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Research Article

FORMULATION AND EVALUATION OF SR MATRIX TABLETS OF GLIPIZIDE USING ION EXCHANGE RESIN

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ABSTRACT

Objective: The aim of present investigation was to develop matrix tablets of glipizide using ion exchnage resin (Cholestyramine resin). The drug delivery system was designed to sustain the release of glipizide which is the drug used to treat diabetes.

Methods: Matrix tablets were prepared by incorporating glipizide-ion exchange resin complex in HPMC K15 matrix. Sodium chloride was added to tablet as a release modifier.

Results: The release profile and retention of glipizide by matrix tablet was influenced by glipizide-ion exchange binding and NaCl which was added as a release modifier. HPMC also has a effect on drug release. Optimization was done using 3^2 factorial design considering two independent factors at three levels. Data was evaluated statistically by Stat Ease Design Expert 8.0.1 software. Software gave two batches which fit our desirability criteria. The drug releases of those batches were compared with the drug release of marketed formulation. The batch F1 showed more similarity factor and so was selected as final optimized batch.

Conclusion: The matrix tablets of glipizide which were prepared usin ion exchange resin showed good sustaining effect. And NaCl acted as release modifier.

Keywords: Sustain release, Chloestyramine resin, HPMC K15M, Sodium Chloride.

INTRODUCTION

For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the desired duration of the treatment [1]. If provided dose size and frequency of administration are correct, therapeutic 'steady-state' plasma concentrations of a drug can be achieved promptly and maintained by the repetitive administration of conventional oral dosage forms. But there are certain limitations associated with it like, fluctuation in plasma drug concentration and so fluctuation at the site of action, frequent dosing etc. These limitations and requirements led pharmaceutical scientists to consider presenting therapeutically active molecules in 'extended-release' preparations. Such delivery systems were aimed at eliminating the cyclical changes in plasma drug concentration seen after the administration of a conventional delivery system. A variety of terms was used to describe these systems such as sustain release, delayed release, repeat action etc [2]. There are many approaches to modify drug release such as coating, embedding drug in polymer matrix etc. One such approach is loading of drug on ion exchange resin to form resinate which then can be formulated in various dosage forms. Common among those dosage forms is tablet. In that generally the resinates are incorporated in polymer matrix and most commonly used polymer matrix material is HPMC. Among different dosage forms, matrix tablets are widely accepted for oral sustained release.Sustained release system have benefits like patient compliance, avoid multiple dosing, cost effectiveness, flexibility, increase the plasma drug concentration, avoid side effects, broad regulatory acceptance and overcome the problems associated with conventional drug delivery system [3]. A major drawback of controlled-release system is dose dumping, resulting in increased risk of toxicity. Because of their better drug-retaining properties drug resinates prevent dose dumping. The polymeric (physical) and ionic (chemical) properties of IER enable drug release more uniformly than that possible with simple matrices (because of physical properties only). Moreover, IER impart flexibility in designing a variety of delivery systems, such as liquids, beads, micro particles and simple matrices [4]. According to WHO, Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipaemia, negative nitrogen balance and sometimes ketonaemia [5]. There are two types of diabetes mellitus type I (Insulin dependent) and type II (insulin independent) [6]. There are mainly two approaches to treat diabetes mellitus [7]. One, to improve insulin availability and other, to overcome insulin resistance. Sulfonylurea class of drug help to improve insulin availability [8]. Glipizide is a drug belonging to sulfonylurea class [9]. It has to be taken before every meal. So its dosing is frequent and is inconvenient to patients. For that reason its sustain release formulation is required.

Kivisto K. T., Neuvonen P. J studied the effect of cholestryamine resin on absorption of glipizide from GIT [10]. They found that cholestryamine resin reduces the absorption of glipizide. So it was evident that glipizide bind to cholestraymaine resin. And, so in present study cholestyramine resin was used to formulate resinate with glipizide.

MATERIAL AND METHODS

Materials

Glipizide was obtained as a gift sample from Lupin Research Park, Aurangabad. Indion 454 was obtained from Ion Exchange India, Mumbai as gift samples. HPMC K15M was obtained from Colorcon Asia Pvt. Ltd. (Goa) as a gift sample.

