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EFFECT OF HYDROPHILIC AND HYDROPHOBIC POLYMERS ON THE MANAGEMENT OF DIABETES USING ANTI-DIABETIC SUSTAINED RELEASE TABLETS BY THE APPLIANCE OF FACTORIAL DESIGN

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ABSTRACT

The consequence of the current study is the preparation and evaluate drug loaded sustained release matrix tablets for "Diabetes Mellitus", using hydrophilic carrier, hydrophobic and pH dependent polymers, by applying 2^3 factorial designs using Box–Behnken design. Glimepiride sustained release tablets were manufactured using a wet granulation technique with 2^3 factorial designs to incorporate a variety of ethyl cellulose concentrations, HPMC K15M, and Eudragit L100 in a variety of variations. The accurate objectives comprise generally to find the levels of the variable that affect the chosen responses and determine the levels of the variable .The quantity of polymers Ethyl cellulose, HPMC K100M and Eudragit L100 was selected as independent variables, X1, X2 and X3 respectively whereas, % swelling index and %CDR was selected as dependent variables. Additional to support Pre formulation studies FTIR and DSC studies were carried out. Interaction of drug with polymers was assessed by FT-IR spectroscopy; results indicated absence of chemical interactions between drug and the polymer. DSC curve of Glimepiride shows a sharp endothermic peak at 200.30°C indicating its crystalline nature and it's compatible with the polymers. Totally sixteen formulations were designed and are evaluated for pre-compression and post-compression studies, *In-vitro* drug release and *In-vivo* studies. The findings revealed that all formulations had been identified within Pharmacopoeia limits, and that the dissolution profiles *in-vitro* of all formulations were matched to various Kinetic models, Polynomial equations were developed for % swelling index and %CDR. The optimized formulation was selected based on the high desirability value (close to 1). From overlay plot and desirability bar graph. The experimental value of prepared optimized formulation from the cross-validation model shows closer value to the predicted values. The prediction variance was less than 5.0 per cent. Lower relative error values suggested that there was near agreement between the experimental values and the expected values for all polymers on the % swelling index and the % release of the drug. So the optimized formulation was subjected to *In-vivo* studies, Blood glucose was estimated using one touch glucometer at specified time points. Histopathological examination (necrotic and fibrotic changes of islets of langerhans) was done.

KEYWORDS

Glimepiride, 2^3 factorial designs, Box–Behnken design, Ethyl cellulose, HPMC K100M and Eudragit L100.

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INTRODUCTION

Oral sustained release drug delivery system

Most of the important medications therapies have been improved by Oral SAR liberate dosage forms (SRDF). The foremost aim of oral SAR medicament

delivery systems (SDDS) is to predict and improve bioavailability of medicaments[1]. But, several physiological difficulties are excluded in the developmental process, Due to the complex gastric emptying and the loss to search and locate the SDDS in the desired GI regions (GIT). This variability leads to uncertain spell and bio - availability for maximum plasma levels[2]. So, for a variety of remarkable medicaments the CRDF (Controlled mechanisms of liberate) approaches has not been appropriate, and In the GIT upper section, i.e. gastrointestinal and bowel, described by a narrow consumption area which is Because of anatomic segments, brief passage spell of the dosage type is due. SRDF of the narcotics exits the high portion of the GIT and enters the remote region with little intake, which contributes to a loss of bioavailability during a fast intake process within short tm periods (less than 6 hours). The main aim of the SR compositions was to change and improve medicament performance, increasing medicament action tm, decreasing the dosage frequency, reducing unfavorable effects, decreasing the required dose and providing the minimum amount of pharmaceuticals on the best route possible[3]. SR dosage forms are compositional to instantly carry a medicament's bl00d level through an initial dose portion to treatment engrossment and then maintain it with the continuation portion for a certain predetermined period. The intake cycle does not impact the SR of medications in the GI tract after oral direction. The key objective of ways of SR dose is to improve medicament treatment assessed by the correlation between benefits and drawbacks of SR device uses[1].

In case of, conventional dosage forms it fails to hold medication bl00d pressures for a long spell within a clinical range. By administrating the medicament repeatedly one can preserve serum engrossment of medications within the clinical range, by using a fixed dosing interval. The high medicament engrossment-tm peaks and troughs are the characters of saw tooth flux, which are latent problems.

The highest intake field (Bowel or upper bowel section), depends on Spell of gastric emptying is typically 2 to 3 hours on average in humans ,this leads to Inconsistent medicament liberate from a method of medicament delivery leading to reduced dosage efficacy. Thus GIT put forwards various advantages during assigning the medicament delivery system in a particular region, specifically for GIT's narrow intake screen medicaments, major intake of the abdomen, intestinal stability issue, alkaline pH solubility, local abdomen activity and colon degradation properties. The medicament should be formulate in a pharmaceutical shape with a small intake vestibule, which may extend the residential gastric tm within the body, which resulting in the better Step of these medicines intake[2].

Glimepiride, an anti-diabetic medicine used as a model to create a sustained release formulation in the treatment of type 2 diabetic mellitus. Glimepiride has a short biological half-life of 5 hours and fast first-pass metabolism which requires many doses every day, which is why a continuous release matrix tablet of Glimepiride was developed in the present study. Glimepiride sustained release matrix tablet is typically taken two times a day at separated doses. The regular dosage starts at 210mg triple a day.

MATERIAL AND METHODS

MATERIAL

Glimepiride was obtained as a gift sample from Zydus pharmaceuticals, Ahmadabad, Gujarat. Ethyl Cellulose-EC 7cps was obtained from DOW Chemicals, U.S, and HPEMC K15M was obtained from Shasun pharmaceuticals, Pondicherry, Tamilnadu and Eudragit L 100 was obtained from Zydus pharmaceuticals, Ahmadabad, Gujarat. All the ingredients used were of analytical grade.

