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Design and Optimization of Hydrodynamically Balanced Oral *In situ* Gel of Glipizide

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ABSTRACT

Objective: The purpose of the present investigation was to formulate hydrodynamically balanced oral *In situ* gel of glipizide inorder to increase the gastric residence time and to modulate the release behavior of the drug. **Material and method:** *In situ*gel formulations were prepared by using different concentrations of sodium alginate, calcium carbonate, trisodium citrate and release retardant polymers. pH triggered ionic gelation is the mechanism involved in the present study. Taguchi L9 OA experimental design was employed for the optimization of formulations. All the formulations were subjected to various evaluation parameters. **Results:** Formulation F9 containing 3% of sodium alginate, 1.0 % of CaCO3, 0.2% of trisodium citrate and 0.5% of HPMC-K100M was selected as optimized batch based on Q12 58.26%, floating time 47.76 sec and drug content 98.2%. The release pattern of drug was found to follow first order. The value of 'n' from Korsemeyer equation was found to be 1.00 indicating the drug release by supercase II. The DSC study revealed that there was no incompatibility. Gastroretentive X-ray imaging study on Albino rabbit demonstrated that it was able to float in the stomach for more than 8hrs. Pharmacodynamic study on Wistar rats demonstrated significant hypoglycaemic activity of the optimized formulation. **Conclusion:** It was concluded that the hydrodynamically balanced oral *In situ* gel of glipizide could be an effective dosage form which remains buoyant and sustain the drug release for 24hrs.

INTRODUCTION

The demand for liquid formulation is particularly strong in geriatric and paediatric market as they are unable to take medications as prescribed because of difficulty in swallowing solid dosage forms which results in ineffective therapy and non-compliance. *In situ* gel drug delivery system, a liquid formulation has become a revolution in oral drug delivery system which is sparked by the advantages of ease of administration, reduced frequency of drug administration, improved patient comfort and compliance. They have been widely proposed as vehicles for sustained drug delivery (Subhashis *et al.*, 2011). *In situ* gel forming preparations are also known as "stimuli-responsive" polymeric drug delivery systems (Vipul and Basu 2013). Glipizide is a second-generation sulfonylurea prescribed to treat type II diabetes that can lower the blood glucose level in humans by stimulating the release of insulin from the pancreatic β cells (Dileep *et al.*, 2003). Drugs like glipizide with short biological half-life (2-5 hours) when administered as conventional solid dosage form do not get enough gastric residence time. In such cases it is to be administered in frequent doses 2.5 to 10 mg per day (Foster and Plosker, 2000) Moreover the site of absorption of glipizide is in the stomach (Jayvadan *et al.*, 2005). Thus, the development of hydrodynamically balanced glipizide *In situ*gel would clearly be advantageous as it improves drug efficacy and decrease dose requirements. Thus, an attempt was made in this investigation to formulate hydrodynamically balanced oral *In situ* gel of glipizide.

Principle of *In situ* gel formation

The main principle involved in the formation of *In situ*gel is the pH induced ionic gelation. Trisodium citrate complexes with free Ca^{++} and maintains the fluidity of *In situ* gel until it reaches the stomach. Once the formulation reaches the stomach, in the presence of acidic environment Ca^{++} get releases and triggers the gelation of sodium alginate.

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Carbondioxide that is released at acidic pH helps the formulation to float on the gastric contents for extended period (Jadhav and Benerjee, 2013).

Sodium citrate + Ca^{++} ⟶ Ca. citrate complex.

Ca. citrate ⟶ (acidic enviroment) Ca^{+2+} CO_2 ↑

MATERIALS AND METHOD

Glipizide was obtained as gift sample from RA chem. Pharma ltd, sodium alginate (Loba Chemie pvt ltd), and calcium carbonate (Finar chemicals ltd.) HPMC K-100-M, K-15M, K-4M (Yarrow Chem Products) trisodium citrate and guargum (SD fine chem. ltd). All other reagents and chemicals used were of analytical grade.