Drug solubility study

The drug solubility study was carried in different buffer solutions with pH 1.2, 6.8, 7.4 and in 0.1N, 0.05N NaOH. The excess amount of drug was added in the buffer solution to make saturated solution. Then saturated drug solutions were sonicated thrice, each time for 10 min. The solutions of Glipizide were kept overnight for attainment of equilibrium with solvent. Prepared solutions were filtered using Whattman filter paper no 42. The filtrate was analyzed spectrophotometrically. The filtered solutions were diluted with buffer solutions if required.

Formulation study

Preparation of GZD-loaded resin complexes

The GZD/resin complexes were prepared by a batch processe. For

the batch method, the previously purified resin particles (500mg of Indion 454)were dispersed in a 1.0% (w/v) drug solution (100 mL) in 0.05 N NaOH under magnetic stirring at room temperature for 5 h. The complexwas separated fromthe supernatant by filtration, washed with water to remove any uncomplexed drugs, and then dried in an oven. In order to investigate how quickly equilibrium could be reached, 0.5mL of supernatant was collected at predetermined intervals during complex formation at room temperature, diluted withwater, and then the drug amount was quantified by UV spectroscopy.

Preparation of tablets

Matrix tablets of glipizide were prepared by direct compression method using 6 mm flat-faced punch of 12 stations (Lab Press Machinery Pvt. Ltd, Ahmadabad, India.) The glipizide-IER complex and the excipients were passed through 60 mesh sieve and thoroughly mixed using a polybag for 10 minutes. PVP K15 was used as binding agent and magnesium stearate, talc were added to the above blend as flow promoters and further mixed for another 10 minutes. In all the formulations the amount of glipizide-IER complex (equivalent to 10mg glipizide) was kept constant.

Preliminary study

In preliminary study tablets were formulated using 20mg, 25mg and 30mg of HPMC K15 and K100. Prepared batches were evaluated for drug release. The tablets formulated using 20mg and 25mg of HPMC showed poor matrix integrity and failed to remain intact for 24 hr.

Factorial study

For the present work 3^2 factorial designs was selected. The two independent variables selected were HPMC K15M (X_1) and NaCl (X_2), and the nine formulations formulated as per the experimental design as shown in table 1.

Table 1: Factorial batches

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide-IER complex	16	16	16	16	16	16	16	16	16
HPMC K15	35	25	25	32	25	30	35	30	30
PVP	5	5	5	5	5	5	5	5	5
NaCl	5	3	4	3	5	3	4	5	4
MCC	36	48	47	38	46	43	37	41	42
Talc	2	2	2	2	2	2	2	2	2
Mg. Stearate	1	1	1	1	1	1	1	1	1

Evaluation of tablets

The tablets were evaluated for various parameters as follows,

Drug content [11]

Drug content was determined by crushing 10 tablets. Powder equivalent to 10 mg of Glipizide was put into 1N NaOH solution. Solution was stirred for 1hr on magnetic stirrer. Then amount of drug present in it was determined spectroscopically at 276 nm.

Determination of stability of complexes

Glipizide –IER complex equivalent to 10mg of Glipizide was dispersed in 50ml of deionised water for 24 hrs. After the period of 24 hrs. amount of drug in water was determined spectroscopically.

Dissolution studies

The *in vitro* releases of drug from tablets of all batches were performed in triplicate using USP apparatus Type I (Basket).

The following conditions were followed to study the in-vitro dissolution study of Glipizide tablets.

a) USP dissolution apparatus: Type I (Basket).

b) Volume of dissolution medium: 900 ml

c) Rotating speed of basket: 50 rpm

d) Temperature: 37±0.50 C

e) Dissolution medium: pH 1.2 (0.1N HCl) first 2 hrs then continue in Buffer pH6.8upto 24 hr.

f) Formulation Sample for dissolution: tablets containing drug-IER complex equivalent to 10 mg of Glipizide

g) Sampling interval: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24 hr.

During dissolution procedure dissolution medium of about 5ml was withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,24 Hr. The volume withdrawn was replaced by fresh volume of dissolution medium.The filtered samples of were analyzed spectrophotometrically at 276 nm and absorbance was noted.

