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Original Article

FORMULATION AND OPTIMIZATION OF NATURAL GUM BASED EXTENDED RELEASE TABLETS OF LOSARTAN USING D-OPTIMAL MIXTURE DESIGN

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ABSTRACT

Objective: Losartan potassium is one of the widely prescribed antihypertensive drugs administered orally and its extended-release tablet formulations are essentially required for the long-acting effect at reduced dosage frequency. The present research was aimed for the development and optimization of an extended-release tablet of losartan potassium, exploring natural gums, i.e., xanthan gum and guar gum as drug release modifiers.

Methods: The tablet formulation was prepared by wet granulation method and the formulation optimization was done by D-optimal mixture design using Design Expert® software. The independent variables studied were xanthan gum (X_1), guar gum (X_2) and lactose (X_3) taking various combinations of the total amount of gum and ratio of xanthan gum to guar gum under the given constraint range. The dependent (response) variables studied were % drug release in 1h (Y_1), 4h (Y_2), 7h (Y_3) and 10h (Y_4). The developed tablets were evaluated for physical properties, i.e., hardness, friability, weight variation as well as the *in vitro* drug release profiles. For optimization studies, the polynomial equations and response surface plots were generated and the optimized formulation was selected on the basis of maximum desirability value.

Results: The developed tablet formulation was found to possess all physical properties within the desired range and showed sustained release profile with ~80% drug release in 10 h duration. The model fitting studies demonstrated best fit in the zero-order model and the slope value of Korsmeyer–Peppas plot was >0.89, suggesting case II transport as a drug release mechanism.

Conclusion: The findings suggested that natural gums-based matrix tablets of losartan could be successfully developed and natural gums can be explored as platform technology as release retardants and in the development of sustained-release matrix tablets of other drugs.

Keywords: Losartan potassium, Xanthan gum, Guar gum, D-optimal mixture design, Extended-release, Matrix tablet

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INTRODUCTION

Losartan is an angiotensin II receptor antagonist used for the treatment of hypertension and diabetic nephropathy by selectively blocking the binding of angiotensin II to the AT_1 receptor [1-4]. The systemic bioavailability of losartan is ~33% showing peak concentration of losartan and its active metabolite in 1 h and 3-4 h, respectively. The terminal half-life of losartan is about 2 h and of the metabolite is about 6-9 h [1-6]. Dosage regimens of losartan are typically 25 mg to 100 mg either once or twice daily. Twice-daily dosing at 50-100 mg/day gives consistently larger trough responses than once-daily dosing at the same total dose [2]. Hence, there was an obvious need of extended-release tablet formulation of losartan in order to get a uniform effect over the entire period of 24 h and to accomplish patient compliance by eliminating the need of frequent drug administration for effective management of hypertension. However, the development of sustained-release and gastroretentive dosage form of losartan has been tried and reported for the same purpose [7, 8].

Hydrophilic matrices are the most commonly used extended-release oral solid dosage forms because of their ability to provide desired drug release profiles for a wide range of drugs, robust formulation, cost-effective manufacturing and broad regulatory acceptance of the polymers [9-11]. Gums are a type of hydrophilic matrices used for obtaining extended-release profile [12]. Xanthan gum is an extracellular polysaccharide secreted by the micro-organism *Xanthomonas campestris* and consists of D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid [13]. Xanthan gum has high drug retarding ability as compared to widely used polymer hydroxypropyl methylcellulose [14]. The drug release from xanthan gum matrices follows a zero-order model that conforms to case–II diffusion [15, 16]. Guar Gum is another gum obtained from the ground endosperms of seeds of *Cyamopsis tetragonolobus* (Linn.) [17]. It consists mainly of a high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages [18]. Recently, the potential of guar gum as an inexpensive and flexible carrier for oral extended-release tablet of diltiazem have been reported [19]. Combination of xanthan gum and guar gum was recently explored for the formulation of matrix tablets for oral controlled delivery of dipyridamole where the ratio of xanthan to gaur gum had equal or dominant role as controlling factor on the kinetics of drug release compared to content of polymer blends [20].