Experimental design

The QbD of 2^3 factorial designs was used to evaluate the impacts of three independent parameters and their impact on the physicochemical properties of tablets. During the optimization of SR tablets, the concentrations of Ethyl Cellulose (A), HPMC K15M (B), and Eudragit L 100 (C) were chosen as independent parameters, while the %Swelling index (%SWI) and % cumulative drug release (% CDR) were chosen as dependent (response) factors. As shown in (Table No.1), each independent component was assigned a low and high level. In accordance

with the factorial design, sixteen preparations of Glimepiride SR tablets (F1-F16) were designed. The Design Expert Software 10 (Stat-Ease Inc., USA) was used to analyze the collected data in order to evaluate the process variables impacting the formulation aspects and to screen optimal formulations using an experimental approach[3]. It is a useful tool that modifies each variable at the same time and provides all possible optimum selections.

Preparation of glimepiride matrices tablets

Sixteen different compositions of tablets were prepared using a wet crumble technique as reported. A dry mixture was drawn and sufficient granular agent capacity (5 percent of the ethane solution PVP-K90), which comprises 2.5mg Glimepiride of the drugs, monomers (HPEMC K15 M), EC and Eudragit L100 and filler talc. Slowly added PVP Ethanol solution. The mass was sifted across 20 meshes after adequate cohesiveness was achieved. The crumbles had been dried for 1 hour at 55^{o}C. These granulate blend were combined with magnesium stearate (1.6 percent W / W), the proper lubricant and then compressed with a round, flat-faced 10-mm-diameter, 16-station tablet CMPSN machine. All compressed tablets were detained at room temperature in a jar that was tightly airborne. Detailed compositions of the various compositions prepared using 2^3 factorial designs as mentioned in (Table No.1).

CHARACTERIZATION OF SR TABLETS

Measurement of tablet hardness

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Difficulty is a function of the pressure exerted and therefore the variables that make the force differ. The added friction used to produce the tablet raises the hardness properties and then the maximum value after the pressure increases causes the tablet to laminate or to shield and therefore the integrity of the tablet is destroyed. Tablets are usually tougher than directly after compaction for several hours after the compaction. When mixed for too long or used in too high concentration, lubricants can influence the toughness of a tablet. The lubricant coats the granules and interferes with the joining of the tablet. Larger tablets have a larger force than a small tablet to inflict fractures (harder).

Friability test

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

Content uniformity

Five pills were individually contemplated and placed in a mortar and pestle. A buffer was extracted with powdered Glimepiride (100mg). The solution was filtered by a membrane of 0.45µm and 226nm of intake measured after appropriate dilution.

Swelling indication

Enlargement of the portion of the tablet excipient means that the solvent absorbs and hence mass and volumes rise. The saturation of capillary spaces in molecules or macro-molecule hydration will cause the liquid absorption through a molecule. The liquid penetrates the molecules by pores and binds to massive molecules; breaks the hydrogen bond and causes molecules to swell. In terms of mass gained by the tablet, the degree of enlargement may be calculated.

The actual tablet of each composition was weighed and placed in a beaker of 50ml pH 1.2 and 7.8. The tablet has been removed and its load has been recorded, and it is still dried on filter paper to extract moisture and its dry load is recorded. Then the Enlarge indications calculated as

$$\% \text{ enlarge indication} = \frac{\text{wet mass-dry mass}}{\text{Dry mass}} \times 100$$

***In vitro* dissolution**

Glimepiride deliver from the SR tablet was tested as a Break up medium at 50rpm and 37 ± 0.5C in 900ml of 0.1N HCL and 900ml of phosphate buffer

7.8 up to 24 hours using a USP Break up paddle assembly. At various stages, a spectrophotometric UV content of 226nm was measured, a purifying and diluting aliquot (1ml) to 10ml and medially dissolved. To preserve the dissolve capacity, the same capacity was replaced by the fresh break up fluid.

Studies of Break up were performed for 24hrs duration, and the value was taken. The cumulative drug deliver percentage was determined using an equation derived from a quality loop.

Data analysis (Curve Fitting Analysis)[5]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the

Data obtained were plotted as:

1) Cumulative percentage drug released Vs time (Zero order plots)
2) Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
3) Log cumulative percentage drug remaining Vs time (First order plots)
4) Log percentage drug released Vs log time (Peppas plots).

SELECTION OF AN OPTIMIZED FORMULATION

A three-factor, two-level QbD was used to optimize the sustained release Glimepiride matrix tablets, using three different polymers. The design setup consisted of sixteen experimental points. Preliminary trial batches of formulations were developed by considering the extreme values of formulation process variables for getting the preferred formulation with high %swelling index (SWI) and high % Cumulative drug release (%CDR). From the preliminary experiments, it was found that the formulation variables such as % of EC, % OF HPMC and % OF EDGT L 100 were the key factors that influenced the %swelling index and % Cumulative drug release. Thus, the impact of these three key, independent formulation factors [A= EC, B= HPMC, and C= EDGT L100] on the high % swelling index and high percent cumulative drug release of the manufactured sustained release tablets was thoroughly examined. For analysis, the actual values of each variable were coded at two levels. For each of the sixteen experimental points, response variables such as % swelling index and % cumulative drug release were examined[6].

ANOVA was used to examine the lack of fit as well as the significance of the linear and interaction effects of the variables on the quality metrics. In ANOVA, the F-value is the ratio of the mean square due to regression to the mean square owing to genuine error. To conduct statistical analysis, the trial version of Design Expert Statistical Software Version 10 was employed.

