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Research Article

Design and Evaluation of Gastro-retentive Drug Delivery System for Glimepiride using Design of Experiment

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ABSTRACT

Glimepiride, oral sulfonyl urea, BCS class-II drug is used to treat diabetes (type-II). Due to its low solubility, it is an ideal candidate for solubility enhancement, leading to better bioavailability and subsequent dose. In the present study, the solid dispersion technique was used to improve the solubility using solvent evaporation method. The solid dispersions were prepared using affinisol 912 as a solubility enhancer. The prepared solid dispersions were evaluated for solubility in 0.1N HCl pH 1.2 and phosphate buffer pH 7.8 medium. The solubility of glimepiride in optimized solid dispersion (SD1) formulation was 682.44 µg/mL compared to 6.88 µg/mL for pure drug in pH 7.8 medium. The solid dispersion (SD1) was further formulated into the tablets. The gastro-retentive and mucoadhesive properties were contributed to the tablets by HPMC K4M and Carbopol 940, respectively. Factorial design (Central composite design) was used to optimize the gastro-retentive tablets. The tablet formulations showed good mucoadhesive properties and drug release up to 12 hours in pH 1.2 with 0.5% SLS medium. The optimized formulation (F2) showed cumulative drug release up to $97.20 \pm 0.99\%$ in 12 hours. The drug release kinetics also showed that the drug is release by dissolution and diffusion from the drug matrix. The gastro-retention studies in rabbits also showed the tablets remain within the GIT up to 12 hours as confirmed by x-ray images.

INTRODUCTION

Gastro-retentive drug delivery systems are among the preferred dosage forms in recent times and most of them are commercially viable. Gastro-retentive dosage forms prolong the stay of the drug within the stomach, thereby improving absorption as most of the drugs are primarily absorbed there.^[1,2] Systemic availability of drugs can be improved using these systems due to site-specific absorption.^[3] Many techniques are reported that can extend the dosage forms' gastric residence time such as mucoadhesive, bio-adhesive, expandable, magnetic, super-porous hydrogel, high-density (sinking), or low density (floating) systems.^[4] Amongst them, floating drug delivery systems allow the formulation to remain buoyant within the stomach with no effect on gastric emptying rate, thereby enabling prolonged release of the drug, making it potentially more effective than conventional dosage

forms. Several floating systems have been developed including: the gas generating system, raft forming system, colloidal gel barrier system, microporous compartment system, floating microsphere system, and the low-density system.^[5]

Many orally administered drugs present poor bioavailability when administered as conventional dosage form, i.e., the rate and extent to which drugs are absorbed in the systemic circulation is less than desirable. Absorption may be as small as 30% or less of the orally administered dose for some drugs. As a result an ample dose is often required to be administered to achieve the therapeutics. As a result, conventional dosage forms may prove costly with expensive drugs, and the unabsorbed drug may also have unwanted side effects within the gastrointestinal tract. In addition, poorly absorbed drug, especially biopharmaceutical classification system (BCS)

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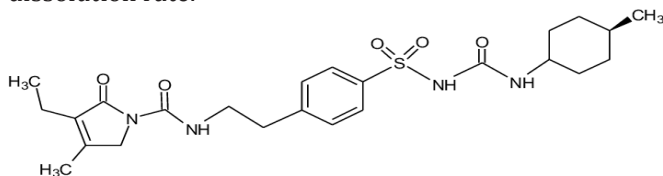
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class II and IV often display large inter and intra-subject variability in bioavailability. The modified release drug delivery system may address this issue with improved residence time in the stomach.^[6]

Glimepiride, third-generation sulfonyl urea, is used as an oral hypoglycemic agent to treat non-insulin dependent diabetes mellitus (type II). It induces hypoglycemia by stimulating the release of insulin from pancreatic beta cells and increasing peripheral tissue sensitivity towards insulin. It also advances the movement of sugar from the blood into the cells that require it.^[7] It is grouped under BCS Class-II drugs and exhibits poor aqueous solubility. In acidic and neutral pH, glimepiride shows extremely low solubility at room temperature (<0.004 mg/mL), while in pH greater than 7, a slight increase in the solubility is observed (~0.02 mg/mL). It might result in poor dissolution rate and low bioavailability.^[8]

Following to oral administration, glimepiride gets quickly absorbed by the liver and undergoes first-pass metabolism. The solubility-related issues of the drug cause hurdle in the development of drug delivery formulations. Several investigations are reported on the different techniques for augmenting glimepiride's solubility and dissolution rate.^[9,10]



The most interesting way to enhance drug dissolution is to improve the solubility through formulation methodology. Solid dispersion (SD) technique is one of the most utilized pharmaceutical approaches to achieve this effect. Other methods to produce a SD are melting, dissolution in a solvent, or spray drying, depending on the characteristics of the drug and carrier.^[11-13]

The present work aims to improve solubility and thereby dissolution of glimepiride via solid dispersion using commonly employed methods like solvent evaporation. Further solid dispersion was formulated in the form of gastro-retentive tablets that can release the drug for a prolonged duration, subsequently improving the absorption and bioavailability.

MATERIALS AND METHODS

Materials

Glimepiride was obtained as a gift sample from IPCA Laboratories Ltd., Mumbai. Affnisol 912 [Hypromellose Acetate Succinate (HPMCAS)] was obtained as gift sample from Colorcon, USA. HPMC K4M was purchased from Taian Ruitai Cellulose Co. Ltd, China. Carbopol 940, Sodium Bicarbonate, Magnesium Stearate and Purified Talc were purchased from Loba Chemie, India. Microcrystalline Cellulose was purchased from Ankit pulps and boards Pvt.

Ltd., Nagpur, India. Solvents used were dichloromethane and methanol and were purchased from Loba Chemie Ltd.

Characterization of Glimepiride

Glimepiride obtained as gift sample was characterized for melting point. Melting point is the temperature at which the last solid particle of a compact column of a substance in a tube passes into the liquid phase. The melting point was determined by capillary method^[14] and temperature was noted down when the compound starts melting and completely melts.

Standard Curve of Glimepiride

Standard curve of glimepiride was prepared in the concentration range of 1–10 µg/mL in phosphate buffer pH 7.8.

Preparation of Solid Dispersion

Solid dispersion of glimepiride was prepared using Affnisol by solvent evaporation method.^[15]

Accurately weighed amounts of glimepiride alone, Affnisol and a series of mixtures of polymer and drug having a final drug-polymer weight ratio ranging from 1:1 to 1:15 were dissolved at 40°C in minimum amount of solvent mixture of methanol and dichloromethane (60:40). The solvent was evaporated under vacuum at 40–50°C.