The computer-aided formulation optimization has been successfully employed in the development of many extended-release products of various drugs where the commonly selected independent variables are quantities of polymers or release modifiers, while the optimized responses invariably were *in vitro* dissolution profile [21-23]. Mixture designs have been widely reported for formulation optimization consisting of multiple excipients, where the characteristics of the finished product usually do not depend on the quantity of each substance but on their proportions. The sum total of the proportions of all the excipients is unity, and none of the fractions can be negative, therefore, the levels of different components can be varied with the restriction that the sum total should not exceed one. In a three-component mixture, only two-factor levels can be independently varied and the remaining factor level is chosen to complete the sum to unity [24].

In the present investigation, it was proposed to develop the extended-release tablet formulation of losartan using xanthan gum and guar gum as release controlling natural gums and formulation optimization using D-optimal mixture design to achieve the desired drug release profile by appropriate contents of natural gums.

MATERIALS AND METHODS

Materials

Losartan potassium was received as a gift sample from Zydus Cadila, Ahmedabad (India). Xanthan gum (Xantural® 75) and polyvinylpyrrolidone K30 (Kollidon®30) were received as a gift sample from Signet Chemical Corporation Pvt. Ltd. Guar gum and Lactose monohydrate were procured from Altrafine Gums, Ahmedabad (India) and SD Fine-Chem Ltd., Mumbai, (India), respectively. All other ingredients used were of analytical grade and procured from SD Fine-Chem Ltd., Mumbai (India).

Preparation of extended-release tablets

The Losartan extended-release tablets (100 mg) were prepared by wet granulation method. The weighed quantity of losartan, xanthan gum, guar gum and lactose monohydrate were sifted through a 60-mesh sieve. The ingredients were mixed by the geometric dilution technique. After blending, granulation was done using a sufficient quantity of 5% polyvinylpyrrolidone solution prepared in isopropyl alcohol. The wet mass was first passed through a 12-mesh sieve and then granules were dried in an oven at 40 °C for 90 min. Then the granules were passed through a 25-mesh sieve. Finally the granules were lubricated with 1% magnesium stearate, 1% talc and 1% aerosil by blending for 3 min. The granulation blend of the extended release tablet was compressed into tablets by using 10 mm circular die and punches on a rotary tablet compression machine (Karnavati).

Optimization study using DoE (Design of experiments)

The formulation optimization was done by D-optimal mixture design using Design-Expert software, selecting three independent and four dependent variables. The amount of xanthan gum (A), guar gum (B) and lactose (C) were selected as the independent variables along with the constraints imposed on the sum total of all independent variables, on the total amount of gum and on the ratio of the gums. The response variables selected were percent release at 1 h (Y_1), 4 h (Y_2), 7 h (Y_3) and 10 h (Y_4). The independent variables along with the constraints and dependent variables, along with the criteria set for numerical optimization, are shown in table 1.

Table 1: Variables in D-optimal mixture design for losartan 100 mg tablet formulation

Independent variable	Lower limit (mg)	Upper limit (mg)
A: Xanthan Gum (X_1)	1.950	16.250
B: Guar Gum (X_2)	4.875	26.0
C: Lactose (X_3)	179.75	202.5
Constraints Set for the independent variables		
9.75 ≤	Xanthan Gum+Guar Gum	≤ 32.5
0.25 ≤	Xanthan Gum/Guar Gum	≤ 1
Xanthan Gum+Guar Gum+Lactose = 212.250		
Dependent variables with their criteria for optimization		
Percent release in 1 h (Y_1)	10-12	
Percent release in 4 h (Y_2)	38-40	
Percent release in 7 h (Y_3)	62-64	
Percent release in 10 h (Y_4)	80-84	

As suggested by the optimization software, the formulations of sixteen batches were prepared and their respective effects (i.e., response) were determined. The values of factors (independent variable) for sixteen batches as suggested are tabulated in table 2.

Table 2: Formulation factors (independent variables) of optimization batches

Formulation code	A: xanthan gum (X_1) mg	B: guargum (X_2) mg	C: lactose (X_3) mg
LOT-1	11.375	21.125	179.750
LOT-2	6.134	9.303	196.813
LOT-3	11.822	14.991	185.438
LOT-4	6.947	19.866	185.438
LOT-5	7.394	13.731	191.125
LOT-6	1.950	7.800	202.500
LOT-7	4.875	4.875	202.500
LOT-8	7.394	13.731	191.125
LOT-9	6.500	26.000	179.750
LOT-10	10.563	10.563	191.125
LOT-11	7.394	13.731	191.125
LOT-12	7.394	13.731	191.125
LOT-13	6.500	26.000	179.750
LOT-14	7.394	13.731	191.125
LOT-15	16.250	16.250	179.750
LOT-16	4.225	16.900	191.125

