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DESIGNING AND CHARACTERIZATION OF ATENOLOL FAST DISSOLVING ORODISPERSIBLE FILMS USING DIFFERENT POLYMERS

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ABSTRACT

The present research was undertaken with the objective to evaluate the film forming properties of pullulan, hydroxyypropyl methyl cellulose 15cps (HPMC) and poly vinyl alcohol in formulating fast dissolving orodispersible films (FDOF) of atenolol.Solvent casting technique was employed to formulate atenolol FDOF. Glycerin and aspartame was used as plasticizer and sweetening agent.The optimum concentration of plasticizer, polymer and solubilizing agent were developed through morphological characterization such as deformation caused during removing from die cavity, surface stickiness and transparency. The physiological evaluation such as thickness, weight variation, disintegration time, *in vitro* dissolution, drug-excipient studies was also performed.Atenolol FDOF showed optimum thickness, drug content and folding endurance. The disintegration time of formulation PU3 film was found to be 13 sec with *in vitro* drug release of 98.01 % in 105 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. Atenolol FDOF formulated using pullulan and PVA showed complete transparency with smooth surface.Thus based on the results of the present research it can be concluded that polymer pullulan showed optimum characteristics as a film forming polymer for atenolol FDOF when compared to HPMC 15cps and PVA.

KEY WORDS: Fast dissolving films, atenolol, pullulan, solubilizing agent.

INTRODUCTION[1-3]

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 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. 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. Atenolol is β1 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 and DMSO 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

Formulation of atenolol orodispersible films without solubilizing agent

Fast dissolving films of atenolol were prepared by solvent casting technique using selected film forming polymers (HPMC 15 cps, pullulan and PVA). Polymers were weighed accurately according to the formula and soaked in 10 ml of water for 1h for the purpose of

polymer swelling. Simultaneously atenolol was weighed accurately and dissolved in 5ml of distilled water. To this drug solution, polymer solutions, polyethylene glycol (PEG) and glycerinwere added and mixed thoroughly with the help of magnetic stirrer. The solution obtained was further sonicated for 20 min for the removal of air bubbles. The solution was transferred into fabricated glass mould with die cavity of size 2.5×2.5 cm, slowly with continuous thin stream in order to get uniform spread and to avoid bubble entrapment during pouring.It was then kept for 24 h at 40 ^{O}C for drying in vacuum oven. After drying, these films were removed from the petridish, packed in aluminum foil and stored in a desiccator for further studies[1-4].

Table 1.Formulation of atenolol fast dissolving films

Formulations code	Atenolol (mg)	Polymer (mg)	Aspartame (mg)	Glycerin (ml)	Distilled water (ml)
H1	50	100	5	20	10
H2	50	200	5	40	10
H3	50	300	5	60	10
H4	50	400	5	80	10
PU1	50	100	5	20	10
PU2	50	200	5	40	10
PU3	50	300	5	60	10
PU4	50	400	5	80	10
PV1	50	100	5	20	10
PV2	50	200	5	40	10
PV3	50	300	5	60	10
PV4	50	400	5	80	10

Ii. Characterization Of The Developed Formulation

A. Morphological characterization by sensory inspection

1. Detachment, deformation and restoration grading of atenolol FDOF from die cavity.

The characteristics of detachment from the surface of fabricated glass mould with die cavity of size 2.5 × 2.5 cm by individual atenolol FDOF formulated by using different polymers with solubilizing agent was evaluated by grading as per Table 2[6].

Table 2.Grading of detachment characteristic of atenolol FDOF

Level of difficulty experienced	Grade
Easy removability	+ + +
Acceptable removability	+ +
Difficult removability	- -

2. Visual inspection of the films

Atenolol FDOF were inspected visually for transparency characteristics and graded as per Table 3[6].

Table 3. Grading of transparency characteristic of atenolol FDOF

Level of transparency	Grade
Complete transparency	CT
Acceptable transparency	AT
No transparency	NT

3. Surface characteristics

The upper and lower surface was inspected for smoothness, stickiness and uneven surface in the dried atenolol FDOF and graded as per Table 5[6].

