Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Development and Characterization of Oral Dissolving Films of Tadalafil based on Pregelatinized Hydroxypropyl Pea Starch

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ARTICLE DETAILS

Article history:
Received on 03 June 2015
Modified on 13 September
Accepted on 20 September

Keywords:
Pregelatinized Hydroxypropyl Pea Starch,
Oral Dissolving Films,
Polymer,
Tadalafil

ABSTRACT

The aim of the present work was to develop and characterize oral dissolving film of pregelatinized hydroxypropyl pea starch (Lycot RS720®) polymers for oral delivery of tadalafil. ODFs films were prepared by solvent casting technique. Formulations were prepared based on Box-Behnken statistical design with concentrations of Lycot RS720® and glycerin (plasticizer) as independent variables. Two dependent variables considered were tensile strength and drug release. Results revealed that film containing 25% (w/v) of Lycot RS720® and 3% (w/v) glycerin demonstrated more than 90% drug release within 5min. SEM images demonstrated smooth and uniform surface of film suitable for oral mucosa. Thus, this study suggests that pregelatinized hydroxypropyl pea starch can act as a rapid dissolving film forming polymer for oral delivery of a tadalafil.

INTRODUCTION

Fast oral-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid dosage forms. In response to this need, a variety of orally disintegrating tablet (ODT) formats were commercialized, which disintegrate within few minutes when placed in the mouth without drinking water or chewing. Oral drug delivery technology has improved from conventional dosage forms to modified release dosage forms to ODT to the recent oral dissolving films (ODF) [1]. In recent years ODF became a very popular drug delivery system due to the fact that it can deliver the drug directly to the systemic circulation (avoiding the first pass metabolism). It enhances drug efficacy by lowering the dose and improving the onset of action and consequently patient compliance. Oral dissolving film or strip that employs a water dissolving polymer which allows the dosage form to quickly hydrate by saliva, adhere to mucosa, and disintegrate within a few seconds, dissolve and releases medication for oromucosal absorption when placed on the tongue or oral cavity.

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ODF are ideal by patients when suffering from motion sickness, dysphasia and mental disorders while they are unable to consume large amount of water. The advantages of suitable dosing and portability of film have led to an extensive applicability of this dosage form in pediatric as well as geriatric patients [2]. Starch is one of the most widely used as fillers, binders, and disintegrants in the manufacture of solid dosage forms. Although corn starch is one of the most widely used starches in pharmaceutical formulations, starches from other botanical sources have shown different functional properties such as gelling, swelling, and water binding capacity, which are related to their capacity to function effectively as binders and disintegrant in solid dosage forms [3] .In this study a non-GMO pregelatinized hydroxypropyl pea starch (Lycot RS720®) which is chemically modified by etherification with the reagent propylene oxide was used as film forming agent in the mouth dissolving dosage form. Pregelatinized hydroxypropyl pea starch may be partially hydrolysed using acids or enzymes to obtain 'thinned starch' with reduced viscosity. It disperses easily in cold water without formation of lumps and simple heating up to 70° C will develop film forming ability. Due to hydroxypropylation solution does not form

gelation on cooling (no retrogradation and high stability).

Tadalafil is a potent and selective phosphodiesterase-5 inhibitor used for the treatment of erectile dysfunction which was approved by the FDA. Tadalafil is absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved approximately at a mean time of 2 hours after dosing. The recommended dose of tadalafil is 2.5-20 mg [4]. The aim of this work was to develop and characterize an oral dissolving film of tadalafil using a non-GMO pregelatinized hydroxypropyl pea starch and to evaluate Lycot RS720® as film forming agent.

MATERIALS AND METHODS

Materials

Tadalafil was obtained as gift sample from Ami Life sciences Pvt. Ltd. Thane, India pregelatinized hydroxypropyl pea starch (Lycot RS720®) was gifted by Roquette Pharma, Mumbai India. Hydroxypopyl-β-cyclodextrin (HPβCD) was obtained from Wockhardt Pharma, Aurangabad, India, Glycerin were procured from Loba Chemie (Mumbai, India). All other chemicals and solvents were of analytical grade.

Preparation of Tadalafil- HPβCD Inclusion Complex

Inclusion complex of tadalafil with hydroxypopyl-β-cyclodextrin were prepared by kneading method. The mixture of tadalafil and hydroxypopyl-β-cyclodextrin was triturated in a mortar with a small volume of water – methanol (1:2 v/v) solution. The thick slurry that formed was kneaded for 45 min and then dried at 45 ºC. The dried mass was pulverized and sieved through sieve no. 60. Store in cool place and in air tight container [5].