Evaluation of the developed tablets

Tablets were evaluated for the hardness using digital hardness tester (Erweka), friability using Roche friabilator (Electrolab) and weight variation using electronic balance (Shimadzu). The drug content of the tablets was also determined in methanol using Waters HPLC system. The column used was octadecyl silane chemically bonded to silica microparticles (3 to 10 µm) and the mobile phase was 0.1% phosphoric acid: acetonitrile (3:2). The flow rate was kept at 1 ml/min and the injection volume was 20µl [25, 26].

In vitro drug release study of optimization batches

Drug release from extended release tablet was determined by using dissolution test (USP Type II) apparatus (Electrolab). The dissolution study for first two hours was carried out in hydrochloric acid buffer pH 1.2 and then after two hours pH 1.2 buffer was replaced by pH 6.8 phosphate buffer. Tablets were placed in the 900 ml of dissolution media and the rotation of the paddle was fixed at 50 rpm. 10 ml aliquots of dissolution media were withdrawn at suitable time intervals and replaced with same volume of fresh dissolution media after each withdrawal. Aliquots collected were

diluted if required, filtered through Whatman grade filter 41 and then the absorbance of the samples was measured in the first derivative UV spectra at 234 nm using UV spectrophotometer (Shimadzu® UV-1700). The cumulative % drug release was calculated for all the batches.

Prediction of the optimum formulation

In order to obtain the optimized formulation, the numerical optimization technique was used and on the basis of the criteria set for dependent variables and the responses of the optimization batches the software gave three formulations with desirability close to 1. The formulation with maximum desirability was selected as the optimum formulation. For validation three batches of selected optimum formula were prepared. The tablets were then evaluated for weight variation, friability, hardness, drug content, swelling index and *in vitro* release profile. The comparison of the responses of the optimized batch suggested by the software with the responses of the validation batches was done.

Model fitting of the drug release data

The drug release data of the three validation batches was fitted into various mathematical models and the regression coefficients were determined. The slope of the Korsmeyer Peppas model was also determined in order to determine the possible release mechanism [27-29].

Determination of swelling index

Tablets from each batch were soaked individually in 50 ml of pH 1.2 hydrochloric acid buffer for first two hours followed by pH 6.8 phosphate buffer for next 8 h. Then after the intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h the tablets were removed and the excess media on their surfaces was carefully absorbed using a tissue paper. The percent increase in the weight of the original tablet was calculated (swelling index) and taken as a measure of the water uptake of the matrix.

$$S.I. = \frac{(W_t - W_0)}{W_0} \times 100$$

Where W_t is tablet weight at various time intervals and W_0 is initial weight of tablet [30].

RESULTS AND DISCUSSION

Observations of optimization studies

The hardness of various tablet formulation batches prepared in optimization studies (LOT-1 to LOT-16) was found to be 6 to 8 kg/cm^2 and friability of these respective tablet batches ranged from 0.57% and 0.89% (average 0.68%). The tablet weight of these optimization batches varied between 312.17 and 332.16 mg (average 322.96 mg) and the drug content was found between 96.56% and 102.14% (average 98.87%). The % cumulative drug release of the optimization batches was also studied over the period of 10 h and was found in the range of 68.25% to 96.72%. The detailed data of % cumulative drug release is shown in table 3.

Table 3: Observed response variables of optimization batches

Formulation code	% Drug release at the different time interval			
	1 h (Y_1)	4 h (Y_2)	7 h (Y_3)	10 h (Y_4)
LOT-1	8.12	30.14	52.68	70.24
LOT-2	12.23	48.13	79.32	96.72
LOT-3	8.56	33.19	59.65	79.18
LOT-4	8.99	37.23	62.28	82.05
LOT-5	10.14	39.94	64.23	84.95
LOT-6	13.68	62.14	96.98	93.79
LOT-7	12.94	52.20	94.26	94.99
LOT-8	9.85	40.56	63.64	82.67
LOT-9	8.41	30.25	53.92	71.82
LOT-10	9.13	36.78	61.14	81.18
LOT-11	9.99	40.19	65.11	85.42
LOT-12	10.65	37.96	64.05	83.29
LOT-13	8.05	28.19	54.33	72.83
LOT-14	10.16	41.23	63.19	83.27
LOT-15	7.39	28.88	51.75	68.25
LOT-16	11.01	40.1	65.12	85.36