Desiccation was completed in a vacuum oven until constant weight was achieved and the resulting solids were pulverized. The dried powder was then passed through a 100-mesh sieve and stored in a desiccator until further evaluation.

Characterization of Solid Dispersion

Determination of Percentage Yield

Solid dispersions were collected and weighed to calculate the practical yield. Percentage yield was calculated for each batches of solid dispersion with respect to theoretical yield and practical yield.^[16] The percentage yield was obtained using the following formulae:

$$\text{Percentage yield} = (\text{Practical yield} / \text{Theoretical yield}) \times 100$$

Drug Content

Solid dispersions equivalent to 10 mg of glimepiride was weighed accurately and dissolved in 100 mL of methanol. The solution was filtered, diluted suitably, and analyzed by reverse phase-high performance liquid chromatography (RP-HPLC) using a fixed ratio of buffer and acetonitrile as mobile phase at λ_{max} of 228 nm. The actual drug content was calculated using the following equation as follows.

$$\% \text{ of glimepiride} = (r_u/r_s) \times (C_s/C_u) \times 100$$

Where,

r_u = Peak area of the sample solution,

r_s = Peak area of standard solution,

C_s = Concentration of glimepiride in standard solution (in µg/mL), and



C_u = Concentration of glimepiride in the sample solution (in $\mu\text{g/mL}$).

Determination of Solubility of Glimepiride in Solid Dispersions

The solubility of glimepiride in solid dispersions was determined by the solubility method as per USP at pH 1.2 and pH 7.8. Firstly 250 mL of each media i.e., pH 1.2 and pH 7.8 was placed in a round bottom flask with a stopper, then an accurately weighed amount of powder (solid dispersion) equivalent to 100 mg of glimepiride was put in to the flask.

The flasks with dispersions were placed on water bath shaker and switched on. After 24 hours shaker was stopped and 10 mL of the sample was taken from each flask, filtered through 0.45 μm membrane filter and analyzed for content of glimepiride.^[17]

Evaluation of Powder Flowability

The powder mixtures of all solid dispersions were evaluated for angle of repose, bulk density (BD), tapped density (TD), compressibility index (CI) and hausner's ratio.

Identification of Drug by Fourier Transform Infrared Spectroscopy (FTIR)

The IR absorption spectrum of glimepiride was obtained using FTIR spectrophotometer (FTIR cary-630 with Transmission Module, Agilent technologies). IR spectra of pure drug and solid dispersions containing affnisol were obtained. The individual spectrum of pure drug, affnisol, and overlaid spectra of both were observed to determine the compatibility in the formulation.

Differential Scanning Calorimetry (DSC) Analysis

Analysis of glimepiride, affnisol and solid dispersions were performed by using a differential scanning calorimeter (Perkin Elmer Pyris-6DSC) system equipped with a computer analyzer.

The samples in crimped aluminum pan were heated in inert nitrogen gas ambience at a heating rate of $10^\circ\text{C min}^{-1}$ over at a temperature ranging between $30-300^\circ\text{C}$.^[18]

Formulation of Gastro-retentive Tablets of Glimepiride

The optimized batch of solid dispersion was further fabricated as gastro-retentive tablets. The polymers viz. HPMC K4M and carbopol 940 were used as release retardants and mucoadhesive respectively. Solid dispersion was sifted through ASTM#40, HPMC K4M, carbopol 940, sodium bicarbonate and microcrystalline cellulose (MCC) were sifted through ASTM#50. Solid dispersion, polymers and other excipients were mixed in a blender for suitable time. Lubricants i.e., magnesium stearate and talc were sifted through ASTM#40 and added to blend and blended for 5 minutes. The final blend was

compressed using 8.00 mm, round punches.

Composition of Formulation

The developed gastro-retentive tablets were optimized via design of experiment. Design expert software version 13.0 (trial version) from Stat Ease, Inc., Minneapolis, Minnesota was used to generate the study design. Central composite design (CCD) is one of the most used surface response methodology design. It represents an interaction between the factors and their effect on the magnitude of responses. CCD was applied using two variable factors i.e., concentration of HPMC K4M (X1) and concentration of carbopol 940 (X2) at two levels (-1 and +1) and the design was developed by the inclusion of central point. The center points provide a good and independent estimate of the experimental error. The axial points are taken in a way to ensure rotatability, and the model prediction variance is constant at every point equidistant from the center of design.^[19]

Evaluation of Pre-compression Blend

Pre-compression final blends were evaluated for bulk density, tapped density, carr's index and hausner ratio to determine the flow characteristics of the final blend.

Evaluation Gastro-retentive Tablets of Glimepiride

The gastro-retentive tablets of glimepiride were evaluated for following parameters:

Physical Characterization

Weight variation: 20 tablets of all batches were collected randomly during compression and weight of individual tablets was measured using electronic balance. Weight value was reported in milligrams.

Thickness: The thickness of the tablets is mostly related to the tablet hardness and can be used as initial control parameter. Ten tablets were randomly selected from each formulation and their thickness was measured by using vernier calipers. Thickness values were reported in millimetres (mm).

Hardness: The crushing strength of the tablet was measured using Schleuniger type hardness tester by placing the tablet between the anvils and measuring the force required to break the tablet.

Friability: This friability test was conducted by placing tablets in friabilator (electrolab). Fifty tablets were taken and rotated at 25 rpm for 4 minutes. The tablets were then dedusted and reweighed. The friability was calculated as the percentage of weight loss.

$$\% \text{ friability} = \frac{(\text{Wt. of 50 tablets before rotation} - \text{Wt. of 50 tablets after rotation}) \times 100}{\text{Wt. of 50 tablets before rotation}}$$

Floating Lag Time

One tablet was placed in a dissolution flask containing 900 mL of 0.1N Hydrochloric acid (HCl) pH 1.2 solution.

Subsequently, the time taken by tablet to move from bottom to the top of the flask, in seconds, was measured.

Drug Content (by Content Uniformity)

Uniformity of dosage units was determined to drug content in different batches. The 10 tablets were selected at random and assay was performed for each tablet. 10 tablets were accurately weighed and crushed to a fine powder to prepare the sample solution. The powder was suitably diluted in water-acetonitrile medium with occasional shaking. The samples were filtered through a 0.45 µm membrane filter (Millipore) and 10 µL solution was injected into the system, and the amount of the drug was determined by RP-HPLC at 228 nm against the reference substance.