Formulation Design

Box-Behnken statistical design was used for optimization of oral dissolving films. In this model two factors were evaluated, each at three levels. Low, medium and high levels of each factor were coded as -1, 0 and +1, respectively. The concentrations of polymer (Lycoat® Rs 720), (X_1), and glycerin (X_2) as a plasticizer were selected as independent variables. The response variables tested include tensile strength (Y_1) and % drug release (Y_2) at 300 sec. The selected factor levels are summarized in **Table 1.**

Table 1: Independent variables in formulation design

Factors	**Levels of Independent variables**		
Independent variables	Low (-1)	Medium (0)	High (+1)
X_1= Concentration of Polymer (%w/w)	25	27.50	30
X_2= Concentration of Plasticizer (%w/w)	3	4	5

Preparation of mucoadhesive buccal films

The fast dissolving films of tadalafil were prepared in the laboratory using the pregelatinized hydroxyl propyl pea starch (Lycoat® RS720) by solvent casting method. Tadalafil- HPβCD complex was dissolved in 20 ml methanol and sonicated for 2-3 minutes. Pregelatinized hydroxypropyl pea starch (Lycoat® RS 720) dissolved in distilled water by stirring on magnetic stirrer at 30 rpm. Then both the solutions were mixed and plasticizer glycerin was added, stirred well on magnetic stirrer (rpm 30/min). The above solution was sonicated for 30 min for deaeration. The solution was poured on a petri dish (diameter 8.8cm) and was dried in hot air oven for 24 hr [6]. Then dried film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose (2 × 2 cm^2 per film). The films were stored in desiccators at relative humidity 30-35% until further use. **Table 2** shows the composition of formulated films.

Table 2: Box-Behnken Designs with Response

Run	**Batch**	**Independent variable**		**Dependent Variable**	
		X_1	X_2	Y_1	Y_2
1	F 1	0	0	1.25	85.27
2	F 2	0	0	1.25	85.27
3	F 3	0	-1	1.2	91.12
4	F 4	0	1	1.3	79.71
5	F 5	0	0	1.25	85.27
6	F 6	0	0	1.25	85.27
7	F 7	-1	1	1.0	83.02
8	F 8	-1	0	0.8	84.92
9	F 9	1	-1	2.14	88.02
10	F 10	1	0	2.18	84.58
11	F 11	-1	-1	0.95	95.27
12	F 12	1	1	2.22	81.09
13	F 13	0	0	1.25	85.27

Where X_1 = Concentration of polymer (% w/w); X_2 = Concentration of plasticizer (% w/w);
Y_1 = Tensile strength (Kg/ mm^2); Y_2 = Drug release (%).

Characterization of Oral Dissolving Films

Film Thickness

The thickness of the different films was measured using a digital micrometer (Mitutoyo, Japan) with an accuracy of 0.001 mm. Thickness was measured in ten different locations of the film and the average thickness was used. The standard deviation of thickness was computed from the mean value.

Weight of film

Films (size of 2 × 2 cm^2) were cut from different areas of film. The weight of each strip was taken and the weight variation of six strips was calculated. The standard deviations of weight were computed from the mean value.

Drug Content

A sample of 4 cm^2 was dissolved in 10 ml methanol and shake for 2 minutes to extract drug from formulation and filtered through whatman filter and analyzed spectrophotometrically at 284 nm using distilled water as blank. The mean and standard deviation of drug content of three randomly selected films were calculated. The same procedure adopted for all the batches and drug content was noted.

Folding Endurance

The folding endurance of the strips was determined by repeatedly folding one strip at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good strip property. The number of times of strip could be folded at the same place without breaking gave the value of the folding endurance. This test was carried for all batches for five times [7].

Tensile Strength

Tensile strength of films was evaluated using a Brookfield, USA texture analyzer equipment equipped with a 5N load cell. Films are held between two clamps positioned between 3cm. During measurement the films were pulled at rate of 2 mm/sec. The force and elongation were measured when film breaks [8].

Tensile strength was measured using following formula

$$Tesile\ strength = \frac{Load\ at\ failure \times 100}{Film\ thickness \times film\ width} \quad (1)$$

Surface pH Measurement

A combined pH electrode is used for this purpose. Fast dissolving film was slightly wetted with distilled water. The pH was measured by bringing the electrode in contact with the surface of the film and repeated for three times.