Response surface analysis for various responses

The design was evaluated by a Scheffe's quadratic model. The equation representing the model is given below.

$$Y = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3$$

Where Y is the measured response associated with each factor level combination, β_1, β_2 and β_3 are coefficients of the factors and β_{12}, β_{13} and β_{23} are coefficients of the interaction terms of factors. The table 3 shows the observed responses of various optimization batches. The drug release in 1 h ranged from 7.39% to 13.68%, release in 4 h ranged from 28.19% to 62.14%, release in 7 h from 51.75% to 96.98% and release in 10 h ranged from 68.25% to 96.72%.

All the responses were fitted into various models i.e., first order, second order, quadratic and cubic models and the model with highest regression coefficient was selected for the responses. On the basis of R^2value amongst the responses, release in 1 h and 10 h followed linear model and release in 4 h and 7 h followed quadratic model. In case of release in 4 h, only linear terms of quadratic polynomial equation were found to be significant and in case of release in 7 h linear terms along with β_{23} were found to be significant. Therefore model reduction was done in case of release in 4 h and release in 7 h to improve the model. The coefficients of polynomial equations generated using software and the respective R^2values for various responses are listed in table 4.

Table 4: Polynomial coefficient values for response variables

Coefficient code	Polynomial coefficient values for response variables			
	Y_1	Y_2	Y_3	Y_4
β_1	-0.25888	-8.24695	-10.49607	-0.83574
β_2	-0.12099	-3.51762	-8.93956	-0.48418
β_3	+0.072865	+0.37128	+0.64940	+0.50735
β_{23}	-	-	-0.061085	-
R^2	0.9515	0.9758	0.9810	0.9187

In case of polynomial equation the positive value suggest that the increase in factor favours the response while the negative value suggests an inverse relationship between the factor and response. The presence of more than one-factor term in polynomial equation suggests the presence of interaction and quadratic effects. This also means that the relationship between response and factor is not linear. The effect of factors and their interactions on the response variables can be analyzed in a better way with the help of two-component mix graphs, contour plots and the response surface plots. The two component mix graphs are shown in fig. 1 and the response surface plots are shown in fig. 2.

