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Formulation, Evaluation and Optimization of Tamarind seed polysaccharide based Glipizide Sustained Release Matrix Tablets by 3^2 Full Factorial Design

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Abstract: The present study was undertaken to assess the potential of Tamarind seed polysaccharide (TSP) to act as a matrix former in sustained release matrix tablets of Glipizide. The polysaccharide was isolated and confirmed by phytochemical analysis. The drug and isolated polysaccharide was found to be compatible as confirmed by IR spectral studies and Differential Scanning Calorimetry. The TSP powder was evaluated for its micromeritic properties viz. Bulk density, Tapped density, Angle of repose, Hausner's ratio, Carr's index and the results indicated good flow properties. The isolated polysaccharide was also evaluated for various physicochemical properties such as solubility, swelling index, melting point and viscosity. The optimized sustained release dosage form of Glipizide with TSP was prepared and evaluated using Response Surface Methodology by employing a 3^2 full factorial design. Independent variables studied were concentration of TSP (X1) and type of diluents (Lactose, Starch and MCC) (X2). The dependent variables were percentage drug release at 4h (Q4), 8h (Q8) and swelling index (SI). The formulated tablets were found to have better uniformity of weight and the drug content with low SD values. The *in vitro* drug dissolution study was carried out using USP 22 apparatus II, paddle method and the release mechanisms were explored. The release data was incorporated into various mathematical models and the drug release mechanism of formulations was found to be non Fickian diffusion. Polynomial equations and response surface plots were generated for all dependent variables. It was observed that all the factors had significant contribution on all dependent variables. *In vitro* drug release study was compared with the commercial Glynase XL tablets using the similarity factor (f2). The dissolution study proved that dried Tamarind seed polysaccharide can be used as a matrix forming material for making once daily Sustained release matrix tablets of Glipizide.
Key words: Tamarind seed polysaccharide, sustained release, 3^2 full factorial design, response surface methodology, similarity factor.

Introduction

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration which leads to highest level of patient compliance. Conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [1]. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/ or targeting the delivery of the drug to a tissue. Such dosage form not only increase patient compliance due to reduction in frequency of dosing, but they also

reduce the severity and frequency of side effects, as they maintain substantially constant blood levels and avoid fluctuations associated with the conventional immediate release formulations . Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional system. Among different dosage forms, matrix tablets are widely accepted for oral sustained release [2]. Matrix tablets may be defined as the, oral solid dosage form in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serve as release rate retardants. Matrix tablets release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms [3]. In recent years considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. The drug release from such hydrophilic matrices can be controlled through their physical properties. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are nontoxic and acceptable by the regulating authorities. The various polysaccharides used in drug delivery application are Cellulose ethers [4], Xanthan gum [5], Scleroglucan [6], Locust bean gum [7] and Guar gum [8]. Recently the use of biopolymers derived from agricultural feed stocks has attracted the attention of many researchers for various biomedical applications.

One such cheap and agro-based biomaterial is Tamarind Seed Polysaccharide (TSP) obtained from tamarind seed. TSP is a natural polysaccharide obtained from the seed kernel of *Tamarindus indica* family Leguminoseae. It is a branched polysaccharide with a main chain of β-D-(1,4)- linked glucopyranosyl units, and a side chain of single D-xylopyranosyl unit attached to every second, third, and fourth D-glucopyranosyl unit through an α-D-(1,6) linkage. One D- xylopyranosyl is attached to xylopyranosyl units through a β-D-(1, 2) linkage with a molecular weight of 52350 daltons [9, 10]. It possesses properties like high viscosity, broad pH tolerance and adhesivity [11]. This led to its application as stabilizer, thickener, gelling agent and binder in food and pharmaceutical industries. In addition to these, other important properties of TSP have been identified recently. They include non-carcinogenicity [12], mucoadhesivity, biocompatibility [13], high drug holding capacity [14] and high thermal stability [15]. This led to its application as excipient in hydrophilic drug delivery system [13-14]. The model drug chosen to assess the release behaviour was Glipizide that is BCS class-II drug, with low aqueous solubility and high permeability. Glipizide, is an effective oral antidiabetic (100 times more potent than Tolbutamide in evoking pancreatic secretion of insulin [16,17] requires controlled release formulation owing to its short biological half-life [18] of 3.4 ± 0.7 h and is rapidly eliminated. Hence sustained release formulation is needed for Glipizide for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficiency, to reduce G.I disturbances and to enhance patient compliance. A few controlled release formulations of glipizide are available commercially.

Material and Methods:

Tamarind kernel powder was obtained as gift sample from Meckoni Impex, Surat, Gujarat. Glipizide was obtained as gift sample from Horizon Bioceuticals Pvt. Ltd. Magnesium Stearate, Lactose, Starch and Microcrystalline cellulose (MCC) were purchased from CDH (P) Ltd, New Delhi, India. Absolute ethanol was purchased from Merck Ltd., India. All the chemicals used were of A.R grade.

