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Formulation and Evaluation of Floating and Mucoadhesive tablets containing Glipizide

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ABSTRACT

In the present study, Glipizide, a drug mainly preferred for type-II diabetes, is formulated in the form of floating mucoadhesive tablets to improve its bioavailability. Hydroxy Propyl Methyl Cellulose K200M, Sodium Carboxy Methyl Cellulose, Carbopol 974P, Karaya gum, Chitosan, and Xanthan gum were used as mucoadhesive polymers in designing of the floating mucoadhesive tablets. Different proportions of glipizide and polymer were used to prepare tablets. Pre-compression evaluation studies evaluated the powder blend of Glipizide mucoadhesive tablets (Pre-compression blend). It concluded that the blend had good flow property and better compressibility by interpreting the data obtained from the test. Hence the floating mucoadhesive tablets were prepared by direct compression technique. The results of floating lag time, and buoyancy studies suggested that formulations had a satisfactory floating ability. The release profile of the active pharmaceutical ingredient (glipizide) from the prepared dosage form indicated a controlled and enhanced drug release for a period of 12hrs. *An in-vivo* study done for selected formulation. By the interpretation of data obtained from all the evaluation studies (Pre-compression test, floating property, drug release profile, & *in-vivo* study) concluded that formulation GF8 containing drug: Carbopol 974P (1:2) was optimized. The drug release kinetics of the formulation GF8 followed the Higuchi model with a regression value of 0.993.

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INTRODUCTION

The most acceptable route of drug administration is the oral route, which gives more patient compliance with systemic drug release. The majority of drugs ($\geq$ 90%) are administered through an oral dosage form. In conventional dosage form, the formulation resides in the stomach for a limited period. Due to these properties, the active pharmaceutical ingredients having an absorption window in stomach hampered the bioavailability. Oral controlled dosage form represents the widest advisable dosage form to design the controlled and prolonged drug action to achieve various benefits and minimizing the cons of conventional therapy. Conventional dosage form gives different patterns of drug release rate, which is majorly affected by gastric residence time (GRT) / gastric emptying time (GET) for formulations (Shaikh and Molvi, 2016; Rouge *et al.*, 1996; Streubel *et al.*, 2006).

Gastric emptying time for tablets (Formulation) can be modified by altering the different parameters of

tablets like density, size, and gas generating agents, which help the dosage form to retain in the stomach for a prolonged interval of time (Mayavanshi and Gajjar, 2008). The gastro retentive dosage form is the most advisable technique to enhance the residence time of dosage form in the stomach (Pattanayak *et al.*, 2018).Gastro retentive drug delivery system (GRDDS) can be elaborated as a modified technique of dosage form which can remain in the upper region of gastrointestinal track(GIT) for a long duration of time by altering the gastric emptying time as well as release the drug for a systemic and controlled manner, and then metabolized (Prajapati *et al.*, 2013). In the present scenario, the different approaches for the gastro retentive drug delivery system are established to enhance the upper GI residence time. The primary objective of the gastro retentive drug delivery system is to overcome the problems related to other oral drug delivery systems, which will be more beneficial towards the patients (Bardonnet *et al.*, 2006; M.Saritha and G.Eswer, 2011; Someshwar *et al.*, 2011).

There are different parameters listed out which effects on the GRT of a dosage form among theme one parameter is 'fluid level.' The fluid level in the stomach is not constant always. This creates a problem for GRDDS to float for a desired duration of time and to give drug release in a controlled and systemic way in the stomach (Gupta *et al.*, 2009). GRDDS is effective for a drug which is having high absorption properties in the stomach or for the drug, which unstable in alkaline pH due to poor solubility and a narrow of absorption window (Gade *et al.*, 2009). The GRDDS have low bulk density than fluids of upper GIT due to which it floats for a prolong period without hampered by gastric emptying time. Due to prolong the floating time in the fluid of upper GIT, the desired amount of drug can release from the dosage form slowly (Varma *et al.*, 2010). So to overcome the problems of low gastric retention time, a new delivery system is designed, which is a combination of the Floating & Mucoadhesive technique. In the present work Glipizide, an antidiabetic drug is formulated with a different type of controlled release and mucoadhesive polymers in different concentrations to optimize a formulation, which will help to overcome the above-said problems.