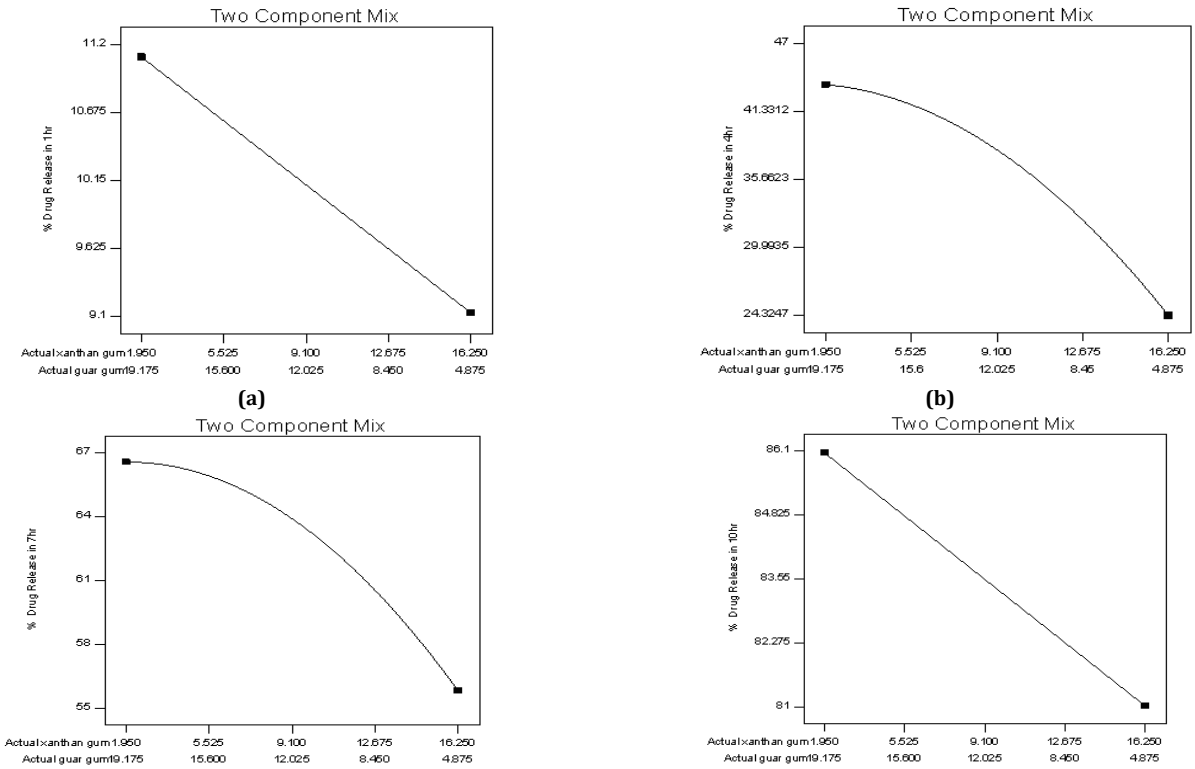

Fig. 1: Two component mix graph showing the effect of xanthan gum and guar gum on (a) % drug release in 1 h (b) % drug release in 4 h (c) % drug release in 7 h (d) % drug release in 10 h

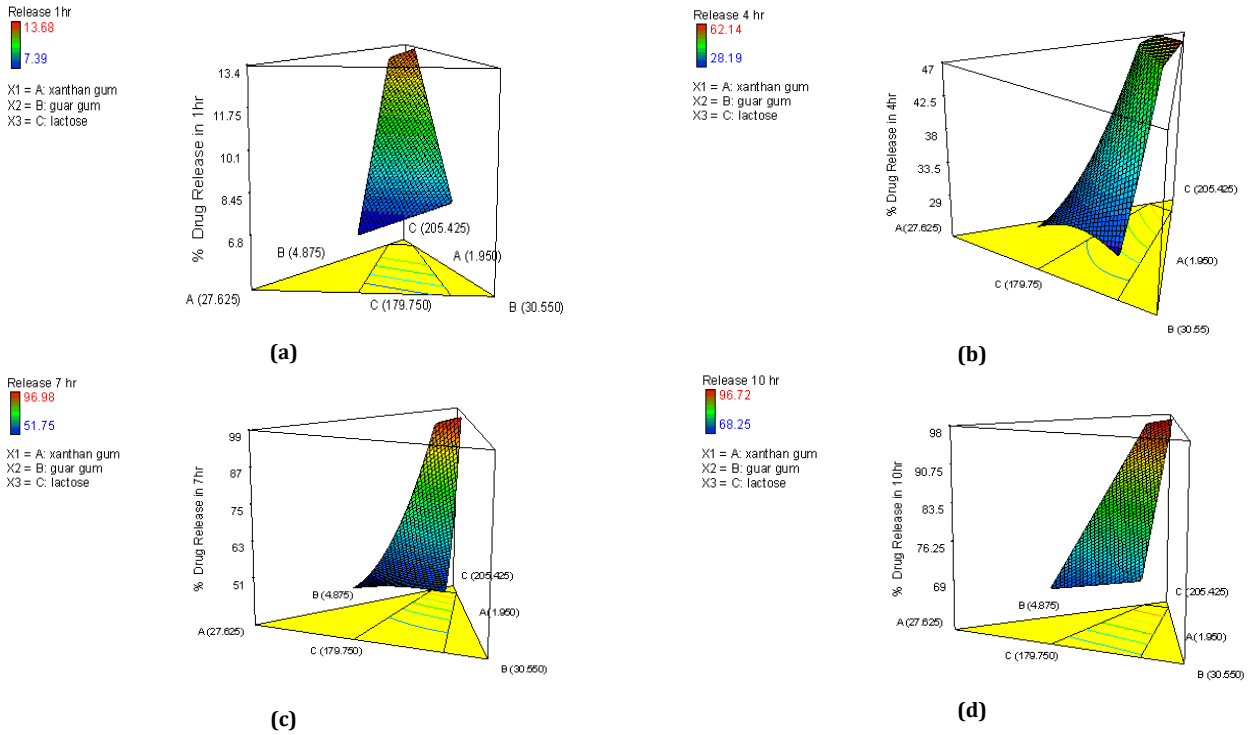

Fig. 2: Response surface plot showing the effect of xanthan gum, guar gum and lactose on (a) % drug release in 1 h (b) % drug release in 4 h (c) % drug release in 7 h (d) % drug release in 10 h

These plots clearly show the linear relationship between factors and release in 1 h and release in 10 h and non-linear relationship between factors and release in 4 h and 7 h. The two-component mix graph and response surface plot showed a decreasing trend in the value of percent drug release in 1 h, 4 h, 7 h and 10 h with an increase in the amount of xanthan gum and guar gum and an increasing trend with an increase in the amount of lactose. Since effect of xanthan gum is more prominent than guar gum and lactose, therefore, on replacing xanthan gum by guar gum (keeping lactose constant), the release increases.