In-vitro Bioadhesion Study

In-vitro tablet bioadhesion studies were done using rabbit gastric mucosa. The gastric mucosa was used immediately for this study. The detachment force, i.e., the force required for separating the tablet from the gastric mucosa surface was determined using a modified 2-arm balance. The rabbit gastric mucosa was fixed to the outer surface of the bottom of 100 mL beaker with cyanoacrylate adhesive and then placed in a 1000 mL beaker. 0.1N HCl pH 1.2 solution was added into the beaker up to the upper surface of the gastric mucosa such that the media remains just above the mucosa. The tablet was fixed to the bottom of the modified stainless steel pan with cyanoacrylate adhesive. A preload of 50 g was placed on the pan for 5 minutes (preload time) to establish adhesion bonding between tablet and gastric mucosa. The preload and preload time were kept constants for all the formulations. After preload time, preload was removed from the pan and water was then added into the beaker from a syringe at a constant rate. The addition of water was stopped when the tablet detached from rabbit gastric mucosa. The weight (mass) of water required to detach the tablet from gastric mucosa was noted down. The mass (in grams) required to detach the tablet from the mucosal surface gave the measure of bioadhesive strength. Force of adhesion was calculated from following formula:
 Force of adhesion (N) = Bioadhesive strength × 9.81/ 100
 Bond strength (N/m²) = Force of adhesion/ disk surface area

In-vitro Drug Release (Dissolution)

Dissolution studies of gastro-retentive tablets of glimepiride (n=6) were carried in 900 mL of 0.1N HCl with 0.5% SLS w/v, using type II (Paddle type) apparatus at 50 rpm with temperature maintained at 37±0.5°C and sampling was done at 1, 2, 4, 6, 8 and 12 hours. 10 mL aliquots of samples withdrawn at above mentioned time intervals and filtered through millipore filters of pore size 0.45 µm with replacement. The content of glimepiride in the samples was determined using RP-HPLC at 228 nm. Percent drug release was then calculated.

Powder X-ray Diffraction (P-XRD) Studies

The P-XRD studies were conducted for solid-state characterization of the drug, polymer, solid dispersion and optimized formulation. The diffraction pattern of samples was recorded by X-ray diffractometer, Bruker AXS D8 Discover equipped with a general area detector diffraction system (GADDS). Light source: CuKα X-ray, at a voltage of 40 kV.

Drug release Kinetics

The *in-vitro* release kinetics of the optimized formulation containing the matrix of HPMC K4M and carbopol 940 was determined by applying various equations and kinetic parameters. Dissolution data obtained during 0~12 hours was fitted to zero-order, first-order, Higuchi and Hixson-Crowell equation. The correlation coefficient (r²) was used as an indicator of the best fit for each of the models applied. According to the literature,^[20] drug release from a hydrophilic matrix is governed by the following sequential processes: primarily, hydration or swelling of the tablet matrix, which results in gel formation; secondly, dissolution of the embedded drug into the hydrated matrix/gel; thirdly, diffusion of the solubilized drug molecules through the hydrated matrix; and finally surface erosion and/or dissolution of the formed gel-matrix.

Stability Studies

The stability studies were conducted according to ICH [Q1A (R2)] and WHO guidelines to assess the stability of drug formulation. Optimized tablets were filled in amber-colored glass bottles stopper with rubber cock and then loaded into stability chambers maintained at 40 ± 2°C and 75 ± 5% RH for 3 months. At the end of 3 months samples were collected and analyzed for physical appearance, drug content and *in-vitro* drug release to determine any deviation.^[21]

In-vivo Radiographic Studies

In-vivo gastro-retention (buoyancy) studies were performed for optimized formulation using radiography technique. Gastro-retentive tablets were made X-ray opaque by replacing glimepiride solid dispersion in formulation with 25 mg of barium sulphate (BaSO₄). The tablets were prepared as per the previously mentioned method all other ingredients were constant except diluent (microcrystalline cellulose), which is used to make up the weight. The protocol for *in-vivo* gastro-retention studies on rabbits was conducted and examined by a radiographic method.^[22] The animal experiment study was approved by Institutional Animal Ethical Committee (838/PO/Re/S/04/CPCSEA-02). The study was conducted on six albino rabbits of either sex weighing between 2.1–2.7 kg (2.4 ± 0.2 kg). The animals were kept in individual cages, and the experiments were conducted under hygienic conditions in the room at a temperature maintained at around 25°C. Animals were kept on fasting overnight for



12 hours before the study except for water ad libitum. One tablet was administered to each animal via an especially designed oral gastric tube and 25 mL water in a fasted state. The animals were barred from eating or drinking during the study. X-ray photographs of the animals were taken by holding them in upright posture. The animals were exposed to x-rays in the abdominal region only at different time intervals of 0, 1, 2, 4, 8 and 12 hours. The tablet that remained in gastric cavity were visible in the x-ray images.

RESULTS AND DISCUSSION

Characterization of Glimepiride

Melting Point: The melting point of glimepiride was 207–209°C which is in compliance with the theoretical value.

Standard Curve of Glimepiride

The standard curve of glimepiride within the concentration range of 1–10 µg/mL (Fig. 1) was almost linear with r^2 value of 0.998.

Preparation of Solid Dispersion

Solid dispersion of glimepiride-affnisol in different ratios i.e. 1:1 (SD1), 1:5 (SD2), 1:10 (SD3) and 1:15 (SD4) were prepared by solvent evaporation method. All the batches

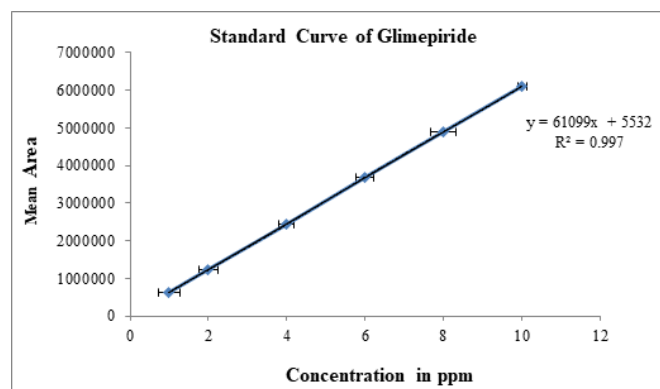


Fig. 1: Standard curve of glimepiride

Table 1: Percentage yield and drug content of solid dispersion of Glimepiride

S. No.	Formulation	% Yield (w/w)	Drug Content (%)
1	SD1	68	98.5%
2	SD2	72	96.8%
3	SD3	70	97.6%
4	SD4	69	97.5%

were prepared in triplicate and evaluated for the following parameters.