Swelling Studies

Swelling index was determined to study and compare the hydration characteristics of film polymers. Films were weighed individually (designated as W_1) and placed separately in glass plate containing phosphate buffer pH 6.8. At regular intervals samples were removed from the glass plate and excess water was removed carefully by using filter paper. The swollen films were reweighed (W_2). The swelling index of each system was calculated using the following formula [9].

$$SI = \frac{W2-W1}{W1} \times 100 \quad (2)$$

Morphology Study

The surface morphology of film was examined by a scanning electron microscope (JEOL Model JSM - 6390LV, Japan).Film was sputtered for 2 minutes at 25 mA with gold-palladium. The polymeric films were coated in order to study the film property. The coated assembly was then mounted on an aluminium stub and analysis was performed at 15kV accelerating voltage in a scanning electron microscope [10].

Organoleptic Evaluation of ODFs in Human Volunteers

Taste evaluation study was conducted on 12 healthy adult male human subjects, and to evaluate mouth feel, palatability in oral cavity for F11 formulation. The volunteers were asked to restrict their tongue moments during the test. The bitterness score was rated as 0-good, 1-not bitter, 2- slightly bitter or 3-very bitter by the participants [11].

In Vitro Drug Release Studies

The drug release study was performed in 900 ml (phosphate buffer solution pH 6.8) using USP type II dissolution test apparatus. Paddle speed and bath temperature were set at 50 rpm and 37.0±0.5 °C respectively. Five milliliters sample was withdrawn at specific intervals replaced with a fresh dissolution medium. These samples were filtered using a filter paper of pore size 0.45µm. The concentration of samples was analyzed in an ultraviolet spectrophotometer (UV-1700, Shimadzu, Japan) at 284 nm.[12].

Ex- vivo Permeation Study

Ex vivo permeation study of film was carried out using porcine buccal mucosa on Franz diffusion cells of diameter 2.76 cm^2 and volume of 25 ml which were placed on magnetic stirring unit (Whirlmatic, Spectralab, India). The diffusion media was continuously stirred with the help of a tiny star headed magnetic stirrer moving at around 300 rpm. Phosphate buffer pH 6.8 was used as receptor solution. The temperature was maintained at 37 ± 5 ºC with the help of circulating water. The diffusion was carried out for 30 min. At predetermined time intervals of 5, 10, 15, 20, 25, 30 min, 5.0 ml samples were withdrawn and replaced with fresh pH 6.8 phosphate buffer. These aliquots after analyzed using UV spectrophotometer (1800, Shimadzu, Japan) at 284 nm [13].

Stability Studies

The accelerated stability studies were carried out according to International Conference on Harmonization (ICH) Q1 A (R2) guide lines [14]. Optimized batches (3 samples) were sealed with aluminium foil and were kept under ambient temperature and moisture condition (40 ± 2 ºC and 75 ± 5% RH) for a period of 3 months in stability chamber. The samples were withdrawn at 30, 60 and 90 days interval and evaluated for drug content.

RESULTS AND DISCUSSION

Tadalafil is a low solubility compound and as the in vivo absorption of Class II drugs (low solubility and high permeability) is typically dissolution rate-limited, inclusion complexation with HPβCD was developed to enhance the solubility and dissolution of tadalafil. Solubility studies on inclusion complex (1:4 tadalfil to HPβCD ratio) reveals marked improvement in solubility of tadalafil (data not shown). Equivalent amount to 10 mg tadalafil of inclusion complex was selected in formulation of film.

Box–Behnken statistical experimental design gives 13 runs. The ranges of Y_1 and Y_2 are 0.95 kg/mm^2, 95.27%, respectively for all the responses observed for 13 formulations prepared were simultaneously fitted to first order, second order and quadratic models using Design Expert 8.0.1. It was observed that the best fitted model was quadratic and the comparative values of R^2, SD, and % CV are given in **Table .3** along with the regression equation generated for each response. It is evident that all the two independent variables, namely the concentration of polymer (X_1), concentration of plasticizer (X_2), respectively have interactive effects on the two responses, tensile strength (Y_1) and drug release (Y_2). A positive value represents an effect that favors the optimization, while a negative value indicates an inverse relationship between the factor and the response.