MATERIALS AND METHODS

Glipizide was obtained from Triveni Chemicals through the supplier. The polymers like HPMC K200M (Masareddy *et al.*, 2010), sodium carboxymethylcellulose (NaCMC), Carbopol 974P, Karaya gum, Chitosan, Xanthan gum and other remaining excipients like sodium bicarbonate, magnesium stearate, talc, lactose too obtained from S. D Fine Chemicals. The remaining additives utilized in this work belong to the laboratory scale.

Precompression evaluation

Solubility Studies

The solubility of Glipizide (Banker and Rhodes, 2002; Peddapalli *et al.*, 2018), was studied in 0.1N HCL (pH 1.2) solution by phase equilibrium method. In a 20 ml vial, 10 mL above resolution, an excessive amount of drug was taken. The above vials were sealed by closures (rubber caps) and mixed properly by rotary shaker for overnight at the reasonable climatic condition. After that, the drug solution was passed into 0.2 μm Whatmann's paper. Followed by it was scanned through UV spectrophotometer 227nm. The calibration curve for Glipizide was done using the above acidic solution, and the solubility of Glipizide was estimated from the slope of the calibration curve. The same method was carried out for 3 times to find out the mean of the result.

Drug-excipient compatibility studies

Fourier transform infrared spectroscopic studies

FT-IR spectrophotometer was performed to check the compatibility between the drug-excipient by the non-thermal analysis. The spectrum for the sample was scanned in the frequency of 450-4000 cm^{-1}.

Pre-compression Evaluation

Preformulation study is a group of studies which deals with the physicochemical parameter of the drug, also helps in designing of dosage form, and also provides an outline for the selection of pharmaceutical additives or excipients.

Compressibility index

It reflects the assessment for inter particulate interactions of powder. The compressibility index (percentage compressibility) of the API was calculated by using the following formula.

$$I = (\frac{DT - Db}{DT})100$$

Where, I = Compressibility index

Dt= Tapped density of sample.

D_b= Bulk density of the sample.

Hausner's ratio

It reflects the flow properties of the powder sample and is calculated by the following formula

$$I = (\frac{DT - Db}{DT})100$$

Where, H =Hausner's ratio

D_t= Tapped density of the sample.

D_b= Bulk density of the sample.

Angle of repose

It also reflects the flow property of the powder sample and determined from the height and radius of the pile obtained by the powder sample. It is expressed as

$$\theta = \tan -1 \left(\frac{h}{r}\right)$$

Where, θ= angle of repose

h = height in cm

r = radius in cm.

Preparation of Floating mucoadhesive tablets

The direct compression method is opted to formulate Floating mucoadhesive tablets containing Glipizide; Different batches were developed by changing the ratio of HPMC K200M, Na CMC, Carbopol 974P, Karaya gum, Chitosan, and Xanthan gum. Sodium bicarbonate is helped to float the tablets. Talc and magnesium stearate and lactose are used as a lubricant, glidant, and diluent, respectively. The drug, polymers, sodium bicarbonate, and lactose were correctly mixed for 15 min until they formed a homogeneous mixture. Followed by talc and Magnesium Stearate are added as lubricating agents. The above powder mixture was combined homogeneously by using a polyethylene bag. Finally, the tablets were prepared by a 6 mm diameter to die in a 9-station rotary punching machine (Lab Press, India). Table 1 shows the different formulation approaches (Hemnani *et al.*, 2011).

Post- compression Evaluation

Physicochemical characterization for prepared formulation

The formulated Glipizide Floating mucoadhesive tablets were studied for the following mentioned test

1. Weight variation
2. Thickness
3. Hardness
4. Friability
5. Drug Content

Weight variation

This test is carried out by a random selection of 20 tablets and followed by weighed accurately. The mean weight of 20 tablets calculated and followed by compared with the weight of the tablet individually. (Al-Saidan *et al.*, 2005; Alhamdany and Abbas, 2018; Nokhodchi *et al.*, 2012). Not more than two tablets should not deviate from the average weight by ± 10 %. The percent deviation was calculated as follows:

% Deviation =

$$\left(\frac{Individual\ weight\ -\ Mean\ weight}{Mean\ weight}\right) \times 100$$

Tablet Thickness

From the production level, physical shape (thickness and diameter) for the tablets was monitored properly. Various parameters have an impact on thickness like compression force, the configuration of the die, and the rotation of machine per minute (RPM) of the compression machine. Hence these criterions are essential for acceptance of formulation, tablet uniformity, and packaging. The Digital Vernier caliper was utilized to examine the physical shape of the tablets (Damien *et al.*, 2010). The tablets (10 tablets for each formulation) were selected randomly, and the mean was calculated. The standard deviation for thickness was calculated.

