WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 5, 923-935. Research Article ISSN 2277 – 7105

INFLUENCE OF SOLUBILIZING AGENTS ON ATENOLOL FAST DISSOLVING ORODISPERSIBLE FILMS OF PULLULAN

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Article Received on
21 May 2014,

Revised on 15 June 2014,
Accepted on 09 July 2014

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ABSTRACT

The present research study is aimed at developing and characterizing the influence of solubilizing agent such as tween 80 and dimethyl sulfoxide (DMSO) on the morphological and physicochemical characteristic of fast dissolving orodispersible films (FDOF). Pullulan is used as film forming polymer and glycerine was incorporated as plasticizing agent. The embodiment of atenolol as antihypertensive drug, in FDOF was achieved by solvent casting technique. Atenolol is β1 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 also attempts to correlate the effect of concentration of pullulan and solubilizing agent on the disintegration time and drug release profile. The atenolol FDOF were characterized for physical appearance, deformation caused during removing from die cavity, disintegration time, *in vitro* dissolution, etc. The optimum concentration of plasticizer, polymer and solubilizing agent was developed on the basis of flexibility, tensile strength and stickiness of the film. 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. The disintegration time of formulation PUD7 film was found to be 10 sec with *in vitro* release of 99.27 % in 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. Atenolol FDOF formulated using DMSO showed optimum results as compared to tween 80 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.

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

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

Methods

Phase I. Embodiment of atenolol fast dissolving orodispersible film (FDOF).

Formulation of atenolol FDOF without solubilizing agent

Fast dissolving orodispersible films of atenolol were prepared by solvent casting technique using pullulan as film forming polymers. Polymersolution was obtained by mixing accurately weighed pullulan in 10 ml distilled water as given in table 1 and allowing the solution to swell, by keeping it undisturbed for 1 h. Simultaneously accurately weighed atenolol was dissolved in 5ml of distilled water. Polymer solutions was added to drug solution under continuous stirring condition, further glycerin and aspartame were added as plasticizer and sweetner respectively and thoroughly mixed using magnetic stirrer. The solution obtained was sonicated for 20 min, to remove entrapped air. The formulation was slowly poured, as a continuous thin stream into the fabricated glass mould with a die cavity of dimension 2.5×2.5 cm (i.e. 6.25 cm^2) to ensure uniform spread and avoid air bubble entrappement, and was dried for 24 h at 40 °C in vacuum oven. The dried films were collected, packed in aluminum foil and stored in a desiccator until used for further study[4, 5].

Formulation of atenolol FDOF with solubilizing agent

Atenolol FDOF were formulated by solvent casting technique using pullulan as film forming polymer and selected solubilizing agent such as tween 80 and DMSO. Polymer solution was obtained by mixing accurately weighed pullulan in 10 ml distilled water as given in table 1 and allowing the solution to swell, by keeping it undisturbed for 1 h. Simultaneously 50 mg of atenolol was dissolved in 0.5ml of solubilizing agent. Polymer solutions was added to drug solution under continuous stirring condition, further glycerin and aspartame were added as plasticizer and sweetner respectively and thoroughly mixed using magnetic stirrer. The solution obtained was sonicated for 20 min, to remove entrapped air. The formulation was slowly poured, as a continuous thin stream into the fabricated glass mould with a die cavity of dimension 2.5×2.5 cm (i.e. 6.25 cm^2) to ensure uniform spread and avoid air bubble

entrappement, and was dried for 24 h at 40 °C in vacuum oven. The dried films were collected, packed in aluminum foil and stored in a desiccator until used for further study[4, 5].

Table 1. Formulation of atenolol fast dissolving orodispersible films

Formulations code	Drug (mg)	Pullulan (mg)	Tween 80(ml)	DMSO (mg)	Glycerin 20% mg)	Aspartame 10% (mg)	Distilledwater (ml) upto
PU1	50	100	---	---	20	5	10
PU2	50	200	---	---	40	5	10
PU3	50	300	---	---	60	5	10
PU4	50	400	---	---	80	5	10
PUT5	50	100	40	---	20	5	10
PUT6	50	200	40	---	40	5	10
PUT7	50	300	40	---	60	5	10
PUT8	50	400	40	---	80	5	10
PUD5	50	100	---	40	20	5	10
PUD6	50	200	---	40	40	5	10
PUD7	50	300	---	40	60	5	10
PUD8	50	400	---	40	80	5	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 FDOFwere 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 FDOFobtained 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].

