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Research

Formulation, Optimization And Evaluation Of Novel Biomaterial As A Sustained Release Excipient

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Abstract:

Natural materials have been gaining lot of interest in the field of drug delivery because they are readily available, cost effective, eco-friendly, capable of multitude of chemical modifications, potentially degradable and compatible due to their natural origin. The present study was an attempt to evaluate the natural *Samanea saman* seed gum (SSSG) as a novel persistent release excipient in tablet dosage form. The gum powder was evaluated for different physicochemical properties as per Indian Pharmacopoeia standards. The water uptake study was performed by capillary method, surface morphology and crystallinity of gum was studied by using scanning electron microscopy (SEM) and X-Ray diffraction (XRD) respectively and drug-excipient interaction was studied by FTIR. Matrix tablets of Valsartan, as model drug, were formulated by wet granulation method. PEG 4000 was used as pore former in combination with SSSG for the controlling drug release profile. A 3^2 full factorial design was applied with SSSG and PEG 4000 as independent variables while the percent drug released in 12 hrs and the time required for a given 50% of drug to be released (t_{50}%) were selected as dependent variables. The developed matrix tablets were evaluated for post compression and in-vitro drug release kinetics and all results passed as per IP standards. All the formulations developed were found to follow zero order drug release kinetics. The drug release retardation was observed with an increase in the SSSG concentration and decreased concentration of PEG 4000. The similarity factor (f2) was calculated for optimized batch considering mean in vitro drug release data of marketed Valsartan SR tablet as a reference standard. It is concluded that the desired drug release pattern can be obtained by using optimized combination of SSSG and PEG 4000.

INTRODUCTION

Over the last few decades the field of drug delivery has grown and progressed at remarkable rate. The scientific field of drug delivery is highly interdisciplinary. The rapid advances made in the design and developments of new drug delivery systems were fueled predominantly by advances made in polymer chemistry. On the other hand, the obvious need to find a new material for the growing research effort in drug delivery provided the force for the development of a wide range of new polymers. Continued improvement and accelerating research and development in polymeric materials has played a vital role in the progress of most controlled release technologies. In the past several years, there has been considerable increase in interest in these technologies, as it is shown by the increasing number of publications and patents in the field of controlled drug release systems using synthetic as well as naturally occurring polymeric materials (1).

Plant products can serve as an alternative to synthetic products. Herbs are non polluting renewable resources for sustainable supplies of cheaper pharmaceutical products. Today we have a number of plant based pharmaceutical excipients like natural gums. Natural materials have been gaining lot of interest in the field of drug delivery because they are readily available, cost effective, eco-friendly, capable of multitude of chemical modifications, potentially degradable under natural or physiological conditions and compatible due to their natural origin (2). A number of researchers have explored utility of plant based materials as an emulsifying, suspending, binding, disintegrating agent and as sustained release and controlled release matrix tablets (3-10) by the pharmaceutical industry. Past research have studied and acknowledged various natural gums like agar, konjac, guar gum, chitosan, xanthan gum, sodium alginate and locust bean gum for potential pharmaceutical and biomedical applications.

Samanea saman (Jacq) Merr is a large umbraculiform tree growing over 20 meters height with a stout trunk about 1.5 meters in diameter, and with a large spreading canopy providing shade. Alkaloids are said to be abundant in the barks, stems, leaves, and seeds. Leaves and stems have Saponin and tannin; gum is present in the trunk. Additionally steroids, cardiac glycosides, terpenoids are also present in the plant. Samanea saman seed gum (SSSG) mainly composed of polysaccharide containing galactomannan (4:1 ratio) of D-mannose to D-galactose. The galactomannan composed of 1,4 linked β-D-mannose, 1,4,6 linked β-D-

mannose and terminal α-D-galactose (11). SSSG showed the hydrocolloid type of nature which hydrates on contact with water. During earlier study, the binding and hydrocolloid properties of SSSG were evaluated. (12, 13). In the present study, an effort has been made to evaluate SSSG, a natural material, as a sustained release matrix forming agent in tablet formulations.

Valsartan inhibits angiotensin II receptors, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow. It is used orally for the treatment of hypertension and has a low bioavailability of 23%, because of its poor absorption in the lower gastrointestinal tract. It undergoes little or no hepatic metabolism and its elimination half-life is 6 hrs. Therefore, it was selected as a suitable drug candidate to design sustain release matrix tablet with a view to improve its oral bioavailability and to achieve a subsequent reduction in its dosage and dosing frequency. (13,14)

MATERIALS AND METHODS

Materials

Valsartan was procured from Indoco Remedies Ltd, Navi Mumbai, as a gift sample. Legumes of Samanea saman were gathered from Nasik, Maharashtra. All other chemicals such as dicalcium phosphate, magnesium stearate, hydrochloric acid, disodium hydrogen phosphate and potassium dihydrogen phosphate, used for the preparation of tablets and their analysis were of analytical grade and obtained from Loba chemie., Mumbai, India. Valstan SR tablets was procured from local pharmacy.

Isolation and purification of gum from seeds

The gum extraction process from Samanea saman pod seeds involved stirring seed powder in water using a mechanical stirrer at 60°C for 4 hr, followed by overnight soaking. The resulting solution underwent filtration, and the filtrate was subjected to ethanol treatment to precipitate the gum. To ensure that any remaining ethanol was removed, the dried gum was further dried in an oven at 40ºC for three to 4 hr after being ground into a powder using a mortar and pestle.(6,7)

Physicochemical evaluation of Samanea saman gum

The macroscopic studies were carried out for organoleptic properties like color, odor and taste of the Samanea saman gum. Gum was evaluated for solubility, loss on drying for moisture content evaluation, total ash and acid insoluble ash determination, pH determination, swelling index and viscosity. The dried purified gum was used for the identification of different phytoconstituents like alkaloids, phenolic, flavonoids, proteins,

Tablet 1: Compositions of Preliminary trial sustained release matrix tablets of Valsartan

Ingredients (mg)	**Batch code**							
	A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**
Valsartan	100	100	100	100	100	100	100	100
DCP	123	111.75	100.5	89.25	78	82.5	80.25	78
SSSG (%)	11.25 (5%)	22.5 (10%)	33.75 (15%)	45 (20%)	56.25 (25%)	45 (20%)	45 (20%)	45 (20%)
PEG 4000	-	-	-	-	-	6.75 (3%)	9 (4%)	11.25 (5%)
PVP(K-30)	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25
Magnesium stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Talc	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

amino acids, saponins, and carbohydrates by using different qualitative chemical tests. (11-13)

Characterization of Natural gum as Polymer (SSSG)

The isolated mucilage was characterized for solubility, moisture content, limit test, Angle of repose, bulk density, tapped density, Carr's index, Hausner ratio, photomicroscopic study, FTIR, X- ray diffraction, swelling index, water retention capacity, viscosity measurement, water sorption capacity, hydration capacity and melting point as per the standard procedures (15-17).