RSM polynomial second-order equation was used to optimize the Glimepiride SR tablets, taking into account the total desired value. A numerical optimization technique was used to find a point with the highest percentage of swelling index (SWI) and cumulative drug release. Experiments were carried out under the desirability conditions and experimental and predicted values compared to validate the model. The best conditions were selected. The runs were conducted three times in optimized conditions to confirm the results.

CHARACTERIZATION OF OPTIMIZED GLIMEPIRIDE SR TABLETS

Fourier transmitter infrared (FTIR) spectroscopy

In order to test the interaction of specific composition Non-API with Glimepiride, rock-solid admixtures were organized by combining the product with each composition excipient separately in a ratio of 1:1 and placed in air-tight containers at 30 + 20c/67 + 5 percent RAH. The solid admixture was defined by the usage of Fourier Trans type Infrared Spectrographs (FT-IR).

Differential Scanning calorimeter (DSC)

The thermal study of Glimepiride and Glimepiride SR tablets were analyzed using DSC (NISHKA LAB, Hyderabad). About 10 mg of samples was placed in aluminum crimp cells and heated from 20 to 300°C with a scanning rate of 10°C/min in a nitrogen ambiance.

***In vitro* dissolution by HPLC Method**

On a 5-micron-octadecyl-silane (ODS) column (250 to 4.6mm) methanol-buffered (pH = 7.8) 40:60 vl/vl was introduced as a mobile-phase at 1ml/min flow speeds, and PdA-detector was used to measure at

228nm. The correlation co effective (r2) for Glimepiride was observed to be 0.998 over 5 to 30µg/ml.

***In-Vivo* Studies**

Blood plasma glucose was estimated using one touch glucometer at specified tm points. Pancreatic tissue sections were fixed in formaldehyde (4g/L) and then surrounded in paraffin. The paraffin- surrounded sections were subsequently stained with Hematoxylin and Eosin stain. Histopathological examination (necrotic and fibrotic changes of islets of langerhans) was done by a pathologist who was bounded to the treatment designs used in the experiment.

Statistical examination

The mathematical analysis was carried out using the version 9.05. SPSS software kit with the one-way ANOVA and the multi-package Duncan analyses. In each sampling category the final values were multiplied ±SD for 10 rats. A p value <0.05 was assumed to suggest a meaningful discernable correlation[7].

RESULTS AND DISCUSSION

Optimization of formulations

RSM has been used for GMP-SR tablets optimization. The values predicted have been estimated by the model fitting technique and have been found to correlate sufficiently with the actual values. After careful analysis, the actual values have been adapted to regression models. Fitted answer surface may actually produce poor and defective results without checking the adequacy of the model. Therefore, the adequacy of the model must be monitored. The chronological model sum of squares and model summary statistics were used to determine the adequacy of models among numerous models representing response parameters of GMP-SR tablets. The chronological model sum of squares has the highest "predicted R^2" and "adjusted R^2" values and indicated P 0.01 for a quadratic model; thus, the quadratic model was chosen for further analysis.

Results revealed that the % SWI varied from 49.4% to 76.3% and %CDR varied from 72.4% to 88.4%. For obtaining the pragmatic relationship between the experimental results based QbD, the following polynomial equations in terms of coded units were generated.

$$\% \text{ SWI} = +67.90 - 6.49\ A + 7.18\ B + 1.44\ C + 0.1602\ AB - 5.11\ AC + 1.39\ BC - 1.19A^2 + 0.0044\ B^2 - 1.13\ C^2$$

$$\% \text{ CDR} = +74.49 - 2.79\ A + 5.21\ B + 2.44\ C - 0.0338\ AB - 3.07\ AC - 0.1508\ BC - 0.1131A^2 + 0.4600\ B^2 + 6.41\ C^2$$

From the polynomial equations, the overall desirability values for all formulations were calculated and found highest (0.974) with the F5 formulation (A- EC-100mg, B-HPMC K15M-150mg and C-EDGT-L100-125mg). Thus, F5 formulation was measured as an optimized formulation. The ANOVA results and statistical parameters for the QbD are shown in (Table No.2). The model is highly significant as evident from F-test value being 242.91 for % SWI and 269.10 for % CDR. respectively, with $P < 0.05$.

The coefficient of determination (R^2 value) is the best measure of the degree of fit, for %SWI is 0.9977 and their adjusted R^2 is 0.9936 and the corresponding R2 value for %CDR is 0.9979 and their adjusted R^2 is 0.9942. In general, the higher the coefficient of variation (CV) value, the lower the experiment's reliability. The CV value in the current design was low (1.26 and 0.59) that statement a higher level of reliability of the experiments performed. It is implied from very lower value of $P < 0.05$ and higher R^2 value that the selected model is highly significant and sufficient to represent the relationship between the response and independent variables. Response of the hypothesized model, the optimized form of Glimepiride-SR tablet was predicted to yield R1 (%SWI), R2 (%CDR), values of 89.1%, and 94.8%, respectively, when A (EC), B (HPMC K15M), and C (EDL L100) values were 100mg, 150mg and 125mg. A new optimized Glimepiride-SR tablet was prepared with these levels of the independent variables, which yielded the R1 (%SWI), R2 (%CDR) values of 86.7% and 93.73%, respectively. And their % prediction error was found to be 0.439 for %SWI and 0.951 for % CDR. From the final formulation's result of each response parameter. With a low bias percentage, it was

discovered that the actual values of each response were much closer to the value of the prediction (Table No.2). The optimized form of Glimepiride-SR tablet (F5) was also found to be reliable and prudent, with the highest desirability (0.974) value for the formulation[8].

