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Formulation of Mouth Dissolving Strips of Metoprolol Succinate Using Locust Bean Gum

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Abstract

The current project was carried out to investigate the use of locust bean gum as a film forming agent in the development of fast dissolving oral strips that can be utilized for the drug administration in urgent situations such as convulsive seizures, hypertension and dysphasia. Oral strips of locust bean gum were formulated using solvent casting method containing metoprolol succinate as model drug. (T1-T9) placebo films were formulated initially using different concentrations of locust bean gum to assess the film forming ability of the locust bean gum. Crospovidone and PEG-200 were used as disintegrating agent and plasticizer respectively. Stability against moisture was improved by addition of beeswax. Formulated films (T1-T9) were evaluated for their appearance, film forming capacity, moisture permeability, weight variation and thickness. Placebo film formulations T4 and T6 consisting of locust bean gum (0.6 gm), beeswax (0.1 gm) and crospovidone (4%), 0.3 and 0.9 ml of PEG-200 respectively were selected for drug loading. Drug loaded films (F1 and F2) were characterised for parameters such as weight variation, film thickness, folding endurance, drug content uniformity, *in vitro* disintegration time, *in vitro* drug release, tensile strength and surface pH. Composition F2 comprising of locust bean gum (0.6 gm) and 0.9 ml of PEG- 200 was chosen as optimized formulation. Stability studies of optimized drug loaded formulation was done as per ICH guidelines of stability. Locust bean gum appears as a good candidate to be utilized as a natural film former in the formulation and development of oral strips/ films.

Keywords: Locust Bean; Oral fast Dissolving Film/ strips; Metoprolol succinate

1. Introduction

Oral fast dissolving tablets and Oral strips/films have been used as alternative to conventional oral dosage forms to deliver the drugs under emergency conditions and where patient find difficulty in swallowing the tablets and capsules. Fast onset of action obtained by administration of oral fast dissolving films prove them as ideal and distinctive pharmaceutical dosage forms that was emerged in late 1970s [1]. Oral films are projected for paediatric, geriatric, bedridden, or unable patients who are not in conscious state and are unable to take medicine independently [2]. It is difficult to swallow tablets or capsules in situations such as during allergic reactions or coughing, in motion sickness and in case of non availability of water. The concept of fast-dissolving drug delivery systems has been developed to assist such disabled patients [3]. Oral films/ oral strips are a form of novel drug delivery system that when placed on tongue rapidly disintegrates on coming in contact with saliva and release the content for absorption through oral mucosal [4]. Film formers are one of the major components in the formulation of oral films. Natural polymers are widely used as an alternative to synthetic polymers (HPMC, EC) due to ease of availability, biocompatibility and biodegradability. Some of natural filming polymers used are sodium alginate, pullulan gum, gelatin, pectin and rosin.

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Locust bean gum (LBG) is a polymer of natural origin which is extensively used as thickening and suspending agent in the oral drug delivery systems due to its bio-degradability, low toxicity, and availability at low cost [5]. Locust bean gum belongs to the category of galactomannans is a polysaccharide composed of mannose and galactose units [6]. Metoprolol succinate is β1 selective adrenoreceptor blocker used in the treatment of high blood pressure, angina and myocardial infarction. The oral bioavailability of the metoprolol succinate is low with elimination half life of 3-4 hr as in liver it undergoes extensive first pass metabolism [7]. In the present investigation oral films of locust bean gum were formulated using metoprolol succinate as a model drug to explore the film forming potential of locust bean gum.

Experimental

Materials:

Metoprolol succinate was procured as a gift sample from Cipla Pharma, Mumbai, India. Crospovidone was obtained from Yerrow Chem. Mumbai, India. Locust bean gum was received as a gift from lucid laboratory Pvt. Ltd. Hyderabad, India.

Methods

Preformulation studies

Standard calibration curve of Metoprolol Succinate

Stock solution (A) was prepared by dissolving metoprolol succinate (100 mg) in 100 ml of phosphate buffer pH 6.8. 10 ml of stock solution A was further diluted to 100 to prepare solution B. From of solution B working standards were prepared within a conc. series of 5 to 30 µg/ ml and absorbance was taken at λ_{max} 223 nm by means of double beam systornics spectrophotometer - 2202 [8].