Isolation of TSP

The isolation of TSP was carried out by method reported earlier [11]. To 20 g of tamarind kernel powder, 200 ml of cold distilled water was added to prepare slurry. The slurry was then poured into 800ml boiling distilled water. The solution was boiled for 20 minutes with continuous stirring. The resulting clear solution was kept overnight so that most of the fibers settle down. The solution was then centrifuged at 5000 rpm for 20 min. The supernatant solution was separated and poured into twice the volume of absolute ethanol by continuous stirring to obtain the precipitate. The precipitate was collected and washed twice with absolute ethanol and dried at room temperature for 2 days. The dried product was grounded and passed through BSS # 60 and stored in dessicator till further use.

Evaluation of isolated TSP powder

1) **Phytochemical examination:** Ruthenium red test and Molisch's test were performed to confirm the presence of polysaccharide.
2) **Micromeritic properties of TSP:** Bulk density, Tapped density, Angle of repose, Hausner's ratioandCarr's index was determined.
3) **pH of 1% solution:** The pH was measured using a digital pH meter.

4) **Physicochemical properties of TSP**: Various physicochemical properties such as solubility, swelling index, melting point, moisture content and viscosity were determined.
5) **Compatibility studies:** Pure drug (Glipizide) and their physical mixtures drug and polymers were examined by Fourier Transform Infrared (FT-IR) spectra. The spectra were recorded in a Thermo-IR 200 FTIR spectrophotometer. Each spectrum was derived from 25 single average scans collected in the range of 4000-400 cm-1 at the spectral resolution of 20 cm-1. DSC curve of pure drug (Glipizide) and their physical mixtures drug and polymers were obtained by a Differential Scanning Calorimeter at heating rate of 10°C/min from 30 to 300°C in nitrogen atmosphere (30mL/min).

Preparation of Glipizide matrix tablets:

Matrix tablets were prepared by direct compression method. Glipizide (10mg) was blended with Tamarind seed polysaccharide (10%, 20% and 30%)) with diluents (Lactose, Starch and MCC). The mixture was blended with 1% Magnesium stearate and mixed for 5 minutes. This mixture was compressed using 8 station rotary tabletting machine (Cadmach) with flat punch of 8mm diameter. The compositions of tablets were varied by using polymer in different ratios and using different diluents and is represented in Table-2

Evaluation of Tablets

1) Granular analysis: Bulk density, Tapped density, Angle of repose, Carr's index and Hausner's ratio of the prepared granules were determined.
2) Post compression analysis: The prepared tablets were evaluated for weight variation test, hardness, friability and content uniformity. Hardness was determined by using Monsanto hardness tester. Friability was determined using Roche friability testing apparatus. Uniformity of weight and content uniformity were performed according to the I.P method

Measurement of swelling index:

Six tablets were weighed individually (W1) and placed separately in Petri dishes containing 25 ml of phosphate buffer pH 7.4. At regular intervals of 0, 2, 4, 6, 8, 10 and 12h the tablets were removed carefully from the petridishes and excess water was removed using filter paper without pressing [19]. The swollen tablets were re-weighed (W2) and the swelling index of each tablet was calculated using the equation:

$$Swelling\ Index = \frac{W2 - W1}{W1} \times 100$$

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

Drug release studies were carried out using USP dissolution test apparatus-II. The study was conducted at 37ºC and 50 rpm. The dissolution medium used was 900ml of phosphate buffer pH 7.4 and study was carried up to 24 hours. 5ml of sample was withdrawn at different time intervals and replaced with fresh medium in order to maintain sink condition. The withdrawn samples were diluted suitably and drug content was estimated spectrophotometrically at 223 nm.

Release Kinetics:

To analyze the mechanism of drug release from the matrix tablets, the release data was fitted into various mathematical models viz., Zero order, First order and Higuchi equation.[20] The dissolution data was also fitted to the well known experimental equation (Korsmeyer Peppas equation), which is often used to describe the drug release behaviour from polymer systems.[21]

$$log\ (M_t - M_f) = log K + n log t$$

Where, Mt is the amount of drug release at time t, Mf is the amount of drug release after infinite time; K is a release rate constant incorporating structural and geometrical characteristics of the tablet and n is the differential exponent indicative of the mechanism of drug release. To clarify the release exponent for the different batches of matrix tablets, the log value of % drug was plotted against log time for each batch according to the above equation. A value of n=0.5 indicates Fickian (case I) release; $0.5 < n < 1$ for non-Fickian (anomalous) release; $n > 1$ indicates super case II type of release. Case II gradually refers to the erosion of the polymeric chain and

anomalous transport (non- Fickian) refers to a combination of both diffusion and erosion controlled drug release. [22]

Experimental design:

A full 3^2 factorial design was developed where the concentration of the TSP (X1) and the type of diluent (lactose, starch and MCC) (X2) were selected as factors. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the factorial design. The percent of drug release in 4h, 8h and swelling index (SI) were taken as response variables. The factors and levels of experimental design were given in Table 6 and 7. The response surface graphs and mathematical models were obtained from DOE software.

Statistical analysis:

The results from statistical analysis of the factorial design batches were performed by multiple regression analysis using Microsoft excel. To evaluate contribution of each factor with different levels on responses, two way analysis of variance (ANOVA) was performed using Graph pad, India. To graphically demonstrate the influence of each factor on responses, the response surface plots were generated using DOE software.