Table 3: Fitting To the Data

Quadratic model	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Y_1	0.9585	0.9289	0.7052	0.13	9.13
Y_2	0.8662	0.8395	0.7097	1.61	1.88

Three dimensional contour plots were prepared for both responses **(Figure 1A & 1B**).These plots are known to study the interaction effects (studying the effects of two factors at one time) of the factors on the responses. The R-squared values of Y1 and Y_2 were found to be in the range of 0.7052-0.7052, 0.7097-0.8395, respectively.
The model proposes the following polynomial equation for effect on tensile strength.

$$Y_1 = +1.25=0.55X_1+0.34X_2+7.500\ X_1\ X_2 +0.71X_{12}+0.052X_2 \quad (3)$$

Where, Y_1 is tensile strength, X_1 is the polymer concentration, and X_2 is the concentration of plasticizer. The quadratic model was found to be significant with F-value 32.37 ($P < 0.0001$) which implies that the model is significant. Tensile strength of films increases with increase in glycerin concentration at same concentration of Polymer (Lycoat®). The combine effect of factor X_1 Polymer (Lycoat®RS 720) and X_2 (glycerin) can be further elucidated with the help of response surface plot **Fig 1A.** High level of factor X_2 gave high value of significance at all the levels of factor which indicates that the factor X_2 has signicant positive effect on tensile Strength. The increase in tensile Strength was observed due to increase in concentration of glycerin and Polymer (Lycoat® RS720).

The model proposes the following polynomial equation for effect on drug release

$$Y_2 = +85.70-1.21X_1-4.41X_2 \quad (4)$$

The F-value of 32.38 implies the model is significant ($P < 0.0001$). Therefore this model can be used to navigate the design space.

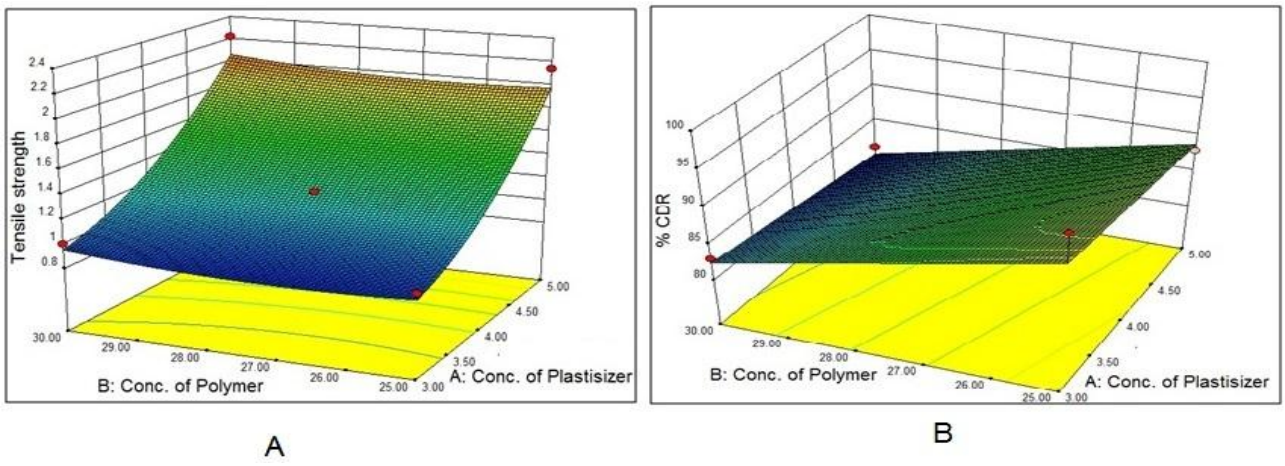

Figure 1: Effect of independent variables on tensile strength (A) and percentage drug release (B)

Table 4: Characterization of the Oral Dissolving Films

Formulation Code	Thickness Uniformity (mm) ± SD	Weight Uniformity (mm) ± SD	Drug Content (%)	Folding Endurance	Tensile Strength (Kg / mm²)	Surface PH study ± SD	Swelling Index ± SD
F 1	0.20 ± 0.005	54.5 ± 0.005	97.81	284	1.25	6.65	33.45
F 2	0.20 ± 0.005	54.5 ± 0.005	97.81	284	1.25	6.65	33.45
F 3	0.24 ± 0.005	55.1 ± 0.005	98.90	332	1.2	6.72	34.44
F 4	0.28 ± 0.01	54.6 ± 0.005	99.32	291	1.3	6.69	35.04
F 5	0.20 ± 0.005	54.5 ± 0.005	97.81	284	1.25	6.65	33.45
F 6	0.20 ± 0.005	54.5 ± 0.005	97.81	284	1.25	6.65	33.45
F 7	0.29 ± 0.01	56.1 ± 0.005	98.25	291	1.0	6.62	41.52
F 8	0.20 ± 0.005	56.3 ± 0.005	99.11	295	0.8	6.82	42.44
F 9	0.20 ± 0.005	54.4 ± 0.005	99.54	341	2.14	6.69	30.55
F 10	0.20 ± 0.005	54.5 ± 0.005	99.76	285	2.18	6.75	30.67
F 11	0.28 ± 0.01	56.2 ± 0.005	99.97	356	0.95	6.63	43.73
F 12	0.20 ± 0.005	54.3 ± 0.005	99.32	289	2.22	6.76	34.34
F 13	0.20 ± 0.005	54.5 ± 0.005	97.81	284	1..25	6.65	33.45