Compatibility study

Compatibility study between drug and selected excipients were carried out using FTIR analysis. Spectra of metoprolol succinate, locust bean gum and physical mixture of metoprolol succinate and locust bean gum was analyzed using Alpha T Bruker. FTIR spectrum was recorded using KBR pellet method and scanned between the ranges of 4000-500 cm^{-1} wave number.

Formulation of films of gum of Locust bean

Formulation of placebo film of Locust bean gum

Placebo films using locust bean gum (T1-T9) were formulated as per the composition give in (Table 1). LBG 0.5, 0.6 and 0.7 gm were dissolved in water (75 ml) at 70ºC for 2 h using water bath to form a clear solution and homogenised at 12000 rpm for 2 min. To each of the composition 0.3, 0.6 and 0.9 ml of PEG 200 was added as plasticiser, 0.1 gm of beeswax was added to modify the film forming property of locust bean gum. Crospovidone was added in the concentration ranging from 2-6% as disintegrating agent. The resulting compositions were homogenised at 18000 rpm for 5 min and heated at 40ºC. The films were casted by spreading on plastic petri plates and dried at 60ºC. The dried films were separated from petri plates and incise into 2x2 cm^2 pieces. The placebo films (T1-T9) were characterized for surface roughness, imperfection, ease of separation from petri plate without breaking and *in vitro* disintegration time. Evaluation parameters of placebo films are summarized in the (Table 2).

Preparation of Drug loaded film

Composition T4 and T6 on the basis of their good film forming capacity were chosen for drug loading. Drug loaded fast dissolving film formulations (F1&F2) containing metoprolol succinate as an active ingredient were formulated as per the composition given in (Table 3) using solvent casting method.

Evaluation of Drug loaded Fast dissolving films [9-11]

Appearance of Films

Films were examined to check any kind of imperfections in appearance such as smoothness, transparency, color etc.

Film Forming Capacity

Film forming ability of a polymer was judged on the basis of its ability to cast into poor, average, good and excellent films.

Thickness of the Film

Vernier caliper was used to determine thickness at different points such as 4 corners and centre of the individual film. Mean± SD is determined.

Weight Variation of the Film

To ensure uniformity in weight, films were weighed individually and average deviation was calculated.

Folding Endurance

It was measured by folding the films repeatedly at the same point until it breaks. Test was done on three films selected randomly from each batch.

In vitro Disintegration Time

In vitro disintegration time was measured in 10 ml of Phosphate buffer (pH 6.8). The time when the film breaks was noted as disintegration time. Same procedure was repeated thrice and calculated as mean ±SD.

In vitro dissolution test was conducted using in 900ml Phosphate buffer pH 6.8 (37ºC and 50 rpm) using official basket type apparatus (Lab India DS-8000). Samples were taken out at different time intervals and analyzed with double beam UV spectrophotometer [12].

Table 1 Composition of placebo oral fast dissolving films using locust bean gum.

Ingredients	T1	T2	T3	T4	T5	T6	T7	T8	T9
LBG (gm)	0.5	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7
PEG-200(ml)	0.3	0.6	0.9	0.3	0.6	0.9	0.3	0.6	0.9
Beeswax(gm)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Crospovidone (%)	2	2	2	4	4	4	6	6	6
Water(ml)	75	75	75	75	75	75	75	75	75

Table 2 Evaluation of placebo films

Parameters	T1	T2	T3	T4	T5	T6	T7	T8	T9
Film forming capacity	Poor	poor	average	good	Very good	excellent	average	Not formed	Not formed
Physical Appearance	brittle	Not formed	hazy	Transparent	Hazy	Transparent and clear	brownish	brittle	brittle
In-vitro disintegration time (sec)	28±0.51	-	172±0.12	60±0.58	24±0.50	18±0.34	85±0.31	33±0.31	121±0.12

Table 3 Composition of drug loaded fast dissolving films

Ingredients	F1	F2
LBG	0.6 gm	0.6 gm
Drug	25 mg	25 mg
PEG 200	0.3 ml	0.9 ml
Bees wax	0.1 gm	0.1 gm
Crosspovidon	4%	4%
Water up to	75 ml	75 ml

Release Kinetic study

Drug release mechanism from the formulated films was studied by fitting the drug releases data into different kinetics models. The drug release order was recognized by analyzing zero-order and first-order release profiles and the mechanism of release of drug was established using Higuchi and Korsmeyer-Peppas model [12].