Tablet Hardness

The hardness of a dosage form explains as a force necessitates / adequate to break it in two parallel plates. Tablets need durable resistance power for additional mechanical shocks. Every batch of pills was taken (6 tablets), and hardness was estimated by Monsanto hardness tester, and the average was calculated (Gopalakrishnan and Chenthilnathan, 2011). It is expressed in Kg/cm^2.

Friability

The hardness of a tablet is not sufficient to express the resistance due to loosening their crown positions during compression. Accordingly, to cross-check the strength of the tablet, another measure for the tablet was proposed i.e., friability (Roche friability). A set of pills that were selected for the test is to get the mechanical force (shock and abrasion). Roche friability, which rotates at 25 rpm speed for 4 minutes (Saumya and Dharmajit, 2012).

The initial weight of tablets was noted down before the test. After the test, the pills were then de-dusted and reweighed. They are finally expressed in the percentage of friability.

Friability (%) =

Table 1: The Composition of Floating Mucoadhesive Tablets of Glipizide

Ingredients	GF 1	GF 2	GF 3	GF 4	GF 5	GF 6	GF 7	GF 8	GF 9	GF 10	GF 11	GF 12	GF 13	GF 14	GF 15	GF 16	GF 17	GF 18
Glipizide	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
HPMC K200 M	5	10	15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Na CMC	-	-	-	5	10	15	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 974P	-	-	-	-	-	-	5	10	15	-	-	-	-	-	-	-	-	-
Karaya gum	-	-	-	-	-	-	-	-	-	5	10	15	-	-	-	-	-	-
Chitosan	-	-	-	-	-	-	-	-	-	-	-	-	5	10	15	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	10	15
NaHCO3	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Lactose	73	68	63	73	68	63	73	68	63	73	68	63	73	68	63	73	68	63
Total Weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

$$\frac{Initial\ weight\ of\ 10\ tablets - final\ weight\ of\ 10\ tablets\ (W)}{The\ initial\ weight\ of\ 10\ tablets\ (Wo)} \times 100$$

Where, W_o is the initial weight of the tablets (Preweighed)

W is the final weight of the tablets (Reweighed)

Assay

Randomized selection of tablets (6 Tablet for each formulation) was carried out to find out the percentage of active pharmaceutical ingredient available in each formulation. Equivalent to the weight of each formulation, the powder was taken and dissolved in 100 ml of 0.1N HCl by stirring for 10 min. The membrane filter (0.45 μ) was used for straining the above solution and diluted suitably followed by measuring absorbance by using a UV-Visible spectrophotometer at 237nm using pH 6.8 phosphate buffers (Kumar *et al.*, 2011).

***In vitro* Buoyancy studies**

It mainly reflects two parameters i.e., floating lag time and total floating time. These two values are finding out by putting formulation in 0.1N HCL. The Floating Lag Time (FLT) is denoted as the time taken by the formulation to reach the top of the medium, and the Total Floating Time (TFT) was determined by noting down the duration of floating time (Gade *et al.*, 2009).

***In vitro* release studies**

The release study was carried out by the USP type II dissolution test apparatus. In Floating mucoadhesive tablets were release the medicaments from a single surface, so to maintain an *in vitro* gastric condition, the formulation was partially covered by an impermeable membrane and followed by it was adhered to a glass slide (2x2 cm) cyanoacrylate adhesive. Then the slide was placed in the 900 ml of pH 1.2 HCl buffer, and paddle speed was 50 rpm at a temperature of 37 $\pm$ 0.5 °C. A fixed amount of test solution withdrawn at fixed time intervals up to 12 h and scanned by spectra at 237nm after appropriate dilution (Vyas and Khar, 2002; Sayeed *et al.*, 2010).

***In vitro* bioadhesion strength**

Ultra Test Tensile strength tester was used to measure the adhesion strength of tablets. 25 kg load cell was set. A membrane was attached to an adaptor, and the Floating mucoadhesive formulation (sample tablet) was attached to adaptor having a similar size using a by adhesive. 100 μl of 1% w/v mucin solution was applied on the membrane, and immediately the formulation was allowed to come in contact with the mucosa. After a certain period, the upper adapter was withdrawn at 0.5 mm/sec until the tablet was completely separate from the membrane. The area under the force-distance curve was helped to determine the work of adhesion.