Kinetics of drug release

The dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model. The observations were summarized in the Table 7.

In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e. release exponent was calculated. The n value is used to interpret the release mechanism as shown in Table 2.

Table 2: Interpretation of diffusional release mechanism

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5 <n <1	Anomalous transport
1.0	Case II transport
Higher than 1.0	Super Case II transport

Analysis of data by Design Expert software

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively . The statistical treatment and interpretation of data was done by Stat Ease Design Expert 8.0.7.1 software. The analysis of variance (ANOVA) is represented in table 6. The data were also subjected to 3-D response surface methodology to study the interaction of independent variables.

Optimization and comparison with marketed preparation

Optimization was performed using Design Expert 8.0.7.1 software to obtain optimized batch. Comparison of drug release profile of desirable batches was done with the drug release profile of marketed preparation to obtain final optimized batch.

RESULT AND DISCUSSION

Drug solubility study [12]

Solubility profile of Glipizide indicated that the drug is freely soluble in methanol and practically insoluble in water which complies with the BP standards. The results of Glipizide solubility in various media are shown in Table 3. Glipizide showed pH dependent solubility. At lower pH, the solubility was less and as the pH was raised from acidic to pH 7.4, the solubility drastically improved.[45] This is due to

the fact that drug is a acidic drug and so is less soluble at lower (i.e. acidic) pH but it's solubility increases as pH increases and is maximum at higher (i.e. basic) pH.

Table 3: Drug solubility study

Solvent	Solubility mg/ml (mean±S.D.)
0.1N HCl	0.093±0.01
pH 6.8 Phosphate buffer	0.321±0.082
pH 7.4 Phosphate buffer	0.890±0.082
0.1 N NaOH	132.69±5.6
0.05 N NaOH	123±4.4

GZD loading on IER

Different ratios of GZD-IER were tried for getting the optimized ratio. Among them 1:2 ratio i.e. one part of IER to two parts of GZD was found to be optimized ratio. Further increasing the concentration of drug showed no further improvement in amount of drug bound to IER. Equilibrium time was found to be 1 hr.

Confirmation of drug loading on IER

From weight difference before and after drug loading :

The weight of IER added to drug solution before drug loading gains weight because of drug loading. It was confirmed from the study that the IER gained weight in proportion of % binding achieved.

From FTIR

From FTIR drug loading can be confirmed. In the FTIR spectrum of glipizide - IER complex the peak corresponding to the groups of the drug which bind to IER are vanished. The IR spectrum of Glipizide shows prominent peak corresponding to –NH at 3323.25 which is absent from the IR spectrum of drug-IER complex. It shows that after ionization of –NH gr. it gives negative ($-N^-$) nitrogen atom which is anion and it binds to IER.

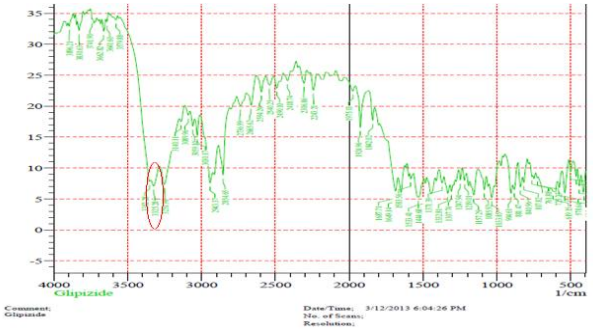

Fig. 1: FT-IR of Glipizide

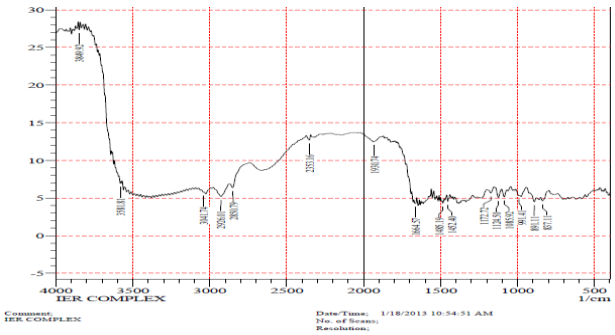

Fig. 2: FT-IR of Glipizide-IER complex

From DSC

The thermal behavior of the pure drug shows endotherm at 215.43 corresponding to melting. Indion 454 shows endotherm near 253.48° whereas resinate shows endotherm near 195.46°C thus indicating complexation.