Preparation of *In situ* gel (Subhashis *et al.,* 2011) Sodium alginate at various concentrations (0.25% to 3% w/v) was dissolved in deionised water with varied concentration of trisodium citrate (0.15% and 0.2% w/v) under continuous stirring on magnetic stirrer at 70^0 C. After cooling to below 40^0C, various concentrations of calcium carbonate (0.5% to 1.5% w/v) and release retardant polymers were added in respective batches under continuous stirring. Then required quantity of oil (liquid paraffin) and surfactant (Tween 80) was taken in another beaker and placed on magnetic stirrer then water was added drop by drop to make an emulsion and weighed quantity of drug was added to it while continuous stirring. Polymeric solution was added to the beaker containing drug solution. Methyl paraben and propyl paraben were added in 9:1 ratio. Finally volume was made up to 100% with distilled water. Resultant solution was stirred well.

Preliminary studies

Preliminary studies were carried out inorder to optimize the concentration of gelling agent, floating agent and fluidity maintaining agent at a concentration of sodium alginate (0.25% to 3% w/v), calcium carbonate (0.5% to 1.5% w/v) and trisodium citrate (0.15% and 0.2% w/v) respectively.

Optimization using Taguchi OA L9 experimental design

Taguchi OA experimental design **(**Indira and Lakshmi, 2012) was used to study the effect of different polymers like HPMC K-15M, HPMC K-100M and xanthan gum at three different levels of 0.25%, 0.5%, and 1% shown in table no. 1. Three factors (independent variables) such as concentration of gelling agent, drug release retardant polymers and concentration of drug release retardant polymers were studied at all the three levels. Percent drug release (Q12) was taken as the response (dependent variable). An L9 orthogonal array was used for choosing the best and optimized formulations. Table no 2 shows Taguchi experimental trials. The software used was Minitab-15 English. The resultant formulations were studied for various evaluation parameters.

Evaluation parameters of *In situ* floating gel

Physical appearance and pH

Physical appearances of hydrodynamically balanced in situ gels were observed and the pH of the *In situ* gel was measured on a standardized digital pH meter at room temperature by taking adequate amount in a 50 ml beaker (Panwar and Chourasiya, 2012).

In-vitro gelling capacity

Invitro gelling capacity can be evaluated visually. It was measured by placing 5 ml of the gelation solution (0.1N HCL, pH 1.2) in a 15 ml borosilicate glass test tube. With the help of pipette one ml of formulation was transferred slowly in to test tube. When the formulation comes in contact with 0.1N HCL, it was immediately converted into stiff gel like structure. Invitro gelling capacity was graded into three categories based n gelation time and time period for which formed gel remains intact.

(+) - Gelation after few minutes but disperse rapidly

(++) - Immediate gelation remains intact for 12 hours

(+++) - Immediate gelation remains intact for more than 24 hours (Kubo *et al.,* 2003)

In vitro buoyancy study

It was carried out using Type II USP dissolution apparatus. The medium used was 0.1N HCl. The temperature of the bath and medium was maintained at 37 ± 0.5°C. 10ml of the formulation was transferred to 900 ml of 0.1N HCl with the help of syringe then floating lag time and floating time was noted (Rishad *et al.,* 2010).

Swelling index

Formed gel of 100mg was weighed accurately (W1) and placed in a petri dish containing 50ml of 0.1 N HCl. It was kept aside for 24 hrs. After 24 hrs gel was weighed (W2) and swelling index was calculated using the following formulae: (Ganapati *et al.,* 2009).

$$W2\text{-}W1/W1 *100$$

Where, W1 = Initial weight of gel (100mg)

W2 = Weight of gel after 24hrs

In vitro dissolution study

It was carried out using dissolution test apparatus USP type II (Paddle). 900 ml of dissolution medium was used (0.1N HCL, pH 1.2 medium). The temperature and speed of the apparatus were maintained at 37±0.5^{0}C and 50 rpm respectively. Five ml of the formulation equivalent to 10mg of drug was placed into dissolution vessel. Aliquot of 5ml was withdrawn at regular intervals of time and replaced with fresh medium. Dissolution test was carried out for 24hours. Withdrawn samples were analysed for drug concentration at maximum wavelength (λmax) of drug 275.8 nm against the medium as the blank by using Elico SL 164 double beam UV-Visible spectrophotometer (Subhashis *et al.,* 2011).

Table 1: Taguchi L^9 orthogonal array (3^3) design of experiment.

Independent variables	Level 1	Level 2	Level 3
Factor A	1%	2%	3%
Factor B	Xanthan gum	HPMC K15M	HPMC K100M
Factor C:	0.25%	0.5%	1%

Where
Factor A: Concentration of gelling agent
Factor B: Type of release retardant polymer
Factor C: Concentration of release retardant polymer

Table 2: Taguchi experimental runs formulae.

