International Journal of Drug Delivery 4 (2012) 113-124

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Formulation and evaluation of controlled porosity osmotic pump tablets of Glimepiride

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Abstract

A Controlled porosity of the membrane is accomplished by the use of pore former. The usual dose of glimepiride was 4 mg to be taken twice daily. The plasma half life of glimepiride was 5 h. Hence, glimepiride was chosen as a model drug with an aim to develop a controlled release system for 24 h. Sodium chloride was use as osmogent. Cellulose acetate was used as the semi permeable membrane. The porous osmotic pump contains pore forming water-soluble additive (Poly ethylene glycol 400) in the coating membrane which after coming in contact with water, dissolve, resulting in an *in situ* formation of microporous structure. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain and concentration of pore former on the *in vitro* release was studied using 2^3 full factorial design. The effect of pH and agitation intensity on drug release was also studied. It was found that drug release rate increased with the amount of osmogent because of increased water uptake. Drug release was inversely proportional to membrane weight gain. Surface plot is also presented to graphically represent the effect of independent variables on t_{90}. Optimized formulation was found to release above 90% of glimepiride at a zero order rate for 24 h.

Keywords: Controlled porosity osmotic pump, glimepiride, osmogent, pore former, factorial design

Introduction

In recent years, considerable attention has been focused on the development of novel drug delivery systems. Once daily controlled release preparation is often desirable. However, drug release from oral controlled release dosage forms may be affected by pH, gastric motility, and presence of food. One practical approach with a potential to overcome these disadvantages is the osmotic drug delivery system where osmotic material have been used extensively in the fabrication of drug delivery systems [1].

The historical developments of osmotic systems include seminal contributions such as the rose nelson pump, higuchi leeper pumps, alzet osmotic pump, elementary osmotic pump and push pull osmotic pump. The osmotic drug delivery systems suitable for oral administration typically consist of compressed tablet core that is coated with a semi permeable membrane that has an orifice drilled on it by means of a laser beam. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume which pushes the drug solution or suspension out of the tablet through one or more delivery ports. To obviate the need for complicated laser drilling, tablets coated with a membrane of controlled porosity have been described. These membranes consist of leachable material which dissolves upon contact with water, leaving behind the pores through which the drug solution is pumped out. Drug release from these systems is independent of pH and hydrodynamic conditions of gastro-intestinal tract to a large extent, and release characteristics of delivery system [1-3].

Glimepiride, an oral hypoglycemic agent, is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus. It is practically water-insoluble, but the absolute bioavailability is close to 1. Thus, it belongs to class 2 of biopharmaceutics classification system. Glimepiride has a relatively short elimination half life (5 h), thereby requiring twice daily dosing in large number of patients, which often leads to non-compliance. Thus, there is a strong clinical need and market potential for a dosage form that will deliver glimepiride in a controlled manner to a patient compliance [4-6].

Materials and Methods

Materials

Glimepiride was obtained as gift sample from Zydus cadila, Ahmedabad. Micro crystalline cellulose was obtained from FMC biopolymers, USA. Cellulose acetate, Acetone, PEG 400, Nacl, Magnesium stearate and talc were obtained from S.D. fine chemicals, Mumbai.

Methods

Drug-excipient compatibility study

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm^{-1} by KBr disc method using FTIR spectrophotometer [7].

Experimental design

A number of preliminary experiments were conducted to determine the formulation and parameters by which the process resulted in controlled porosity osmotic pump tablets. A full factorial 2^3 design was employed for the optimization procedure. The drug:osmogent ratio (X_1), concentration of pore former (X_2) and % weight gain (X_3) were selected as the independent variables, where as t_{90} i.e. the average time required to release 90 % of glimepiride (Y) was chosen as the dependent variables. Table 1 summarizes these factors with corresponding levels and the responses studied, where as experimental formulations are listed in Table 2. The factors were selected to measure the change in response from one extreme factor to another and for determining interactions, if any, among the factors with their best levels for optimizing the considered experimental responses [8].

Preparation core tablets (S_1 to S_8)

The formulations SP_1 to SP_8 were prepared by direct compression method. The formulation ingredient quantity was selected as per trial and error method. This trial and error method was also supported by extensive literature review for nearby optimize quantity of each ingredients in this study. All the ingredients were passed through sieve # 60 separately, weighed and mixed in geometrical order. Then lubricant and glidant (standard sieve # 120) were added and mixed for further 5 minute. The resulting powder mixtures were then compressed into tablets using a rotary tablet machine fitted with 6 mm flat faced punches. Formulae of different core formulation (SP_1 to SP_8) of glimepiride were listed in Table 2 [7].

Preparation of coating solution

Coating solution was prepared by mixing required quantity of cellulose acetate (semi permeable membrane) and PEG 400 (pore former and plasticizer) in acetone and stirred on magnetic stirrer to get homogeneous coating solution. The coating composition for glimepiride core formulation was listed in Table 2 [7].