Similarity Factor (f2) analysis:

In-vitro release profile of Glipizide from selected TSP matrix tablet formulation and the marketed sustained release tablets were performed under similar conditions. The similarity factor between the two formulations was determined using the data obtained from the drug release study. The data was analyzed by the formula:

$$f_2 = 50\log \{[1 + (1/N) \Sigma (Ri - Ti)^2]^{-0.5} \times 100\}$$

where N = number of time points, Ri & Ti = dissolution of reference and test products at time 'i'. If f_2 is greater than 50 it is considered that the two products share similar drug release behaviors.

Result and Discussion

Table 1: Micromeritic properties of TSP

Sr.no	Parameters	Values observed
1	Bulk density	0.64 g/cc
2	Tapped density	0.78 g/cc
3	Angle of repose	17.5°
4	Carr's index	30.5°
5	Hausner's ratio	1.15
6	Loss on drying	17%
7	Ph	6.8

The polysaccharide was isolated from the seeds of *Tamarindus indica* using aqueous extraction followed by precipitation using acetone as non-solvent. The yield of the TSP was calculated with respect to the weight of Tamarind kernel powder and was found to be 70%. Extracted polysaccharide was analyzed for various chemical tests. Molisch's test developed violet green color at the junction of the two layers showed presence of carbohydrate in it. The absence of starch was confirmed by iodine test, showed no color change on addition of iodine solution. The presence of polysaccharide was further confirmed by Ruthenium solution which showed development of pink color. The micromeritic properties of isolated TSP are tabulated in Table no.1. The viscosity of 1% w/v solution of the polysaccharide was found to be 515-349 cps at various shear rates. The pH of the isolated polysaccharide was found to be 6.8 ± 0.25 and melting point was found to be 235-242°. TSP was found to be quickly soluble in warm water forming viscous colloidal solution. The compatibility between the drug and the isolated polysaccharide (TSP) was found to be good by the FTIR and DSC studies. The FTIR spectrum of TSP, Glipizide and physical mixture of TSP and Glipizide is given in Fig. 1. It can be used as standard spectrum for quality control and determination of the purity of TSP. The spectra of TSP display a characteristic broad peak at 3260.34 cm^{-1}representing hydroxyl (OH) groups of glucan backbone.

Peak at 2918.69 cm^{-1} can be attributed to C-H stretching of alkanes. Peak appearing at 1018.19 cm^{-1} is due to C-O-C stretching of cyclic ether.Cyclic C-H bending was confirmed by the peak at 755.77 cm^{-1}.