Material(%w/v)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide (10mg/5ml)	200	200	200	200	200	200	200	200	200
Liquid paraffin (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tween 80 (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium alginate (%)	1	2	3	1	2	3	1	2	3
Calcium carbonate (%)	1	1	1	1	1	1	1	1	1
Trisodium citrate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Xanthan gum	0.25	-	-	0.5	-	-	1	-	-
HPMC K-15M	-	0.5	-	-	1	-	-	0.25	-
HPMC K-100M	-	-	1	-	-	0.25	-	-	0.5
Na. propyl and methyl parabens	9:1	9:1	9:1	9:1	9:1	9:1	9:1	9:1	9:1
Distilled water(ml)	Upto 100ml								

Table 3: Results of evaluation parameters for the Taguchi experimental batches.

Formulation code	pH	Floating lag time (sec)	Floating time(hrs)	Swelling index (%)	Drug content (%)	Viscosity (cps)	Q12 (%)	Sedimentation ratio (Hu/Ho)
F1	7.36±0.03	29.34±4.28	>24	42.03±1.35	89.56±0.46	115 ±10	99.21±0.71	0.93
F2	7.54±0.01	30±2.64	>24	43.02±1.79	83.42±0.53	127±30	99.97±0.32	0.95
F3	7.61±0.04	32.57±2.64	>24	47.54±2.55	91.5±0.4	150±25	99.84±0.41	0.97
F4	6.98±0.06	34.66±1.63	>24	58.9±1.79	95.96±0.37	240±30	66.52±0.36	0.95
F5	6.94±0.05	34.66±2.51	>24	59.77±2.64	92.4±0.49	257±20	88.58±0.57	0.96
F6	7.35±0.01	33.66±1.64	>24	55.22±1.60	94.8±0.46	216±40	91.32±0.54	0.95
F7	7.35±0.04	46.66±2.3	>24	68.79±1.81	90.5±0.53	295±10	60.16±0.51	0.98
F8	6.94±0.01	45.06±2.45	>24	61.44±3.24	96.4±0.38	310±10	87.67±0.21	0.99
F9	7.23±0.04	47.76±5.45	>24	72.39±1.72	98.2±0.55	320±10	58.26±0.21	0.99

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

Table 4: Model dependent kinetic analysis of the dissolution profiles.

Formulation code	Zero order release	First order release	Higuchi release	Korsmeyer-Peppas release		Release mechanism
Parameter	r^2	r^2	r^2	r^2	n	
F1	0.933	0.99	0.84	0.84	0.64	Anomalous transport
F2	0.96	0.963	0.89	0.93	1.08	Super case II
F3	0.96	0.965	0.89	0.937	0.97	Super case II
F4	0.92	0.98	0.84	0.88	0.69	Anomalous transport
F5	0.96	0.97	0.89	0.93	1.10	Super case II
F6	0.96	0.97	0.89	0.95	0.91	Super case II
F7	0.99	0.98	0.88	0.95	0.75	Anomalous transport
F8	0.95	0.98	0.86	0.87	0.80	Anomalous transport
F9	0.96	0.97	0.91	0.95	1.00	Super case II

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

Table 5: Stability study of optimized formulation F9.

S.No	Evaluation parameters	Initial	1st week	2nd week	3rd week
1	Physical appearance	Milky white	Milky white	Milky white	Milky white
2	pH	7.23±0.04	7.05±0.01	7.16±0.15	7.18±1.23
3	Gelling capacity	+++	+++	+++	+++
4	Floating lag time(sec)	46.66±2.3	40.67±0.06	45.05±0.45	42.60±0.04
5	Floating time(hrs)	>24hrs	>24hrs	>24hrs	>24hrs
6	Viscosity (Cps)	320±20	310±30	320±30	330±20
7	Drug content (%)	98.2±0.55	98.9±0.95	98.2±0.67	98.4±0.75
8	Q24	98.93±0.01	97.67±0.45	98.01±0.89	98.26±1.74
9	Hu/Ho	0.99	0.98	0.99	0.99
10	Redispersibility	Good	Good	Good	Good

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

Curve fitting analysis

The mechanism of glipizide release from *In situ*gel was studied by fitting the dissolution data of optimized formulation in the following model dependent kinetics.