Table 5: Stability Study of Optimized Batch **F 11**

Evaluation Parameters	Before Stability	After 1 month	After 2 month	After 3 month
Thickness (mm)	0.28 ± 0.01	0.28 ± 0.01	0.28 ± 0.01	0.27 ± 0.09
Weight variation (mg)	56.2 ±0..005	56.1 ±0..009	56.1 ±0..006	56.1 ±0..003
Drug Content (%)	99.97	99.76	99.54	99.32

The contour plots **Fig 1B** showed the effect of different independent variables on percentage drug release (Y_2). Percentage drug release decreases as the amount of polymer increases since the drug remains inside the polymer matrix and vice versa. The increase in rate of drug release at 25% could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the drug. Moreover, the hydrophilic polymers would reach out and hence, create more pores and channels for the drug to diffuse out of the patches. The drug release pattern in the oral dissolving films (ODF) is also affected by the concentration of plasticizer (X_2) and followed a direct relationship when the amount of plasticizer increases drug release decreases.

Characterization of Oral Dispersible Films

Film Thickness

The thickness of each film was determined at ten different positions and the thickness was noted between 0.20 – 0.29 mm (**Table 4)**.The values were uniform for the films within the respective

group of formulation type. This depicts that the film cast was uniform.

Weight of Film

The weight variation values of film (2X2 cm^2) for formulations F1 to F13 were found to be between 54 and 56 mg. The proportional gain in weight of films was observed as the thickness of films increased.

Drug Content

Despite of amount of drug and polymer in formulation the drug content was found between 97.81 to 99.97 %. The content uniformity was observed in all formulations **Table 4.**

Folding Endurance

The folding endurance of films was found to increase with decrease in glycerin concentration. Formulations F3, F9 and F11 showed folding endurance values more than 300. Folding endurance values for films more than 300 indicates high mechanical strength of these films. This is highly desirable because it would not allow easy dislocation of the films from the site of application or breaking of film during administration and handling.

Tensile Strength

The observation of the data for all formulations for tensile strength was calculated and as given in **Table 4**. Films have sufficient strength to withstand wear and tear occurring during administration and transportation. Tensile strength values for films of more than 0.5 kg/mm^2 indicate good mechanical strength.

Surface pH Measurement

Surface pH for formulation F1–F13 was found to range from 6.62 to 6.82. Since range of the pH of film is near to the salivary pH (6.5–7.2), hence no mucosal irritation was expected at these pH values (**Table 4).**

Swelling index

Swelling behavior of films as a function of time illustrated in Table 4. Swelling index of films was found to increase with increase in polymer concentration. Being hydrophilic polymer lycot RS720 has good swelling behavior at higher concentration. The rapid fluid uptake enabling the polymer to swell and dissolve that has a key role in drug release.

***In vitro* drug release studies**

In vitro drug release study of tadalafil oral dissolving film was carried out in phosphate buffer solution, pH 6.8 the release data of tadalafil were given in **Fig 2**. *In vitro* release study indicated that the release of drug varied from the formulation batches according to the concentration of polymer used. At lower concentration of pregelatinized Pea starch (Lycoat® Rs 720) formulations demonstrated immediate drug release than at higher concentration. The variation of plasticizer concentration does not showed any significant effect on drug release. The F 11 batch shows higher the drug release within 300 sec.