Characterization of Solid Dispersion

Determination of Percentage Yield

The results (Table 1) showed that %yield was found to be 68.0–72.0% which was satisfactory and within the observed concentration range while preparing the solid dispersion by solvent evaporation technique.

Drug Content

Drug content for all the prepared batches of solid dispersions is shown in the Table 1:

Drug content for all the batches was within 96.8–98.5%. The batches prepared with glimepiride-affnisol (1:1) the drug content was 98.5%, for glimepiride-affnisol (1:5). The drug content was 96.8%, for glimepiride-affnisol (1:10) the drug content was 97.6% and for glimepiride-affnisol (1:15) the drug content was 97.5%.

Determination of Solubility of Glimepiride in Solid Dispersions

The solubility of all the batches of solid dispersions of glimepiride was determined in 0.1N HCl pH 1.2 and phosphate buffer pH 7.8.

All the batches (SD1 to SD4) showed improved solubility of glimepiride in both the media compared to the pure drug (Fig. 2). The solubility enhancement may be attributed to the enhanced wettability and more intimate contact between drug and polymer, resulting in reduced crystallinity. The improved solubility of glimepiride in pH 7.8 was compliant with Viana *et al.*

It was also observed that an increase in the polymer concentration did not significantly improve solubility

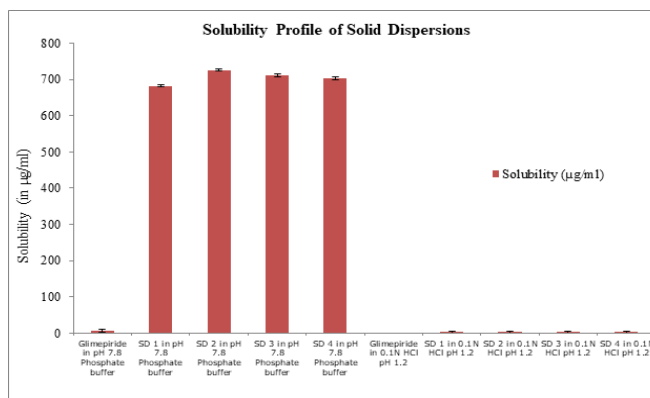


Fig. 2: Solubility profile of solid dispersions

Table 2: Physical properties of Solid Dispersions

Formulation	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
SD1	28.50±1.023	0.66±0.411	0.69±0.265	4.35±1.15	1.05±0.026
SD2	27.21±0.924	0.65±0.374	0.68±0.177	4.41±0.14	1.04±0.014
SD3	24.09±0.157	0.68±0.057	0.72±0.025	5.56±2.04	1.06±0.027
SD4	25.55±0.187	0.64±1.051	0.66±0.202	3.03±1.08	1.03±0.011

and drug:polymer ratio (1:1) yielded the optimum solubility.

Evaluation of Powder Flowability (Tapped and bulk density, Carr's index, Hausner's ratio)

The powder mixtures of all solid dispersions were evaluated for angle of repose, bulk density (BD), tapped density (TD), compressibility index (CI) and hausner's ratio. The results are shown in Table 2.

Identification of Drug by FTIR

Infrared spectrum of glimepiride was characteristics for peak of N-H stretch (secondary amine) at 3389.5 cm^{-1} , 3291.2 cm^{-1} , C-H stretch (aromatic) at 2933.4 cm^{-1} , C-H stretch (aliphatic) at 2882.8 cm^{-1} , C=O stretch at 1707.1 cm^{-1} , N-C=O stretch at 1677.3 cm^{-1} and O=S=O at 1349.3 cm^{-1} as confirmed by peaks (Fig. 3).

Infrared spectrum of solid dispersion (SD1) were prominent for the N-H stretch (secondary amine) at 3389.5 cm^{-1} and 3291.2 cm^{-1} , C-H stretch (aromatic) at 2933.4 cm^{-1} , C=O stretch at 1707.1 cm^{-1} , N-C=O stretch at 1673.6 cm^{-1} , O=S=O groups at 1349.3 cm^{-1} .

Differential Scanning Calorimetry (DSC) Studies

DSC thermogram of glimepiride showed endothermic peak at 212.33°C, indicating its melting point in the range of 210-214°C. Further DSC, thermograms of affnisol also showed endothermic peak at 132.45°C, indicating that drug and polymer possess different melting points. However, the thermogram of optimized solid dispersion (SD1) showed

broad endothermic in the peak of drug (Fig. 4) in remained at around 210.54°C indicating the drug is molecularly dispersed in the polymer.

Formulation of Gastro-retentive Tablets of Glimepiride

The optimized batch of solid dispersion (SD1) was selected for compression to the tablets. Gastro-retentive properties were attributed to the tablets by HPMC K4M and carbopol 940. The composition of formulations is shown in Table 3.

Composition of Formulation

The independent variables [HPMC K4M (X1) and concentration of carbopol 940 (X2)] influencing the bioadhesive strength and cumulative drug release (responses) were optimized by central composite design (CCD) found in response surface methodology of the Design-Expert software at a fixed temperature of $30 \pm 0.5^\circ\text{C}$. The CCD results revealed that the independent variables investigated had significant impacts on bioadhesive strength and cumulative drug release. The obtained experimental data showed that at the optimized HPMC K4M (25 mg) and Carbopol 940 (20 mg) concentration resulted in an optimum bioadhesive strength (9.86) and cumulative drug release (97.05%).

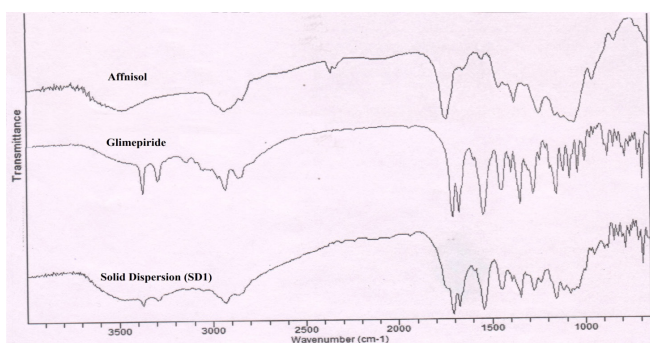


Fig. 3: FTIR spectrum (overlay) of Affnisol, glimepiride and solid dispersion (SD1)