1. Zero order
2. First order
3. Higuchi model
4. Korsemeyer- Peppas equation

Based on the slope and the r^2 values obtained from the above models the mechanism of drug release was determined.

Determination of viscosity

Viscosity of prepared formulations was determined by Brookfield programmable viscometer LV DV-II+PRO using spindle number 62 which was rotated at 100 rpm (Shivaraju *et al.,* 2013)

Determination of drug content

5 ml of *In situ* gel (equivalent to 10 mg of drug) was measured and transferred to 100 ml of volumetric flask containing 0.1N HCL and stirred for 1hour on magnetic stirrer. The solution was filtered and suitably diluted with (0.1N HCl, pH 1.2 medium) and the drug concentration was determined by using a UV-visible spectrophotometer at 275.8 nm against a pH 1.2 medium as blank solution.

Sedimentation property

Sedimentation property of all the formulations was evaluated by visual observation in terms of sedimentation volume ratio and redispersibility (Kirti *et al.,* 2013)

(A) Sedimentation volume ratio = Ratio of the final height (Hu) of the sediment to the initial height (Ho) of the total suspension as the suspension settles in a cylinder under standard conditions.

(B) Redispersibility =. Sediment or formed suspension should be easily dispersed by moderate shaking to yield a homogenous system.

Differential scanning calorimeter (DSC) studies

DSC study was carried out to check the compatibility of drug and excipients. DSC analysis of pure drug and optimized formulation was performed with DSC 60 thermal analyser at heating flow rates of 10^0 C per minute between 50 ^{0}C -300 ^{0}C under static air using aluminium pans.

Stability study

Optimized formulations were placed in amber colored bottles and tightly closed with cotton plug and it should be capped and then stored for 1 month and then subjected to various evaluation parameters.

***Gastroretentive X-ray imaging study (*Basavaraj et al., 2012 and Saphier et al., 2010)**

A protocol for the study was prepared. After approval from Institutional Ethics Committee ID no. GPRCP/IAEC/ 11/13/3/PCE/AE-8, the study was conducted as per protocol. Gastroretentive X-ray imaging study was carried out on one healthy Albino rabbit weighing 2.5 kg which was housed for a minimum of at least 3days prior to the study and had free access to food and water. Animal was fasted for 12 h prior to the study. Optimized glipizide *In situ* gel was prepared by incorporating X-ray opaque material $BaSO_4$ to ensure visibility by X-ray. During the experiment the rabbit was not allowed to eat, but had free access to water. Gastric X-ray imaging was done at predetermined time intervals 0.5, 1, 2 and 8 hrs using an X- ray machine.

Pharmacodynamic study

In vivo evaluation studies for optimized hydrodynamically balanced oral *In situ*gel of glipizide were performed on normal healthy Wistar rats weighing 250 to 300 g each. The approval of the Institutional Animal Ethics Committee was obtained prior to the study. The rats were kept in rat cages, fed with commercial rat pellets and allowed free access to fresh water *Induction of diabetes* (Etuk and Muhammed, 2010)

Wistar rats weighing 250-300g were selected and baseline blood glucose level of each of the animal was taken. 150mg/kg of alloxan monohydrate was administered intraperitoneally to the rats which were fasted for 18 hours prior to the study. After 72 hours of the administration, blood glucose levels in the rats were measured through tail tipping using Glucometer (Easy-Prik blood glucometer). Wistar rats with blood glucose level (> 150mg/dl) were selected for the study.

Animal treatment

Eighteen diabetic rats fasted at least 12hours before the study were selected and divided into three groups (n = 3) labelled I, II and III. Before drug administration, a blood sample as a diabetic control was withdrawn from tail vein of each rat. Pure drug glipizide and hydrodynamically balanced oral *In situ* gel of glipizide were administered orally to each group using stomach intubations. A dose of 800 µg/kg of glipizide was administrated in a suspension form (freshly prepared) for each rat (Jayvadan *et al.,* 2005). Blood samples were collected at predetermined time at every one hour intervals up to 24 hours.

Group I – Disease control

Group II- Treated with optimized formulation

Group III- Treated with pure glipizide

The percentage reduction in blood glucose level at time "t" was measured by using the following equation.