Preparation of Valsartan Matrix Tablet

Matrix tablets of Valsartan were prepared by wet granulation method as per formula given in Table 1. Initially all the ingredients along with the drug were weighed accurately and were passed through 60# sieve. The ingredients and the drug were then mixed in a mortar by geometric progression for a period of 10-15 mins. Distilled water was used as a granulating agent. The wet granules were dried at 50°C for 3 h. the dried granules were passed through 20# sieve and lubricated using magnesium stearate (1%, w/w) and talc (1%, w/w). The resultant granules were compressed in Karnavati tableting machine using 10 mm biconvex punches (18,19). The total weight of the tablet was 250 mg.

Factorial Design (20-23)

A 3^2 full factorial design was constructed where the amounts of SSSG (X1) and PEG 4000 (X2) were selected as the independent variables i.e. factors. The levels of these factors were selected on the basis of initial studies and observations. All the other formulation aspects and processing variables were kept invariant throughout the study period. The data was analyzed using Design Expert Software 13.

Table 2 summarizes the translation of the coded levels to the experimental units used in the study and tablet 3 summarizes the experiment runs and their factor combinations used

Independent Variables:

X1 = SSSG

X2 = PEG 4000

Dependent Variables

Y1 = Release after 12 hours

Y2 = T_{50}%

Table 2: Translation of the coded levels in actual units.

Coded levels	Actual value in %	
	X_1	X_2
-1	15	3
0	20	4
+1	25	5

Tablet 3: 3^2 full factorial design layout, experimental runs and their combinations

Sr. No.	Trial	Coded factor Levels with combinations	
		X_1	X_2
1	F1	-1	-1
2	F2	0	-1
3	F3	+1	-1
4	F4	-1	0
5	F5	0	0
6	F6	+1	0
7	F7	-1	+1
8	F8	0	+1
9	F9	+1	+1

Evaluation of sustained release matrix tablets of Valsartan (13,14,23-27)

The prepared matrix tablets were evaluated for thickness, weight variation, content uniformity, hardness, and friability as per the standard procedures.

Thickness and Diameter: Thickness and diameter of ten tablets were measured using digital Vernier caliper, and the average was calculated.

Uniformity of Weight: Twenty tablets of each batch were weighed individually using electronic balance, and standard deviation was calculated.

Hardness: Tablet hardness was measured using a simple Monsanto hardness tester.

Friability: In this test 20 tablets were weighed and placed in a Roche Friabilator, and then the tablets were subjected to rolling and repeated shocks, resulting from free falls within the apparatus from the height of 6 inches. After 100 revolutions the tablets were removed, de-dusted and weighed again. The friability was calculated as the percentage weight loss.

Uniformity of Content: Previously weighed 20 valsartan tablets were powdered. 5mg equivalent Valsartan tablet powder was dispersed phosphate buffer pH 6.8 and sonicated. The drug content was determined by UV spectrophotometrically.

***In-vitro* drug release study**

USP apparatus II was used to determine in vitro drug release study. The variables maintained are 50 rpm and temperature 37±5ºC. Dissolution media used was 0.1 N HCl (pH 1.2) for an initial 2 h and then phosphate buffer (pH 6.8). The samples were withdraw at one hour interval and analyzed UV spectrophotometrically. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally. The release study was performed in triplicate.

***In-vitro* Drug Release Kinetics**

In order to study the exact mechanism of drug release from the matrix tablets, drug release data was analyzed according to Zero order, First order, Matrix and Korsmeyer Peppas kinetic equation. One of the model-independent approaches to compare dissolution data is similarity factor (f2) and difference factor (f1). The f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between releases profiles increases. Acceptable values are $50 \leq f_2 \leq 100$, which is considered equivalent to a difference in approximately 10 % between the dissolution profiles being compared. If f_2 is greater than 50 it is considered that 2 products share similar drug release behaviors. (28,29)

$$f_2 = 50\ log\left\{\left[1+\frac{1}{n}\sum_{n=1}^{n} W_t\ (R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where, n = number of pull points

W_t= Optional weight factor

R_t= Reference profile at time point t

T_t= Test profile at same time point

RESULTS AND DISCUSSION

Characterization of the Polymer (SSSG)

SSSG comprises of pale white and odorless powder, which hydrate rapidly on contact with water. The powder forms colloidal solution in water and insoluble in alcohol, chloroform. The SSSG showed a loss on drying of 3.2% (w/w), Total ash value 7.5 % w/w, Acid insoluble ash 1.4 % w/w value and heavy metal content all were within official limits. The pH of 1% w/v dispersion of the gum in water was 7.1 which found to be in the neutral