Selection and validation of predicted optimum formulation

The numerical optimization was performed according to the criteria set for the responses, as shown in table 1. The software suggested three solutions out of which the solution with maximum desirability was selected. The selected formulation had a desirability value equal to 0.923 and consisted of 9.242 mg of xanthan gum, 11.740 mg of guar gum and 191.27 mg of lactose. Three batches of the optimum formulation were prepared and were evaluated for various physical parameters and the set responses. The average hardness, friability, tablet weight, and drug content of tablet formulations of optimized validation batches were found to be 6 kg/cm^2, 0.63 %, 323.18 mg, and 99.17%, respectively. Thus all the physical parameters of the optimized validation batches were found to be practically within control. The comparison of the responses, i.e., % drug release of the optimized batch suggested by the software with the responses of the validation batches, is shown in table 5.

Table 5: Responses of the validation batches

Response	Predicted by software	Observed in optimized formulation batches		
		LT-1	LT-2	LT-3
% drug release in 1 h (Y_1)	10.12	9.46	10.23	9.88
% drug release in 4 h (Y_2)	38.0	38.75	37.83	38.05
% drug release in 7 h (Y_3)	64.0	63.54	64.72	63.19
% drug release in 10 h (Y_4)	83.63	83.51	84.34	84.92

Comparison of the observed and software predicted responses showed a good correlation between the observed and predicted values. The drug release profile of optimized validation batches is shown in fig. 3.

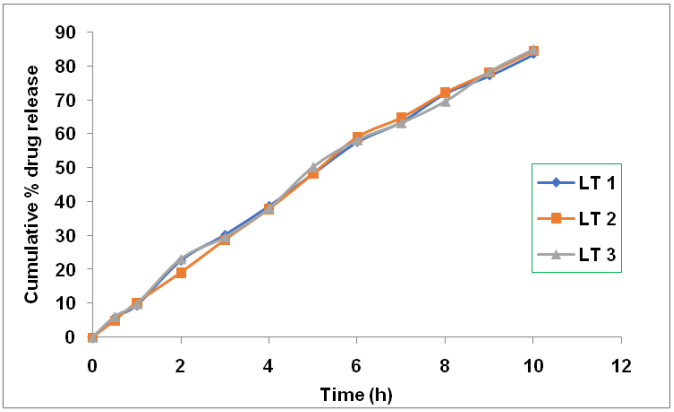

Fig. 3: Drug release profile of the optimized validation batches of losartan tablets

Model fitting of the drug release data

The regression coefficients for various models along with the slope of Korsmeyer–Peppas model is shown in table 6. The regression coefficients for various plots of all the validation batches suggested that the release data showed best fit in zero-order model. In the Korsmeyer-Peppas equation the value of slope for all three batches was found to be above 0.89 which suggests that case-II transport is the mechanism of drug release. Case II transport follows zero order release kinetics. Thus, according to the Korsmeyer-Peppas equation also the release data follows zero-order kinetics.

Table 6: Model fitting of drug release data

Validation batches	Regression coefficients of various models			Slope of korsmeyer peppas
	First order ln m = kt	Higuchi m_0-m = $kt^{1/2}$	Zero order m_0-m = kt	log (m_0-m) = log K+n log t
LT-1	0.9773	0.9589	0.9918	0.9087
LT-2	0.9746	0.9509	0.9931	0.9519
LT-3	0.9662	0.9573	0.9917	0.8969

Swelling index of an optimized batch of tablets

The variation of swelling index of optimized tablet batches is shown in fig. 4. The tablets showed smaller swelling index in the first two hours because xanthan gum swells to a lesser extent in the acidic media and guar gum, being highly swellable polymer allows faster penetration of dissolution medium, which is responsible for the release of drug in the first two hours. The swelling index was found to be higher in the later hours when media was changed to pH 6.8. In pH 6.8 buffer, xanthan gum shows prominent swelling along with the guar gum leading to sustained release throughout the period of next 6 h. This swelling accounts for the drug released in 4 h and 7 h. Thereafter the swelling index reduced because the increase in weight was compensated by erosion. The tablet starts eroding after the period of 8 h and this probably accounts for the release of the drug in the last two hours. The photographs of the swelling study of the optimized formulation are shown in fig. 5.