Percent reduction in blood glucose level at time t (h) =

Glucose conc. at 0 (h) – Glucose conc. at t(h)

Glucose conc. at 0 (h)

Statistical analysis

Obtained data were expressed as mean ± SEM (standard error mean). The data was analyzed by one-way ANOVA followed by Tukey's multiple comparison tests (Amolkumar *et al.,* 2013) using GraphPad prism version 5.0.3.477 (GraphPad Software). Statistical significance was set at 0.001 level ($P<0.001$).

RESULTS AND DISCUSSION

The preliminary batches were prepared by employing varied concentrations of sodium alginate 0.25 to 3%, calcium carbonate 0.5 to 1.5% and trisodium citrate 0.15 and 0.2 %, as a gelling agent, floating agent and fluidity maintaining agent respectively. Formulations containing sodium alginate 0.25% showed improper gelation (+). Formulations containing sodium alginate 0.5%, gel was formed but dispersed after few hours which lead to rapid flow (++) and in the formulations containing 1, 2 and 3% of sodium alginate stiff gel was formed (+++) and remained intact for greater than 24 hours. Thus we can conclude that 1, 2 and 2% of sodium alginate were the optimum concentrations.

Where

(+) - Gelation after few minutes but disperse rapidly

(++) - Immediate gelation remains intact for 12 hours

(+++) - Immediate gelation remains intact for more than 24 hours

Calcium carbonate was used as a floating agent. Upon reaction with gastric fluid, Ca++ ions releases from the calcium carbonate and complexes with sodium alginate resulting in the formation of gel. Calcium carbonate was taken in three varied concentrations 0.5, 1 and 1.5%. Floating lag time and floating time were evaluated and it was found that the formulation containing 1% calcium carbonate exhibited least floating time of less than 60seconds and the floating time greater than 24hours. Thus 1% calcium carbonate was the optimized concentration. Trisodium citrate was used as fluidity maintaining agent. 0.2% concentration of trisodium citrate formulation remains in liquid state before administration.

Physical appearance and pH

The formulations were free running solutions and did not show any gelation at room temperature. All the formulations were milky white in appearance. They had pH in the range of 6.9-7.6 as shown in table no. 3, which was found to be satisfactory for orally administered formulation. Therefore there is no need for adjusting pH.

Invitro-gelling capacity

All the formulations showed immediate gelation (+++) and remain intact for greater than 24hours.

Invitro floating ability

Results from table no. 3 depicts that all the formulations F1 to F9 showed invitro floating lag time of less than 60 sec. The formulation F1 showed least floating lag time 29.34 sec because of low concentration of polymer. The formulation F9 showed highest floating lag time of 47.76 sec because of high concentration of polymer. Floating time was greater than 24hours for all the formulations.

Swelling index

All the formulations exhibited the swelling index in the range of 42-72% shown I table no. 3. *In situ* gel prepared from synthetic polymer (HPMC K100M) has greater percent of swelling index as compared to *In situ* gel prepared from natural polymers (xanthan gum and guargum) within 24 hrs. The highest water uptake of the formulation F9 may be due to highest swelling capacity of gum.

Drug content

Table no 3 depicts the percentage of drug content of all the formulations. The formulation F9 was found to have maximum drug content of 98.2%, indicating homogenous drug distribution throughout the gel.

Viscosity

From table no 3, formulations showed a marked increase in viscosity with increasing concentration of sodium alginate and release retardant polymer. Increasing the concentration of sodium alginate and release retardant polymer in the formulation simultaneously increased the viscosity. Viscosity results of all the formulations concluded that formulation can be easily given orally within this range.

Invitro drug release

The invitro drug release data at 12hrs was given in table no. 3 and drug release profiles showed in figure no. 1. The formulations F1, F2 and F3 exhibited 99.21, 99.97 and 99.84% of drug release in 12hrs respectively. Formulations F4, F5 and F6 exhibited 66.52, 88.58 and 91.32% of drug release in 12 hrs respectively. Formulations F7, F8 and F9 exhibited 60.16, 87.67 and 58.26% of drug release in 12 hrs respectively.