Force of adhesion =

$$(\frac{Bioadhesion\ strength}{1000})\times 9\cdot 8$$

Bond strength =

$$\frac{Force\ of\ adhesion}{Surface\ area}$$

Moisture absorption

Before the study Floating, mucoadhesive tablets (6 from each formulation) were dehumidified by vacuum oven, if any, followed by immediately partially covered with a water-insoluble backing membrane. The above tablets were exposed to the surface of the agar media (5% m/v) for 1h (Kharia *et al.*, 2010). After the completion of the specified time, the weight of formulation was noted moisture absorption was calculated:

% Moisture Absorption =

$$(\frac{Final\ weight\ -Initial\ weight}{Initial\ weight})\times 100$$

Kinetic analysis of dissolution data

To analyze the *in vitro* release data various dynamic models were used like Zero-order model (Cumulative % drug released versus time), First-order model (Log cumulative percent drug remaining versus time), Higuchi's model –Cumulative percent drug released versus square root of time, Korsmeyer equation / Peppa's model – Log cumulative % drug released versus log time (DM *et al.*, 1995; Peppas, 1985; Korsmeyer *et al.*, 1983; Hixson and Crowell, 1931).

***In vivo* studies - Pharmacokinetic studies**

To determine the peak plasma concentration, pharmacokinetic studies were carried out. The *In vivo* studies were carried out on male Wistar rats weighing range from 250-300 gm. They were housed in polypropylene cages and had free access to food and water. The formulation for the test was formulated according to the doses of anti-diabetic drugs, which were calculated as per the bodyweight of animals. The proposed proof on the animal was approved by the Institutional Animal Ethical Committee (IEAC), which is recognized by the Committee for the Purpose of Control and Supervision of Experiments on Animal (CPCSEA). The optimized Floating mucoadhesive matrix tablets were administered orally. Blood samples were collected for over 24h according to a predetermined sample collection schedule. Various pharmacokinetic parameters like C max, T max, AUC were determined (Hixson and Crowell, 1931; Shin *et al.*, 2010).

RESULTS AND DISCUSSION

The solubility studies indicated that the drug has less solubility in water as compared to methanol and 0.1N HCl.

Drug –Polymer Compatibility Studies by FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). From the FTIR data, it was evident that the drug and excipients doses not have any interactions. Hence they were compatible, as mentioned in Figure 1&Figure 2.

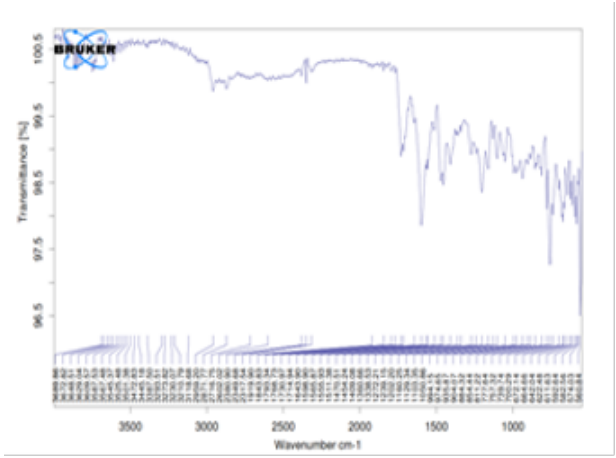

Figure 1: FTIR of Glipizide pure drug

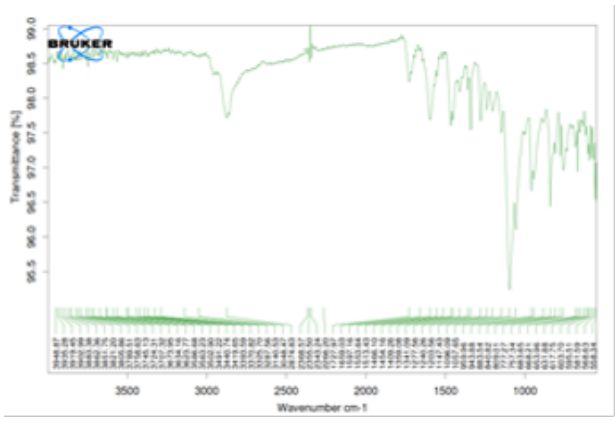

Figure 2: FTIR Spectra of Mixture Drug+Polymer Physical

The angle of repose for all formulations was in the range of 22.29 to 29.36, as mentioned in Figure 3. This suggested that the powder blend has excellent to moderate flow property. The above results showed that the pre-compressed mixture has a good Compressibility index and Hausner's ratio, as mentioned in Figure 4 &Figure 5. This is an indication that the mixture had good compression properties