Table 5.Grading of surface feel characteristic of atenolol FDOF

Level of surface characteristics	Grade
Upper sticky	USt
Lower sticky	LSt
Upper and Lower sticky	ULSt
Upper and Lower smooth	ULSm

B. Physicochemical Characterization

4. Variation of mass

The mass of atenolol FDOF was determined by an analytical balance with five decimal places. The study was carried out on all atenolol FDOF obtained from each formulation batch. The mean weight of film as well as the deviation from the mean was calculated and recorded separately for individual atenolol FDOF in Table 6[7].

5. Film thickness

Film thickness was determined using the micrometer screw gauge. Each atenolol FDOF was measured at five different positions (central and the four corners) and the mean thickness was calculated and reported separately for individual atenolol FDOF in Table 6[7].

6. Folding endurance

Folding endurance was determination of folding capacity of the film when subjected to frequent extreme condition of folding. Each 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 for that individual film and reported in Table 6[7].

7. Surface pH

The surface pH of atenolol FDOF was determined in order to investigate the possibility of any side effects for *in vivo* studies. As an acidic or alkaline pH may cause irritation to the oral mucosa, hence an attempt was made to formulate atenolol FDOF with surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The experiments were performed in triplicate, and average values were reported separately for individual atenolol FDOF in Table 6[7].

8. Measurement of Tensile Strength and Percentage Elongation

The instrument, which was designed in our laboratory, as per literature specification was used for the measurement of tensile strength. The strips were clamped at the static end and were 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 results are shown in Table 7[8].

The tensile strength was calculated using Allen's formula. a, b, L are the width, thickness and length of the films. ΔL is the elongation at break.

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

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

9. *In vitro* disintegration studies

a. Petridish method

In a clean dry petridish, 2 ml of simulated saliva was poured and one film was placed on the surface of the simulated saliva and the time was recorded for the film to completely disintegrate and reported separately for individual atenolol FDOF in Table 6[8].

b. Slide frame method

The slide frame method was performed to compare and verify the reliability of results of petridish method. Atenolol FDOF were stored in slide frames and therein positioned planar. The slide frames with the oral films were laid on a petridish and one drop of simulated saliva was added by 10 ml pipette. The time taken for the drop to dissolve that portion of the film and form a hole was recorded and reported separately for individual atenolol FDOF of selected polymers with solubilizing agent, in Table 6[8].

10. Drug content estimation

Individual film of size 6.25 cm^2 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 7[9].

11. *In vitro* dissolution studies

The dissolution study was performed in 100 ml of simulated salivary fluid 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 UV spectrophotometer at 224.6 nm. The cumulative percentage drug release was calculated and graphed as cumulative percentage of drug release vs time (sec) (Fig. 2) [10].

12. Compatibility studies by IR spectral analysis

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. It was scanned from 4000 - 600 cm^{-1} in a Bruker 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. 3[10].

RESULTS AND DISCUSSION

A. Morphological Studies By Sensory Inspection

The morphological studies performed by sensory inspection of atenolol FDOF is reported in Table 6; the data indicates that formulation of atenolol FDOF containing HPMC 15cps gave satisfactory films with formulations coded as H2 and H3 where as films coded H1 and H4 displayed stickiness on upper surface.

Atenolol FDOF containing pullulan as film forming agent coded PU1 and PU2 formulation showed slight deformation while detaching from the die cavity but later when kept undisturbed, complete restoration was observed. Whereas formulation coded PU3 and PU4 possessed optimum morphological properties.

Polyvinyl alcohol (PVA) films indicated optimum detachment factor, transparency and smoothness factor with visual inspection and handling.