Dip coating method

In the present study, dip coating method was used to coat the tablets. The formulations SP_1 to SP_8 were used as the core tablets. The weighed core tablets were dipped into coating solutions by holding with forcep and after dipping were placed on a glass plate (smeared with PEG 400) for drying in air for 15 minutes at room temperature. The tablets were then dried at 60 C in an oven for 30 minutes. During drying, the tablets were rotated occasionally. The tablets were subjected to coat about 5 % w/w, 8 % w/w and 10 % w/w of total weight of tablet [9].

Evaluation of controlled porosity osmotic pump tablets [10-15]

Evaluation of powder blend [10-15]

The flow property of core material ready to compress was evaluated by measuring bulk density, tapped density, hausner's ratio, carr's index and angle of repose.

Evaluation of core tablets [7]

Tablets were evaluated for hardness by using a Monsanto type hardness tester. Friability of the tablets was evaluated by a Roche Friabilator (Mumbai, India). Thickness of the tablets was measured by using Vernier calipers.

Weight variation

The tablets were randomly selected from each batch and individually weighted. The average weight and standard deviation of 20 tablets were calculated.

Content uniformity

Five tablets were taken and finely powdered. The quantities of the powder equivalent to 4 mg of glimepiride were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with phosphate buffer (pH 7.4) solution and mixed thoroughly. The solution was made up to volume and filtered and the absorbance of the resulting solution was measured at 228 nm by using UV-visible double beam spectrophotometer.

In vitro drug release study of factorial design formulations (SP_1 to SP_8) [15]

In vitro release of glimepiride from factorial design formulations was carried out by using USP type II apparatus at a rotation speed of 50 rpm and at 37 ± 0.5 C using 900 ml phosphate buffer pH 7.4 as the dissolution media. At appropriate time intervals, dissolution samples were withdrawn and filtered. Samples were analyzed at 228 nm by using UV-visible double beam spectrophotometer. The amount of glimepiride dissolved in the dissolution media was then determined from the calibration curve and the cumulative percentage of glimepiride released was calculated.

Release kinetics

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* drug release study were fitted with various kinetic equations namely zero order (% release vs t), first order (log% unrelease vs t) , higuchi matrix (% release vs square root of time). In order to define a model which will represent a better fit for the formulation, drug release data further analyzed by Korsmeyer Peppas equation, $M_t/M = kt^n$, where M_t is the amount of drug released at time t and M is the amount released at time , the M_t/M is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent, a measure of the primary mechanism of drug release. R^2 values were calculated for the linear curves obtained by regression analysis of the above plots [16-18].

Statistical analysis

Polynomial models, including interaction terms for all response variables using multiple linear regression analysis using Microsoft Excel 207. A polynomial model together with interaction terms was generated for the response variable (Y) by means of multiple linear regression analysis. 3D response plots were constructed using sigma plot software. One optimum checkpoint was selected by layout grid search techniques, performed over the entire experimental domain. Values were predicted for the drug:osmogent ratio, concentration of pore former, % weight gain using a mathematical model developed for the optimized formulation. The formula of checkpoint formulation is shown in above Table 3 [6]. These predicted values were compared with the resulting experimental values and the percentage bias was calculated.

$$\text{Bias } (\%) = \frac{(\text{experimental value} - \text{predicted value}) \times 100}{\text{experimental value}}$$

To study effect of pH on *in vitro* drug release

In order to study the effect of pH of the release media, release study of optimized formulation (SP_9) were carried out in dissolution apparatus USP type II in 0.1 N HCl, phosphate buffer pH 6.8, phosphate buffer pH 7.4 medium for 24 h with the temperature maintained at 37 ± 0.5 C. Samples of 5 ml were withdrawn at specific time intervals, filtered and analyzed at 228 nm by using UV-visible double beam spectrophotometer.

To study effect of agitation intensity on *in vitro* drug release

In order to study the effect of agitation intensity of the release media, release study of optimized formulation (SP_9) were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP type II at 50, 100, and 150 rpm for 24 h with the temperature maintained at 37 ± 0.5 C. Samples of 5 ml were withdrawn at specific time intervals, filtered and analyzed at 228 nm by using UV-visible double beam spectrophotometer.

Results and Discussion

Drug-excipients compatibility study

The FTIR spectra of pure glimepiride and physical mixture are shown in Figure 1 and Figure 2 respectively. The major peak of glimepiride in FTIR spectrum due to amide showed peak at 3367 and 3180 cm^{-1}, alkane in conjugation showed peak at 2860 cm^{-1}, amide with para substitution showed peak at 877 cm^{-1}. All the above peaks were also present in physical mixture confirming the presence of drug in the physical mixture without any interaction (Table 4).

Evaluation of controlled porosity osmotic pump tablets

Evaluation of powder blend

The results of powder blend of formulations SP_1 to SP_8 are shown in Table 5.

The results of angle of repose, bulk density, tapped density, carr's index and hausner's ratio indicates that powder blend has good flow property with good compressibility and suitable for direct compression method.