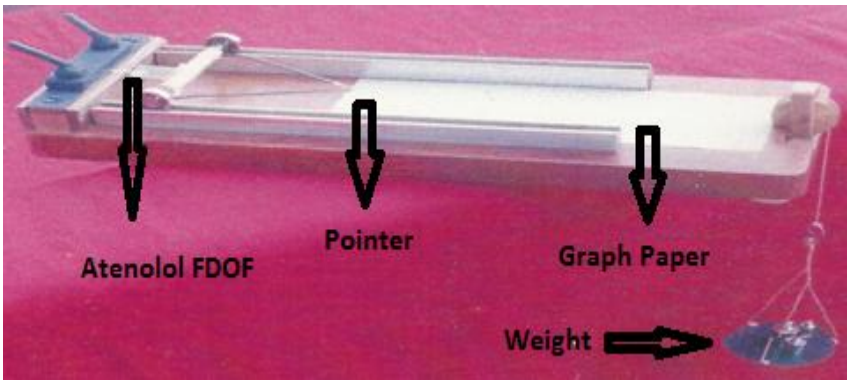

Fig. 1.Apparatus for the measurement of tensile strength and percentage elongation

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. Percentage moisture content

The test was carried out to evaluate the integrity of the films at dry condition. IRmoisture balance model A was employed to perform the test. The housing was raised and then the film previously weighed, was carefully placed on the disposable pan, so that the disposable pan did not tilt and remained in horizontal position. The temperature of 37 ± 2 °C was set and the study was conducted for 1 h. The film was collected and weight was determined using digital weighing balance. Percentage reduction in weight at the end of 1 h was determined by rotating the scale until the pointer returned to the index mark. The results are given Table 7[9]. The number displayed was percentage moisture lost based on the initial weight of the sample. Percentage moisture on dry bases was calculated by the formula,

$$\% \text{ Moisture } = \frac{100\ (P)}{100 - P}$$

Where; P = Percentage of moisture lost by sample in given time.

11. 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].

12. *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].

13. 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 5; the data indicates that PU1 and PU2 formulation without solubilizing agent showed slight deformation while detaching from the die cavity but later when kept undisturbed, complete restoration was observed, rest all the atenolol FDOF possessed optimum detachment, deformation and restoration factor when withdrawing from the fabricated glass mould with die cavity of size 2.5×2.5 cm. The data further indicated optimum transparency and smoothness factor with visual inspection and handling of atenolol FDOF.

Table 5.Grading of atenolol FDOFby sensory inspection

Formulation code	Detachment factor	Transparency factor	Smoothness factor
PU1	+ +	CT	ULSm
PU2	+ +	CT	ULSm
PU3	+ + +	CT	ULSm
PU4	+ + +	CT	ULSm
PUT5	+ + +	CT	ULSm
PUT6	+ + +	CT	ULSm
PUT7	+ + +	CT	ULSm
PUT8	+ + +	CT	ULSm
PUD5	+ + +	CT	ULSm
PUD6	+ + +	CT	ULSm
PUD7	+ + +	CT	ULSm
PUD8	+ + +	CT	ULSm

B. Physicochemical characterization

The preliminary physicochemical characterization performed on atenolol FDOF are reported in Table 6. Variation of masses was found in the range 50 mg to 58 mg. Film thikness was reported in between 0.71 to 0.79 mm and folding endurance was more than 200 foldings at a single point. The data of variation of mass, thickness test and folding endurance were reported to be satisfactory.The surface pH of all the 48 atenolol orodispersible film formulations were recorded at 6.78 which are close to normal, indicating no irritation to the oral mucosa upon insertion. Disintegration test were performed by two methods, namely petridish test and slide frame test, showed approximately similar values between the methods; indicating reliability of any one method to be used in the future research study.