Stability Studies

Optimized film composition was chosen for stability studies. The film samples were packed in aluminum foil and maintained at room temperature and at 40ºC with 75% relative humidity in stability chamber for 3 months. The stability test parameters used were disintegration time, *in vitro* drug release, drug content and general appearance at different time points say 15, 30, 45, 60 and 90 days [13].

RESULT AND DISCUSSION

Preformulation studies

The standard calibration curve of metoprolol succinate was plotted by UV spectrophotometric analysis as given in the (Figure 1). The plot showed equation as $y = 0.427x + 0.036$ and measured R^2 value as 0.993.

The FTIR spectra of metoprolol succinate, locust bean and (1:1) their mixture depicted in (Figure 2 a, b and c) respectively. FTIR spectra of metoprolol succinate showed characteristic peaks of -N-H stretching at 3429.80 cm^{-1}, -C-H stretching at 2981.46 cm^{-1} succinic acid at 2508.79-2422.38 cm^{-1}

C=C stretching at 1616.77, C-O-H bending at 1413.20 cm^{-1}, C-CH_3 bending at 1381.12 cm^{-1} and =C-O stretching at 1241.06 cm^{-1}. Spectra of locust bean gum showed O-H stretching at 3426.04 cm^{-1}, C-H stretching at 2925.54 cm^{-1}, stretching due to galactose and mannose ring at 1642.29 cm^{-1}, symmetrical deformation of CH_2 and COH group is shown in the range between 1301.46-1414.67 cm^{-1} primary alcoholic –CH_2OH group stretching at 1026.78 cm^{-1}. It was found that all characteristics peaks of drug are present in the FTIR of mixture, so there was no interaction between locust bean gum and drug and was found to be compatible.

Evaluation of Films

The results of evaluation of F1 and F2 film compositions are shown in the (Table 4). The appearance of F1 film formulation was found to be transparent and hard on the other hand F2 formulation was found to be transparent and soft with may be due increased amount of PEG-200, weight of both the formulation was found to be uniform, thickness of both the formulations were almost comparable showing not much difference. Folding endurance of F1 formulation was found to be better than F2 formulation which may be due to oily nature of F2 formulation. Both formulations were found to be neutral. Water vapour permeability of film formulation plasticized with increased amount of PEG-200 (0.9 ml) was found. Based on *in vitro* drug released characteristics F2 formulation was selected for scanning electron microscopy. The results of scanning electron microscopy of placebo and drug loaded F2 formulations are shown in (Figure 4 a and b) which demonstrated the smooth surface without visible aggregation of drug particles indicating uniform dispersion of drug particles.

Results of *in vitro* released kinetic studies are depicted in (Table 5). The Korsmeyer-Peppas was shown to be most appropriately fit kinetic model giving R2 (correlation coefficient) value of 0.992. The value of n corresponding to 0.5<n<1.0 describes non-fickian diffusion of drug which involve a combination of both diffusion of surrounding fluid followed by erosion of polymeric matrix to release the drug. Results of stability testing of optimized film composition is shown in (Table 6 and Figure 5) which indicated that selected composition remain stable for the period of 3 months. d to be less which may be due to hydrophobic nature of PEG-200 and therefore permeability to decreases with increasing amount of plasticizer. Tensile strength of F2 formulation is more than F1 which suggests that F2 formulation has better elasticity, flexibility and can withstand more strain before rupturing which is found to be ideal for normal handling and packaging [12]. Results of *in vitro* dissolution studies as shown in (Figure 3) indicates that almost 90% and 99% drug get released from F1 and F2 formulations respectively in 30 min.