Evaluation of core tablets

The mean value of friability, thickness, weight and content uniformity of prepared core tablets of glimepiride are shown in Table 6.

Tablets prepared by direct compression technique showed uniform thickness, diameter and acceptable weight variations limit as per pharmacopoeial specifications.

Hardness was found in the range of 4 to 4.5 kg/cm^2 for all the formulations of the core tablet and the friability for all formulations was found to be less than 1% indicating sufficient mechanical integrity and strength of the prepared tablets.

The drug content for all formulations of core tablet was performed in triplicate. The drug content was between 99.0 to 101.0 % which is within the pharmacopoeial limit i.e. 90.0 to 110.0 %.

In vitro drug release study of factorial design formulations.

The results of *in vitro* release of glimepiride from different factorial formulation SP_1 to SP_8 are shown in Figure 3 to 4.

It can be evident Figure 3 to 4 that the cumulative percentage drug release from the formulation prepared by using 2^3 full factorial design were found to be SP_1 (97.96 % in 24 h), SP_2 (94.28 % in 24 h), SP_3 (96.20 % in 20 h), SP_4 (94.75 % in 22 h), SP_5 (99.90 % in 20 h), SP_6 (98.48 % in 22 h), SP_7 (96.00 % in 16 h) and SP_8 (92.30 % in 20 h).

Release kinetic

The *in vitro* release profile of formulations (SP_1 to SP_8) was analyzed by various kinetic models are shown in Table 7. The kinetic models used were zero order, first order, higuchi and korsmeyer peppas equations. The release rate constants were calculated from the slope of the respective plots. Higher correlation was observed with zero order plots (r^2 = 0.98-0.99) than first order and higuchi equation. It was observed from zero order plots that the drug release from controlled porosity osmotic pump tablets (Table 7). To find out release mechanism, the *in vitro* release data were applied in korsmeyer peppas equation. In the formulations under study, the value for n was found to be in the range of 0.85 to 1.80 (Table 7) indicating that the release mechanisms followed zero order case II transport and super case II transport as the case may be.

Statistical analysis

Experiments were carried out to determine the mathematical relationship between the factors acting on the system and the response of the system. The statistical evaluation of experimental outcomes was processed to find the optimum levels of drug:osmogent ratio, concentration of pore former and % weight gain that would provide controlled release of glimepiride form the formulations. A first order polynomial regression equation that fitted the data is as follows

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

Where b_0 is the arithmetic mean of all the quantitative outcomes of the eight experimental runs, b1–b3 are the estimated coefficients from the observed experimental values of Y for X_1, X_2, and X_3. The interactions terms XiXjXk (i, j, and k = 1, 2, and 3) shows how the change in response occurs when two or more factors are simultaneously changed. The equation represents the quantitative effect of factors (X_1, X_2, and X_3) upon the response Y. In the osmotic drug delivery system t_{90} is highly desirable parameter. In present study t_{90} was strongly influenced by % weight gain and composition.

$$Y = 19.71375 - 1.58875X_1 - 1.31625X_2 + 1.18375X_3 + 0.03875X_1X_2 - 19.875X_2X_3 + 0.3875X_1X_3 + 0.0125X_1X_2X_3$$

The p value of coefficients from Table 8 suggests that % weight gain have a significant effect on t_{90}. The negative sign of coefficients of X_1, X_2 and the interaction terms X_1X_3 indicate a negative effect on t_{90}. However, the coefficient values for interaction terms X_1X_2, X_1X_3, X_2X_3 and $X_1X_2X_3$ shows that their interaction was not statistically significant (p> 0.05, Table 8), hence they were omitted from full model to generate the reduced model. The coefficients X_1, X_2 and X_3 were found to be significant (p< 0.05, Table 8), hence they were retained in the reduced model.

$$Y = 19.71375 - 1.58875X_1 - 1.31625X_2 + 1.18375X_3$$

The value of R^2 was found to be 0. 9990 which indicate a highly significant and linear relationship between X_1, X_2 and X_3.

Full and reduced model for lag time of rupture

The full model for t_{90} was developed by using the coefficients. The significance level of coefficient β_{12}, β_{23}, β_{13} and β_{123} were found to at p > 0.05, hence it was omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 8. The coefficients β_1, β_2 and β_3 were found to be significant at p < 0.05, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient β_{12}, β_{23}, β_{13} and β_{123} contribute significant information for the prediction of t_{90} or not. The results for testing the model in portions are shown in Table 9. The critical value of F for = 0.05 is equal to 8.94 (df = 6, 3). Since the calculated value (F = 1.00) is less than critical value, it may be concluded that the interaction term β_{12}, β_{23}, β_{13} and β_{123} does not contribute significantly to the prediction of t_{90} and therefore can be omitted from the full model

Figure 5 and 6 showed the response surface plot and Counter plot of durg:osmogent ratio (X_1) and % weight gain (X_2) versus t_{90} respectively. The plot was drawn using Sigma Plot Software 11.0 demonstration version. The data demonstrate that both X_1 and X_2 affect the t_{90}. It may also observed that the X_1 and X_2 appear to favour the preparation of controlled porosity osmotic pump tablets of glimepiride. It can say that the t_{90} may be changed by appropriate selection of the X_1 and X_2 levels. The area in counter plot (Figure 6) shows if we selected X_1 and X_2 in this range we get the desired release profile of glimepiride tablet.