EFFECT OF PROCESS PARAMETERS ON THE RESPONSE VARIABLE

Effect of Independent Variable on Swelling Index (SWI)

The p-value clearly indicates the remarkable influence of the EC (A), HPEMC K 15 M (B), EL L 100 (C) and their combination respectively in enlarge indication. The EC (A) shows remarkable impact in the enlarge indication (p-value < 0.0010) and HPEMC K 15 M (B) also shows remarkable impact in the enlarge indication (p-value < 0.0010). The EL L 100 (C) alone shows remarkable impact in the enlarge indication (p-value less than 0.0001). It clearly shows that the HPEMC K 15M and EL L 100 influence the enlarge indication a lot compared to that of EC (A). The combination of EC, HPEMC K 15 M (AB), HPEMC K 15M, EL L 100 (BC) have synergistic effect on enlarge indication, in case of EC, EL L 100 (AC) has greater antagonistic effect on enlarge indication and it is asserted by respective p-value and coded equation. A synergistic effect was observed in doubling-up the amount of HPEMC K 15 M (B^2) and antagonistic effect was observed in doubling-up the amount of EC (A^2), EL L 100 (C^2).

With the increase in the engrossment of the Ethyl cellulose (EC) and incorporating HPEMCK15M at high level (150mg) with respect to Eudragit L100 at constant level as high. The results of enlarge indication shows decreasing range from 80% to 70% .It concluded that incorporating of aqua phobic monomer at high level, failed to permit the fluid to get swell. This shows the way to fall down of swelling indication range (Figure No.1). However this figure shows there is no interaction between AC and risk factor is at low level. The interaction of Independent Variable Ethyl cellulose and Eudragit L 100 (AC) shown in (Figure No.1). With the increase in the engrossment of the Ethyl clse by maintaining high level of Eudragit L 100, figure shows greater interaction with the two unconstrained pattern at high level and evidenced with the decline of enlarge indication. This is due to enlarge degree decreasing with increasing the engrossment cross linker like Eudragit L 100.The monomer network expands(217), during the intake of fluids, Due to expanding hydrogel network and dissociation of acid molecules, the pH of the fluids decreases, results decreasing in fluid intake. As they are pH sensitive. This shown greater interaction and risk factor

Effect of Independent variable on cumulative drug Deliver (CDR)

The combination effect of two independent pattern (AC) shown greater interaction with antagonistic effect, which is clearly indicated in ANOVA table with least p value (<0.0001) and coded factors as evidence.

The interaction of unconstrained pattern shown by incrementing the engrossment of Ethyl clse (A) and HPEMC K15M (B) at high level, Eudragit L 100 as a constant level was shown in the (Figure No.1). This outcome clearly indicates there is a decreasing in CDR from 84% to 78%, owing to inclusion of aqua phobic monomer, Ethyl clse at high level which retards the drug Deliver from monomers. since they doesn't permit the Transmission of fluid into the tablets that show the way to lack of proper wetting and results , decrease in CDR .It conclude that there is no interaction between two unconstrained pattern (AB) on CDR as responses and with low risk factor.

The result reveals that (Figure No.1). Strong interaction and negative effects observed between two unconstrained patterns (AC), in high engrossment of Eudragit L100. This leads to decrease in %CDR, because of dissociation of acid molecules in Eudragit L100, the pH of the fluids decreases, results decreasing in fluid intake. As they are pH sensitive. This shown greater interaction and risk factor with antagonistic effect.

***In vitro* drug release studies and release kinetics**

Depending on the independent variables, the percent CDR ranged from 72.4 % to 94.6 % for up to 24 hours. With higher levels of HPMCK15M and ED L100 and lower levels of EC, the highest percent CDR (94.6%) was observed. However, at a higher level of EC and ED L100 but a lower level of

HPMCK15M, the lowest percent CDR (72.4%) was observed.

It is critical to understand the release mechanism and kinetics while attempting to build a sustained-release device. The drug release profiles of Glimepiride sustained release tablets followed a biphasic pattern, with a quicker drug release phase (burst effect) followed by a slower controlled drug release phase for 12 hours (Figure No.2,3). As they are a matrix system, the burst effect may be linked to the unbound drug and the drug molecules that are attached to the surface of the sustained release tablet. The pattern of sustained release depends on the rate at which the Swelling Index is emitted, which depends further on the solubility level and diffusion rate of the drug from the polymer matrix[9].

To explore the drug release properties, in vitro drug release data from Glimepiride sustained release tablets were fitted into zero-order, first-order, Higuchi, and Korsmeyer- Peppas models. Table No.4 shows the medication release kinetics data. The Higuchi and Korsmeyer-Peppas equations were demonstrated by comparing the R^2 values of the Glimepiride sustained release tablets. It was, however, best suited to the Higuchi model. The release exponent "n" is more than 0.5, indicating that Glimepiride was released from polymers by a non-Fickan diffusion mechanism. After 10 hours, 51% of the medicine was released, and drug release reached a constant state after roughly 24 hours for the optimum formulation (93.7%). This proves that the formulated Glimepiride sustained release tablets can keep the medicine in the systemic circulation for longer, potentially reducing dose frequency.

FTIR studies

Compatibility studies were performed by using FET-IAR spectrophotography. The IR spectrums of pure Glimepiride drug were compared with IAR spectrums of physical mixture of Glimepiride (EC, HPEMC K15 M and EDGT L100). Some characteristic peaks do not emerge or vanish. This shows that the drug and monomers have no scientific chemical interaction. The presence of peaks in the predicted range suggests that the studies have been carried out are confirmed.