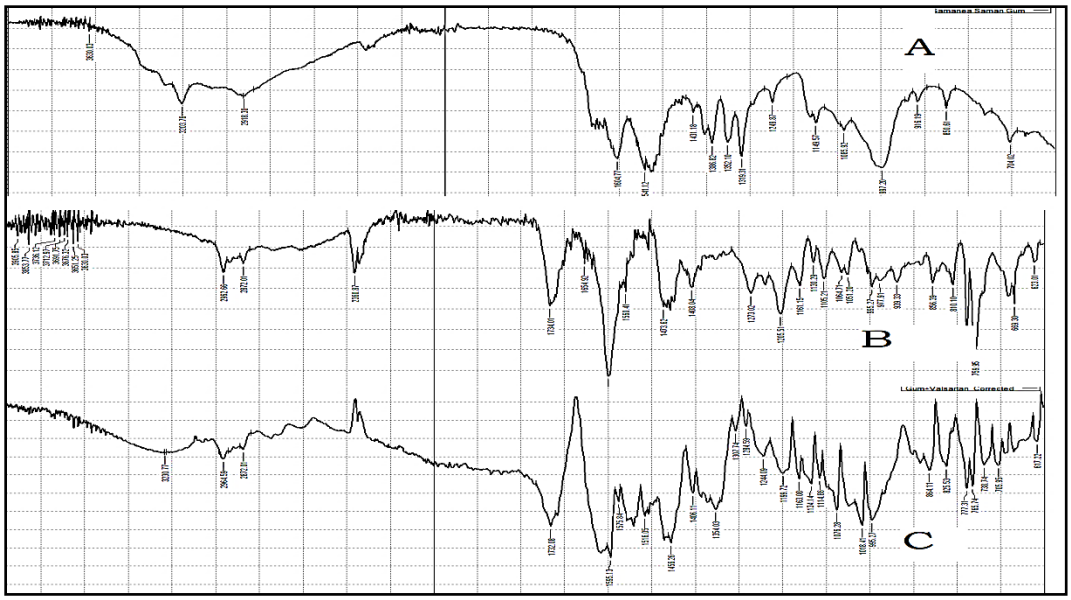

Figure 1: FTIR Spectra of SSSG (A), Valsartan (B) and Valsartan matrix tablet (C)

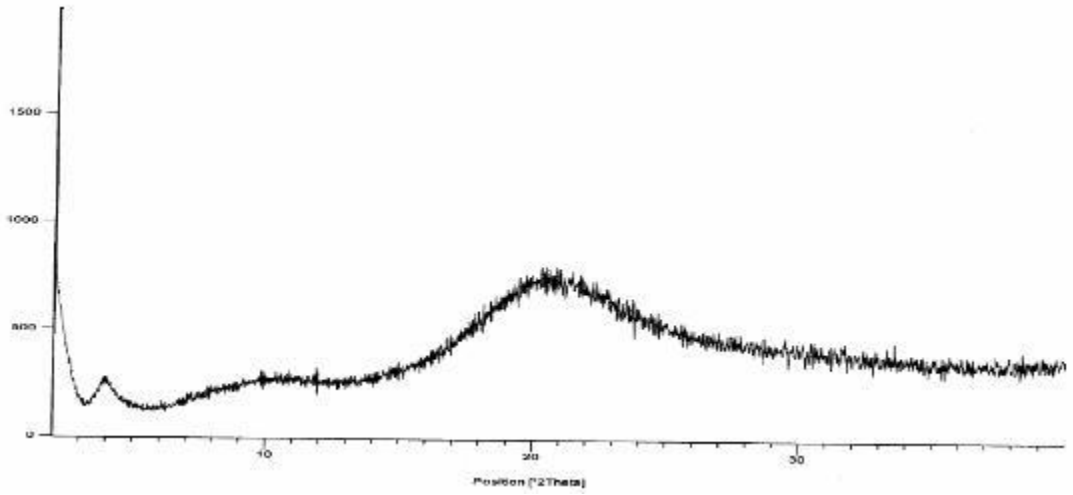

Figure 2: X-Ray diffraction pattern of SSSG

range. The bulk density, tapped density, Carr's index, and Hausner ratio of the SSSG were 0.4861 g/cm^3, 0.623 g/cm3, 25.12 and 1.33 respectively. The Carr's index and Hausner's ratio indicated that SSSG powder is having good flow property and compressibility. The angle of repose was found to be in between 25-30°, indicated that the powder is having good flow property. The swelling index of SSSG was found to be 7.5. The viscosity of 1 % (w/v) dispersion of the SSSG was found to be 16.451 Pas at 25 ^{0}C as determined by Brookfield viscometer. Melting point of SSSG was measured; and it was found that the material showed charring instead of melting in the range of 116-118 ^{0}C.

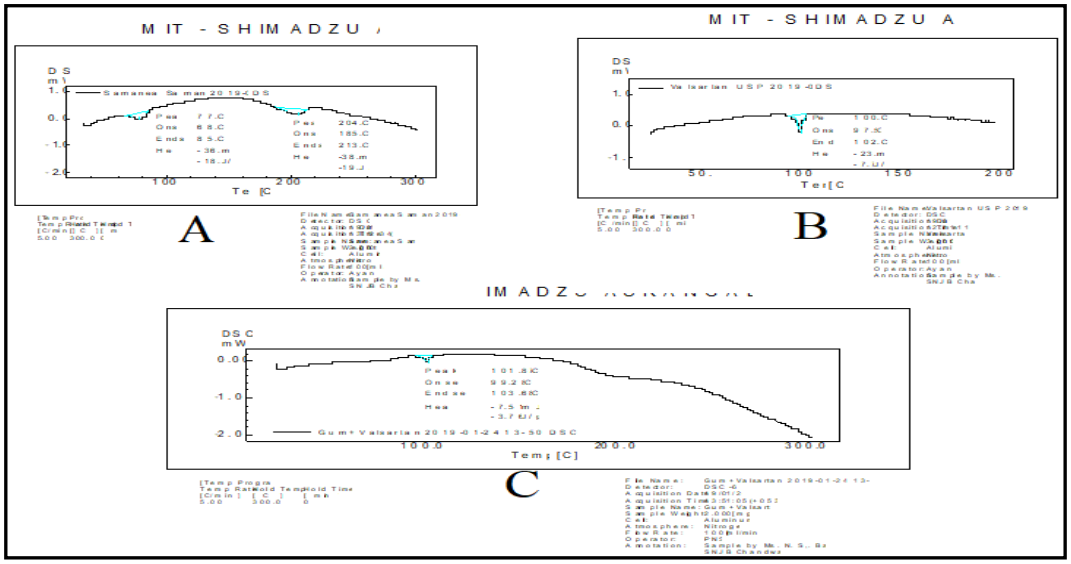

Figure 3: DSC of SSSG (A), Valsartan (B) and Valsartan matrix tablet

Table 4: Evaluation Preliminary trial Valsartan matrix tablets (A1-A8)

Batch code	Uniformity of Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Uniformity of Content (%)
A1	305.85±5.5	3.96±0.052	8.12±0.52	0.308	99.01
A2	306.1±3.6	4.02±0.047	7.61±0.18	0.283	98.76
A3	302.3±4.5	3.99±0.050	7.60±0.55	0.198	98.56
A4	302.25±4.2	3.98±0.052	8.36±0.50	0.206	98.70
A5	299.9±3.8	3.93±0.052	7.42±0.32	0.234	101.22
A6	296.4±2.6	3.92±0.042	7.85±0.42	0.244	98.85
A7	300.3±4.6	3.96±0.052	7.83±0.24	0.265	100.34
A8	302.2±3.7	3.98±0.041	8.66±0.08	0.309	99.04

All values are expressed as mean± SD, n=3

FTIR spectroscopy of SSSG, Valsartan and formulation:

In the FTIR study (Figure 1), the characteristic peaks of N-H stretching, phenyl group, azo group, and N-N bending of the pure drug were almost identical with that physical mixture of drug and excipients which indicates the absence of any drug polymer interaction.