Table 6.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
PU1	50	0.71	>200	6.75	18	17
PU2	52	0.71	>200	6.78	18	17
PU3	53	0.71	>200	6.78	18	17
PU4	55	0.73	>200	6.78	15	14
PUT5	55	0.72	>200	6.78	14	13
PUT6	54	0.72	>200	6.78	12	11
PUT7	58	0.77	>200	6.77	11	11
PUT8	53	0.71	>200	6.78	11	10
PUD5	57	0.77	>200	6.78	12	11
PUD6	56	0.75	>200	6.78	12	10
PUD7	57	0.76	>200	6.78	10	08
PUD8	56	0.79	>200	6.79	11	10

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 99.32 to 99.98% which is complying with the limits mentioned in pharmacopoeia. The characteristics like tensile strength, percentage elongation and percentage moisture content was found to be satisfactory for the fast dissolving films.

Table 7.Mechanical properties,percentage moisture content and drug content estimation of atenolol FDOF

Formulation code	Tensile trength (Kg/mm2)	% Elongation	% Moisture content	%drug content in 6.25 cm^2
PU1	1.58	54.5	2.44	99.56
PU2	1.2	15.1	2.37	99.92
PU3	1.05	10.5	2.55	99.88
PU4	1.24	11.5	2.49	99.32
PUT5	1.59	55	1. 40	99.34
PUT6	1.48	45.8	1.37	99.98
PUT7	1.28	18.3	1.56	99.88
PUT8	1.32	17.3	1.47	99.26
PUD5	1.428	41	2.58	99.34
PUD6	1.1	13.51	2.50	99.98
PUD7	0.90	08.2	2.88	99.94
PUD8	1.02	10.1	3.13	99.32

Atenolol FDOF formulated without solubilizing agent showed optimum drug release of 98.01% in 105 sec with formulation coded PU3 containing 300 mg pullulan. At higher concentration of pullulan i.e. 400 mg in PU4 formulation, 98% the release was reported at 120 sec. when tween 80 was used as solubilizing agent 92.09 % drug was release in 90 sec in formulation coded as PUT7 as compared to other tween 80 formulation. Atenolol FDOF formulated by using DMSO as solubilizing agent and pullulan in concentration of 300 mg i.e. PUD7 showed highest drug release of 99.06% in 90 sec. The drug release form FDOF increased in the presence of solubilizing agent as can be seen from graph (fig. 2).