DSC studies

The DSC thermograms of pure Glimepiride, Glimepiride with polymers are shown in (Figure No.5). The pure Glimepiride showed a single sharp endothermic peak at about 196.2°C and mixture of drug with polymers shows same sharp endothermic peak with the same range, without the disturbing the melting point of pure drug .Indicating its crystalline nature and it's compatible with the polymers.

***In-vivo* Studies**

Induction of experimental diabetes (219)

DM was induced at the rate of 90 m g / kg solubilized in the citrate bfr (0.01 M, pH 4.4) in overnight rats by intra peritoneal injection of the STAZ (1ml/rat) while intra peritoneal citrate buffer-bfr was administered alone by normal control animals. Subsequently, bl00d from O/N-fasted animals was obtained 72 hours after STAZ injection by sin ocular puncture. Fasting plasma glucose levels > 270mg/dl plasma boards were included.

After STAZ treatment, rats were randomly categorized, with 10 animals/grouping. Out of the 3 DM animal category, 2 DM animal categories were given Glimepiride and GSAR (Novel Composition) at the dosage of 100mg/kg as a suspension in 0.5% W/V CMC, by oral gavages, and the third category was used as a DM control.

Estimation of Blood Plasma glucose and Cellular pathological Examination

Blood plasma glucose was estimated using one touch glucometer at specified tm points. Pancreatic tissue sections were fixed in formaldehyde (4g/L) and then surrounded in paraffin. The paraffin- surrounded sections were subsequently stained with Hematoxylin and Eosin stain. Histopathological examination (necrotic and fibrotic changes of islets of langerhans) was done by a pathologist who was bounded to the treatment designs used in the experiment.

Statistical examination

The mathematical analysis was carried out using the version 9.05. SPSS software kit with the one-way ANOVA and the multi-package Duncan analyses. In each sampling category the final values were multiplied ±SD for 10 rats. A p value <0.05 was

assumed to suggest a meaningful discernable correlation[10].

Table No.1: Formulation table of Glimepiride SAR Tablets using Factorial Design and their responses

Run	FC	Factor 1	Factor 2	Factor 3	Response 1	Response 2
		A:EC (mg)	B: HPEMC K15 M (mg)	C:EL L 100 (mg)	SWI (%)	CDR (%)
1	F1	100	50	75	62.18	72.91
2	F2	100	50	125	71.8	84.4
3	F3	150	50	75	58.9	73.47
4	F4	150	150	125	66.5	82.34
5	F5	100	150	125	89.1	94.6
6	F6	150	150	75	71	84.18
7	F7	100	150	75	73.23	83.63
8	F8	150	50	125	49.4	72.4
9	F9	102.5	95	105	71	77.89
10	F10	130	105	75	62.8	79.31
11	F11	150	50	75	55.4	73.47
12	F12	150	50	75	54	74.56
13	F13	130	105	75	64.02	79.3
14	F14	100	95	125	76.3	88.42
15	F15	150	105	125	53.4	78.56
16	F16	102.5	95	105	71.06	78

Table No.2: ANOVA results and statistical parameters of the QbD model

Response No.1: Swelling index

S.No	Source	Sum of Squares	df	Mean Square	F-value	p-value	
1	Block	72.80	1	72.80			
2	Model	1492.91	9	165.88	242.91	< 0.0001	significant
3	A-EC	404.06	1	404.06	591.69	< 0.0001	
4	B-HPEMC K15 M	412.66	1	412.66	604.28	< 0.0001	
5	C-EL L 100	16.50	1	16.50	24.17	0.0044	
6	AB	0.0903	1	0.0903	0.1322	0.7310	
7	AC	250.74	1	250.74	367.17	< 0.0001	
8	BC	15.45	1	15.45	22.63	0.0051	
9	A^2	0.8554	1	0.8554	1.25	0.3139	
10	B^2	8.897E-06	1	8.897E-06	0.0000	0.9973	
11	C^2	1.25	1	1.25	1.83	0.2345	
12	Residual	3.41	5	0.6829			
13	Lack of Fit	1.69	2	0.8442	1.47	0.3594	not significant
14	Pure Error	1.73	3	0.5753			
15	Cor Total	1569.13	15				

Response No.2:% CDR

S.No	Source	Sum of Squares	df	Mean Square	F-value	p-value	
1	Block	21.21	1	21.21			
2	Model	551.18	9	61.24	269.10	< 0.0001	significant
3	A-EC	74.62	1	74.62	327.86	< 0.0001	
4	B-HPEMC K15 M	217.24	1	217.24	954.56	< 0.0001	
5	C-EL L 100	47.78	1	47.78	209.92	< 0.0001	
6	AB	0.0091	1	0.0091	0.0400	0.8493	
7	AC	90.20	1	90.20	396.36	< 0.0001	
8	BC	0.1821	1	0.1821	0.8003	0.4120	
9	A^2	0.0078	1	0.0078	0.0342	0.8605	
10	B^2	0.0964	1	0.0964	0.4236	0.5439	
11	C^2	39.83	1	39.83	175.00	< 0.0001	
12	Residual	1.14	5	0.2276			
13	Lack of Fit	0.5378	2	0.2689	1.34	0.3830	not significant
14	Pure Error	0.6002	3	0.2001			
15	Cor Total	573.53	15				

Table No.3: Comparisons between actual values and predicted values of the final formulation under optimized conditions

S.No	Optimized formulation code	Response	Predicted value	Experimental value	% prediction error
1	OFLMN	% SWI	87.0826	86.7	0.439
		% CDR	94.6368	93.73	0.951

Table No.4: *In vitro* release kinetics of Glimepiride sustained release tablet formulations up to 24 hrs