Post-compression Evaluation

The thickness of the prepared tablets was, as men-

Table 2: Evaluation of floating mucoadhesive tablets of Glipizide

Formulation Code	Thickness (mm)	Average Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)	Floating Lag time (Sec)	Total Floating time(hr)
GF1	4.21±0.22	97.32±0.11	6.1±0.09	0.55±0.07	98.36±0.33	102±0.09	>12
GF2	4.39±0.29	96.10±0.09	6.5±0.05	0.35±0.09	94.15±0.40	95±0.04	>12
GF3	4.20±0.18	99.39±0.15	6.8±0.09	0.48±0.05	95.29±0.29	62±0.05	>12
GF4	4.96±0.27	95.48±0.14	6.3±0.04	0.15±0.08	99.15±0.31	50±0.07	>12
GF5	4.33±0.10	99.83±0.08	6.9±0.08	0.19±0.04	97.39±0.28	45±0.10	>12
GF6	4.75±0.19	100.3±0.16	6.0±0.03	0.49±0.06	99.25±0.36	36±0.08	>12
GF7	4.19±0.17	99.25±0.13	6.4±0.06	0.52±0.07	98.25±0.37	30±0.06	>12
GF8	4.62±0.21	97.64±0.10	6.7±0.04	0.39±0.06	100.0±0.31	35±0.11	>12
GF9	4.81±0.29	99.47±0.27	6.1±0.08	0.31±0.05	95.12±0.27	120±0.08	>12
GF10	4.67±0.17	95.36±0.21	6.8±0.08	0.30±0.04	98.64±0.35	110±0.06	>12
GF11	4.15±0.27	98.61±0.09	6.5±0.10	0.28±0.06	99.20±0.39	125±0.12	>12
GF12	4.21±0.09	95.92±0.16	6.1±0.08	0.21±0.08	95.10±0.34	110±0.09	>12
GF13	4.79±0.19	97.18±0.15	6.9±0.06	0.15±0.07	99.67±0.32	80±0.08	>12
GF14	4.69±0.16	99.86±0.11	6.4±0.09	0.28±0.04	98.33±0.27	60±0.10	>12
GF15	4.91±0.28	100.0±0.08	6.3±0.13	0.19±0.03	99.49±0.30	75±0.13	>12
GF16	4.86±0.24	97.85±0.15	6.0±0.07	0.40±0.05	97.11±0.38	56±0.06	>12
GF17	4.44±0.21	99.90±0.19	6.5±0.05	0.32±0.09	100.0±0.25	35±0.08	>12
GF18	4.52±0.23	96.98±0.23	6.7±0.09	0.10±0.08	97.84±0.29	25±0.05	>12

Each value represents the mean±SD (n=3)