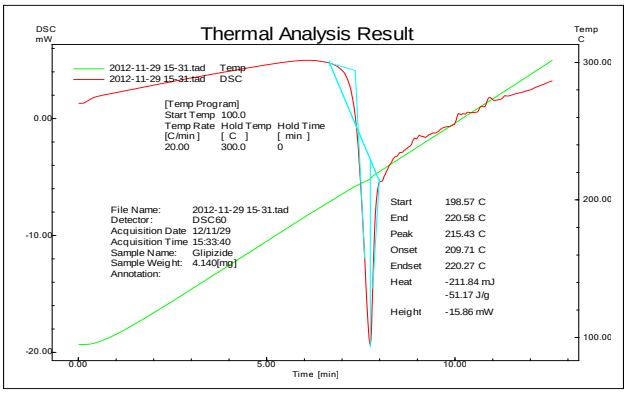

Fig. 3: DSC thermogram of glipizide

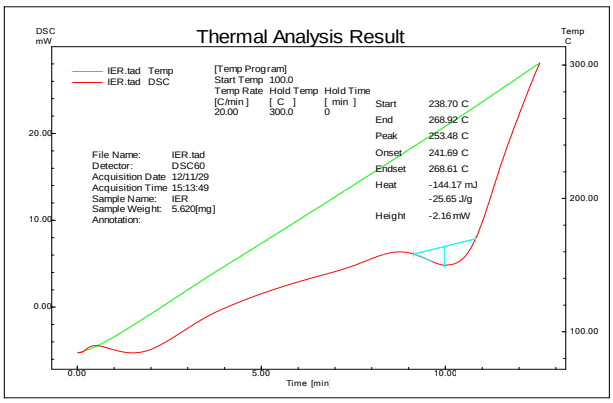

Fig. 4: DSC thermogram of indion

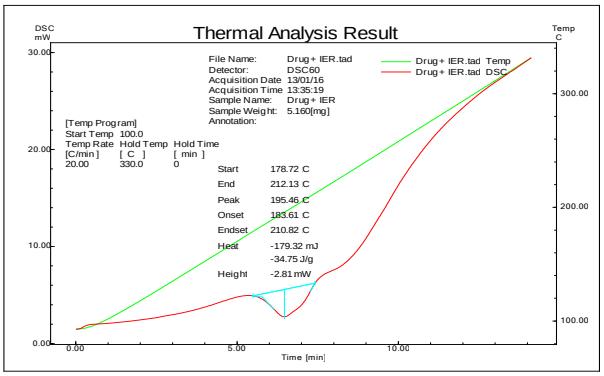

Fig. 5: DSC thermogram of Glipizide-IER complex

Preliminary study

Preliminary study was performed using different concentrations of HPMC K15 and K100.

Preliminary study showed that the drug release was very less. This must be due to tight binding of glipizide to IER. This type of behaviour was in confirmation with what was reported in literature. So, again second set of preliminary batches were prepared. In the second set of study sodium chloride (NaCl) was added as release modifier.

The second set of preliminary study showed that when NaCl was added as the release modifier amount of drug release increases significantly. This is because NaCl provides the ions needed for exchange locally. Whereas, in batches without the NaCl, ions from the medium have to diffuse through the gel layer of HPMC and reach glipizide-IER complex to displace the drug. This can best explained by the diagram shown below,