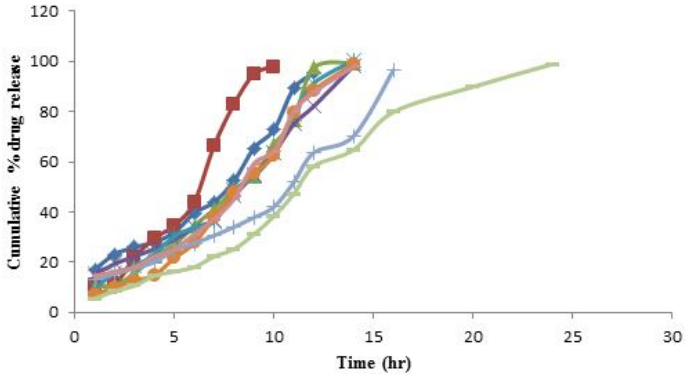

Fig. 1: Cumulative percentage drug release of Taguchi experimental batches.

In the above results, it was observed that as the concentration of polymers increased, there is a decrease in the drug release rate. Increase in concentration of polymer causes increase in viscosity of the gel layer with longer diffusional path. This could cause reduction in drug release.

Formulations containing higher HPMC viscosity grade have slower drug release rates when compared to the formulations with xanthan gum and the formulation containing lower HPMC viscosity grade. The amount of drug release was found to be in the order of HPMC K15M>Xanthan gum> HPMC K100M. Hence the Formulation F9 containing 3% sodium alginate and 0.5% HPMC K100M was able to sustained the drug release for 24hrs and

floating lag time of 47.76 sec with a floating time of greater than 24 hours. Hence F9 formulation (figure no 2) was selected for further short term stability studies.

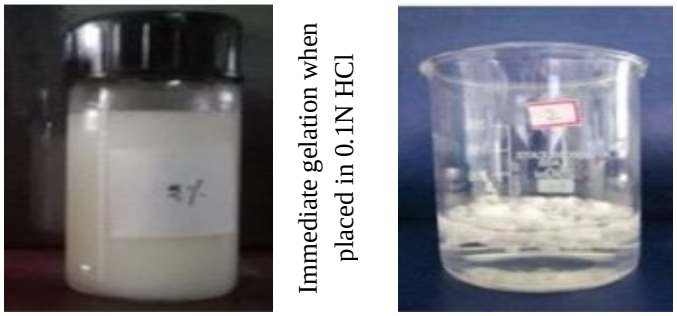

Fig. 2: Optimized formulation containing 3% Sodium alginate

Drug release kinetics

The results obtained from in vitro release studies of the optimised batch (F9) was attempted to fit into various mathematical models.

The regression coefficient r^2values of zero order, first order, Higuchi matrixes, Peppas are tabulated in table no 4 for all the formulations. When the regression coefficient 'r^2' value of zero order and first order plots of optimized formulation (F9) were compared, it was observed that 'r' value of zero order was 0.96 whereas the 'r' value of first order plots was found to be 0.97 indicating that the drug release from the optimized formulation was found to follow first order release kinetics. The 'r' value of Higuchi kinetics was found to be 0.91. The invitro dissolution data as log cumulative percent drug release versus log time were fitted to Korsmeyer Peppas equation, value of the exponent 'n' was found to be 1.00 indicating the drug release by supercase-II.

The mechanism of drug release involves the disentanglement and erosion of the polymer. The release process involves the penetration of water into matrix followed by hydration and swelling of the polymer, and diffusion of the drug dissolved in the matrix.

Based on swelling and erosion studies, it was concluded that polymers undergo swelling as well as erosion during the dissolution study, which indicates that polymer relaxation had a role in drug release mechanism. The obtained invitro drug release data was analyzed by Minitab 15 English software. Signal to noise (S/N) ratio for 'smaller the better' characteristic was chosen since the goal is to minimize the response (dependent variable-Q12). From signal to noise ratio (figure no. 3) it can be inferred that sodium alginate has the greatest influence in sustaining the drug release Q12. The concentration of release retardant polymer has the next greatest influence followed by the type of release retardant polymers. Therefore the order of independent variables on which Q12 depends is Conc. of gelling agent > Conc. of release retardant polymer > type of release retardant polymer. One way ANOVA was used in the analysis of Taguchi design of experiment. ANOVA is used to determine whether the factors are significantly related to the response. It was found that the concentration of gelling agent (sodium alginate) has a significant effect on the drug release