A. Morphological Studies By Sensory Inspection

Table 6.Morphological characterization of atenolol FDOF

Formulation code	Detachment factor	Transparency factor	Smoothness factor
H1	+ +	CT	USt
H2	**+ +**	**CT**	**ULSm**
H3	**+ + +**	**CT**	**ULSm**
H4	+ + +	CT	USt
PU1	+ +	CT	ULSm
PU2	**+ +**	CT	ULSm
PU3	**+ + +**	**CT**	**ULSm**
PU4	+ + +	**CT**	**ULSm**
PV1	+ +	**CT**	**ULSm**
PV2	**+ +**	CT	ULSt
PV3	**+ + +**	CT	ULSt
PV4	+ + +	CT	USt

B. Physicochemical Characterization

The physicochemical characterization performed on atenolol FDOF containing HPMC 15cps, pullulan and PVA as film forming polymers are reported in Table 7.Variation of masses for HPMC 15cps polymeric films was found in the range 55 mg to 64 mg. Film thickness was reported in between 0.78 to 0.81 mm and folding endurance was more than 200 folding's at a single point. The surface pH was recorded at 6.75. Disintegration test showed that as the concentration of the HPMC increased in the film the time required for the film to disintegrate

increased; formulation coded H1disintegreated in 17 sec whereas H4 took 22 sec to disintegrate. Pullulan films of atenolol had mass in the range of 50 mg to 55 mg and thickness was reported between 0.71 to 0.73 mm with folding endurance of more than 200 folds at single point. The films coded PU3 disintegrated within 14 sec when compared with PU1, PU2 and PU4 which disintegrated at 16,16 and 17 sec respectively. The pH was neutral for all the pullulan films.

Atenolol FDOF of PVA showed similar pattern of disintegration as that of HPMC 15cps films i.e. as the concentration of the polymer increased the time for disintegration alsoincreased from 16 sec for PV1 to 21 sec for PV4 atenolol FDOF. the variation of masses was found in the range of 54 to 61 mg whereas thickness was in the range of 0.72 to 0.81.

Table 7.Physicochemical characterization of atenolol FDOF

Formulation codes	Evaluation parameters					
	Variation of mass (mg)	Thickness test (mm)	Folding endurance	Surface pH	Disintegration Test (Sec)	
					Petridish test	Slide frame test
H1	55	0.78	>200	6.75	17	16
H2	58	0.79	>200	6.78	17	17
H3	62	0.81	>200	6.78	20	21
H4	64	0.81	>200	6.78	22	23
PU1	50	0.71	>200	6.78	16	16
PU2	52	0.71	>200	6.78	16	16
PU3	53	0.71	>200	6.77	14	13
PU4	55	0.73	>200	6.78	17	17
PV1	54	0.72	>200	6.78	16	18
PV2	56	0.73	>200	6.78	17	17
PV3	59	0.79	>200	6.78	17	18
PV4	61	0.81	>200	6.79	21	21

The drug content estimation performed on all the atenolol FDOF with size 6.25 cm^2 showed that the formulation contained atenolol in the range of 99.56 to 99.94% which is complying with the limits mentioned in pharmacopoeia. The characteristics like tensile strength and percentage elongation was found to be satisfactory for the fast dissolving films.

Table 8.Mechanical properties, percentage moisture content and drug content estimation of atenolol FDOF

Formulation code	Tensile strength (Kg/mm^2)	% Elongation	%drug content in 6.25 cm^2
H1	1.58	54.5	99.56
H2	1.2	15.1	99.92
H3	1.05	10.5	99.88
H4	1.24	11.5	99.32
PU1	1.59	55	99.34
PU2	1.48	45.8	99.98
PU3	1.28	18.3	99.88
PU4	1.32	17.3	99.26
PV1	1.428	41	99.34
PV2	1.1	13.51	99.98
PV3	0.90	08.2	99.94
PV4	1.02	10.1	99.32

A comparative the drug release data form atenolol FDOF containing all the polymers can be seen from graph (fig. 1).Atenolol FDOF formulated employing different polymers showed the following results. Atenolol FDOF containing HPMC 15cps in concentration of 100 mg coded as H1, had drug release of 94.61% in 135 sec followed by H1, H3, and H4 with 96.91% in 150 sc, 95.62 in 165 sec and 95.61 in 195 sec respectively. Pullulan incorporated FDOF of atenolol recorded 98.01% drug release in 105 sec for PU3 whereas 98.91% in 135 sec, 96.97% in 120 sec and 98.98% in 135 sec for PU1, PU2 and PU4 formulations respectively. PVA FDOF of atenolol had drug release of 98.98% in 135 sec for PV1 followed by 98.91% in 165 sec, 99.12% in 180 sec and 98.79% in 195 sec for PV2, PV3 and PV4 respectively.