X-Ray Diffraction of SSSG:

The X-ray diffraction pattern of the SSSG is shown in Figure 2 of the polymer has shown peaks with low intensity which confirms the amorphous nature of the polymer.

DSC of SSSG, Valsartan and formulation:

In the DSC study (Figure 3), at 100.0 °C endothermic peak for valsartan was obtained, same also observed in a physical mixture of drug and excipients. Therefore DSC data proved that Valsartan and polymers are compatible with each other.

Physicochemical characterization of tablets

The prepared sustain release matrix tablets were evaluated for various parameters. Table 4 showed the results of the evaluation parameters with their standard deviation values.

The tablets evaluated showed the weight variation within ±5% and thus passes the test. Thickness of tablet was in the range of 3.92-4.02 mm. Hardness of tablets was in the range of 7-9 kg/cm^2. Percent weight loss in friability test was found to be less than 0.4% in all the batches. Content uniformity was found within 100 ±2% of the 50 mg of Valsartan.

***In-vitro* drug release profiles:**

Figure 4 shows % drug release of formulation A1-A8 containing SSSG concentration range of 5-25% and PEG 4000 concentration range of 3-5%. As drug had a half-life of 6-7 hrs, for its once daily formulation, hence sustain release was desired for at least 12 hrs. From table and figure it was observed that the formulations with SSSG showed a much more sustain release of the drug. Total amount of drug release from the formulation A3 & A4 up to 10hrs ranged between 50-70%. Other formulations, A1 & A2 indicating complete drug release within 10 hrs at low concentrations of SSSG and A5 indicating incomplete drug release at high concentrations of SSSG. This may be due to the viscosity of

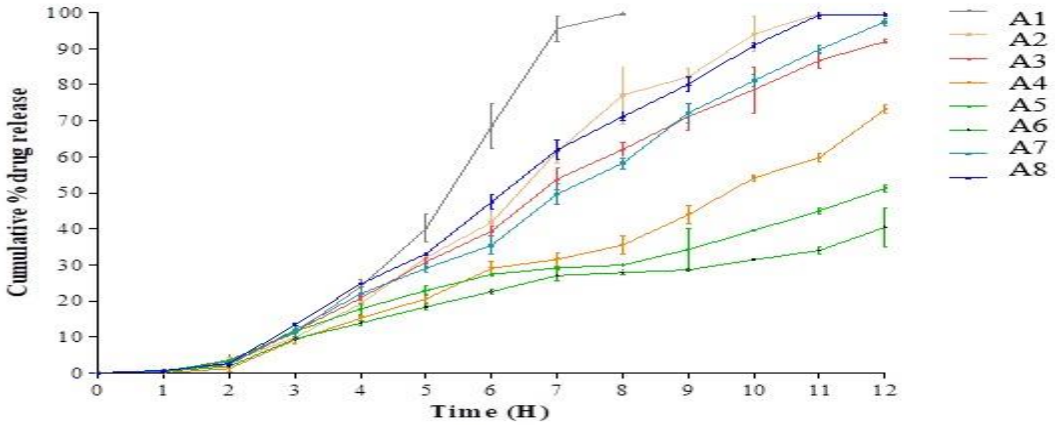

Figure 4: The dissolution profile of matrix tablets (A1-A8) of Valsartan matrix tablet.

polymer present in tablet increases with increase in the hydrogel (SSSG) concentration thus limiting the release of active ingredient. Also with fact that further increase in polymer amount, thicker gel forms inhibiting dissolution medium penetration strongly resulting in significant reduction in release value. For the improvement of drug release, PEG 4000 was added as channeling agent for the A6-A8 formulations. The result showed that there is significant increased in the drug release. As the amount of PEG 4000 (channeling agent) increased in the formulation % cumulative release of the drug increased. From this we can conclude that SSSG is the release controlling agent and PEG 4000 is release improving (channeling) agent. Formulation A4 formulation showed approximate 70% release in 12 hrs., whereas A5 showed 52% of drug release with 20 and 25 % concentration of SSSG gum respectively. Hence further PEG 4000 added in formulations as channeling agent 3, 4 and 5% respectively marked as A6, A7 and A8 code. Further based on in vitro drug release data batch A7 with 20% SSSG and 4% PEG 4000 was selected for optimization.

Factorial Design

In order to control of drug release in 12 hours combination of SSSG polymer and PEG 4000 were used. Preliminary studies indicated that this combination shows the good improvement in drug release. In order to study the influence of combination of two factors on the overall

Table 5: Evaluation data for matrix tablets for formulations F1-F9

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content Uniformity (%)
F1	225.2 ± 4.20	4.08 ± 0.46	7.3 ± 0.36	0.33	99.22
F2	226.66 ± 4.68	3.98 ± 0.057	9.4 ± 0.38	0.46	98.76
F3	224.25 ± 3.52	3.96 ± 0.040	7.5 ± 0.34	0.36	96.77
F4	227.13 ± 3.24	4.08 ± 0.042	8.2 ± 0.46	0.20	99.42
F5	225.9 ± 4.86	4.02 ± 0.046	7.4 ± 0.35	0.45	99.32
F6	225.32 ± 5.6	3.98 ± 0.048	7.5 ± 0.30	0.36	100.45
F7	228.4 ± 3.69	3.96 ± 0.050	8.2 ± 0.22	0.50	99.39
F8	224.6 ± 5.70	3.98 ± 0.041	8.3 ± 0.78	0.52	98.43
F9	229.47 ± 4.38	3.92 ± 0.053	7.8 ± 0.35	0.40	99.78

drug release and to obtain the optimum formulation 3^2 full factorial designs was used. The two factors were the concentration of SSSG and pore forming agent PEG 4000, with 3 levels of it. The obtained tablets were evaluated for various parameters. Table 5 gives the results of the evaluation parameters with their standard deviation values.