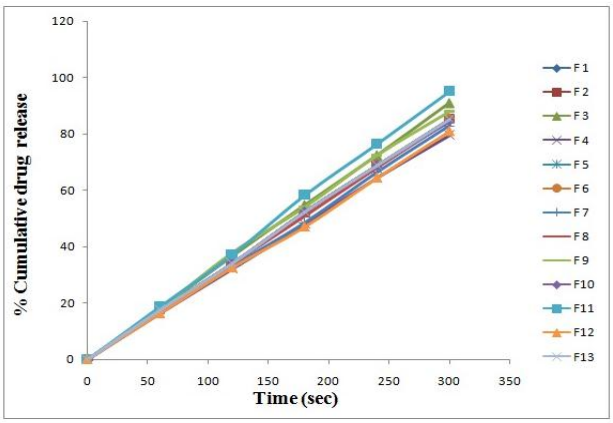

Figure 2: In vitro drug release from all formulation

Optimization of Formulation

The computer optimization technique by the desirability approach was used to produce the optimum formulation. The process was optimized for the response variable Y1 and Y_2. The optimized formula was obtained by setting more than 90% drug release at 5 min and tensile strength greater than 0.5 kg/mm^2. Formulation F11 was found to be optimized formulation which contained 25 % of pregelatinized pea starch as film forming agent and 3% of glycerin as plasticizer.

Characterization of Optimized Formulation

Morphology Study

The morphology of the films was studied using scanning electron microscopy (SEM), at varying magnifications for determination of surface characteristics. The SEM image (**Fig 3)** of optimized formulation shows the surface was smooth and uniform depicting its suitability as oral dissolving films.

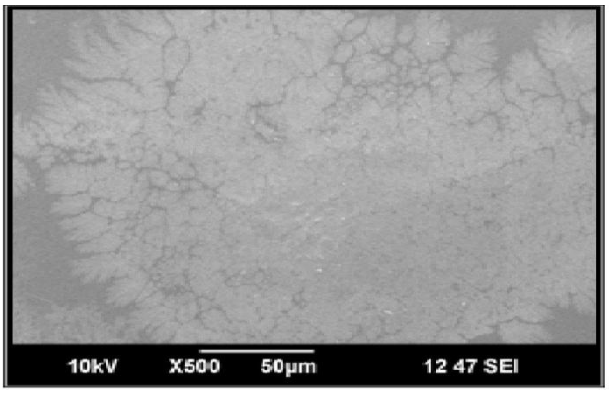

Figure 3: SEM image of polymeric film

Organoleptic Evaluation of ODFs in Human Volunteers

Taste evaluation study was conducted on 12 healthy adult male human subjects, and to evaluate mouth feel, palatability in oral cavity for F11 formulation. The majority of the participants (10 out of 12) found the taste of F11 film was good (score = 0) or non-bitter (score = 1) and was rated as slightly bitter (score >2) by two participants showed formulation F11 had a good mouth feel.

Ex vivo permeation study

Formulation F 11 further subjected to ex vivo permeation studies using the sheep oral mucosa. The percent drug permeated after 30 min was found to be 96.65 % demonstrated faster dissolution of film and rapid permeation of drug across oral mucosa.

Stability Studies

The accelerated stability studies were carried for developed optimized formulation (F11) was analyzed for thickness, weight variation and drug content. Samples were withdrawn at 30 days interval. After 3 months studies, the formulation showed little changes in thickness, weight variation that could be due to loss of moisture at stress conditions. Study of drug content in formulations reveals that there is no significant change in drug content as show in table no. 5

CONCLUSION

In the present study rapid oral dissolving film based on pregeletinized pea starch (LycoatRS720®) which dissolve in oral cavity within few minutes which would provide rapid onset of action. Oral dissolving films were prepared by Box-Behnken statistical design and effect of formulation on tensile strength and drug release were analyzed by applying computer optimization technique. Based on the results of dependent variables, formulation F11 was found to be optimized formulation.

Thus, an attempt of formulating a stable oral dissolving film of tadalafil for treatment of erectile dysfunction using novel modified starch was made by using scalable film casting method. Pre gelatinized pea starch (Lycoat® RS720) showed good film forming agents with rapid dissolution in minimal dissolution media. Thus cheap and abundantly available carbohydrate, pre gelatinized starch (Lycoat® RS720) could be a promising vehicle for rapid systemic delivery of drug through oral route. The in vitro studies have shown that this is a potential drug delivery system for tadalafil with considerable good stability and release profile. However, in vivo studies in human volunteers would be needed to verify findings of in vitro studies.

ACKNOWLEDGEMENT

Authors are thankful to Roquette Pharma, Mumbai and Ami Life sciences Pvt. Ltd. Thane, India for providing gift samples of Lycoat RS720® and tadalafil respectively.

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