintegrated in 13, 12 and 14 sec respectively. Formulation PUT1, PUT2 and PUT3 disintegrated in 15, 16 and 16 sec respectively. The data is given in Table 2.

Table 2. Characterization of atenolol fast dissolving orodispersible films

Evaluation parameters	Formulation codes							
	PUT1	PUT2	PUT3	PUT4	PUT5	PUT6	PUT7	PUT8
Physical appearance	B	B	B	B	T	T	T	T
Texture analysis	R	R	R	R	S	S	S	S
Variation of mass (mg)	50	52	53	55	55	54	58	53
Thickness test (mm)	0.71	0.71	0.71	0.73	0.72	0.72	0.77	0.71
Folding endurance	>200	>200	>200	>200	>200	>200	>200	>200
Tensile strength Kg/mm^2	1.2	1.05	0.90	1.28	1.45	1.48	1.58	1.35
% Elongation	15.1	10.5	5.3	22.3	45.1	51.8	60.5	45.8
Surface pH	6.75	6.78	6.78	6.78	6.78	6.78	6.77	6.78
Petridish disintegration Test (sec)	15	16	16	18	13	12	10	14

B = Blurred, T = Transparent, S = Smooth, R = Rough.

Compatibility studies

The major peaks N – H stretching at 3346.85 cm^{-1} , C –N stretching at 1236.03 cm^{-1}, C=C stretching at 1513.85cm^{-1}, aromatic C – H stretching at 2961.91cm^{-1} of pure drug atenolol were also found in FDOF of atenolol indicating that there is no interaction between drug and polymer. Figure 2 displays the IR spectra of atenolol FDODF.

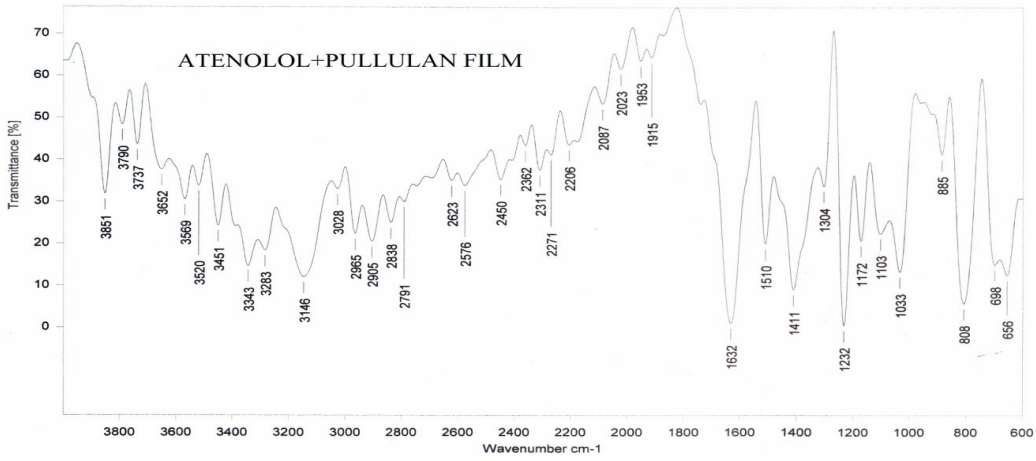

Fig. 2: FT-IR spectra of atenolol fast dissolving orodispersible films.

Drug content estimation

The drug content of atenolol FDOF showed that all the formulations were containing atenolol in the range of 98.02 to 99.98%. The drug content data is shown in the Table 3.

Table 3. Drug content of atenolol fast dissolving orodispersible films

Formulation code	Amount* in 2.5 × 2.5 cm (mg) ± SD	%drug content in 2.5 × 2.5 cm
PUT1	49.78 ± 0.02	99.56
PUT 2	49.96 ± 0.32	99.92
PUT 3	49.94 ± 0.12	99.88
PUT 4	49.66 ± 0.64	99.32
PUT 5	49.67 ± 0.59	99.34
PUT 6	49.99 ± 0.42	99.98
PUT 7	49.94 ± 0.42	99.88
PUT 8	49.63 ± 0.14	99.26

*Average of six determinants.

SD = Standard Deviation.

In vitro dissolution studies

Atenolol fast dissolving films containing pullulan with tween 80 as solubilizing agent displayed highest cumulative percentage of drug release as compared to the formulation without tween 80. Formulation PUT7 released 99.64% drug in 90 sec followed by drug release of 98.01% in 105 sec by PUT3 which is without tween 80. The graphical data is shown in Figure 3.