FMLN code	Zero order		First order		Higuichi	Korsmeyer-Peppa	
	K_0	R	K_1	R	R	n	R
F_1	2.643	0.968	-0.02	0.973	0.978	0.888	0.828
F_2	2.99	0.882	-0.030	0.983	0.976	0.916	0.78
F_3	3.084	0.990	-0.024	0.992	0.964	0.997	0.901
F_4	2.993	0.913	-0.027	0.984	0.984	0.919	0.799
F_5	3.598	0.974	-0.044	0.938	0.988	0.915	0.797
F_6	3.159	0.985	-0.029	0.968	0.979	0.904	0.818
F_7	3.17	0.946	-0.030	0.987	0.987	0.937	0.826
F_8	2.611	0.982	-0.020	0.974	0.974	0.836	0.787
F_9	3.314	0.995	-0.027	0.981	0.952	1.066	0.932
F_{10}	3.112	0.994	-0.026	0.96	0.956	0.939	0.861
F_{11}	3.084	0.99	-0.024	0.992	0.964	0.997	0.901
F_{12}	3.056	0.982	-0.025	0.996	0.977	0.954	0.867
F_{13}	3.112	0.994	-0.026	0.96	0.956	0.939	0.861
F_{14}	3.701	0.984	-0.037	0.973	0.967	1.063	0.909
F_{15}	3.318	0.996	-0.027	0.98	0.952	1.078	0.939
F_{16}	3.106	0.996	-0.025	0.952	0.994	0.983	0.896

Table No.5: Fasting plasma glucose levels of Streptozotocin (STAZ) -induced DM rats at intervals during daily oral administration of optimized Glimepiride SAR Tablets & Glimepiride SAR (GLIMY)

GRP	Treatment	Initial	2hr	12hr	24hr	72hr
I	DM control 1% w/v CMC soln p.o	252.41± 3.38	302.45± 0.855	329.77± 1.11	352.2±1.18	362.46±0.73
II	DM control + Glimepiride SAR (GLIMY) (100mg/kg p.o)	248.84± 0.48	219.62± 1.22	186.23± 1.52	135± 0.70	114.83±2.22
III	DM control + optimized Glimepiride SAR (100mg/kg p.o)	247.89± 1.43	198.12± 0.52	153.10± 2.00	124.2±1.26	111.23±2.94

Table No.6: Statistical Analysis

GRP	INITIAL	2 hr	12hr	24hr	72hr
I	252.41+ 3.38	304.45+0.85	329.77+1.11	352.2+1.18	362.46+0.73
II	248.84+0.48	219.62+1.22***	186.23+1.52***	135+0.70***	114.83+2.22***
III	247.89+1.43	198.12+0.52***	153+2.00***	124.21+1.26***	111.23+2.94***

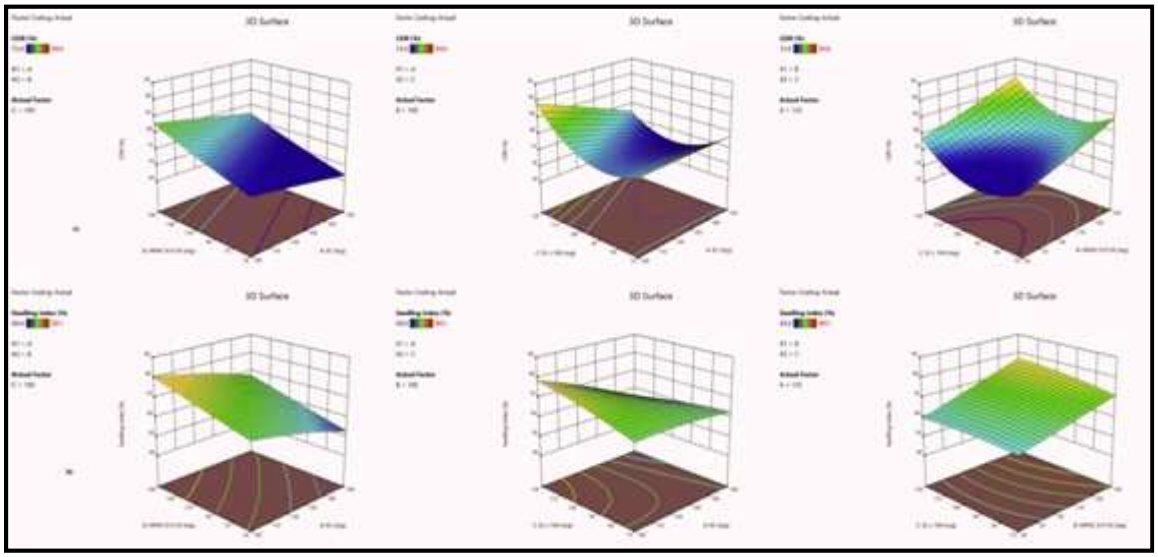

Figure No.1: Response surface plots showing the simultaneous influence of independent variables on response parameters (a) Swelling index and (b) % cumulative drug release of Glimepiride-sustained release tablets within the experimental design