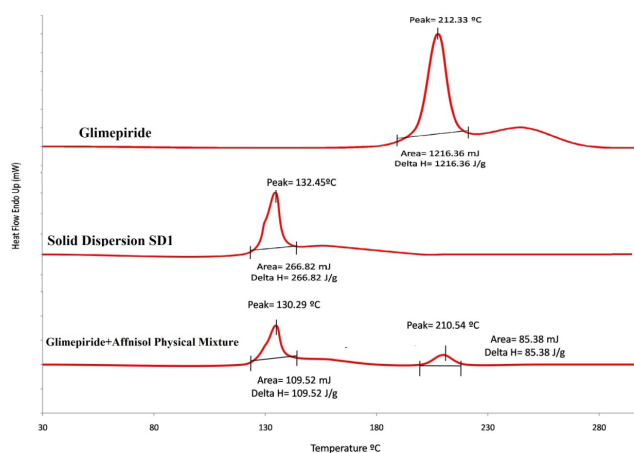


Fig. 4: DSC thermogram of glimepiride, Affnisol and Solid Dispersion (SD1)

Table 3: Composition of gastro-retentive tablets (mg) (F1 to F10)

Composition (in mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Glimepiride SD (eq. to 4mg glimepiride)	8	8	8	8	8	8	8	8	8	8
HPMC K4M	25	25	4	25	10	10	40	40	25	46
Carbopol 940	20	20	20	34	30	10	30	10	6	20
Sodium bicarbonate	20	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose	71	71	92	57	76	98	46	66	85	50
Magnesium stearate	4	4	4	4	4	2	4	4	4	4
Purified Talc	2	2	2	2	2	2	2	2	2	2
Total (in mg)	150	150	150	150	150	150	150	150	150	150



Evaluation Pre-compression Blend of Glimepiride

The batches F1-F10 were evaluated for Bulk density, tapped density, angle of repose, compressibility index and hausner ratio (Table 4).

The values of pre-compression parameters were found to be within limits and all the batches represent very good flow characteristics.

Evaluation Gastro-retentive Tablets of Glimepiride

The average weight of all the batches (F1-F10) was close to the tablets' target weight, i.e. 150 mg, and all the tablets were within the pharmacopoeal limits of weight variation. The thickness and hardness were 3–4 mm and 5–6 kg, respectively. The friability of all the batches was less than 1.0% i.e., within pharmacopoeal limits. The floating time

for all the tablets was less than 1 minute and drug content was also more than 96% for all the batches. The results are shown in Table 5.

In-vitro Bio-adhesion Study

In-vitro bio-adhesion studies performed on Modified two arm balance the results are shown in Table 6 and Fig. 5 and 6.

In-vitro Drug Release (Dissolution)

Cumulative drug release of all the batches of gastro-retentive tablets of glimepiride at the end of 12 hours was more than 90% for all the batches (Fig. 7 and 8).

During the first hour, rate of drug release was significantly higher, and this effect may be attributed to a

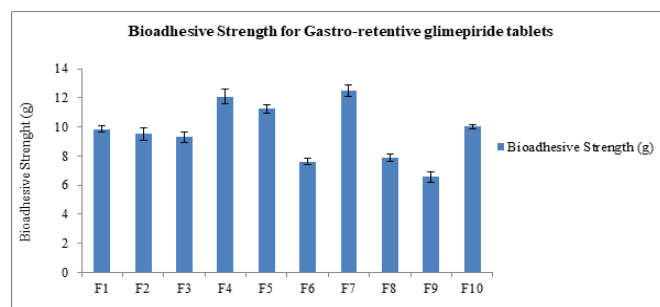


Fig. 5: Bioadhesive strength of F1 to F10

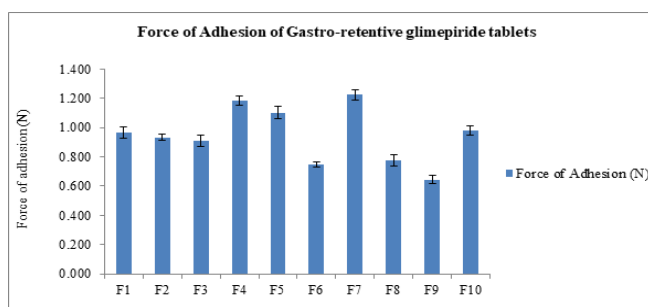


Fig. 6: Force of adhesion for formulation F1 to F10

Table 4: Preformulation study of pre-compression batches of glimepiride blends

S. No.	Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Angle of repose (θ)	Compressibility index (%)	Hausner ratio
1	F1	0.602 $\pm$ 0.007	0.664 $\pm$ 0.006	22.34 $\pm$ 0.008	9.179 $\pm$ 0.009	1.108 $\pm$ 0.008
2	F2	0.656 $\pm$ 0.004	0.740 $\pm$ 0.004	21.38 $\pm$ 0.005	10.199 $\pm$ 0.007	1.118 $\pm$ 0.006
3	F3	0.641 $\pm$ 0.005	0.758 $\pm$ 0.007	22.41 $\pm$ 0.002	12.400 $\pm$ 0.005	1.157 $\pm$ 0.011
4	F4	0.691 $\pm$ 0.001	0.764 $\pm$ 0.003	20.47 $\pm$ 0.006	11.538 $\pm$ 0.002	1.128 $\pm$ 0.006
5	F5	0.660 $\pm$ 0.009	0.750 $\pm$ 0.008	24.34 $\pm$ 0.003	11.158 $\pm$ 0.008	1.110 $\pm$ 0.005
6	F6	0.629 $\pm$ 0.003	0.735 $\pm$ 0.005	22.08 $\pm$ 0.007	13.325 $\pm$ 0.005	1.122 $\pm$ 0.004
7	F7	0.721 $\pm$ 0.005	0.808 $\pm$ 0.002	23.51 $\pm$ 0.001	10.468 $\pm$ 0.011	1.134 $\pm$ 0.008
8	F8	0.604 $\pm$ 0.004	0.668 $\pm$ 0.005	22.57 $\pm$ 0.004	9.397 $\pm$ 0.003	1.101 $\pm$ 0.009
9	F9	0.658 $\pm$ 0.007	0.709 $\pm$ 0.003	21.69 $\pm$ 0.009	11.471 $\pm$ 0.004	1.109 $\pm$ 0.006
10	F10	0.626 $\pm$ 0.006	0.767 $\pm$ 0.009	22.35 $\pm$ 0.002	14.178 $\pm$ 0.007	1.168 $\pm$ 0.010

Table 5: Evaluation of floating gastro-retentive tablets for weight variation, thickness, hardness, friability and floating time.