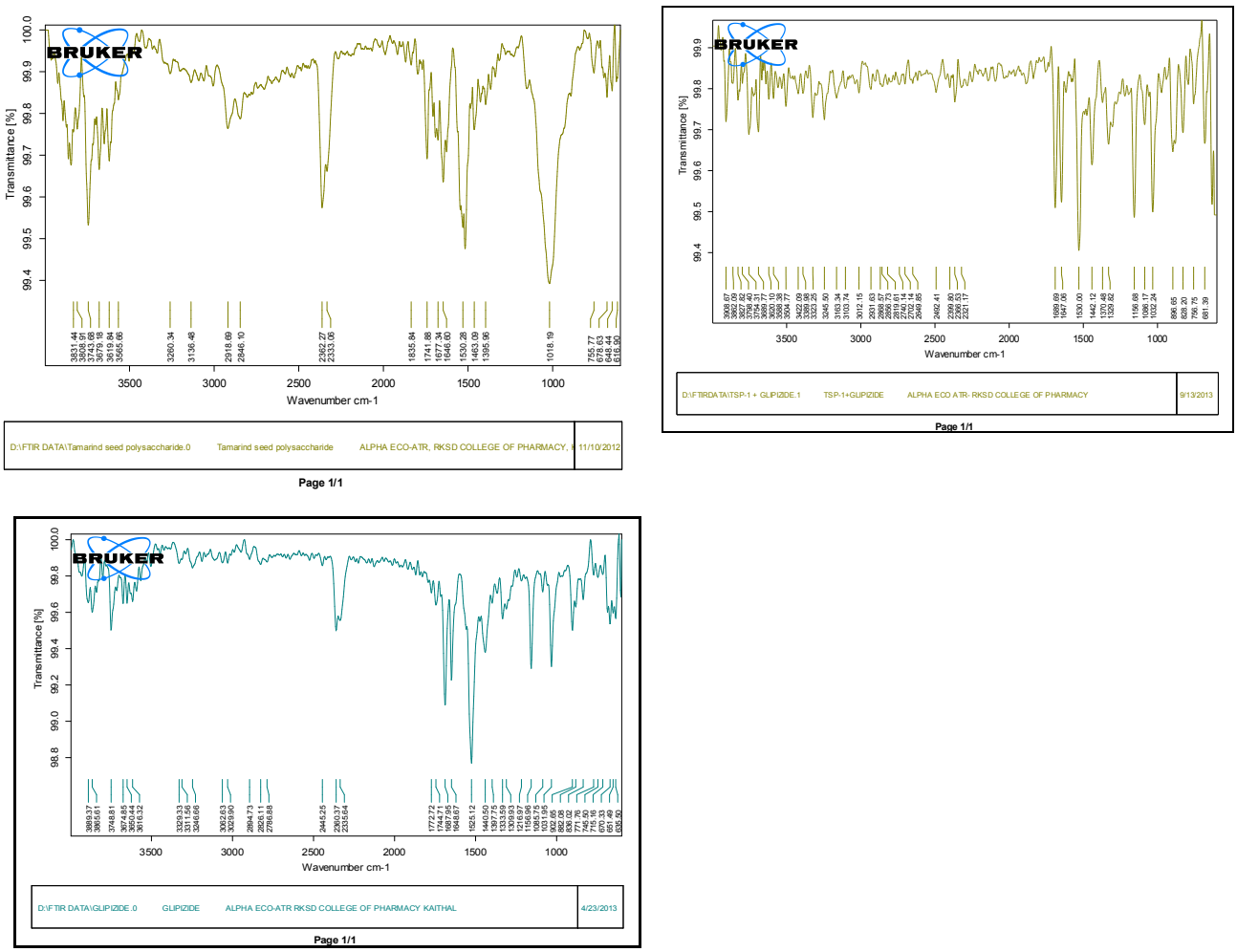
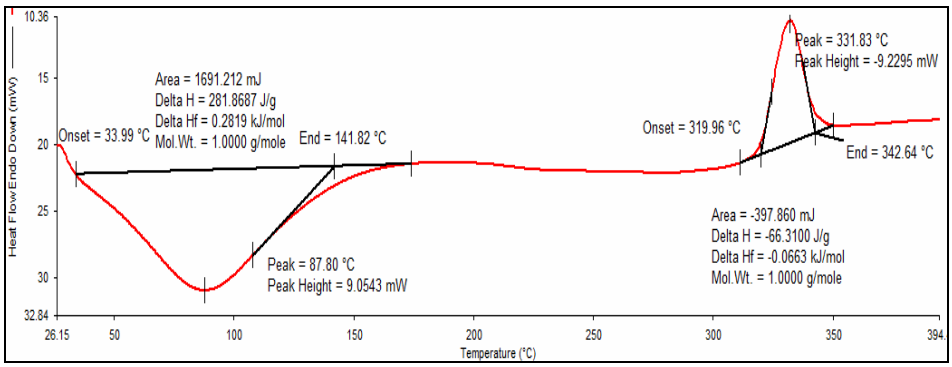


Fig.1: FTIR spectrum of TSP, TSP + Glipizide and Glipizide

The DSC thermogram (Fig.2) of TSP shows broad endotherm at 88.13^0 C with heat of fusion of 249.36 J/g followed by an exotherm at 331.83^0 C with heat flow of 63.62 J/g.