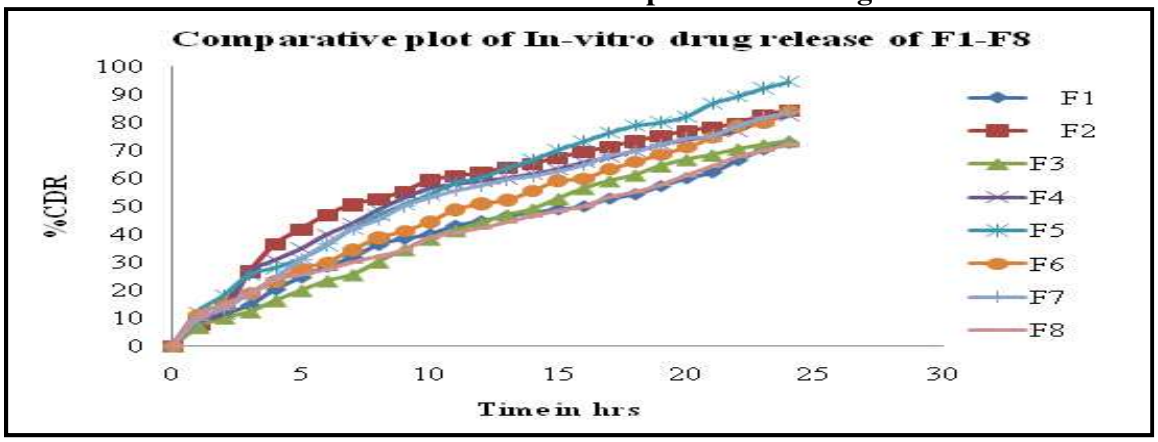

Figure No.2: Comparative Cumulative % Drug Release Profile of F1-F8

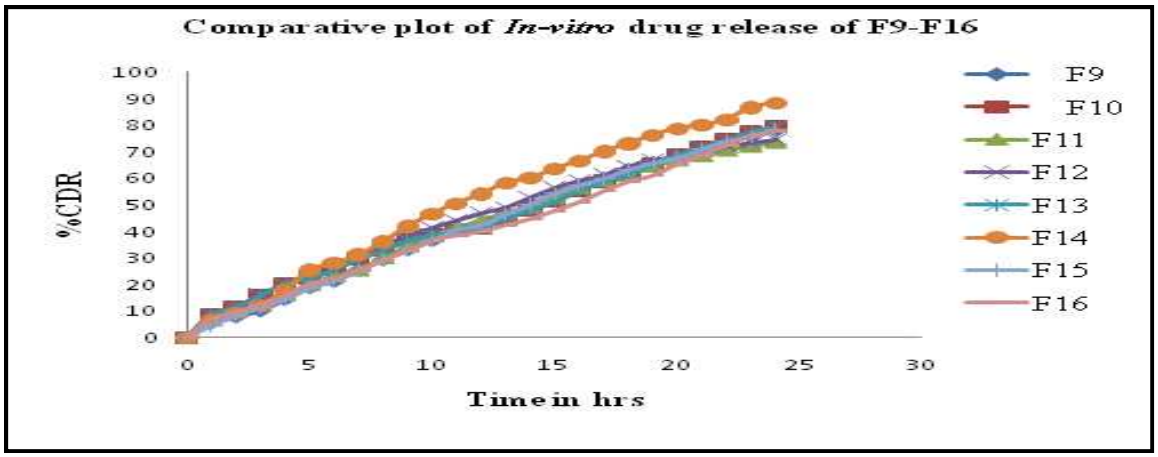

Figure No.3: Comparative Cumulative % Drug Release Profile of F9-F16

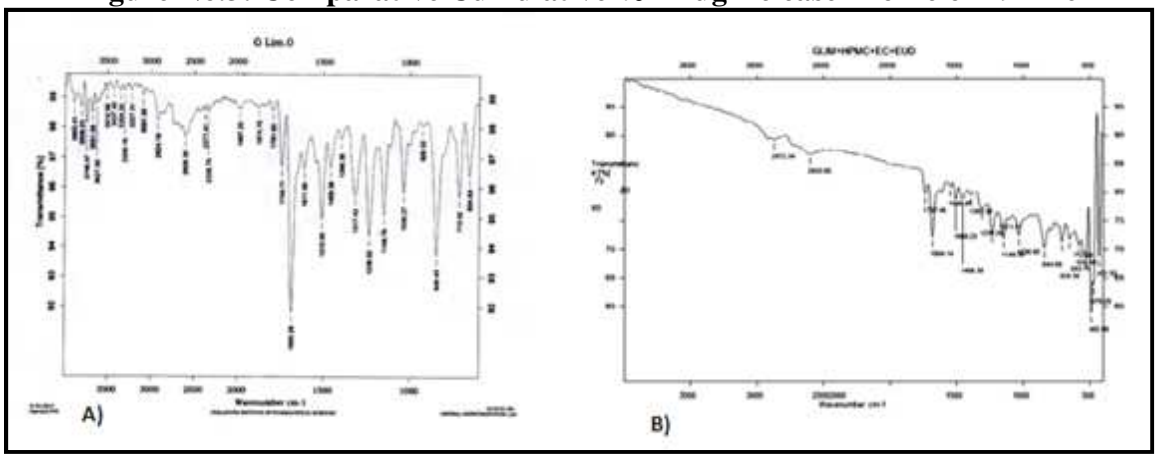

Figure No.4: FTIR spectrum of (A) free Glimepiride, and (B) Glimepiride SR tablet (F5)