Formulation	Average weight (in mg)	Thickness (in mm)	Hardness (kg/cm^2)	Friability (%)	Floating time (Sec.)	Drug Content(%)
F1	151.31 $\pm$ 0.097	3.17 $\pm$ 0.010	5.25 $\pm$ 0.005	0.15 $\pm$ 0.008	45.00 $\pm$ 0.019	98.41 $\pm$ 0.023
F2	149.35 $\pm$ 0.070	3.15 $\pm$ 0.022	5.18 $\pm$ 0.010	0.19 $\pm$ 0.004	51.00 $\pm$ 0.012	99.15 $\pm$ 0.101
F3	152.14 $\pm$ 0.074	3.13 $\pm$ 0.039	5.15 $\pm$ 0.011	0.26 $\pm$ 0.011	48.00 $\pm$ 0.008	97.72 $\pm$ 0.128
F4	148.34 $\pm$ 0.123	3.17 $\pm$ 0.074	5.23 $\pm$ 0.008	0.22 $\pm$ 0.006	38.00 $\pm$ 0.011	98.08 $\pm$ 0.089
F5	151.21 $\pm$ 0.108	3.18 $\pm$ 0.023	5.30 $\pm$ 0.002	0.29 $\pm$ 0.005	41.00 $\pm$ 0.009	97.48 $\pm$ 0.126
F6	149.11 $\pm$ 0.089	3.15 $\pm$ 0.018	5.18 $\pm$ 0.006	0.30 $\pm$ 0.010	48.00 $\pm$ 0.017	96.90 $\pm$ 0.094
F7	153.39 $\pm$ 0.048	3.14 $\pm$ 0.025	5.17 $\pm$ 0.003	0.35 $\pm$ 0.005	50.00 $\pm$ 0.007	97.60 $\pm$ 0.111
F8	151.72 $\pm$ 0.098	3.11 $\pm$ 0.070	5.31 $\pm$ 0.005	0.24 $\pm$ 0.009	52.00 $\pm$ 0.008	97.61 $\pm$ 0.059
F9	148.91 $\pm$ 0.048	3.16 $\pm$ 0.014	5.20 $\pm$ 0.007	0.21 $\pm$ 0.007	46.00 $\pm$ 0.010	98.52 $\pm$ 0.083
F10	151.51 $\pm$ 0.071	3.10 $\pm$ 0.017	5.15 $\pm$ 0.004	0.17 $\pm$ 0.008	49.00 $\pm$ 0.012	98.65 $\pm$ 0.109

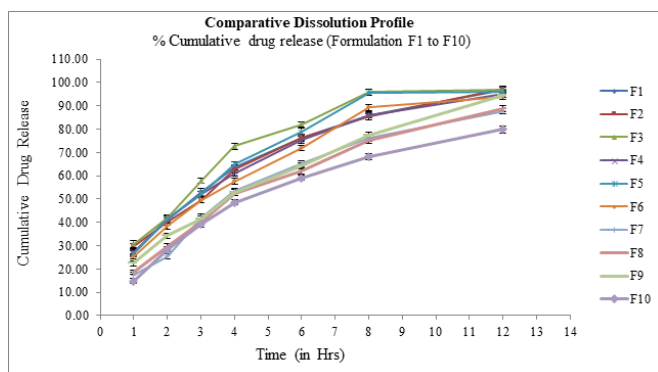


Fig. 7: Comparative dissolution profile for formulation F1 to F10.

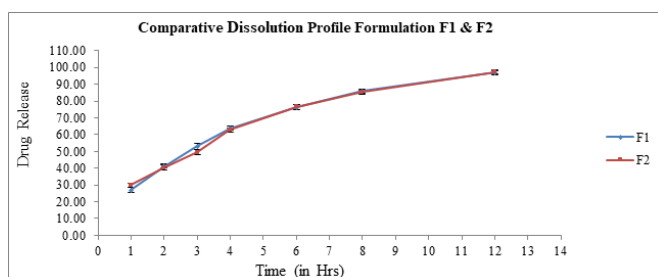


Fig. 8: Comparative dissolution profile for formulation F1 and F2.

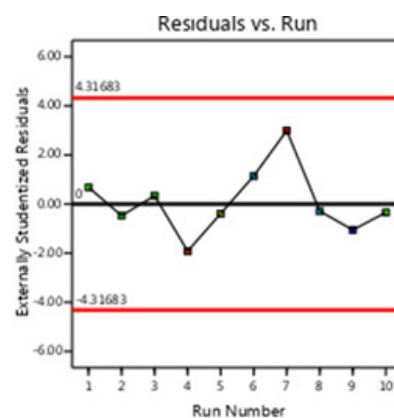
Table 6: Bioadhesion strength of different formulations

Formulation	Bioadhesive Strength (g)	Force of Adhesion (N)	Bond Strength (N/m ²)
F1	9.86±0.19	0.967	277.87
F2	19.51±0.41	0.933	268.01
F3	9.29±0.38	0.911	261.81
F4	12.08±0.52	1.185	340.43
F5	11.23±0.31	1.102	316.48
F6	6.71±0.21	0.747	214.46
F7	12.48±0.40	1.224	351.71
F8	7.90±0.26	0.775	222.63
F9	6.57±0.35	0.645	185.15
F10	10.02±0.15	0.983	282.38

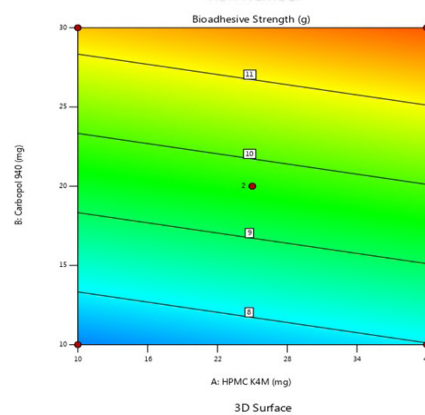
Table 7: Central composite design variables and responses

Run	Factor 1 A:HPMC K4M (mg)	Factor 2 B:Carbopol 940 (mg)	Response 1 Bioadhesive Strength (g)	Response 2 Cumulative Drug Release (%)
1	25	20	9.86	97.05
2	25	20	9.51	97.2
3	4	20	9.29	96.84
4	25	34	12.08	95.1
5	10	30	11.23	96.19
6	10	10	7.61	93.87
7	40	30	12.48	87.8
8	40	10	7.9	88.69
9	25	6	6.57	94.63
10	46	20	10.02	79.82

a)



b)



c)

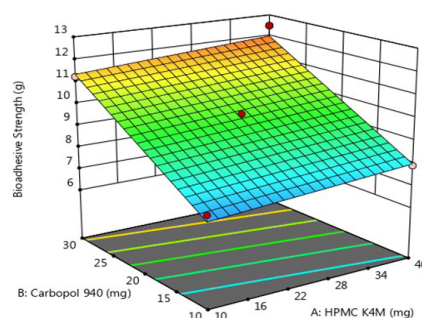


Fig. 9: Plots for Bioadhesive strength F1 to F10 (a = Residual plots, b =Contour plots, c = 3D plots)



higher rate of drug diffusion from the tablet matrix due to high concentration gradient. However, the drug release rate further slowed down due to a decrease in a concentration gradient, and a comparatively slow drug release from the tablets was observed in the later phase. The relationship between variables and its effect on drug release is shown in Table 7. At 12 hours, more than 90% of the drug had been released, indicating that prepared tablets might serve as a

sustained release gastro-retentive dosage form. The effect of variables on bioadhesive strength and cumulative drug release is shown in Fig. 9 and 10.