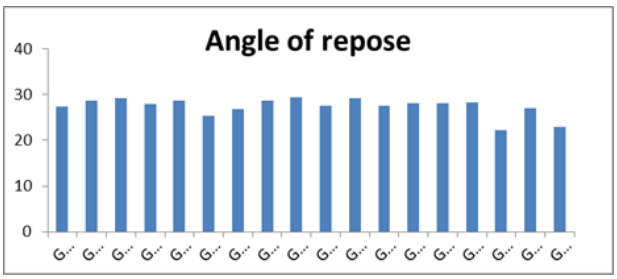

Figure 3: Angle of repose for the obtained formulation

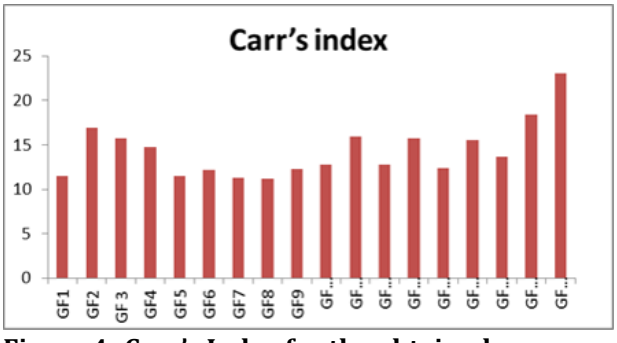

Figure 4: Carr's Index for the obtained formulation

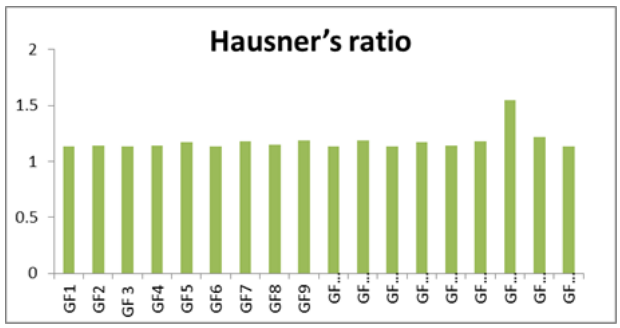

Figure 5: Hausner's Ratio for the obtained formulation

tioned in Table 2 poses in the range between 4.15mm to 4.96mm. The weight variation was in the limit as specified in I.P. The maximum, and minimum hardness of tablets was 6.9Kg/cm^2, and 6Kg/cm^{2}respectively, mentioned in Table 2. This is an optimum hardness for floating mucoadhesive tablet. The friability study depicted that all formulations tend to withstand handling and packing. The maximum floating lag time was 125Sec, as mentioned in Table 2.

In vitro release studies

The minimum drug release was observed for formulation GF6, which contains drug: Na CMC in the ratio

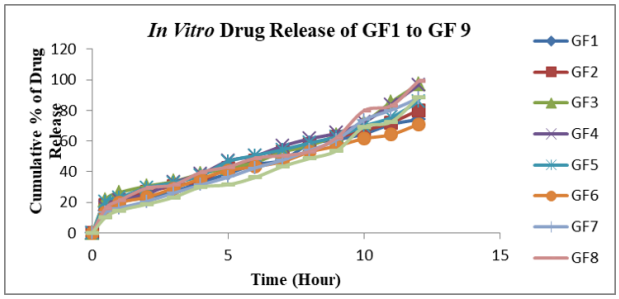

Figure 6: In vitro Dissolution study of RT 1 to RT 9

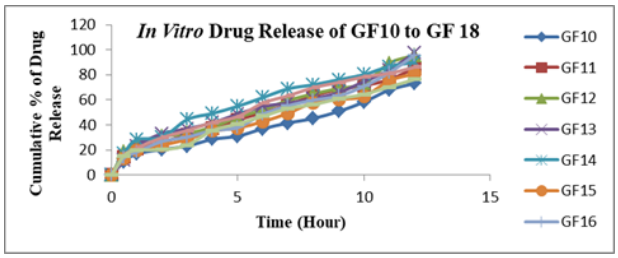

Figure 7: In vitro Dissolution study of RT 10 to RT 18

of 1:3. This may be the reason to provide a high amount of polymer. The maximum drug release is found in formulation GF8, which contains drugs: carbopol 974P in ratio 1:2, as mentioned in Figure 6 &Figure 7. This shows that the drug: carbopol 974P in ratio 1:2 is optimum to achieve a mucoadhesive and free tablet.

In the same way, the moisture absorption and adhesion strength properties presented inTable 3 for the GF8 formulation because the evaluation results of GF8 are better than others, and it also represents the good adhesion strength due to the optimum concentration of carbopol 974P.

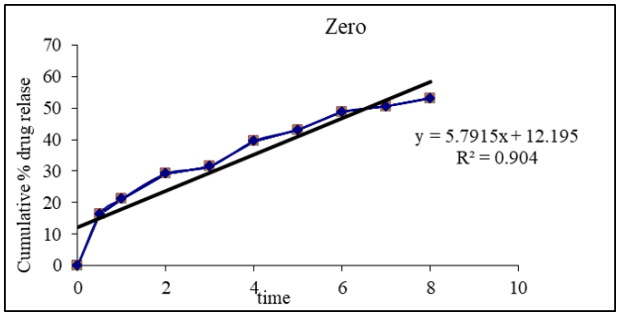

Figure 8: Zero-order plot of optimized formulation

Release kinetics

Data of *in vitro* release studies of formulations, which was showing better drug release, was applied for different release kinetics such as zero, first-order kinetics, Higuchi, and Korsmeyer Peppas of Glipizide release from mucoadhesive tablets given in Figures 8, 9 and 10 &Figure 11.