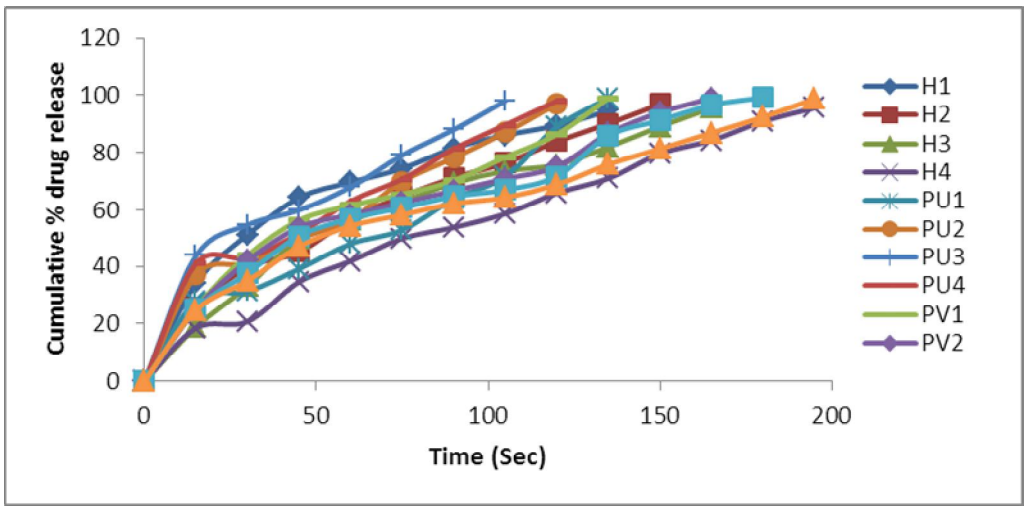

Fig. 1.*In vitro* cumulative percentage of drug release from atenolol FDOF

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} which were present in pure drug atenolol were also found in physical mixture indicating that there is no interaction between drug and polymer (Fig. 2-4).