Validation of statistical model

Further optimization was carried out using grid search technique keeping X_2 as constant (level 1). The formulations whose response has optimal characteristics based on the experimenter's specifications can then be chosen. It clearly evident that X_1, X_2 and X_3 give desired response. Formulation SP_9 was formulated by using -1 (1:1.25 drug:osmogent), -1(10% w/w) and -0.85 (6.8%) as X_1, X_2 and X_3. Formulation SP_9 was optimized formulation that was used for further study. The optimized formulation SP_9 was prepared on the basis of lay out grid search technique the composition is shown in Table 3.

In vitro dissolution study of optimized formulation

The results of *in vitro* release of glimepiride from optimized formulation are shown in Figure 7. It evident that the selection of the optimized formulation on the basis of grid search technique and preparation of the optimized formulation on the basis of it gave us the desired results in terms of time for 90% drug release (21.61 h).

From the results of dissolution profile of check point formulations SP_9 (Figure 7), it was concluded that there is no significant difference in experimental t_{90} than that of predictable one (Table 10).

To study effect of pH on *in vitro* drug release

The results of *in vitro* release of glimepiride from optimized formulation SP_9 are shown in Figure 8.
It suggest that the dissolution data and dissolution profile of optimize formulation SP_9 in pH 1.2 hydrochloric acid, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer solutions respectively. The drug release rate in different dissolution media was almost similar. The pH of dissolution media has not significant impact on the drug release. So, the drug release from controlled porosity osmotic pump tablet was independent on pH.

To study effect of agitation intensity on *in vitro* drug release

The results of *in vitro* release of glimepiride from optimized formulation SP_9 are shown in Figure 9. It clearly evident that the dissolution data and dissolution profile of optimize formulation at 50 rpm, 100 rpm and 150 rpm. The drug release rate at different agitation speed was almost similar. The agitation speed of paddle has not significant impact on the drug release. So, the drug release from controlled porosity osmotic pump tablet was independent on agitation intensity. It could be expected that the release from the developed formulation will be independent of the hydrodynamic condition of the body.

Conclusion

Glimepiride was successfully formulated as controlled porosity osmotic pump tablets to release drug up to 24 h. The rate of drug release from the formulation increased with increased concentration of osmogent or pore former. The optimized formulation displayed desired results in terms of time for 90% drug release (t_{90}) for 21.61 h and mimicking the fluctuating symptoms of diabetes.

Acknowledgment

The authors are thankful to Zydus Cadila, Ahmedabad, Gujarat, India for providing gift sample of glimepiride for research work. The authors are highly thankful to Arihant School of Pharmacy and Bio Research Institute, Adalaj, Gandhinagar, Gujarat, India for providing all the facilities to carry out the work.

Declaration of Interest

The Authors declares that there is no conflict of interest.

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Table 1 Selection of levels for independent variables

Levels	X_1 (Drug:osmogent ratio)	X_2 (Concentration of pore former)	X_3 (% wt gain)
Low (-1)	1:1.25	10% w/w	8%
High (+1)	1:3.75	20% w/w	10%

Table 2 Composition of factorial design formulations for controlled porosity osmotic pump tablets

	Core tablets							
Ingredients (mg)	SP_1	SP_2	SP_3	SP_4	SP_5	SP_6	SP_7	SP_8
Glimepiride	4	4	4	4	4	4	4	4
NaCl	5	5	5	5	15	15	15	15
Lactose	63	63	63	63	63	63	63	63
MCC	25	25	25	25	15	15	15	15
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	100	100	100	100	100	100	100	100
	Coating solution							
Cellulose acetate (% w/v)	4	4	4	4	4	4	4	4
PEG 400 (% w/w of dry polymer)	10	10	20	20	10	10	20	20
Sudan red	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Acetone	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
% wt gain	8	10	8	10	8	10	8	10
Total weight	108	110	108	110	108	110	108	110

Table 3 Composition of controlled porosity osmotic pump tablets of optimized formulation SP_9

Core tablets	
Ingredients (mg)	**SP_9**
Glimepiride	4
NaCl	5
Lactose	63
MCC	25
Mg Stearate	1.5
Talc	1.5
Total weight	100
Coating	
Cellulose acetate (% w/v)	4
PEG 400(% w/w of dry polymer)	10
Sudan red	q.s
Acetone	q.s
% weight gain	6.8
Total weight	106.8

Table 4 FTIR interpretation data of glimepiride and physical mixture

FTIR peak at cm^{-1}		Interpretation
Glimepiride	**Physical mixture**	
3367, 3180	3300-3500	Primary amide stretching (2bands)
2860	2850	-C-H stretching alkane
1680-1630	1684	-C=O stretching
877	876	Amide with para substitution