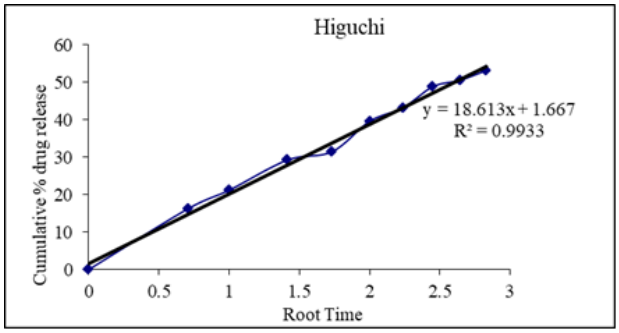

Figure 9: Higuchi plot of optimized formulation

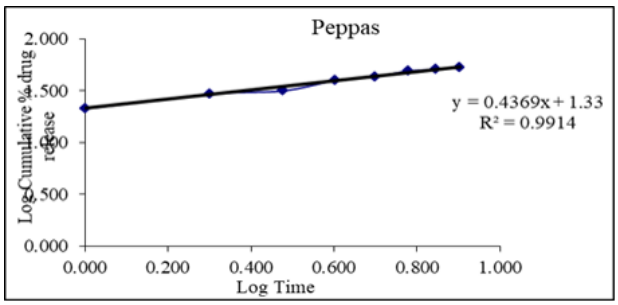

Figure 10: Koresmeyer-Peppasplot of optimized formulation

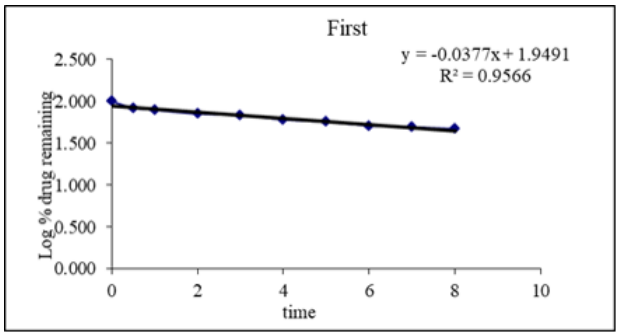

Figure 11: First order plot of optimized formulation

Based on all studies, GF8 formulation was found to be better when compared with all other formulations. This formulation was following the Higuchi mechanism with a regression value of 0.993.

In vivo Studies - Pharmacokinetic Studies

The pharmacokinetics parameters are mentioned inTable 4, Mean time to reach peak drug concentration (T_{max}) and maximum drug concentration (Cmax) were 3.92 hours and 629.0 mg/mL, respectively. The values for C_{max}, T_{max}, AUC were represents the sustain release pattern, as mentioned in Table 4.

Table 3: Moisture absorption, adhesion strength values of selected formulations

Formulation Code	Moisture absorptior	Bioadhesion strength	
		Peak detachment force (N)	Work of adhesion (mJ)
GF8	46±0.25	3.6±0.22	12.42±6.16

Each value represents the mean±SD (n=3)

Table 4: Pharmacokinetic parameters of optimized formulation

S.No	Parameter	Glipizide
1	Cmax	629.0 ng/mL (±94.2)
2	T max(hr)	3.92hours(±0.89)
3	AUC	3430ng·h/Ml(± 882)

CONCLUSION

Glipizide, was formulated as Floating mucoadhesive tablets to improve its bioavailability. HPMC K200 M, Na CMC, Carbopol 974P, Karaya gum, Chitosan, Xanthan gum were selected as polymers. The pre-compression blend of Glipizide Floating mucoadhesive tablets was characterized with respect to all the pre-compression parameters. It found that all the results reflected that the blend was having a good flow of nature and better compression properties. Peak detachment force (N) and work of adhesion were also represented good adhesion activity.

Glipizide GF8 formulation was considered as an optimized formulation because of proper drug release (99.11 %) in 12 hours, Moisture absorption(46±0.25), Peak detachment force (N) (3.6±0.22N), Work of adhesion (12.42±6.16mJ). GF8 formulation follows the Higuchi mechanism with a regression value of 0.993. The in-vivo pharmacokinetic studies showed that the drug reaches the maximum concentration in 3.92 hr. The C_{max} and AUC data predicts that the drug has excellent oral bioavailability. Further studies can be carried out using different drugs to correlate the data.

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