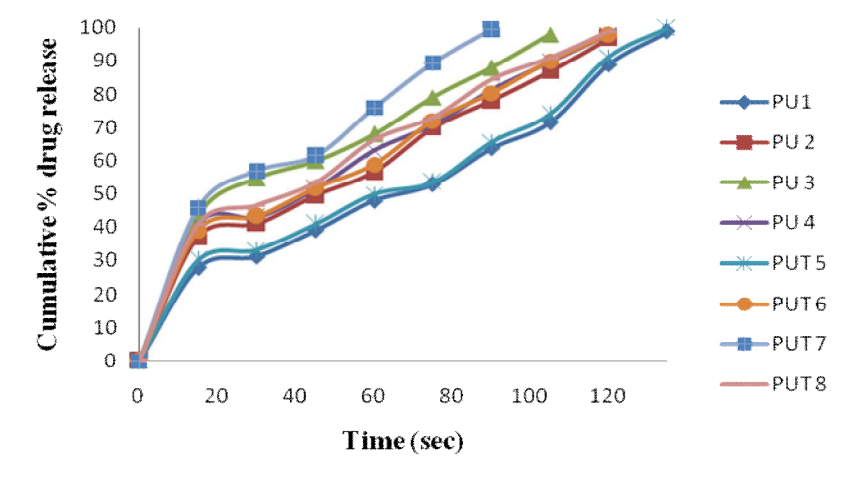

Fig. 3: Cumulative percentage of drug release of atenolol fast dissolving films.

Stability studies

Stability studies performed at three different temperature and percentage relative humidity conditions, on all the atenolol FDOF showed no appreciable change in drug content, *in vitro* petridish disintegration test, surface pH and drug release profile. The study reveals that the stability of the formulation at different temperature and humidity conditions.

DISCUSSION

Atenolol FDOF was formulated according to the principle of solvent casting method with and without solubilizing agent i.e. tween 80. The formulated FDOF of atenolol were characterized by various methods. It can be seen from the results that the formulation containing solubilizing agent showed better characteristics. The films containing tween 80 coded as PUT5, PUT6, PUT7 and PUT8 showed highest level of transparency and smoothness on both the surfaces as compared with Put1, PUT2, PUT3 and PUT4 which were blurred and the upper and lower surface was rough. The tensile strength and percentage elongation was better in case of formulation with tween 80. All the formulations of atenolol showed optimum characteristics with variation of masses, thickness, folding endurance and drug content estimation. The *in vitro* drug release studies showed 99.64% release of atenolol from formulation PUT7 in 90 sec which was quickest when compared with other formulations. The release pattern is as follows PUT7>PUT3>PUT8>PUT6>PUT4>PUT2>PUT5>PUT1. The results of *in vitro* disintegration studies using petridish method showed the following pattern with respect to quick disintegration time: PUT7>PUT6>PUT5>PUT8>PUT1>PUT2>PUT3>PUT4.

The accelerated stability data revealed that after 6 months, the formulations were found to be stable at different conditions of temperature and relative humidity, i.e. 40 °C/ 75 % RH ± 5, 25 °C/ 60 % RH ± 5 and 2 °C/ 45 % RH ± 5 respectively. The characteristics like physical appearance, surface pH, folding endurance, drug content and cumulative percentage drug release studies, showed similar results when compared with the results before the stability studies. This indicated the formulations are stable when exposed to different temperature and humidity conditions.

CONCLUSION

The present research is an attempt to prove that a sparingly water soluble drug like atenolol can be formulated in the form of fast dissolving orodispersible films; As the literature reports that fast dissolving orodispersible films are more suitable for water soluble drugs than drugs which are poorly water soluble.

Atenolol FDOF was prepared by using solvent casting principle. Different concentration of film forming polymer i.e. pullulan with and without solubilizing agent tween 80 was used to formulate FDOF of atenolol.

Formulation coded PUT7 showed optimum results when compared to the other seven formulations. The *in vitro* disintegration showed that films disintegrated completely in 10 sec when kept in 2 ml simulated saliva in a petridish and cumulative percentage drug release was found to be 99.64% in 90 sec, which can be concluded as superior than formulated batches. The films formulated by incorporating a solubilizing agent i.e. tween 80 had better visual characteristics and disintegrating time than those without tween 80.

Hence it can be concluded atenolol FDOF with optimum physical appearance, disintegration and drug release can be formulated successfully by using pullulan as film forming agent and tween 80 as a solubilizing agent.

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