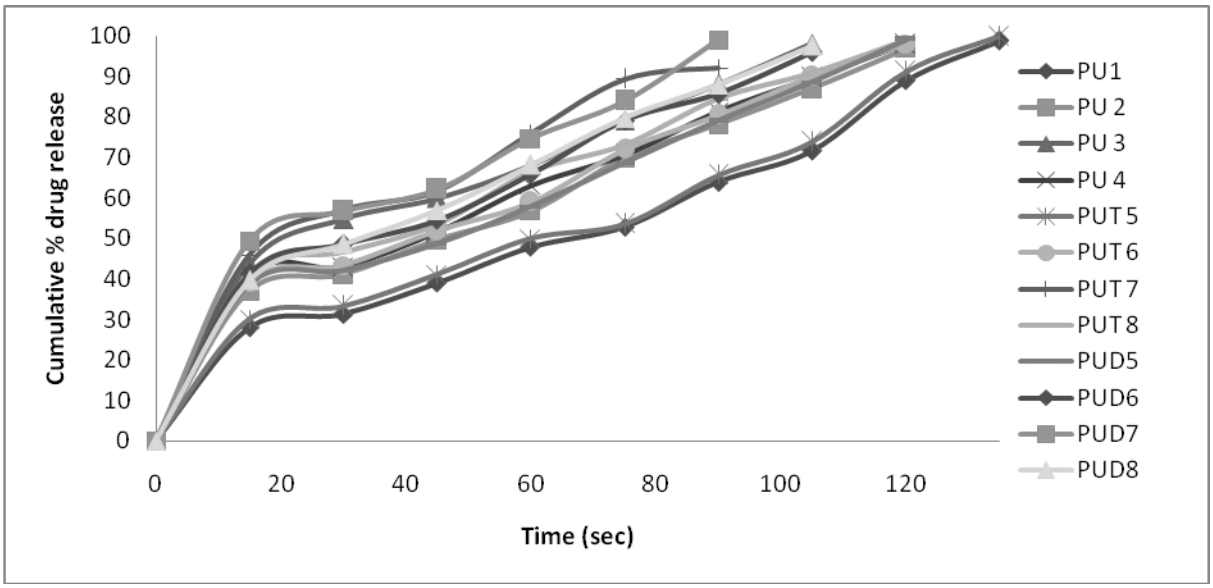

Fig. 2.*In vitro* cumulative percentage of drug release from atenolol fast dissolving orodispersible films containing tween 80 and DMSO.

Following is the comparison of drug release pattern from the formulation of atenolol FDOF having optimum concentration of polymer and solubilizing agent. The release pattern is as follows PUD7>PUT7>PU3>PUD8>PUD6>PUD5>PUT8>PUT6>PUT4>PUT2>PUT5>PU1. 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. 3).

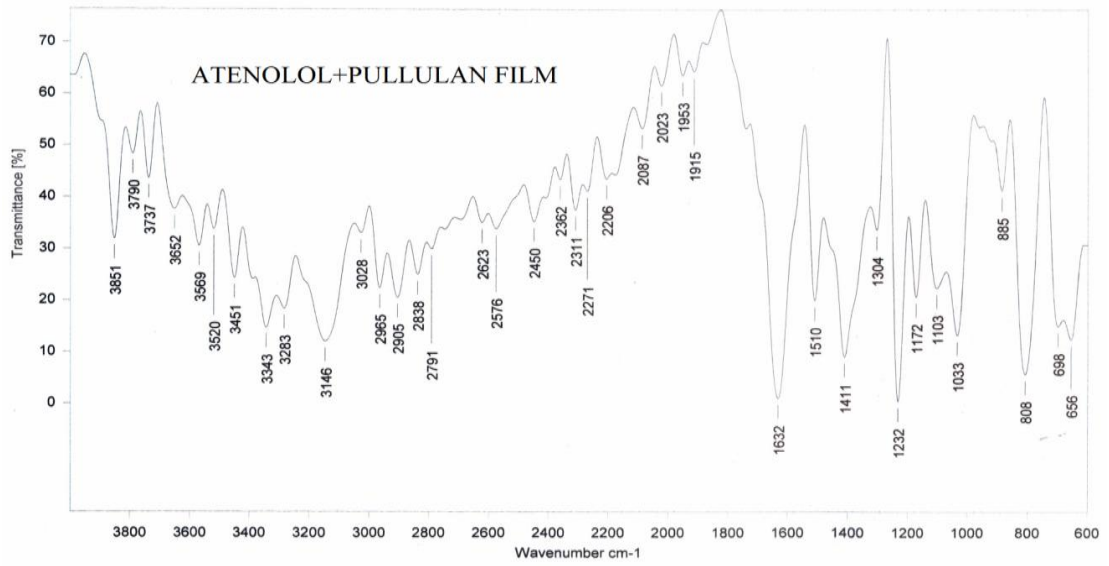

Fig. 3.FTIR spectra of atenolol and pullulan

CONCLUSION

Atenolol FDOF of size 6.2 cm^2(2.5×2.5 cm)was prepared by using solvent casting principle. Pullulan was used in different concentration as film forming agent with DMSO and tween 80 as solubilizing agent.

The morphological characterization of atenolol FDOF revealed that by adding solubilizing agent the properties of the FDOF can be enhanced to optimum extent without increasing the bulk of the formulation. The important parameters of FDOF such as disintegration time and drug release was also concluded optimum by comparing the results from table 6 and graph shown in fig. 2. The optimum formulation was concluded as PUD7 having pullulan in the concentration of 300 mg and solubilizing agent DMSO 40 mg as it showed disintegration time of 10 sec and 99.06% drug release in 90 sec. 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 DMSO as a solubilizing agent.

ACKNOLEDGEMENT

The authors express their sincere gratitude to the NITTE University for constant motivation and providing necessary facility to carry out the research work.

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