Table 5 Evaluation of powder blend

Formulation code	Bulk density* (gm/ml)	Tapped density* (gm/ml)	Hausner's ratio*	Carr's Index* (%)	Angle of repose (°)
SP_1	0.220±0.020	0.250±0.025	1.14 ± 0.026	12.59 ± 0.40	24.18
SP_2	0.271±0.002	0.321±0.005	1.18 ± 0.025	15.26 ± 0.57	26.45
SP_3	0.293±0.015	0.352±0.017	1.20 ± 0.023	16.54 ± 0.33	23.57
SP_4	0.225±0.020	0.256±0.029	1.14 ± 0.026	12.10 ± 0.44	28.28
SP_5	0.270±0.002	0.322±0.010	1.19 ± 0.025	16.14 ± 0.57	26.30
SP_6	0.257±0.015	0.301±0.015	1.17 ± 0.023	14.61 ± 0.39	25.34
SP_7	0.246±0.015	0.298±0.027	1.21 ± 0.023	17.44 ± 0.43	27.90
SP_8	0.228±0.020	0.259±0.015	1.14 ± 0.026	11.96 ± 0.42	26.11

* Values are mean ± SD, (n=3)

Table 6 Evaluation of core tablets

Formulation code	Diameter* (mm)	Weight variation	Thickness* (mm)	Hardness* (kg/ cm²)	% Friability	Content uniformity* (%)
SP_1	6.36± 0.01	Pass	2.25± 0.27	4±0.19	0.3976	99.51±0.25
SP_2	6.36± 0.01	Pass	2.23± 0.35	4±0.47	0.3952	98.19±0.29
SP_3	6.36± 0.01	Pass	2.19± 0.25	4±0.28	0.4955	99.11±0.34
SP_4	6.36± 0.01	Pass	2.21± 0.27	4±0.19	0.3456	99.59±0.25
SP_5	6.36± 0.01	Pass	2.14± 0.35	4±0.47	0.3842	98.49±0.29
SP_6	6.36± 0.01	Pass	2.18± 0.25	4±0.28	0.4165	98.51±0.34
SP_7	6.36± 0.01	Pass	2.24± 0.27	4±0.19	0.3878	99.54±0.25
SP_8	6.36± 0.01	Pass	2.29± 0.35	4±0.47	0.3459	98.29±0.29

*** Values are mean ± SD, (n=3)**

Table 7 Drug release kinetic data of formulation SP_1 to SP_8

Formulation	Regression coefficient (R)							
	Zero order		First order		Higuchi		Krosmayer-peppas	
	K_0	r^2	K_1	r^2	K_h	r^2	n	r^2
SP_1	4.37	0.989	0.14	0.817	19.46	0.992	1.18	0.935
SP_2	4.13	0.993	016	0.787	25.05	0.991	1.64	0.953
SP_3	4.95	0.993	0.14	0.714	27.12	0.978	1.11	0.945
SP_4	4.35	0.995	0.13	0.870	24.73	0.969	1.33	0.943
SP_5	4.77	0.982	0.11	0.876	26.60	0.994	0.85	0.966
SP_6	4.40	0.982	0.09	0.836	25.96	0.993	0.98	0.959
SP_7	5.50	0.998	0.09	0.924	27.32	0.981	0.79	0.991
SP_8	4.74	0.995	0.11	0.818	25.42	0.984	0.83	0.986

K: release rate constant, r^2: coefficient of determination, n: release exponent

Table 8 Regression Statistics for Y

Regression Statistics for Y	
Multiple R	0.995371
R Square	0.990763
Adjusted R Square	0.983836
Standard Error	0.324788
Observations	8
Coefficients	**P-value**
β0 = 19.71375	6.90E-09
β1 = -1.58875	0.000158
β2 = -1.31625	0.000330
β3 = 1.18375	0.000499
β12= 0.038	0.31
β13= -19875	1.12566
β23= 0.3875	0.067809
β123 = 0.02125	0.98

Table 9 Calculations for testing the model in portions

	t_{90}					
	DF	SS	MS	F	R^2	
Regression						
FM	7	45.6815	7.6135	210.75	0.9992	F_{cal} = 1.00
RM	3	45.2632	15.087	143.02	0.990	
Error						F_{cri} = 8.94
FM	1	0.0036	0.0036	-	-	
RM	4	0.4220	0.105	-	-	DF = (6,3)

DF: degree of freedom, SS: sum of squares, MS: mean of squares, F: Fischer's ratio, R^2: regression coefficient, FM: full model, RM: reduced model.