Powder X-ray Diffraction (P-XRD) Studies

The Powder XRD studies were carried out for solid-state characterization of the drug, polymer, solid dispersion and optimized formulation.

XRD patterns of glimepiride show sharp, intense peaks notably at 2θ diffraction angles of 6° , 13° , 18° , 19° and 21° indicating glimepiride was in the crystalline state (Fig. 11). The reduction or disappearance of peaks intensity in glimepiride GR Tablets (F2) formulation indicates that glimepiride may have undergone solid-state transition to amorphous form or crystalline was reduced.

Drug Release Kinetics

Evaluation of drug release kinetics and applying the best fit by correlation coefficients revealed that the Higuchi ($r^2 = 0.991$) and Hixson-Crowell ($r^2 = 0.992$) equations seemed to be better fit than the first-order ($r^2 = 0.977$) and zero-order equation ($r^2 = 0.866$). The drug release was both diffusion and erosion dependent as indicated from the best fit model (Table 8).

The correlation of Higuchi (diffusion) and Hixson-Crowell (erosion) kinetic equations suggests that the co-dependent diffusion/erosion mechanism is the main drug release mechanism from these tablets. The above results show that the drug release in optimized formulation (F2) containing HPMC K4M (25 mg) and

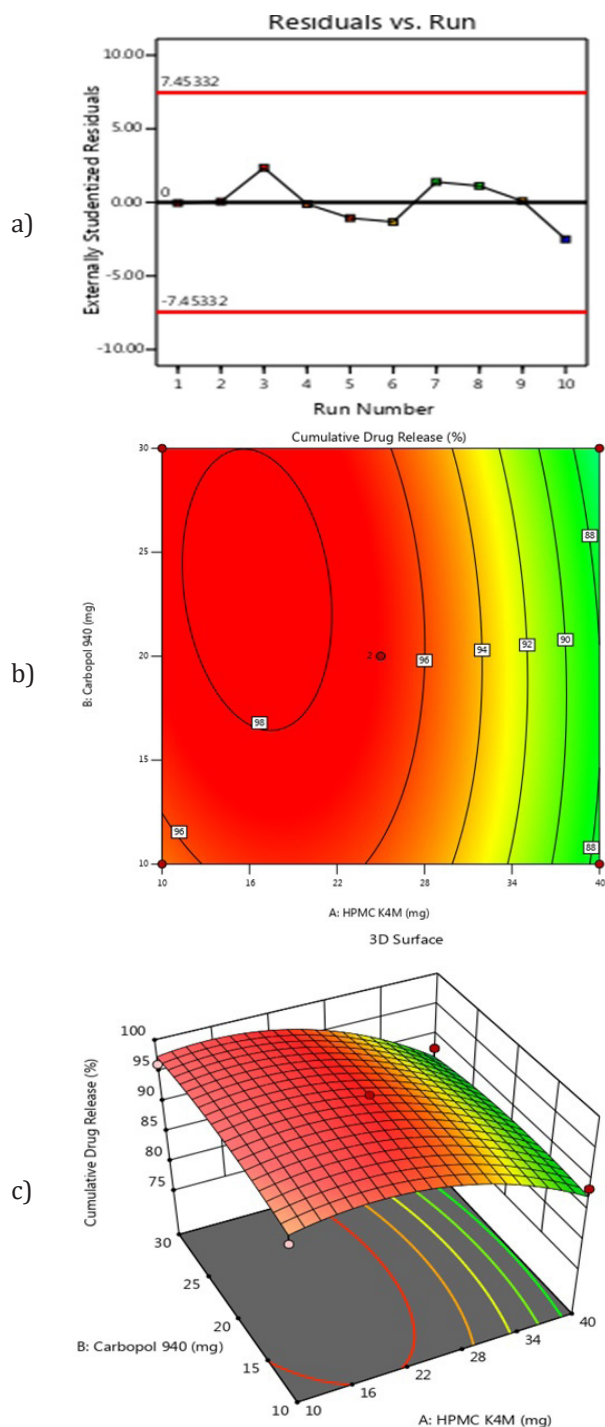


Fig. 10: Plots for cumulative drug release F1 to F10 (a = Residual plots, b = Contour plots, c = 3D plots)

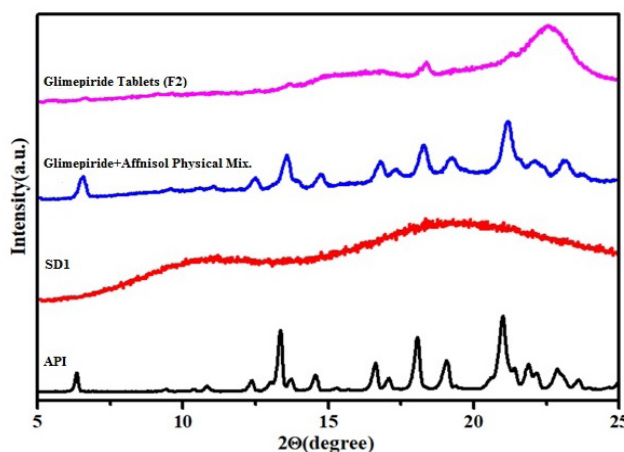


Fig. 11 : XRD pattern of Glimepiride (API), Affnisol, Solid dispersion and glimepiride tablets

Table 8: Release kinetics of glimepiride tablets

S. No.	Model	Correlation Coefficient (r^2)
1	Zero Order	0.866
2	First Order	0.977
3	Higuchi	0.991
4	Korsmeyer-Peppas	0.935
5	Hixson-Crowell model	0.992