The tablets evaluated showed the weight variation within ±7.5% and thus passes the test. Thickness of tablet was in the range of 3.92 to 4.08 mm. Hardness of tablets was in the range of 7.4 to 8.3 kg/cm^2. Percent weight loss in the friability test was found to be less than 0.52 % in all the batches. Content uniformity was found within 100 ±2% of the 50 mg of Valsartan.

***In-vitro* drug release profiles**

The result shows that less % drug released during first 2 h in 0.1 N HCl. Valsartan is a weakly acidic drug with pKa of 4.37; as a result, it is practically insoluble in acidic solution. Thus, the lower solubility of Valsartan in 0.1 N HCl accounted for its less % release of the drug. It can be observed from the result that, as the proportion of polymer in tablets increased from the 15 to 25%, there was a decrease in the release rate, and release of Valsartan was extended with 99% and 60% of the drug getting released from the tablets of batches F1 and F9, respectively. Earlier studies have also reported the decrease in the release rate of drug with increase in the proportion of matrix polymer. The decrease in the release rate of drug from the matrix tablets with increase in the polymer proportion can be attributed to increase in the gel strength and to the formation of gel layer with longer path of diffusion, resulting in reduction of diffusion coefficient of the drug. As the total percentage of matrixing system increased in the formulations, more controlled release effect was observed for formulations F1-F9 retarded the drug release. Formulations with more amount of PEG 4000 showed lesser hardness in the formulation, resulting in lesser sustaining effect. Also formulations with more amount of SSSG showed more hardness in the formulation, resulting in good sustaining effect. From this we can conclude that SSSG is the release controlling agent and PEG 4000 is the channeling agent and both are required in optimum amount to attain the predetermined release profile of the drug from matrix tablet.

SSSG used release controlling agent in the matrix formulations and. As the amount of the PEG 4000 increased in the formulation, there was a remarkable increase in % cumulative release of Valsartan from the formulations.

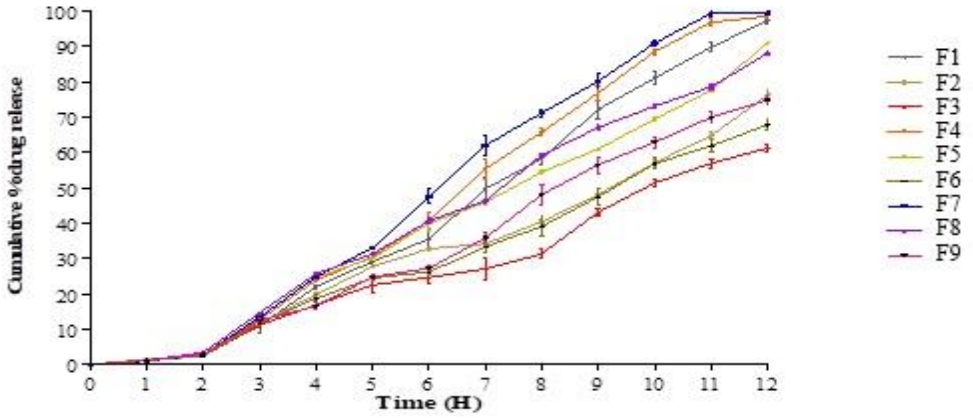

Figure 5: The dissolution profile of matrix tablets (D1-D9) of Valsartan.

Table 6: The dissolution models for matrix tablets (F1-F9) of Valsartan

Formulation code	R^2				n
	Zero order	First order	Higuchi	Korsmeyer Peppas	Korsmeyer Peppas
F1	0.982	0.776	0.936	0.964	1.28
F2	0.979	0.890	0.948	0.928	1.32
F3	0.973	0.932	0.945	0.963	1.29
F4	0.982	0.778	0.962	0.944	1.38
F5	0.987	0.848	0.937	0.929	1.40
F6	0.986	0.952	0.949	0.904	1.46
F7	0.980	0.742	0.966	0.972	1.28
F8	0.992	0.909	0.980	0.965	1.42
F9	0.983	0.926	0.932	0.978	1.39

The release kinetics of the matrices is shown in Table 6. The best fit model representing the mechanism of drug release from the matrices was of zero order. This is further confirmed by Korsmeyer–Peppas model, the value of n is greater than 1 showing case II drug release or anomalous drug release, indicating that two or more mechanisms for drug release are involved, that is, diffusion, erosion, and chain relaxation.

It is evident that the initial drug release from matrices containing SSSG is because of erosion, but after sometime, the matrices begin to swell causing water uptake leading to formation of fronts and decreased erosion that leads to decreased release rate. But, in this

study, use of PEG 4000 helped in maintaining a balance between matrix swelling and erosion as PEG 4000 is highly soluble and is greatly susceptible to disintegration. This helped in maintaining the zero order release throughout the experiment showing time-independent release profile, which can be clearly depicted from Figure 5. The combination of both can lead to control of drug release producing greater therapeutic effects with minimum side effects.

Optimization data analysis ***(***21-23***)***

polymer and channelling agent. A 3^2 full factorial design was constructed where the amounts of SSSG (X_1) and PEG 4000 (X_2) were selected as the independent variables i.e. factors. The levels of these factors were selected on the basis of initial studies and observations. All the other formulation aspects and processing variables were kept invariant throughout the study period. Polynomial models including interaction and quadratic terms were generated for the entire response variables using multiple linear regression

Table 7: Layout of Design Actual.

Std	Run	Factor 1 A: Gum (SSSG)	Factor 2 B: PEG 4000	Response 1 Q_{12} (%)	Response 2 T_{50} (Hr)
2	1	20.00	3.00	76.226	9.3
7	2	15.00	5.00	97.896	6.26
5	3	20.00	4.00	90.988	7.32
9	4	25.00	5.00	74.764	8.20
6	5	25.00	4.00	67.833	9.28
1	6	15.00	3.00	97.507	6.76
4	7	15.00	4.00	98.838	6.58
8	8	20.00	5.00	88.426	7.30
3	9	25.00	3.00	61.523	9.81

Various computations for the current optimization study were performed using Design Expert® software (Design Expert trial version 13.0; State-Ease Inc., USA). A two factor three level full factorial design was used for systemic study of combination of natural

analysis (MLRA) approach. The general form of the MLRA model is represented in the Equation

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where Y is the dependent variable; b_0 is the arithmetic average of all the quantitative outcomes of nine runs. b_1, b_2, b_{12} are the estimated coefficients computed from the observed experimental response values of Y and X_1 and X_2 are the coded levels of the independent variables. The interaction term (X_1X_2) shows how the response values change when two factors are simultaneously changed. The polynomial terms (X_1^2, X_2^2) are included to investigate nonlinearity.