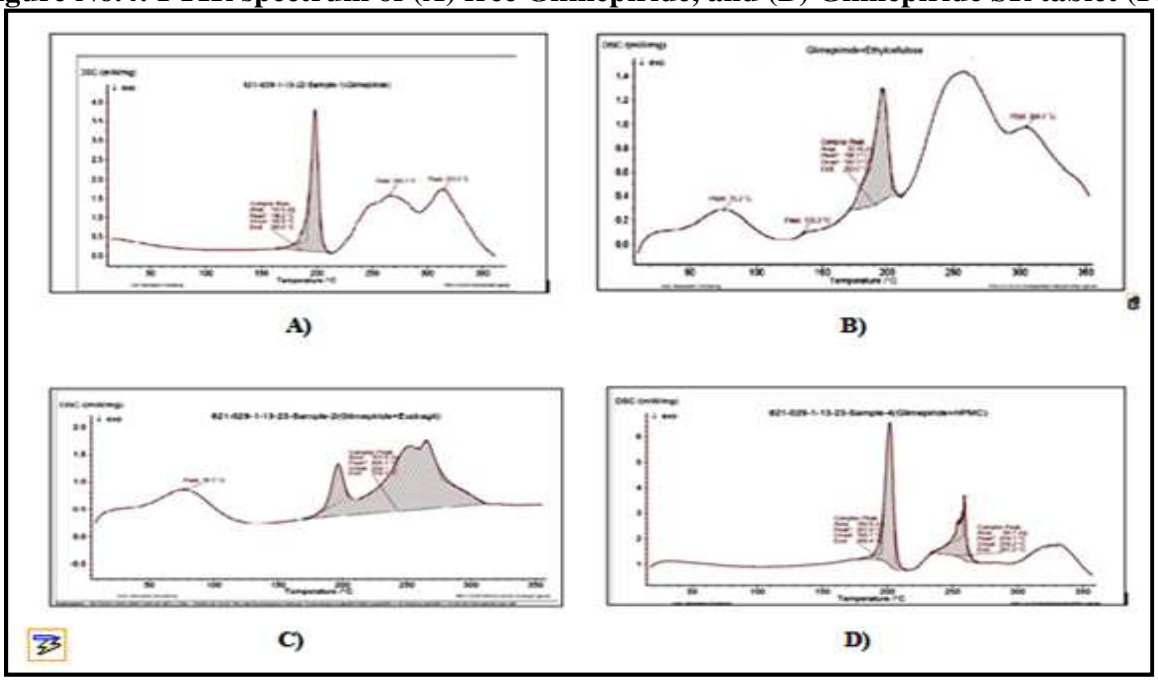

Figure No.5: DSC thermograms of (A) Pure Glimepiride; (B) Glimepiride-EC, (C) Glimepiride-EL 100 and (D) Glimepiride- HPMC K15 M

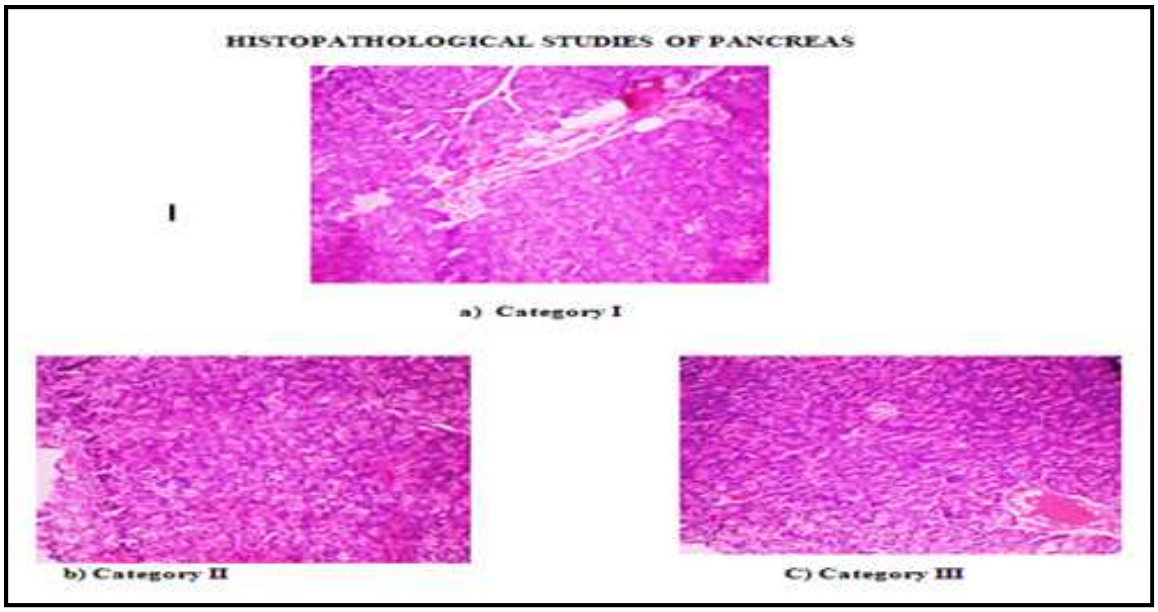

Figure No.6: Histopathological Studies of Pancreas

CONCLUSION

The formulation process variables of Glimepiride-Sustained release tablets were optimized by QbD of RSM. To validate the model, actual and predicted values of the responses at optimized conditions were processed, and the results indicate that the difference between predicted value generated and actual value measured. Confirming the reliability of the model. Moreover, in this study, optimized Glimepiride-Sustained release tablet have shown with better %SWI and %CDR with high desirability value. The *in vitro* drug release kinetics revealed that the release of Glimepiride from the Sustained release tablets followed non-Fickian's mechanism. The burst release of Glimepiride at the initial stage may help in achieving minimum therapeutic concentration, and the secondary sustained release characteristic helps in maintaining the therapeutic concentration. This helps to improve patient compliance, reduce the dose frequency and minimize the incorporation of polymers over the sustaining for the duration of 24 hrs. Results in reduction of dose dumping and reduce the toxicity for effective diabetic therapy. So QbD of RSM technique is the promising method to reduce the consumption of polymers in sustaining the drug and also it gives the appropriate concentration of polymers to be used in the delivering the drug.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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