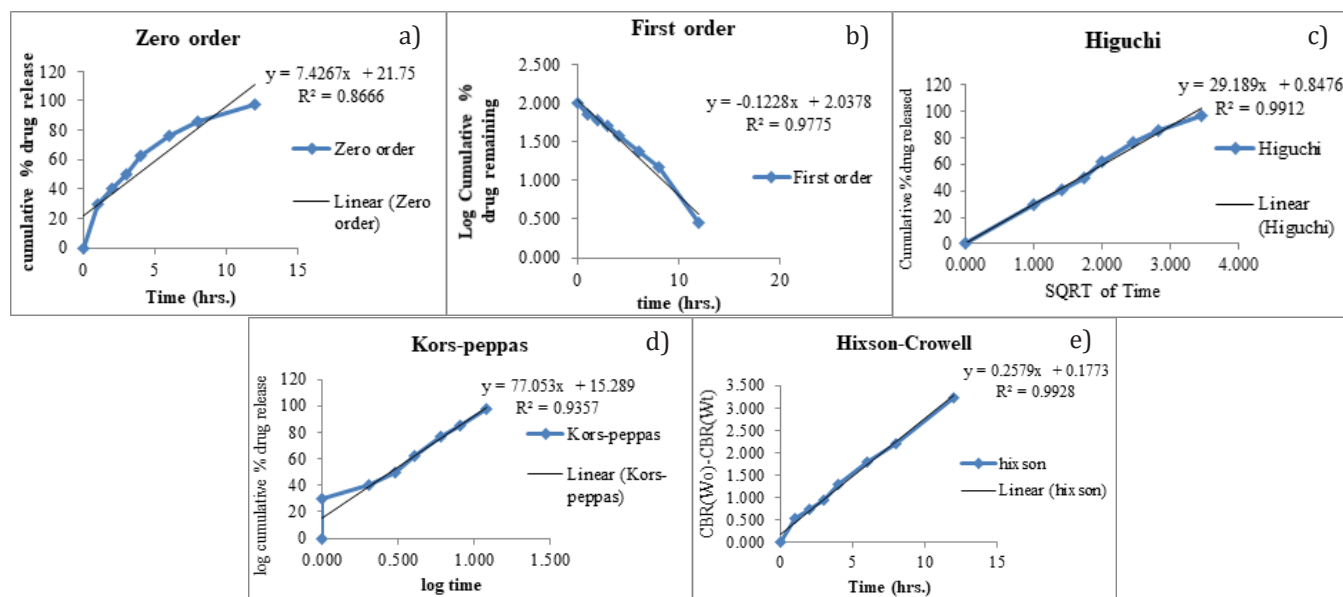


Fig. 12: Kinetic models of the optimized formulation (a = Zero order, b = first order, c = Higuchi, d = Kors-peppas and e = Hixson Crowell)

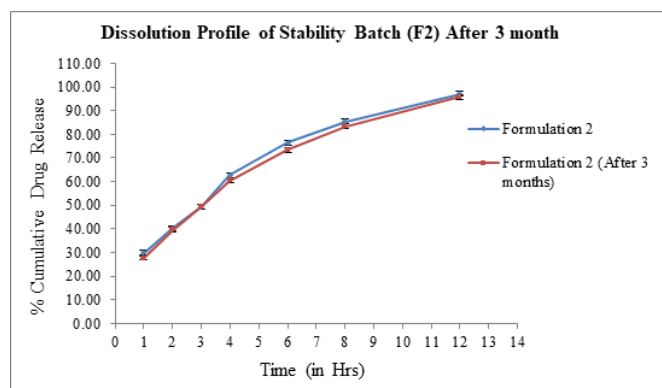


Fig. 13: Dissolution profile of the optimized formulation (F2) at initial and after 3 months

carbopol 940 (20 mg) was primarily dependent on drug diffusion and supplemental polymer erosion (Fig. 12). In conclusion, the developed optimized formulation (F2) drug was successfully released *in-vitro* for 12 hours compared.

Stability Studies

The optimized gastro-retentive tablets of glimepiride solid dispersion (F2) were stable with cumulative drug release up to 95.94% in 12 hours after 3 months of stability (Fig. 13). The difference in drug release from initial to 3 months is less than 2% which complies with ICH guidelines of stability. The stability study suggests that the formulation is stable and robust.

In-vivo Radiographic Studies

In-vivo gastro-retention (buoyancy) studies were performed for optimized formulation using the radiography technique. The animals were exposed to x-rays in the abdominal region only at different time intervals of 0, 1, 2, 4, 8 and 12 hours. The tablets remained in the gastric cavity were visible in the x-ray images (Fig. 14).

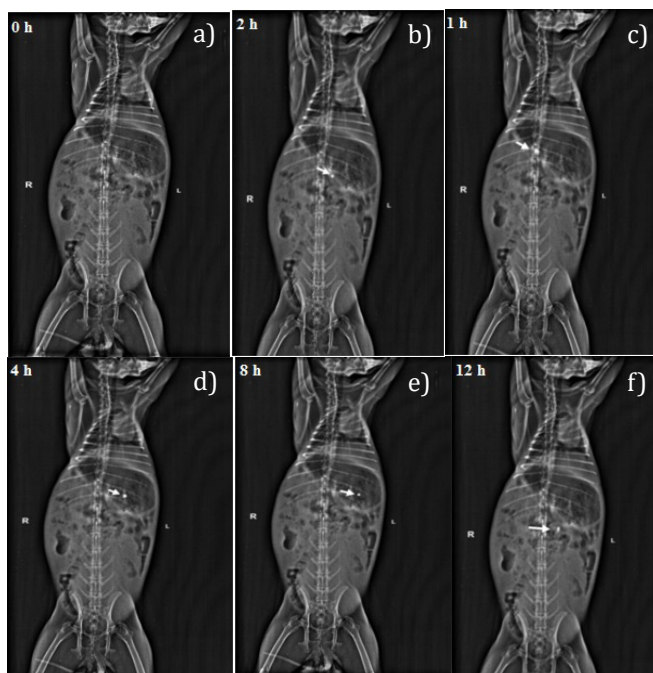


Fig. 14: X-ray images of rabbit (a = 0 hr, b = 1 hr, c = 2 hr, d = 4 hr, e = 8 hr and f = 12 hrs)

The radiographic images reveal that the tablet floated as soon as it came in contact with gastric fluid and remained attached to gastric mucosa during the early stages for more than two hours and remained in floating condition for more than eight hours. The tablets were visible after 12h of ingestion and proved that the formulation has potential for gastro-retention.

CONCLUSION

In the present study, solubility of glimepiride (BCS class-II drug) was successfully enhanced by formulating