The polynomial equations can be used to draw conclusion after considering the magnitude coefficient and the mathematical sign that the coefficient carries. A high positive or negative value in the equation represent that by making a minor change in the setting of that factor one may obtain a significant change in the dependent variable.

Statistical validity of the polynomials was established on the basis of analysis of variance (ANOVA) provision in the Design Expert software. Level of significance was considered at $p < 0.05$. The best-fitting mathematical model was selected based on the comparison of several statistical parameters, including the coefficient of variation (CV), the multiple correlation coefficient(R^2), the adjusted multiple correlation coefficient (adjusted R^2), and the predicted residual sum of squares (PRESS), provided by the software. PRESS indicates how well the model fits the data, and for the chosen model, it should be small relative to the other models under consideration. The 3-D response surface graphs and the 2-D contour plots were also generated by the Design Expert® software. These plots are very useful to see interaction effects of the factors on responses. Subsequently, the desirability approach was used to generate the optimum settings for the formulations.

Linear model:

$$Y = b_0 + b_1X_1 + b_2X_2 \quad \ldots\ldots (2)$$

2FI (interaction) model:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 \quad \ldots (3)$$

Full and Reduced Model assessment for the dependent variables:

The ranges of responses Y_1 and Y_2 were 63.20–98.78% and 6.20–9.86 hrs, respectively. All the responses observed for nine formulations prepared were fitted to various models using Design Expert software. It was observed that the best-fitted models were linear. The values of R^2, adjusted R^2, predicted R^2, SD and %CV are given in Table 8, along with the regression equation generated for each response.

Table 8: Summary of results of regression analysis for responses Y_1 and Y_2

Models	R^2	Adjusted (R^2)	Predicted (R^2)	SD	% CV
Response (Y_1) Linear model	0.9389	0.9152	0.8455	4.36	5.22
Response (Y_2) Linear model	0.9419	0.9192	0.8565	0.41	4.97

Table 9: Analysis of variance for response Y_1 (Q_{12}).

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Significance
Model	1476.49	2	738.31	40.02	0.0004	S
X_1-Gum(SSSG)	1362301	1	1359.24	72.42	0.0001	S
X_2-PEG 4000	113.58	1	132.87	6.02	0.0501	NS
Residual	113.78	6	18.96			-
Cor Total	1584.41	8				-

*S indicates significant #NS indicates non-significant

A) Model for Q_{12}:

Model equation

$Q_{12} = 126.65243 - 3.01231X_1 + 4.32875X_2$ ……(4)

Statistical validation of the polynomial equations generated by Design Expert and estimation of significance of the models was established on the basis of analysis of variance provision of the software as shown in Table 9.

The Model F-value of 40.02 implies the model is significant. There is only a 0.04% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In Table 9, p values for response Y_1 (Q_{12}) represent that the linear contribution (X_1) is significant model term and the linear contribution (X_2) is non-significant model term. The values obtained for main effects of both the independent variables from Equation 4 indicate that SSSG has greater but negative effect on the response Y_1(Q_{12}), confirming the release rate retarding ability of SSSG. From the Figure 6 and 7 of the response curve of Q_{12} for matrix system, it is observed that as the concentration of SSSG in the formulation increases from -1 level (15%) to 0(20%) and +1 level(25%), Q_{12} of Diclofenac decreases significantly. On the other hand, the PEG 4000 has a comparatively greater but positive influence on the response Y_1 (Q_{12}), showing the rapidly dissolving feature of the PEG 4000

Table 10: Analysis of variance for response Y_2 (T_{50} %).

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Significance
Model	12.46	2	6.22	39.83	0.0003	S
X_1-Gum(SSSG)	9.32	1	9.34	62.35	0.0002	S
X_2-PEG 4000	3.14	1	3.08	21.06	0.003	S
Residual	0.92	6	0.16			-
Cor Total	12.98	8				-

*S indicates significant #NS indicates non-significant

facilitating the drug release through the tablet matrices.

A) Model for* T_{50}*:

Model equation

T_{50} =5.76866 +0.2510 X_1 - 0.72800 X2 …….. (5)

Statistical validation of the polynomial equations generated by Design Expert and estimation of significance of the models was established on the basis of analysis of variance provision of the software as shown in Table 9.

The Model F-value of 41.03 implies the model is significant. There is only a 0.03% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.05 indicate model terms are significant. In Table, P-values for response Y_2 (T_{50}) represent that the linear contributions (X_1 and X_2) significant model terms, represented in Table by S. Values greater than 0.1000 indicate the model terms are not significant. Values greater than 0.1000 indicate the model terms are not significant.

The values obtained for main effects of both the independent variables from Equation 5 indicate that SSSG has positive effect on the response Y_2 (T_{50}), confirming the release rate retarding ability of SSSG. From the Figure 6 and VII of the response curve of T_{50} for matrix system, it is observed that as the concentration of SSSG in the formulation increases from -1 level (15%)to 0(20%) and +1 level(25%), T_{50} i.e. time required for 50% of drug release (Valsartan) increases significantly. On the other hand, the PEG 4000 has a comparatively greater but negative influence on the response Y_2 (T_{50}), showing the pore forming ability and facilitating the drug release through the tablet matrices. The effect of PEG 4000 was thrice time greater but opposite effect than SSSG on the T_{50}. From the Figure of the response curve of T_{50} for matrix system, it is observed that as the concentration of PEG 4000 in the formulation increases from -1 level (3%) to 0

(4%) and +1 level (5%), T_{50} i.e. time required for 50% of drug release (Valsartan) decreases significantly.