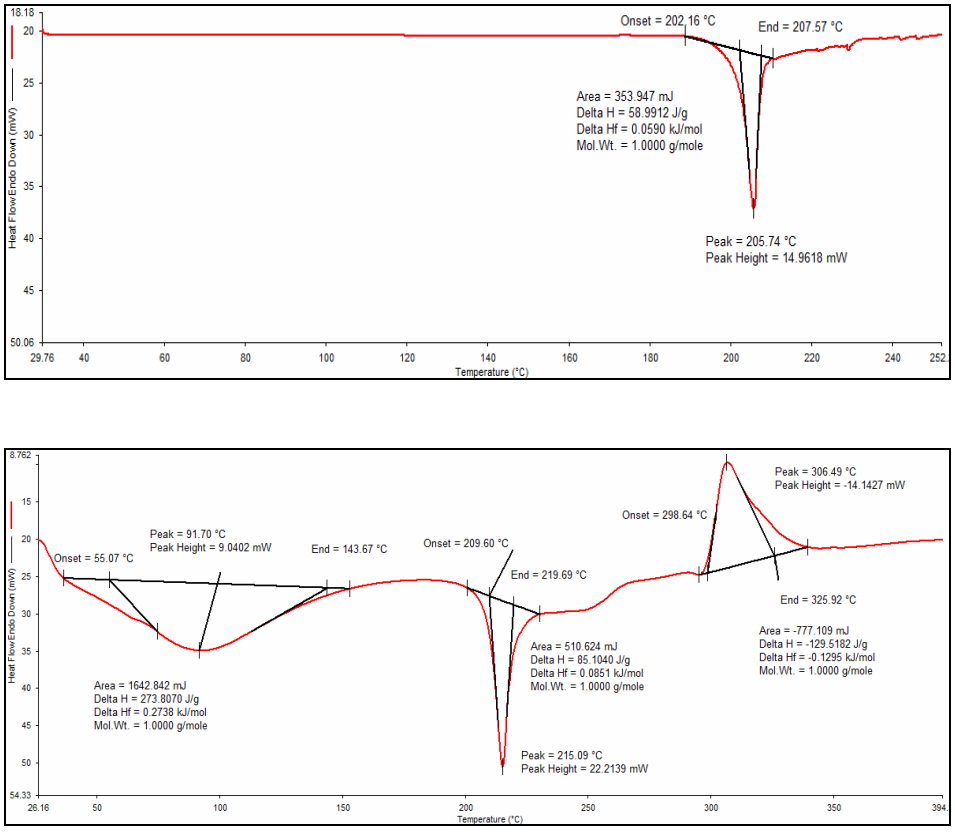


Fig. 2 DSC thermograph of TSP, Glipizide and TSP + Glipizide

The glipizide matrix tablets using TSP as matrix former were prepared by direct compression method (Table 2). The granules were characterized with respect to angle of repose, bulk density and tapped density. The angle of repose less than 25° indicates satisfactory flow behaviour. Physical characteristics of the prepared granules are given in Table 3. The matrix tablets were evaluated for hardness, friability, content uniformity, uniformity of weight and *in vitro* drug release studies. The hardness of the tablets in all the batches was found to be in the range of 5.8 – 6.9 Kg/cm^2. The friability of the tablets was in the range of 0.17 – 0.76 %. The drug content was found to be uniform for all the batches of tablets prepared and was found to be within 95±2% of labeled claim. Evaluation data of the matrix tablets were given in Table 4. The hardness and friability values indicated good handling properties of the prepared matrix tablets. The prepared matrix tablets were also studied to *in vitro* drug release studies. Table 5 indicates the data analysis of release profiles according to different kinetic models. Drug release from the matrix tablets was found inversely proportional to the concentration of gum and depends on type of diluent. The drug release fitted zero order kinetics and mechanism of release is by diffusion and polymer erosion. The Formulation F8 showed a slow and complete drug release of 98.05±0.57% over a period of 12 hr. The 'n' value of formulation F8 from Korsmeyer-Peppas equation was found to be 0.825 indicating that the release mechanism was non-Fickian or anomalous release ($0.5 < n < 1$). It showed that the release was dependent on both drug diffusion and polymer erosion. R2 value (i.e., 0.992) was maximum for zero order plot, therefore release kinetics fits zero order plot**.**

Table 2: Composition of Glipizide matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide	10	10	10	10	10	10	10	10	10
TSP	20	40	60	20	40	60	20	40	60
Lactose	168	148	128	-	-	-	-	-	-
Starch	-	-	-	168	148	128			
MCC							168	148	128
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

Table 3: Pre compression physical parameters of Glipizide granules

Formulation Code	Angle of repose (%)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's Ratio
F1	22.71±0.033	0.545±0.004	0.596±0.025	8.12±0.192	1.10±0.005
F2	20.55±0.004	0.536±0.015	0.626±0.015	8.45±0.115	1.05±0.004
F3	21.54±0.324	0.614±0.022	0.656±0.032	8.02±0.134	1.14±0.096
F4	19.56±0.015	0.616±0.016	0.666±0.012	8.52±0.118	1.10±0.035
F5	20.45±0.025	0.596±0.014	0.625±0.025	10.12±0.065	1.14±0.045
F6	21.80±0.032	0.526±0.015	0.595±0.014	9.72±0.112	1.04±0.065
F7	19.45±0.025	0.636±0.021	0.715±0.015	9.15±0.115	1.11±0.075
F8	22.45±0.015	0.539±0.020	0.626±0.018	8.55±0.105	1.12±0.064
F9	20.15±0.050	0.612±0.032	0.646±0.021	9.22±0.145	1.10±0.085

Table 4: Post compression parameters of Glipizide tablets

Formulation	Weight Variation(mg)	Hardness kg/cm²	%Friability	%Drug content	Thickness (mm)
F1	200.7	6.0	0.29	93.28	2.23
F2	200.4	6.2	0.32	95.35	2.19
F3	199.8	6.4	0.17	96.34	2.22
F4	201.2	6.9	0.19	93.28	2.20
F5	200.1	6.1	0.24	98.88	2.17
F6	200.25	5.8	0.56	97.75	2.15
F7	200.35	5.9	0.55	98.45	2.03
F8	199.8	6.0	0.59	94.45	2.02
F9	201.2	6.2	0.45	97.65	2.31

Table 5: Mathematical modeling of matrix tablets

Formulation	Correlation Coefficients (R^2)				Release exponent 'n'
	Zero order	First order	Higuchi	Korsmeyer Peppas	
F1	0.980	0.734	0.954	0.961	0.672
F2	0.971	0.825	0.946	0.926	0.715
F3	0.945	0.901	0.991	0.962	0.562
F4	0.968	0.815	0.955	0.955	0.706
F5	0.950	0.774	0.898	0.924	0.677
F6	0.948	0.898	0.954	0.969	0.678
F7	0.892	0.745	0.938	0.952	0.689
F8	0.992	0.710	0.978	0.990	0.825
F9	0.930	0.824	0.934	0.989	0.601

A 3^2 factorial design was adopted to optimize the formulation variables. In the present design, concentration of TSP (X_1) and type of diluent (X_2) were selected as independent variables. Percentage drug release at 4h, 8h and swelling index (S.I.) were taken as dependent variables. The application of an empirical polynomial equation to the experimental results facilitates the optimization procedure. The general polynomial equation is as follows:

$$Y= b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response on nine runs and b_1 is the estimated coefficient for factor X_1. The main effects (X_1 X_2) represent the average values of change in factors from low to

high value. The interaction terms ($X_1^2$and X_2^2) are included to investigate nonlinearity. The drug release at Q_4 and Q_8 and swelling index for nine batches showed wide variations and the results are given in Table 8. The data clearly indicates that the values of dependent variables strongly depend on the independent variables. ANOVA data of the dependent variables is given in Table 9.The polynomial equations are given below and the regression coefficients are given in Table 8.