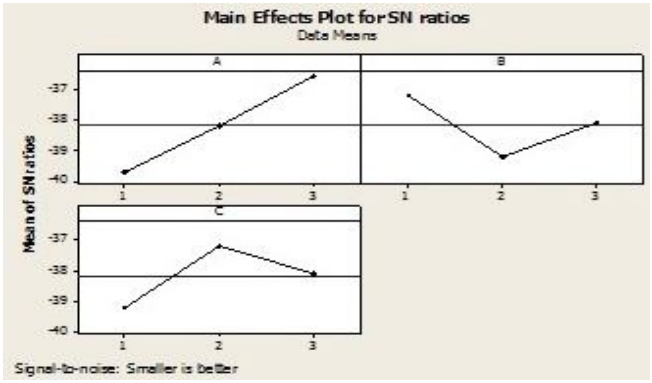

Fig. 3: Signal to noise ratio.

Sedimentation properties

Table no. 3 shows the sedimentation properties of different formulations. As viscosity increases, sedimentation rate decreases. Also the redispersibility was found to be good in all the formulations.

DSC analysis of drug and optimized formulation

Figure no. 4 shows the DSC curve of pure glipizide. Pure drug showed a single sharp endothermic peak at 217 ^{0}C which was ascribed to drug melting and optimized formulation F9 (figure no. 5) showed melting endothermic peak at 208^{0}C.

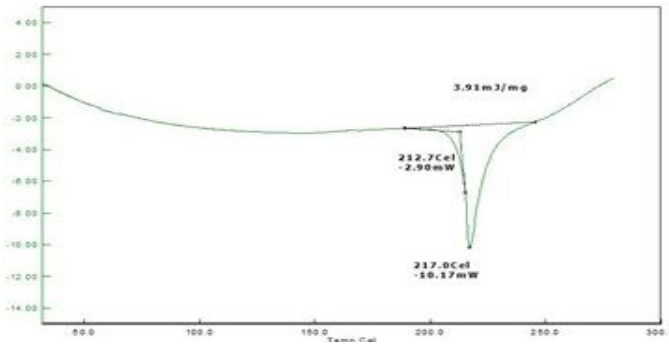

Fig. 4: DSC of pure drug.

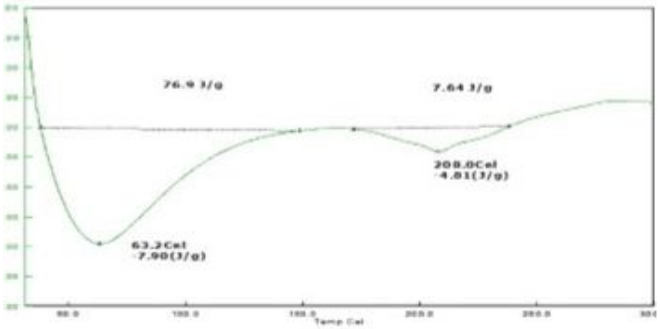

Fig. 5: DSC of the optimized formulation F9

Decrease in intensity of peak in the optimized formulation may be due to the baseline shifting. Endothermic peak corresponding to

melting point of glipizide in the optimized formulation F9 did not show any significant shift. Thus the finding of DSC study confirmed the absence of interaction between drug and excipients used in *In situ* gel.

Stability studies

The stability of this optimized formulation was known by performing stability for one month at room temperature on the optimized formulation (F9). The formulation was found to be stable with insignificant change in the appearance, pH, gelling capacity, floating ability, redispersibility studies and Q24 as shown in table no 5. Viscosity was increased slightly due to the hydration of polymers.

Gastoretentive X-ray imaging study

From the figure no. 6: image-I was taken at the end of 0.5 hour after the administration of gelling solution. The gel formation was seen, and a slight opacity is seen in the gastric region due to release of Barium sulphate till a stable gel structure was formed. Images – 2, 3, and 4 were taken at the end of first, second and eight hour respectively. Image 3 revealed the intactness of the formed gel and slight change in the size of the formed gel than seen in image 2. This may be due to the dissolution of the content. In image 4 the gel structure shows decrease in opacity and slight withering. This is attributed to release of the entrapped barium sulphate from the gel mass.