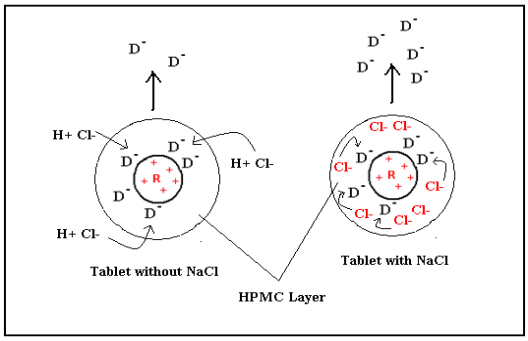

Fig. 6: Effect of NaCl on drug release

Dissolution studies

The factorial design batches were formulated and in vitro release was studied. Formulations containing higher amount i.e. 5mg of NaCl (F1 and F8) showed higher drug release after 24hrs. The most successful formulation was F8 containing 30mg of polymer HPMC K15M and 5mg of NaCl which gave drug release of about 99% after 24hrs. The response from the dissolution study taken was Q_{24} The response Q_{24} of the formulations F5 differed from F1 and F8 though they contained same amount of NaCl. This is because batch f5 containing 25mg of HPMC K15 could not retain its matrix integrity for 24hrs. It disintegrated early so the NaCl escaped into dissolution medium and thus the ions needed for exchange were not available in near vicinity. And it gave low drug release. The Q_{24} i.e. drug release after 24 hrs for formulations F1, F5 and F8 were 97±2.1,77±2.3 and 99±3.1 respectively.

However, with constant polymer concentration and increased NaCl concentration (3mg, 4mg and 5mg respectively) showed increased Q_{24}. Same trend was observed for formulations containing progressively less polymer concentration, except for formulation containing 25mg of HPMC K15 (due to the reason explained above). The release profile of the drug from the formulation was as follows, F6>F9>F8, F4>F7>F1 which depicts the significant effect of NaCl.

Further no characteristic trend can be observed for dissolution up to 1hr. This may be due to the time taken by the polymer in the tablet to get hydrated before changing from glassy state to rubbery state. Thus during first hour of dissolution, there was no significant polymer chain reaction due to which the rate controlling gel barrier could not be formed.

Thus in study IER was a main rate controlling polymer. It can be confirmed from the fact that the batch P1 which was formulated using only glipizide-IER complex (i.e. which did not contain HPMC) showed drug release in sustained manner. HPMC K15M was the secondary rate controlling polymer. The main purpose it served was of forming a HPMC Gel layer containing NaCl around the glipizide-IER complex and of preventing NaCl ions from escaping into dissolution medium. NaCl acted as a release modifier.

Most successful batch was F8 with 30mg HPMC K15M and 5mg NaCl. The result of cumulative drug release (%) of all formulation batches were as per table 9.

Kinetics of drug release [13]

In present study the dissolution were analyzed by PCP Disso Version 2.08 software to study the kinetics of drug release mechanism. The results showed that most of the factorial design batches followed matrix model.In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e. release exponent was calculated. The n value is used to interpret the release mechanism as shown in Table 5.Then values were found to be between 0.5-1, indicating non-fickian diffusion or anomalous transport. The n (0.5<n<1) value also revealed the drug release mechanism via diffusion coupled with erosion.

Table 4: Comparative drug release of batch F8 and marketed preparation

Time	Cumulative Drug Release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	6.898±2.1	13.653±1.01	17.838±1.98	15.507±1.01	13.761±2.08	15.138±2.05	12.861±0.83	16.731±1.66	19.17±2.21
1	9.8982±2.3	15.084±1.81	16.623±2.4	16.407±2.21	15.345±1.98	17.631±2.13	14.499±1.26	25.011±1.63	20.385±2.35
2	20.3553±1.7	15.399±2.01	18.531±2.10	16.731±2.52	19.485±1.78	16.353±2.69	22.563±1.55	31.419±1.45	24.201±1.64
3	41.3865±1.1	28.26±2.11	37.593±0.551	29.592±2.3	32.346±1.44	27.936±2.54	38.628±1.86	48.555±1.66	41.337±1.25
4	47.2347±3.1	30.519±2.23	39.24±1.221	32.751±1.78	38.916±0.35	31.392±1.98	42.363±2.11	52.578±1.53	45.36±1.17
6	54.225±1.2	37.791±1.78	40.473±0.97	37.935±1.88	46.728±2.98	37.638±1.57	46.683±2.51	56.403±1.93	49.185±1.65
8	63.8073±1.71	40.014±2.05	44.748±1.46	41.22±1.45	51.417±1.99	43.515±1.69	51.822±2.01	63.549±1.12	56.331±1.11
10	68.6835±1.77	44.532±0.38	51.651±1.73	47.88±1.66	55.728±2.21	51.075±1.58	55.152±3.34	69.021±2.21	61.803±1.64
12	71.4618±2.1	49.176±1.99	57.483±2.02	49.806±2.01	63.657±2.10	57.24±1.11	61.236±1.13	76.167±2.05	68.949±2.02
24	97.4304±1.2	69.723±1.87	75.123±2.11	69.048±1.78	77.265±1.19	83.214±2.21	93.699±2.00	99.38±3.0	98.162±1.12