$Q_4 = 15.57 - 8.61X_1 + 13.52X_2 - 3.0X_1X_2 + 7.91X_1^2 + 16.4X_2^2$
$Q_8 = 43.64 - 15.08X_1 + 8.71X_2 + 3.93X_1X_2 - 1.45X_1^2 + 29.57X_2^2$
$S.I. = 76.77 + 5.48X_1 + 20.36X_2 - 1.55X_1X_2 - 7.67X_1^2 + 0.195X_2^2$

Table 6: Factors and levels of the factorial design

Factor/level	-1	0	+1
X1(concentration of TSP)	10%	20%	30%
X2(Type of diluent)	Lactose	Starch	MCC

Table 7: Independent and Dependent variables of formulations in a 3^2 full factorial design

Sr. no	Formulation code	Coded factor levels X1	X2	Percent drug released Q4	Q8	Swelling index SI
1	F1	-1	-1	32.24	84.52	44.75
2	F2	0	-1	20.75	65.60	53.91
3	F3	1	-1	18.19	40.50	55.80
4	F4	-1	0	27.95	52.42	61.15
5	F5	0	0	18.20	41.35	75.68
6	F6	1	0	16.40	34.25	78.15
7	F7	-1	1	68.90	94.02	85.35
8	F8	0	1	40.57	83.12	101.12
9	F9	1	1	42.85	65.74	90.20

Table 8: Summary of regression output of significant factors for the measured responses

Parameters	Coefficients of regression parameters b_o	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
Q_4	15.57	-8.61	13.52	-3.00	7.91	16.40	0.9660
Q_8	43.64	-15.08	8.71	3.93	-1.45	29.576	0.9681
SI	76.77	5.483	20.36	-1.55	-7.67	0.195	0.9785

Table 9: Analysis of variance (ANOVA) for dependent variables in factorial design

For Q_4				
	SS	DF	MS	F value
Regression	2241.118	5	448.223	17.069
Residual	78.775	3	26.258	
Total	2319.894	8		
For Q_8				
Regression	3635.012	5	727.002	18.242
Residual	119.555	3	39.851	
Total	3754.567	8		
For SI				
Regression	2796.96	5	559.391	27.323
Residual	61.418	3	20.472	
Total	2858.378	8		

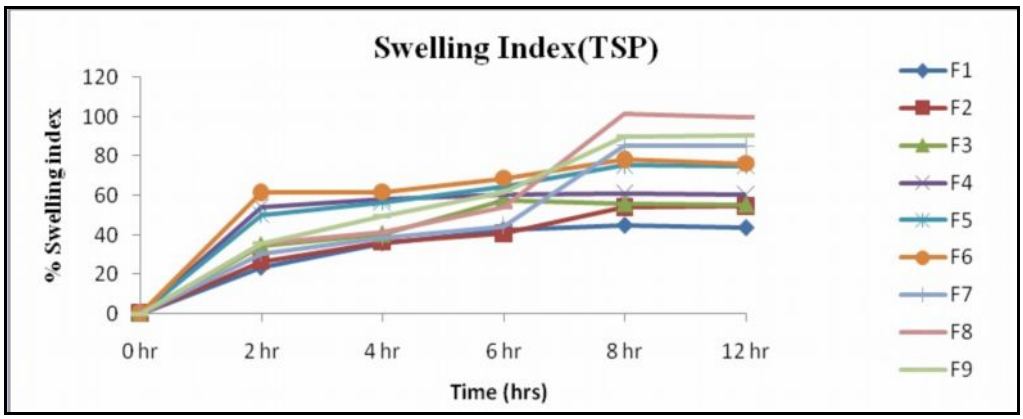


Fig 3: Percentage Swelling Indices of F1– F3 (TSP-Lactose), F4- F6 (TSP-starch), F7- F9 (TSP-MCC)