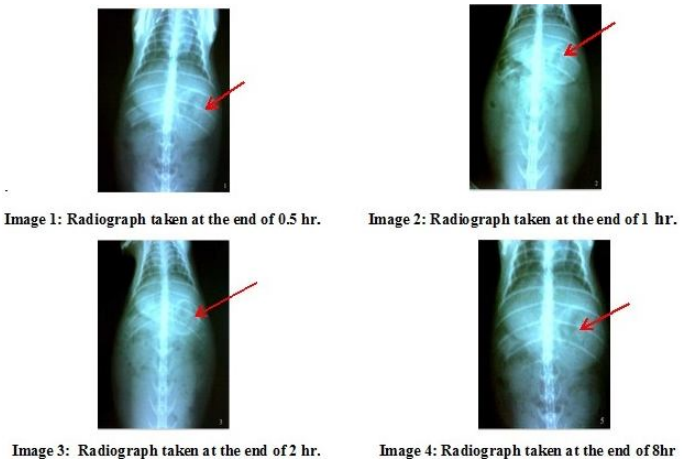

Fig. 6: Gastroretentive X-ray imaging of rabbit stomach.

Performance of pharmacodynamic activity of the optimized formulation on Wistar rats

Intraperitoneal administration of 150mg/kg of alloxan monohydrate induced hyperglycaemia (Blood glucose level ≥150mg/dl) in about 75% of the treated rats. The peaks blood glucose levels reached in alloxan induced hyperglycaemia rats were 318±34.7 with the mean 220 mg/dl.

Invivo efficiency of the optimized batch F9 was performed in healthy normal Wistar rats by measuring the hypoglycaemic effect which was produced after oral administration. When pure glipizide suspension was administered, a rapid reduction in blood glucose levels was observed and maximum reduction of 48.86% was observed within 2 hours after oral administration. Blood glucose levels were recovered rapidly to the normal level within 8 hours (figure no. 7). In the case of glipizide *In situ* gel (optimized formulation F9), the reduction in blood glucose levels was slow and reached maximum reduction within 6 hours after oral administration .

This reduction in blood glucose levels was sustained over longer periods of time (14 hours). Significant hypoglycemic effect was maintained only from 1 to 4 hours after oral administration of pure glipizide in suspension form, whereas in the case of glipizide *In situ* gel, significant hypoglycemic effect was maintained for a period of 2 to 14 hours. Therefore the optimized glipizide sustained release hydrodynamically balanced oral *In situ* gel is significantly more effective than the immediate release formulation of glipizide in reducing fasting plasma glucose levels

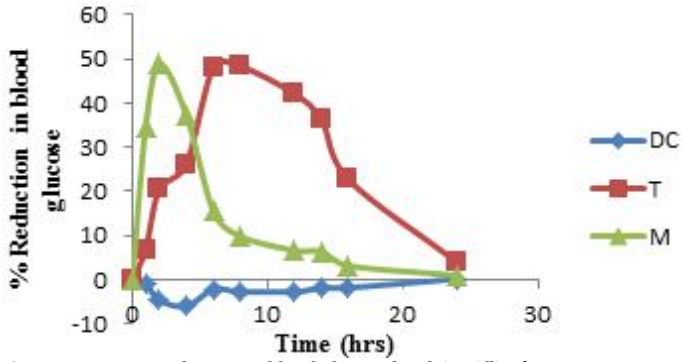

Fig. 7: Percentage reduction in blood glucose level (mg/dl) of Wistar rats.
Where: Group I (DC) - Disease control;
Group II (T) - Treated with optimized formulation;
Group III (M) - Group treated with pure glipizide.

Statistical analysis

Obtained data were expressed as mean ± SEM (standard error mean). The data was analyzed by one-way ANOVA followed by Tukey's multiple comparison tests using GraphPad prism version 5.0.3.477. (GraphPad Software). The statistical significance was set at 0.001 level ($P<0.001$). It was observed that the optimized formulation F9 shows a significant hypoglycemic effect when compared to that of pure glipizide.

From all these results it was concluded that the hydrodynamically balanced oral *In situ* gel of glipizide may effectively decrease the blood glucose level.

CONCLUSION

The above results clearly indicate that the optimized formulation was able to float in the stomach for extended period of time sustaining the drug release for 24 hrs. Pharmacodynamic activity of the optimized formulation clearly demonstrates that it shows significant hypoglycemic effect for 2-14 hrs over the pure glipizide. Further pharmacokinetic studies are needed for determining the ADME pattern of the optimized formulation.

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