ANOVA Study

Evaluation and interpretation of research findings are utmost important and the p-value serves a valuable purpose in these findings.Table 6 shows ANOVA for the dependent variables Q_{24}. The coefficients of X_1 and X_2 were found to be significant at $p<0.05$, hence confirmed the significant effect of both the variables on the selected responses. Increasing the concentration of the HPMC K15M resulted in the decrease in the release of Glipizide from the tablet. However, the increase in concentration of the NaCl resulted in increase in drug release.

Overall both the variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 8.0.7.1 software. However, both the variables favour the preparation of controlled release tablets of Glipizide.

Response surface plot

The quadratic model obtained from the regression analysis used to build a 3-D graphs in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots. The response surface plots were generated using Design Expert 8.0.7.1 software presented in Figure 8 to observe the effects of independent variables on the response studied such as Q_{24}.Graphical presentation of the data helped to show the relationship between the response and the independent variables. The information given by graph was similar to that of mathematical equations obtained from statistical analysis. The response surface plots showed that various combinations of independent variables X_1 and X_2 may satisfy any specific requirement (i.e. maximum drug release) while taking into consideration of various factors involved in dosage form.

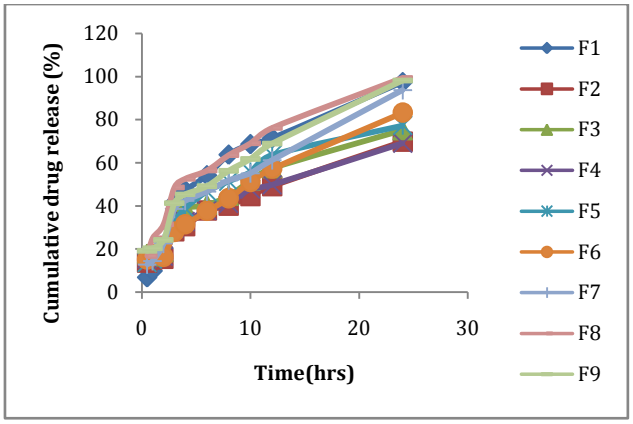

Fig. 7: % cumulative drug release of factorial batches

Table 5: Kinetics of drug release

Form-ulation	R^2					N	K
	Zero Order	1st order	Matrix	Peppas	Hixson Crowell		
F1	0.9846	0.9912	**0.9946**	0.9443	0.9645	0.6744	0.0074
F2	0.9316	0.9316	**0.9769**	0.9655	0.9316	0.5182	0.0089
F3	0.8697	0.8698	**0.9836**	0.9544	0.8698	0.5514	0.0080
F4	0.9021	0.9021	**0.9809**	0.9506	0.9021	0.4653	0.0100
F5	0.8859	0.8860	**0.9836**	0.9760	0.8860	0.5567	0.0099
F6	0.9640	0.9641	0.9509	**0.9300**	0.9641	0.5317	0.0095
F7	0.9596	0.9596	0.9614	**0.9882**	0.9596	0.5725	0.0096
F8	0.7194	0.9196	**0.8620**	0.7458	0.7195	0.3531	0.0176
F9	0.9339	0.9340	**0.9676**	0.9540	0.9339	0.4669	0.0131

Table 6: ANOVA Study

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	P Value	Model
Model	1227.11	5	245.42	31.86	0.0084	Significant
X_1	240.67	1	240.67	31.24	0.0113	Significant
X_2	450.67	1	450.67	58.50	0.0045	Significant
X_1X_2	100	1	12.98	0.0367	-	-
$(X_1)^2$	355.56	1	46.15	0.0065	-	-
$(X_2)^2$	80.22	1	10.41	0.0483	-	-
Residual	23.11	3	7.70	-	-	-
Core Total	1250.22	8	-	-	-	-