Table 10 The experimental and predicted values for responses Y

Formulation code	t_{90} (h)		
	Experimental value	**Predicted value**	**% Bias**
SP_9	21.68	21.61	0.3228

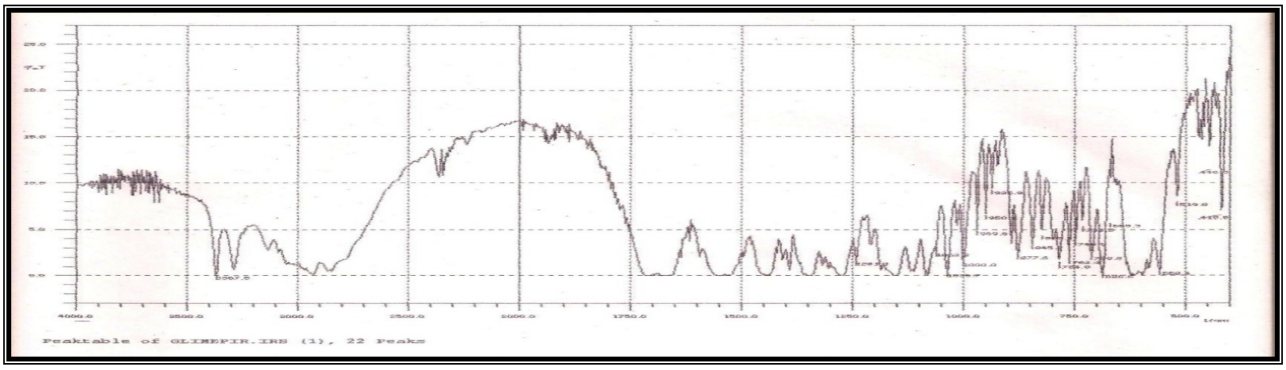

Figure 1 FTIR Spectra of glimepiride

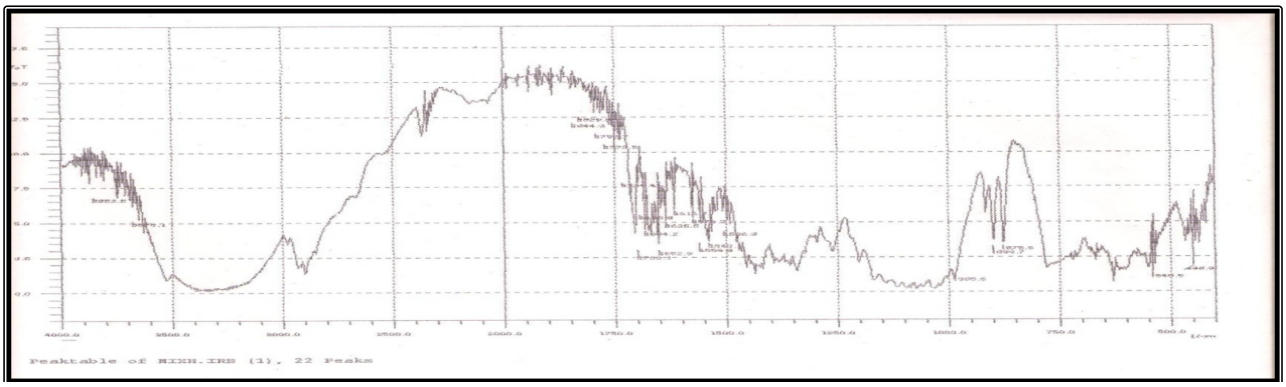

Figure 2 FTIR spectra of physical mixture

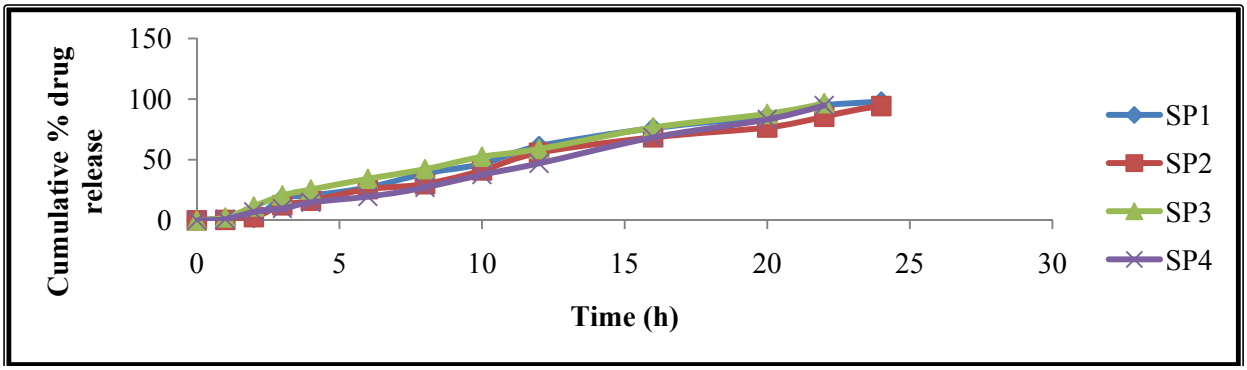

Figure 3 *In vitro* release of glimepiride from the SP_1 to SP_4 formulations