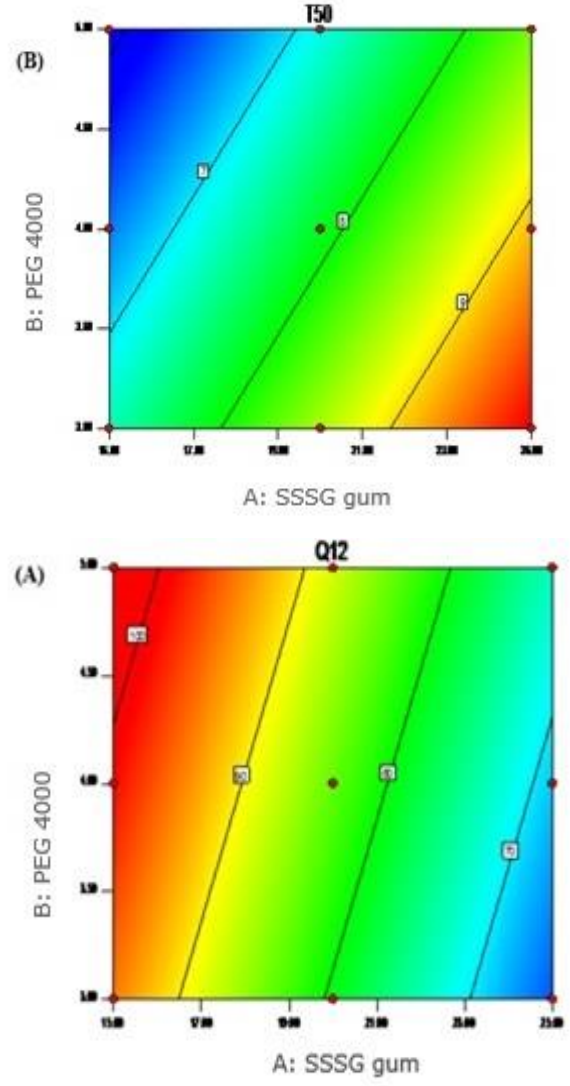

Figure 6: 2D Contour plot for Q_{12} and T_{50} for matrix system

VALIDATION OF OPTIMUM FORMULATIONS:

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent

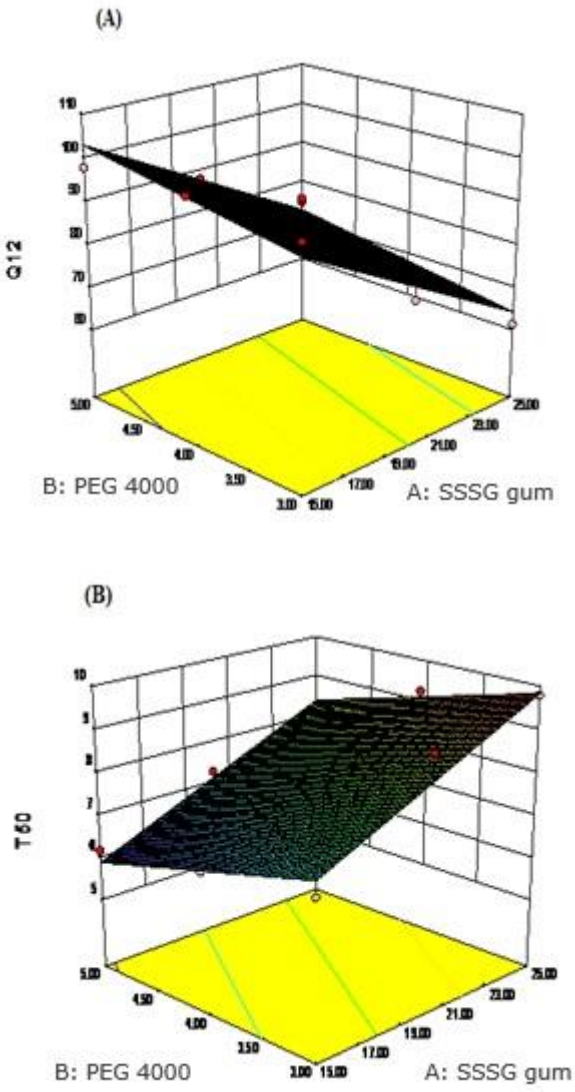

Figure 7: 3D response curve of Q12 and T50 for matrix system

(response) variables Y_1 and Y_2. The optimum formulation was selected based on the criteria of attaining the maximum value of Q_{12} and minimum value of T_{50} %.

Table 11: Predicted and observed response variables of the Valsartan matrix tablet.

Responses	Formulation	Predicted Value	Observed value	Prediction error* (%)
Y_1	F_1	96.91	93.45	-3.03
	F_2	75.82	80.14	4.17
	F_3	63.02	63.83	5.08
	F_4	98.67	97.78	-0.20
	F_5	91.04	86.06	-7.98
	F_6	68.28	70.06	1.20
	F_7	97.78	99.11	5.36
	F_8	88.22	87.04	-0.011
	F_9	75.36	74.98	-2.49
Y_2	F_1	6.54	5.84	5.15
	F_2	9.14	8.59	-6.63
	F_3	9.18	9.83	0.51
	F_4	6.00	6.62	0.60
	F_5	7.41	7.87	6.63
	F_6	9.85	9.11	-1.51
	F_7	6.63	5.90	-4.53
	F_8	6.98	7.15	-1.78
	F_9	7.88	8.39	2.56

* Prediction error (%) = (Observed value- Predicted value)/Predicted value*100.

Y_1 and Y_2 are drug release in 12 hrs and time required for 50% drug release, respectively. The result in Table 11 illustrates the comparison between the observed and predicted values of both the responses Y_1 and Y_2 for all the formulations presented. It can be seen that in all cases there was a reasonable agreement between the predicted and the experimental values, as prediction error was found to vary between 7.98% and 0.011%. For this reason it can be concluded that equations describe adequately influence of the selected independent variables on responses under study. This indicates that the optimization technique was appropriate for optimizing matrix tablet formulation. The linear correlation plots drawn between the predicted and experimental values for all the batches of the tablets are shown in Figure 8, which demonstrated high values of R^2 (0.929 and