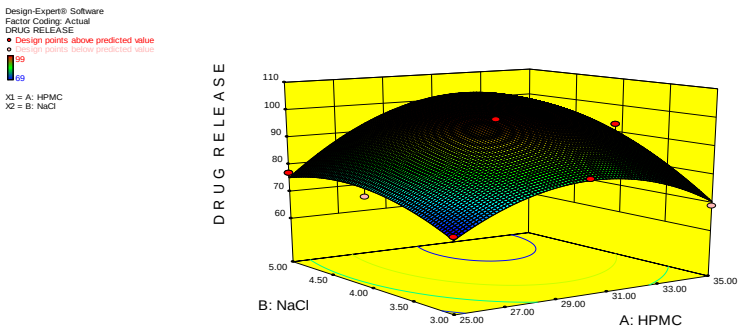

Fig. 8: 3D surface plot.

Optimization

Optimization was performed using design expert 8.0.7.1 software. Numerical optimization and graphical optimization methods were used for optimization of formulation.

Numerical optimization

Goals were set for maximization of drug release at 24 hrs. Software generated optimal solutions. It gave two solutions. As shown in diagram below,

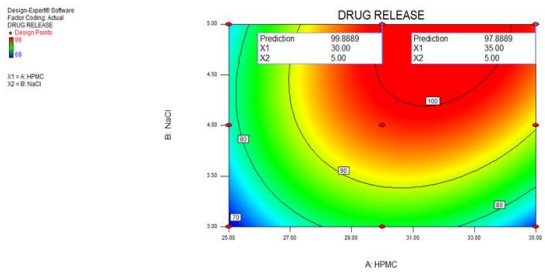

Fig. 9: Numeric optimization contour plot.

Graphical optimization –After setting minimum or maximum limits for drug release in range of 85% to 100%,software created an overlay graph highlighting the area of operability. As shown below,

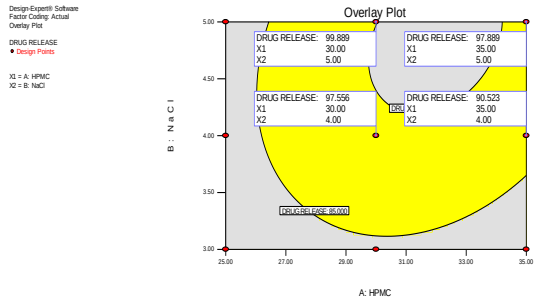

Fig.10: Graphical optimization overlay plot

From the optimization methods 2 batches were found to be in desirability range. Those were, F1 and F8. The drug releases of those two batches were then compared with that of marketed formulation to get final optimized batch.

Comparison with marketed preparation (Calculation of similarity factor)

Similarity factor (F_2) was calculated using formula [14],

$$f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

Where, n = number of time points

R_t = % API dissolved of reference product at time point x, T_t = % API dissolved of test product at time point x

If the value of $F_2 \geq 50$ then the profiles are regarded as similar [15]. Values of F_2 for both the batches were greater than 50. But value of F1 batch was more than that of F8 Batch so, F1 batch is selected as final optimized batch. The results are shown in table 7.

Table 7: Similarity factor for batch F1 and F8

Time (Hrs)	Release profile	
	Marketed	F1
0.5	**8.51**	6.893
1	12.22	9.8982
2	25.13	20.3553
3	35.35	41.3865
4	42.57	47.2347
6	51.2	54.225
8	63.03	63.8073
10	69.05	68.6835
12	72.48	71.4618
24	99.7	97.4304

CONCLUSION

Development of sustained release matrix tablets of Glipizide has a great significance to overcome problems associated with conventional dosage forms. Modified release drug delivery is the most versatile technique for treatment of diabetes mellitus.

Glipizide is an antidiabetic drug belonging to sulfonylurea class. It is a low dose drug. Low dose drugs are particularly difficult to formulate using ion exchange resin (IER),because if some small amount of drug remain permanently bound to IER, it can create problem in therapeutics owing to small dose of the drug. So, present study aims at formulating matrix tablets of glipizide using IER eliminating above stated problem.