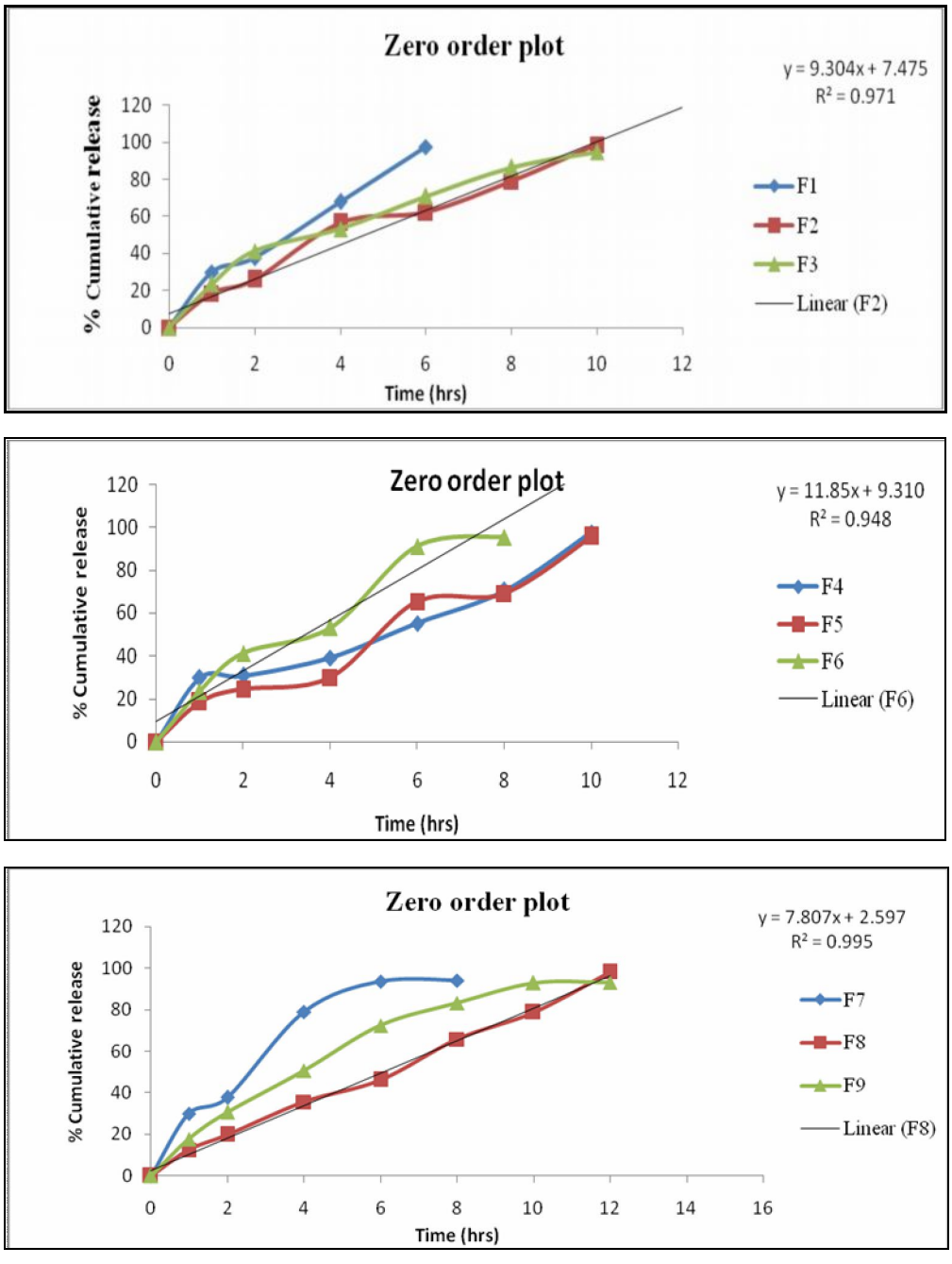


Fig 4: Cumulative % release of F1–F3 (TSP-Lactose), F4-F6 (starch), F7- F9 (MCC)