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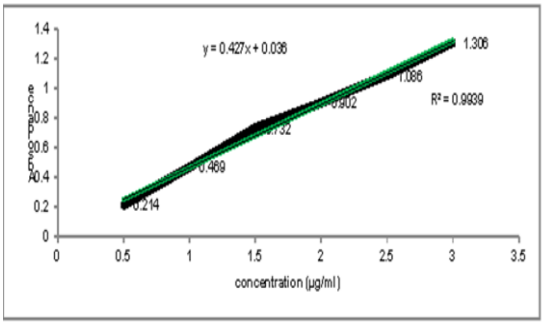
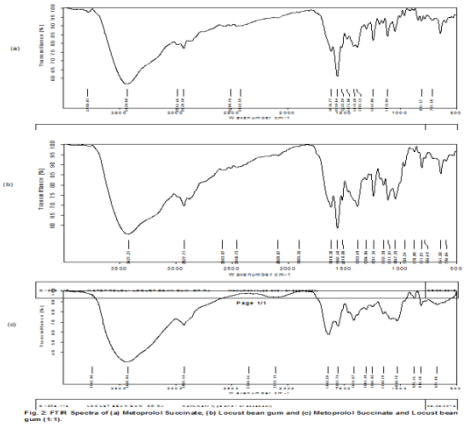


Figure 1. Standard calibration curve of metoprolol succinate

corresponding to 0.5<n<1.0 describes non-fickian diffusion of drug which involve a combination of both diffusion of surrounding fluid followed by erosion of polymeric matrix to release the drug. Results of stability testing of optimized film composition is shown in (Table 6 and Figure 5) which indicated that selected composition remain stable for the period of 3 months.



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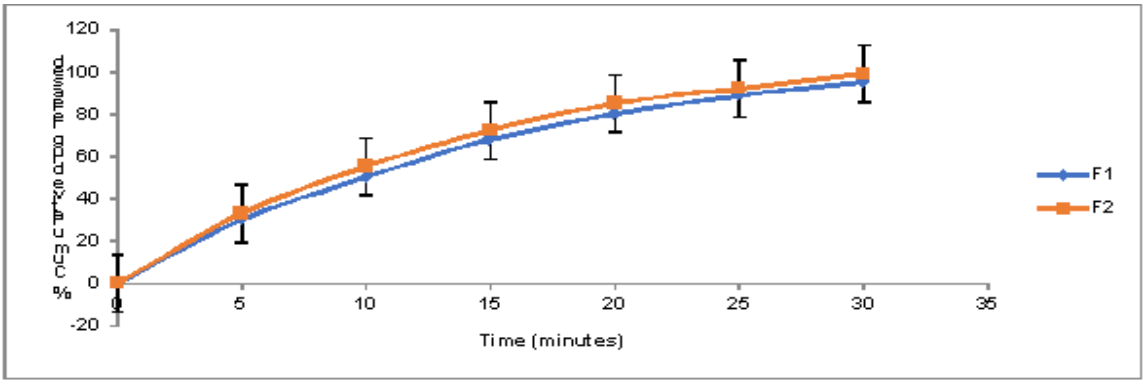

Figure 3. *In vitro* dissolution of F1 and F2 formulations in Phosphate buffer pH 6.8

Table 4 Evaluation of drug loaded F1 and F2 formulations

Parameters	**F1**	**F2**
Appearance	Transparent and oily	Transparent and clear
Thickness (mm)	0.04±0.2	0.045±0.2
Weight (mg)	32.3	33.2
Folding endurance	400	350
Surface pH	7.0	7.0
In- vitro disintegration time(sec)	24±0.34	18±0.50
Water vapour permeability ($gm^{-1}s^{-1}Pa^{-1}$)	$2.0x10^{-14}$	$1.8x10^{-14}$
Tensile strength (MPa)	12.24± 2.34	13.84±2.82
% elongation	323.2± 1.41	320.4±2.30
% drug content	98.8%	99.2%

Table 5 *In vitro* drug released kinetic studies

Formulation	**Kinetic Model**				
	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer Peppas (R^2)	Value of n
F1	0.895	0.912	0.905	0.986	0.86
F2	0.899	0.902	0.951	0.992	0.84

Table 6 Stability studies of optimized F2 film composition

Formulation	**Parameters**			
	Appearance	Disintegration Time (sec)	*In vitro* drug release	Drug content (%)
F2	clear, transparent	18.2±0.50	99.0%	99.2

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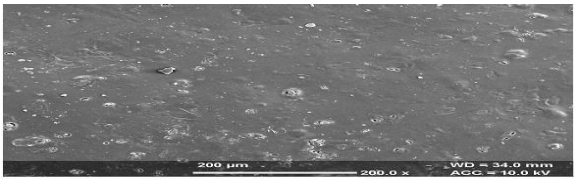
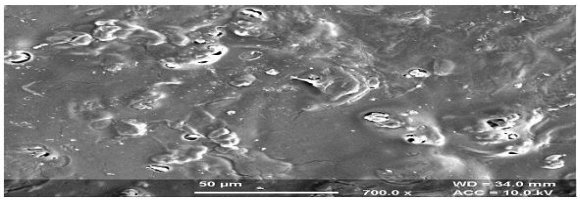
explain large numbers of abbreviations and acronyms after the conclusion part.