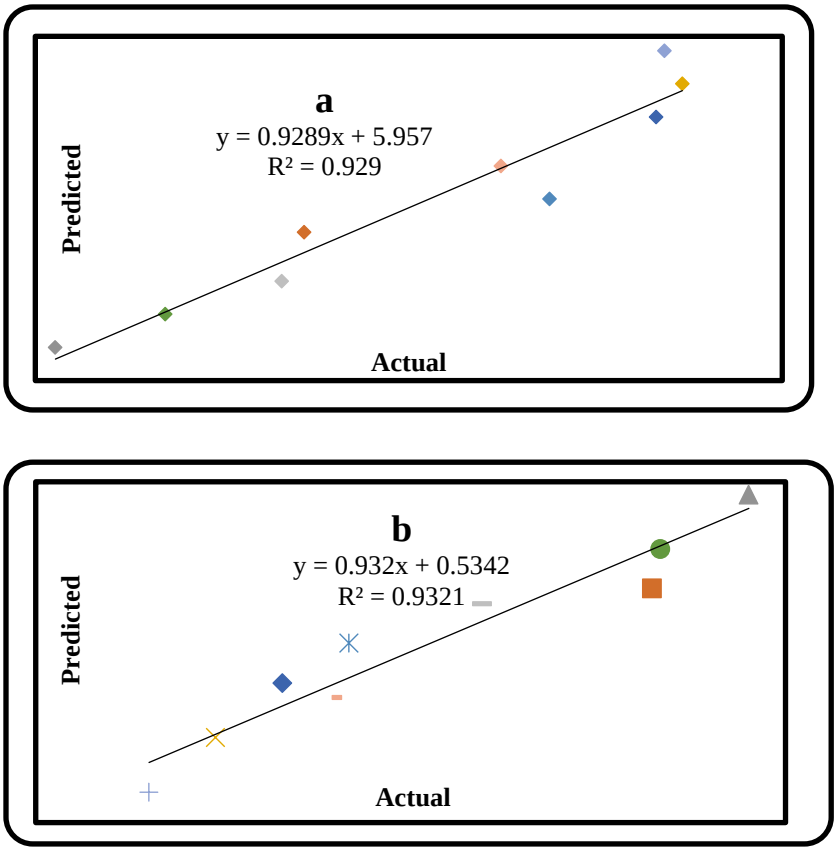

Figure 8: Correlation between actual and predicted values for (a) Q_{12} and (b) T_{50}%.

0.932). Thus, the low magnitudes of error as well as the values of R^2 in the present investigation prove the high prognostic ability of the optimization technique by factorial design.

Optimization of the formulation

Optimization of formulation was done on the basis of results obtained in the above formulation and required drug release. The optimized batch (V1) was having the composition containing SSSG (17.56%) and PEG 4000 (3.88 %) which showed a good desired release patterns.

The tablets evaluated showed the weight variation within limit and thus passes the test. Thickness of tablet was in the range of 3.95-4.08 mm. Hardness of tablets was in the range of 7-9 kg/cm^2. Percent weight loss in the friability test was found to be less than 0.4%. Content uniformity was found within 100 ±1% of the 50 mg of Valsartan.

Comparison of optimized formulation with marketed Formulation:

Optimized formulation V1 was compared with marketed formulation (Valstan SR). The f_2 value of marketed formulation and optimized formulation V1 was found to be 62.36 which indicate that the release profile of optimized formulation is close to similar that of the marketed tablet as shown in figure 9.

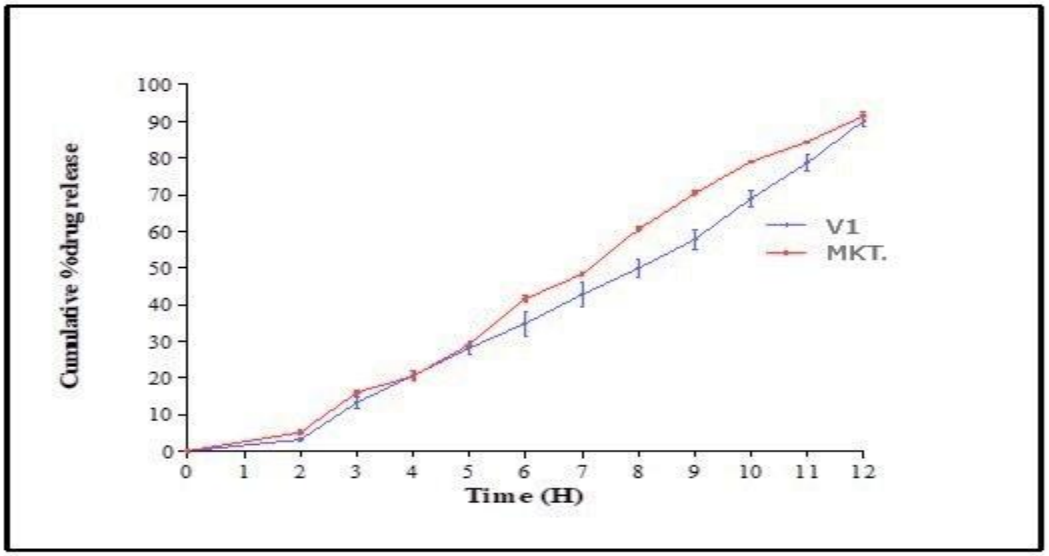

Figure 9: Dissolution profile of marketed and optimized formulation

CONCLUSION:

The present study, sustained release matrix tablets were prepared by using SSSG, to evaluate the *Samanea saman* seed gum as a natural sustained release excipient in matrix tablet dosage form. For the study purpose, Valsartan was selected as the model drug. Optimization studies with 3^2 full factorial design were carried out using SSSG (X_1) and PEG (X2) as variable factors and by keeping both constant which were selected based on preliminary trials. From the mathematical models generated, an optimal formulation comprising of SSSG (17.56%) and PEG 4000 (3.88 %) was identified to provide desired values for percentage drug released at a 12 hr (90.26%) and the time required for a given percentage of drug to be released ($t_{50\%}$) (7.5 hrs.). Both the factors were found to significantly affect the drug release from the matrix tablets. Sustained drug release following zero-order kinetics and showed the case II drug release or anomalous drug release, indicating that two or more mechanisms for drug release are involved, that is, diffusion, erosion, and chain relaxation. The f_2 value of the marketed sample (Valstan SR) and optimized formulation V_1 was found to be 62.36, which indicate that the release profile of optimized formulation is similar to that of the marketed tablet. The matrix tablets of Valsartan can be successfully used as sustained release oral drug delivery system. FTIR studies suggest the absence of any significant interaction between the polymers and the drug in the formulation. The above study suggests that the SSSG has good release retardant property in tablet formulation. In combination with channeling agent PEG 4000 it showed the good release properties. The

gum might be useful for producing matrix forming agent for sustained drug delivery in tablet formulations for other drugs too.

Declaration of interest: The authors report no conflicts of interest.

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