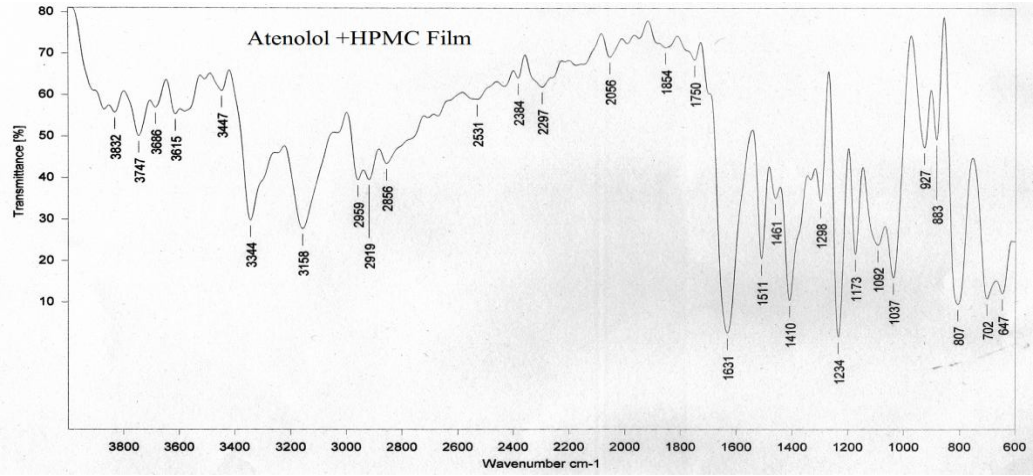

Fig. 2.FTIR spectra of atenolol and HPMC 15cps

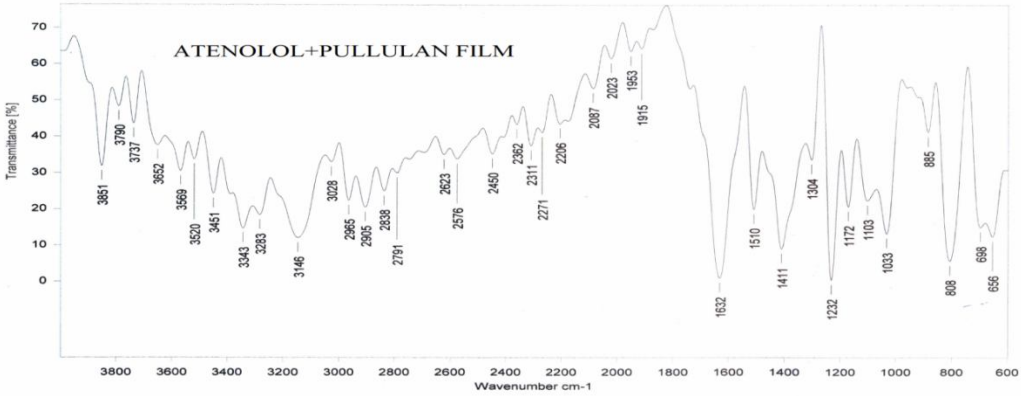

Fig. 3.FTIR spectra of atenolol and pullulan

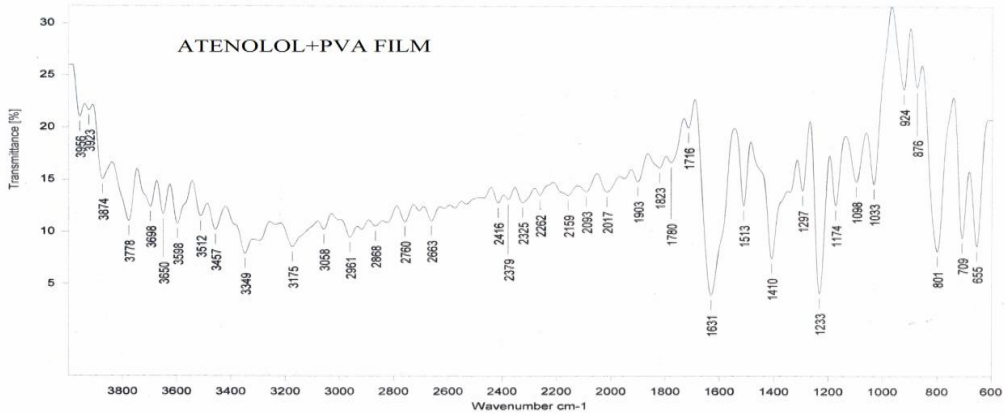

Fig. 4.FTIR spectra of atenolol and pullulan

CONCLUSION

Atenolol FDOF of size 6.2 cm^2(2.5×2.5 cm)was prepared by using solvent casting technique. HPMC 15cps, pullulan and PVA were incorporatedat varying concentration as film forming polymers. The morphological characterization by sensory inspection of all atenolol FDOF showed satisfactory performance with respect to detachment, transparency and smoothness factors. The results of Table 6 revealed optimum morphological characteristics for formulations H3, H4, PU3, PU4, PV3 and PV4; that means that as the concentration of polymer increased the morphological characters improved. Physicochemical characterization of atenolol FDOF shown in Table 7 indicated that, all the formulation had optimum variation of mass, thickness and folding endurance. The surface pH was found to be neutral indicating its safetyin intraoral environment. The disintegration time test showed optimum disintegration time of 13 sec for PU3 followed by PV1 and H1 formulations at 16 sc and 17 sec respectively. Table 8 data proved that the tensile strength and % elongation were satisfactory for all the atenolol FDOF's, with optimum drug content in the range of 99.2 to 99.9%. *In vitro* drug release concluded optimum drug release of 98.01% in 105 sec for PU3 formulation followed by 98.98% and 94.61% drug release in 135 secfrom PV1 and H1 atenolol FDOF respectively (Fig.1). The IR studies, showed no drug-polymer interaction (Fig.2-4). The results and discussion of atenolol FDOF formulated using HPMC 15cps, pullulan and PVA as film forming polymers concluded that pullulan at concentration of 300 mg has optimum physical appearance, disintegration and drug release which is best suited to be used as film forming polymer for atenolol FDOF.

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