(a)



(b)

Figure 4. Surface morphology of (a) Placebo film and (b) Drug loaded F2 formulation

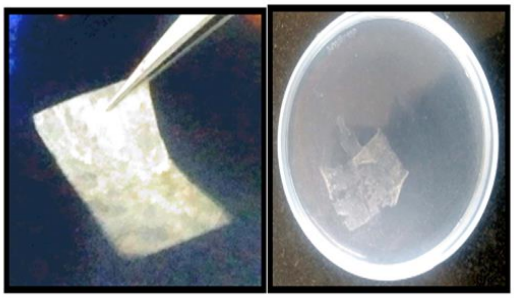


Figure 5. a) Optimized F2 film formulation. b) Disintegration of F2 formulation

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Conclusion

The research work done indicated that oral fast dissolving strips/ films of locust bean gum as natural film forming polymer are stable and can be successfully used for the development of oral fast dissolving films for the delivery of drugs in diseased conditions where fast onset of action is desirable.

Conflict of interest

The authors have no conflict of interest to proclaim.

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2. References

[1] R.P. Dixit, S.P. Puthli, Oral strip technology: overview and future potential, Journal of controlled release : official journal of the Controlled Release Society 139(2) (2009) 94-107.

[2] C. Gijare, A. Deshpande, Orodispersible Films: A Systematic Patent Review, Recent patents on drug delivery & formulation 12(2) (2018) 110-120.

[3] M. Scarpa, S. Stegemann, W.K. Hsiao, H. Pichler, S. Gaisford, M. Bresciani, A. Paudel, M. Orlu, Orodispersible films: Towards drug delivery in special populations, International journal of pharmaceutics 523(1) (2017) 327-335.

[4] E.M. Hoffmann, A. Breitenbach, J. Breitkreutz, Advances in orodispersible films for drug delivery, Expert opinion on drug delivery 8(3) (2011) 299-316.

[5] F.S. Mostafavi, R. Kadkhodaee, B. Emadzadeh, A. Koocheki, Preparation and characterization of tragacanth-locust bean gum edible blend films, Carbohydr Polym 139 (2016) 20-27.

[6] Ö.A. Bozdemir, M. Tutb_, Plasticiser Effect on Water Vapour Permeability Properties of Locust bean gum--Based Edible Films, Turkish Journal of Chemistry 27 (2003) 773-782.

[7] P. Js, Design, Evaluation and Characterization of Rapidly Dissolving Oral Strips of Metoprolol Succinate, Journal of Pharmaceutical Analytics and Insights (ISSN 2471-8122) 1 (2016).

[8] K.R.V. Kulkarni M.N, Sakarkar D.M, Development and validation of spectrophotometric method for determination of metoprolol succinate., International Journal of ChemTech Research 1(4) (2009) 1273-1277.

[9] F. Rezaee, F. Ganji, Formulation, Characterization, and Optimization of Captopril Fast-Dissolving Oral Films, AAPS PharmSciTech 19(5) (2018) 2203-2212.

[10] P. Prabhu, R. Malli, M. Koland, K. Vijaynarayana, U. D'Souza, N. Harish, C. Shastry, R. Charyulu, Formulation and evaluation of fast dissolving films of levocitirizine di hydrochloride, International journal of pharmaceutical investigation 1(2) (2011) 99-104.

[11] A. Mahesh, N. Shastri, M. Sadanandam, Development of taste masked fast disintegrating films of levocetirizine dihydrochloride for oral use, Current drug delivery 7(1) (2010) 21-7.

[12] A. Allam, G. Fetih, Sublingual fast dissolving niosomal films for enhanced bioavailability and prolonged effect of metoprolol tartrate, Drug design, development and therapy 10 (2016) 2421-33.

[13] A. Pethe, R. Desai, Formulation, optimization & evaluation of mouth dissolving film of nifedipine by using design of experiment, Asian Journal of Pharmaceutical Sciences 11 (2016) 74-76.