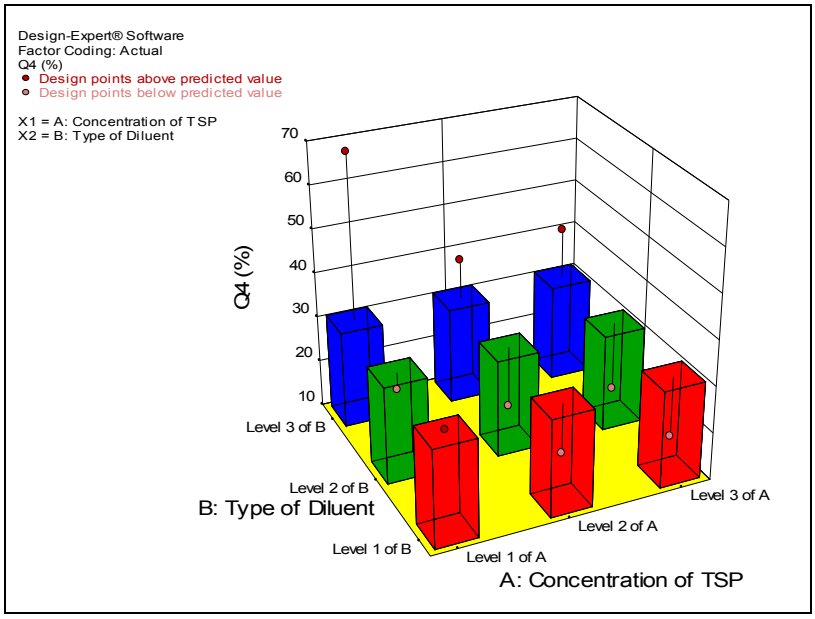


Fig.5: Response surface plot of tablet formulations after 4 hours dissolution

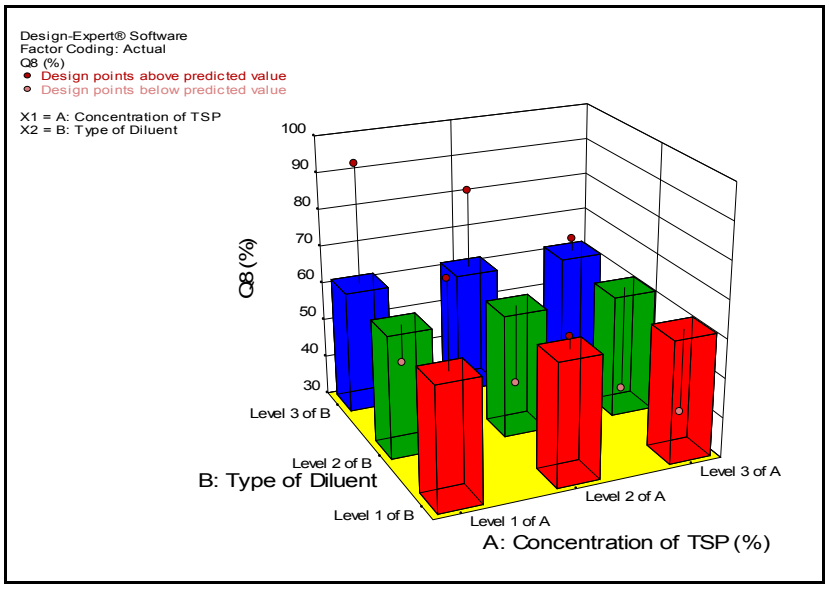


Fig.6: Response surface plot of tablet formulations after 8 hours dissolution

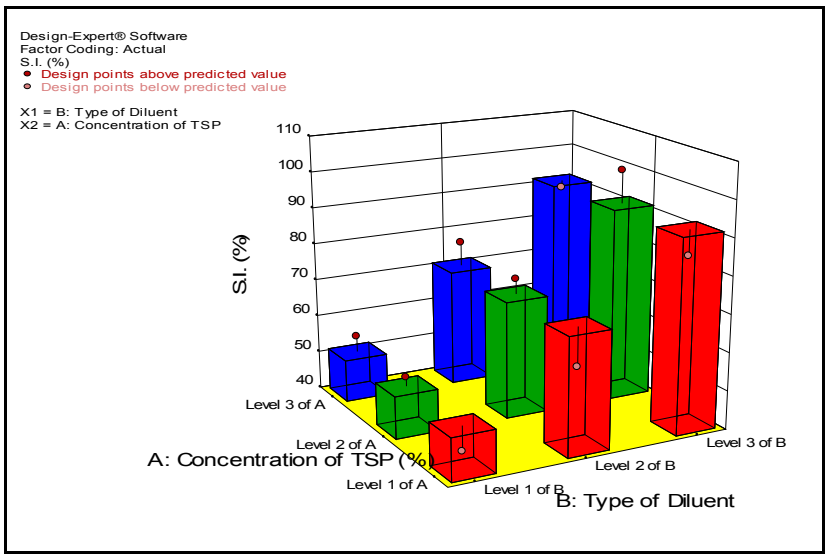


Fig.7: Response surface plot of tablet formulations showing the effect of polymer on swelling index (S.I.)

The high levels of correlation coefficients for the dependent variables indicate a good agreement between the dependent and independent variables. The polynomial equation can be used to draw a conclusion by considering the magnitude of the coefficients and the mathematical sign it carries (+ or -). Positive sign before a factor in the equation represents that the response increases with the factor, while a negative sign indicates that the response and the factor have inverse relationship.

From the above equations it can be concluded that the release of drug from matrix tablets is inversely related to the amount of polysaccharide (X_1) and positively related to the type of diluent (X_2). The magnitude of coefficients indicate that the release of drug after 4h and the swelling index are dependent on the type of diluent while the release after 8h is dependent on the concentration of polysaccharide. It also indicates that the release of drug initially depends on the diluent but eventually the release is controlled by the concentration of TSP. Similarity factor analysis between the formulations F8 and marketed product for the drug release showed an f_2 factor of 68.67, which is greater than 50, which confirmed that the release of the drug from the prepared matrix tablets is similar to that of the marketed tablet.

Conclusion

Sustained release matrix tablets of glipizide with satisfactory release characteristics were successfully prepared by direct compression method using tamarind seed polysaccharide as matrix former and different diluents (lactose, starch and MCC). Response surface methodology was adopted for understanding the change of responses and effect of formulation variables. Study indicated that increase in amount of TSP in the tablets resulted in a reduction in the release rate. The calculated release exponents (n values) of F8 (0.825) was non-Fickian or anomalous release mechanism with zero order kinetics (R^2=0.992). It was concluded that TSP with MCC at high concentrations were able to produce desired effects.

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