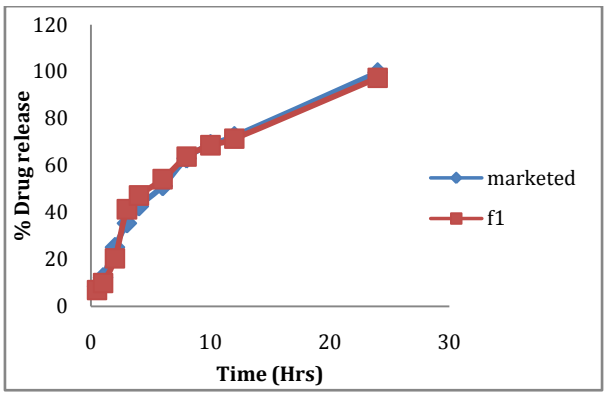

Fig. 11: Comparative drug release of batch F1 and marketed preparation.

Table 8: Comparative drug release of batch F8 and marketed preparation

Concentration	Release profile	
	Marketed	F8
0.5	8.51	16.731
1	12.22	25.011
2	25.13	31.419
3	35.35	48.555
4	42.57	52.578
6	51.2	56.403
8	63.03	63.549
10	69.05	69.021
12	72.48	76.167
24	99.7	99.38

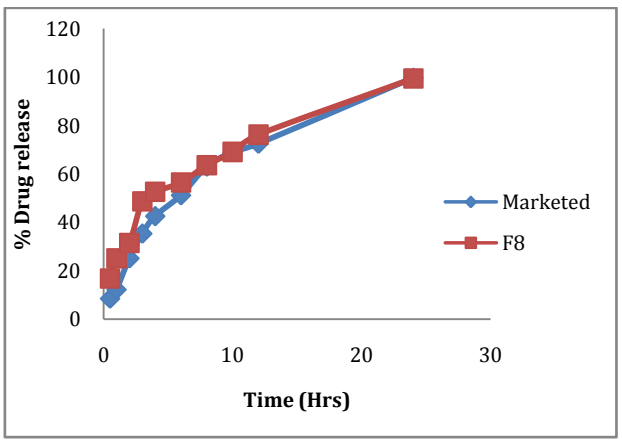

Fig. 12: Comparative drug release of batch F8 and marketed preparation

Firstly, different ratios of glipizide and IER were tried to get an optimum ratio at which maximum drug loading was achieved. The optimum ratio of drug and IER was found to be 2:1 (i.e. two parts of glipizide and one part of IER). Also the equilibrium time (i.e. time beyond which no more drug binding could be achieved) was found to be 1hr.

Preliminary batches were prepared using 25mg, 30mg, 35mg concentration of HPCM K15 and HPMC K100. Those batches were evaluated for drug release. It was found that the drug release was

very less from them which may be attributed to strong glipizide-IER bindng. It was in confirmation with the literature. So, other set of preliminary batches were prepared containing 5mg of NaCl as a release modifier. It was found that drug release was significantly increased.

For further development of the dosage form factorial design concept was applied. The effect of two factors (HPMC K15 and NaCl) was studied at 3 levels (25mg, 30mg, 35mg and 3mg, 4mg, 5mg respectively). Factorial batches were prepared and evaluated for drug release and other physical parameters. The results of drug release study were analyzed by using Expert Design 8.0.7.1 software and optimized batches were found out. The software gave two results [(1) 35mg HPMC, 5mg NaCl and (2)30mg HPMC,5mg NaCl] which fit our criteria of desirability. The drug releases of those two batches were compared with the drug release from marketed formulation (GLYNASE XL-10). Among them batch containing 35mg HPMC and 5mg NaCl showed higher similarity factor and so was selected as final optimized batch.

It can be concluded from the results that drug release through the formulation containing IER can be increased by incorporating a little amount of salt such as NaCl in it. The salt provides locally the ions which are required for exchange. Also the result showed that gel layer containing ions must be present in near vicinity because the tablet which disintegrated showed less drug release than those which were intact.

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