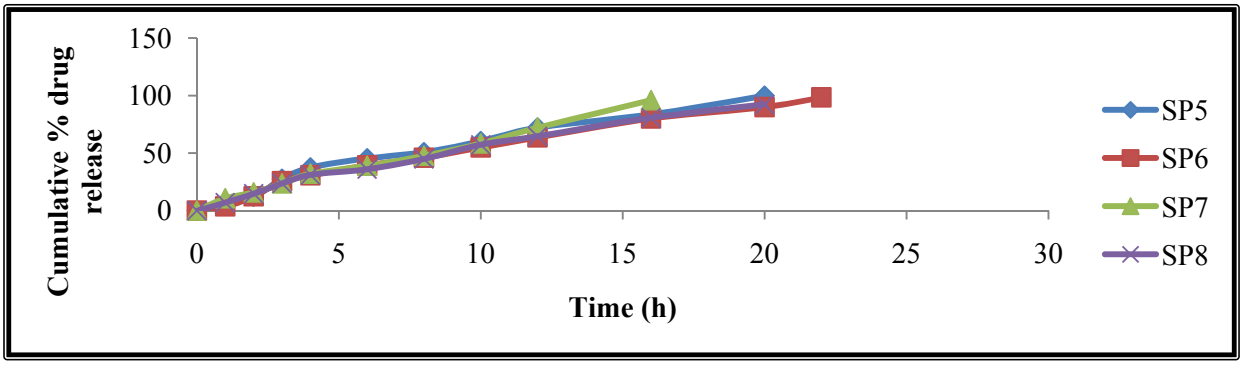

Figure 4 *In vitro* release of glimepiride from the SP_5 to SP_8 formulations

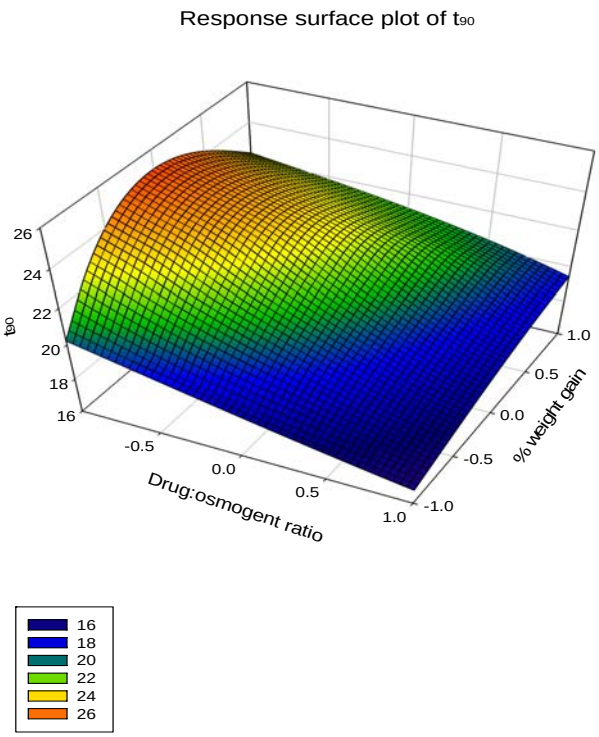

Figure 5 Response surface plot showing the influence of % weight gain and drug:osmogent ratio on response Y i.e. t_{90}.

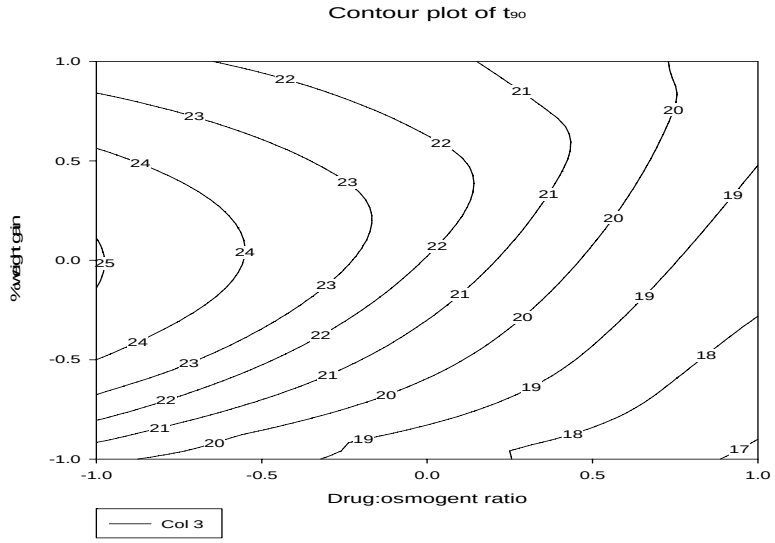

Figure 6 Contour plot showing relationship between drug:osmogent ratio and % weight gain on t_{90}