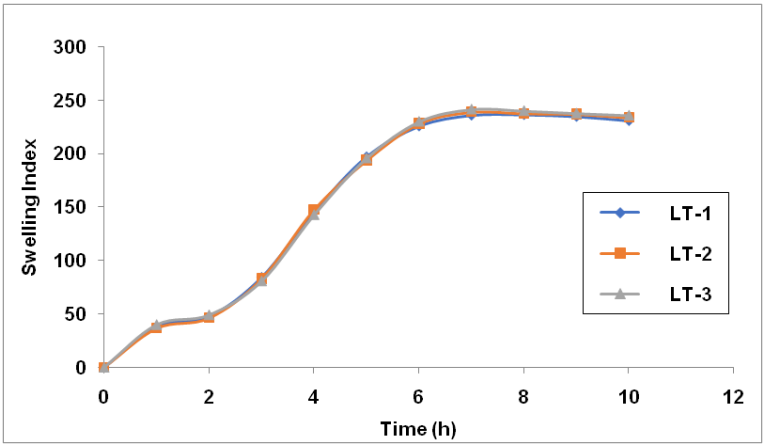

Fig. 4: Swelling index v/s time plot for optimized validation batches of losartan tablets

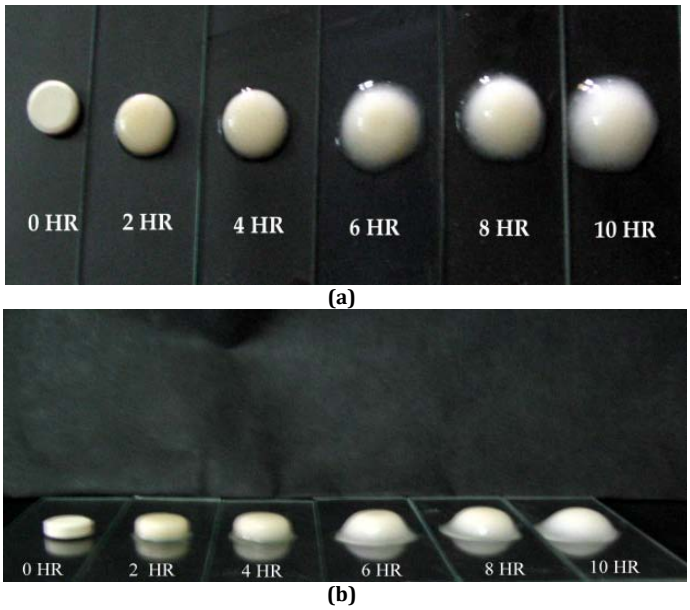

Fig. 5: Swelling of the tablets at different time intervals (a) Top view (b) Side view

The high swelling capacity of xanthan gum helped in sustaining the drug release in later hours. Though the xanthan gum and guar gum individually have already been investigated earlier in matrix tablet formulation for sustained drug release [31], in the present work combination of these two gums was explored for sustained release of losartan potassium from matrix tablet as both the gums had their own effect on release kinetics. Resultantly, the combination of gums showed desired sustained drug release profile.

CONCLUSION

The extended-release tablet formulation of losartan was successfully prepared using xanthan gum and guar gum and the drug release profile of losartan from the tablet was optimized using a D-optimal mixture design. The polynomial equations and response surface plots helped in understanding the effect of gums on the drug release profile. The validation of the optimization methodology was done by formulating three batches and determining their responses. The model fitting of the release profile suggested that the release profile showed the best fit in the zero-order model, and Korsmeyer–Peppas plot suggested case-II transport as the probable release mechanism of losartan. According to the swelling study, the desired release profile was the result of the swelling and erosion process. Thus, the combination of natural gums like xanthan gum and guar gum can be used in order to obtain the desired drug release profile and the optimization of these polymers to obtain the desired drug release profile can be successfully done by optimization techniques.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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