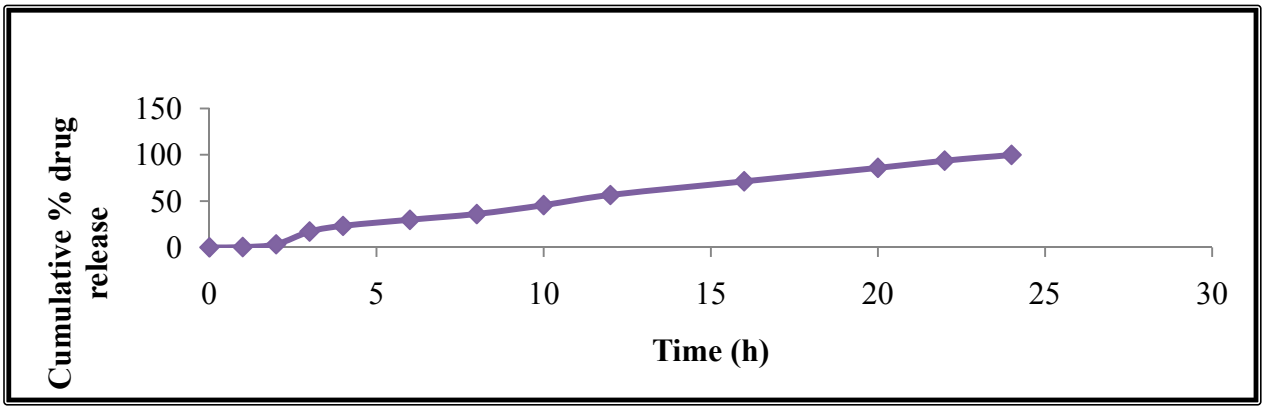

Figure 7 *In vitro* release of glimepiride from SP_9 formulation

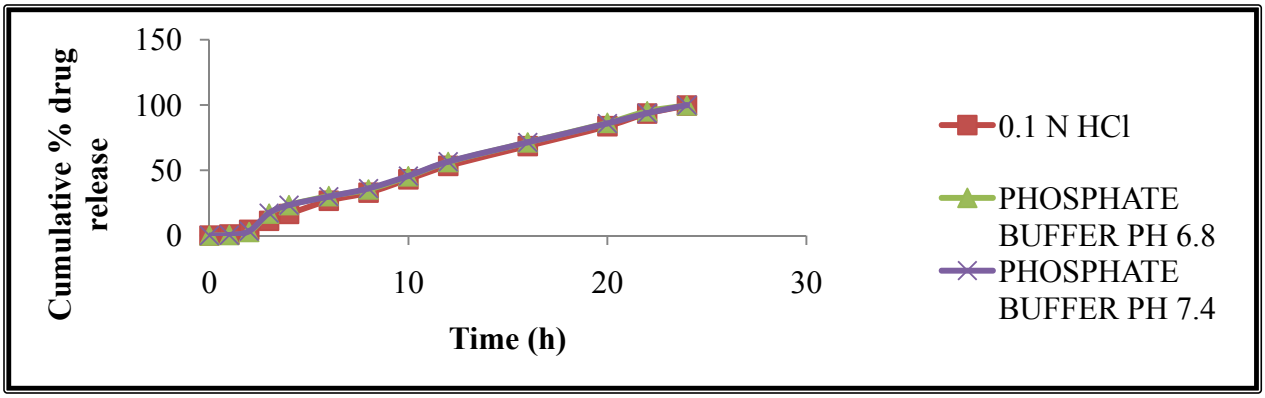

Figure 8 *In vitro* release of glimepiride from SP_9 formulation in 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4

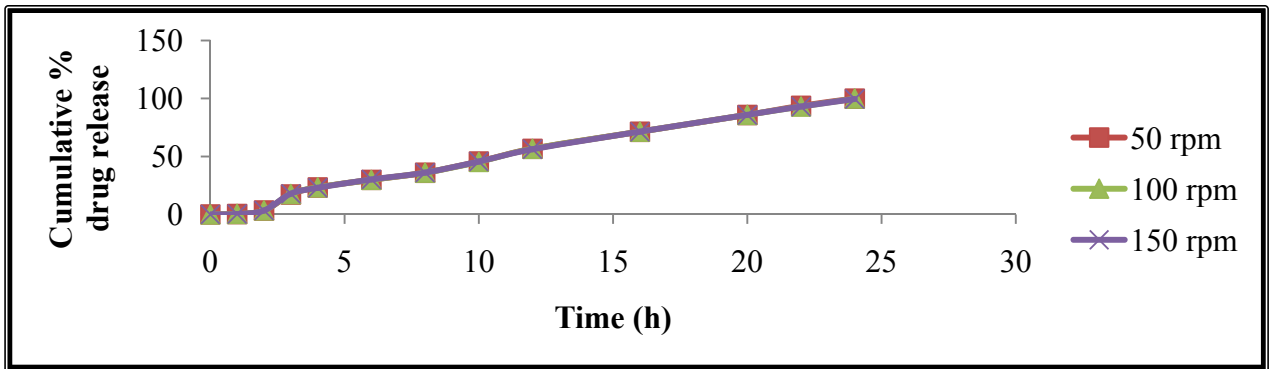

Figure 9 *In vitro* release of glimepiride from SP_9 formulation at 50 rpm, 100 rpm and 150 rpm