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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF GLIPIZIDE

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Abstract:

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. Floating tablets are drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose in stomach region. The purpose of study was to develop the Gastro retentive floating tablets of Glipizide, and anti-diabetic drug so as to increase the gastric residence time thereby prolong the drug release. Bulk density of these tablets is lower than the gastric content so, they remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. In the present study tablets were prepared by direct compression method using different polymers like Carbopol, HPMC, MCC and sodium bicarbonate as gas generating agent, lubricants and glidants. Prepared tablets were evaluated for different parameters like Hardness, Friability, uniformity of weight, invitro buoyancy and invitro dissolution studies. Among all the formulations F5 containing HPMC K15M (60 mg), Carbopol 940 (40 mg) and MCC (52 mg) was optimized as it has shown best results in terms of buoyancy and drug release.

Keywords: Glipizide, Gastro retention, Buoyancy, Carbopol, HPMC, MCC.

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INTRODUCTION:

Oral route of drug delivery has gained higher level of patient compliance due to the ease of administration, but it has limitation for class of drugs with poor absorption window through out the GIT. Various oral controlled delivery systems have been designed which can overcome these problems and release the drug to maintain its plasma concentration for a longer period of time. This has led to the development of oral gastroretentive dosage forms. Gastroretention is essential for drugs that are absorbed from the stomach. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT),i.e. gastro retensive dosage form (GRDFs or GRDS).

GRDFs extend significantly the period of time over which the drug may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyancy in the stomach for a prolonged period of time without affecting the gastric emptying rate. While the system is floating on the gastric contents the drug released slowly at a desired rate from the system [1]. After the drug release the residual system is emptied from the stomach. Carbonates or bicarbonates, which react with gastric acid or any other acid (e.g., citric or tartaric) present in the formulation to produce CO2 , are usually incorporated in the dosage form, thus reducing the density of the system and making it float on the media. To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system[1], lowdensity systems[1], raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems.Stomach Specific Floating Drug Delivery

Kshirsagar et al [2]., have developed a hydro dynamically balanced system of metformin as a single unit floating tablet. Various grades of low-density polymers were used for the formulation of this system. They prepared by physical blending of metformin and the polymers in varying ratios. The formulation was optimized on the basis of *in-vitro* buoyancy and *in-vitro* release in simulated gastric fluid pH 1.2. Tablets prepared with HPMC K15M and carbopol showed best *in-vitro* percentage release and selected as a optimize formulation. All the formulations were robust tablets with optimum hardness, consistent weight uniformity with low tablet friability. *In-vitro* drug release tests of the tablets indicated the sustained release of metformin HCl was reported.

K.Karunakar et. Al[3]., prepared and evaluated floating drug delivery system of Lamivudine. Floating matrix tablets of Lamivudine were developed to prolong gastric residence time and increase its bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by direct compression technique, using polymers such as hydroxyl propyl methyl cellulose (HPMC E15), Ethyl cellulose and Xanthan gum combination and other standard excipients. Sodium bicarbonate was incorporated as a gas generating agent. The effects of different concentrations of HPMC, EC and Xanthan gum on drug release profile and floating properties were investigated. Comparable release profiles between the commercial product and the designed system were obtained. The model fitting showed that the optimized formulation F2 formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (r). While tablet hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

Varun Dasari et. Al[4]., Formulation of potent drug molecules as dosage form still draws continuous interest and challenges against its optimization towards pharmacokinetics parameters like absorption, bioavailability, onset of action, duration of action Besides it has been proved that by increasing gastric retention time will increase the drug absorption effectively. Lamivudine is an potential anti-HIV agent, used for the long term treatment of HIV-1 infection. It is approved by the U.S Food and Drug Administration (FDA). The dissolution characteristics of optimized multi unit formulation MF8 is compared with that of the pure drug and Marketed formulation (EPIVIR). Compatibility among the drug and optimized polymer i.e., Geleol Pastilles was assessed by performing IR spectroscopy studies Characteristics with the aid of Geleol Pastilles as polymer. , very promising in vitro results were observed with multi unit floating formulations of 24 Lamivudine, further there is a scope to conduct the bioavailability studies in human volunteers to know the exact pharmacokinetics of the developed multi unit GFDDS of Lamivudine.

Ravi Kumar et al [5] have prepared and evaluated the floating tablets of famotidine. Floating tablet were developed using gas-forming agents, like sodium bicarbonate, citric acid and hydroxypropyl methylcellulose (HPMC) and carbopol 934P. The

prepared tablets were evaluated in terms of their precompression parameters, physical characteristics, *in-vitro* release, buoyancy, buoyancy lag-time and swelling index. The formulations were optimized for the different viscosity grades of HPMC, carbopol 934P and its concentrations and combinations. The results of *in-vitro* release studies showed that the optimized formulation (F12) could sustain drug release (98%) for 24 h and remain buoyant for 24 h. Optimized formulation (F12) showed no significant change in physical appearance, drug content, total buoyancy time or *in-vitro* dissolution study after storage at 45 °C/75% RH for three months.

Parikh et al[6].,have done the project work on preparation of floating drug delivery system of atenolol by direct compression method. They performed the pre and post compression studies using IP standard formula and procedure. The hardness of all formulations was found to be in the range of 3.5 - 4.0 kg/cm^2. They found that among all formulations, batch A4 was best formulation and showed very slow release i.e. 52.67% in 12 hour. The drug release of other formulations like A1 to A3 exhibited 96.56%, 81.83%, 69.23% in 12h respectively. The formulations with natural polymers guar gum and xanthum gum have shown better sustained release effect than HPMC different grade.

Aim of this study is to formulate and evaluate gastric retentive floating tablets of Glipizide using various polymers like HPMC K15M and carbopol 940. Tablets were prepared by using direct compression technique and evaluated for different physicochemical parameters like weight variation, wetting time, water absorption ratio, hardness, friability, drug content and in vitro release.

MATERIALS AND METHODS:

Glipizide was procured from Alkem Pvt, Mumbai, HPMC K15M was supplied by Colorcon, Carbopol 940, MCC, Sodium bicarbonate, magnesium stearate, Talc was obtained from SD Fine –Chem pvt, Mumbai.

Ultraviolet Visible (UV-visible) spectroscopy:
Construction of Calibration Curve:
Preparation of Stock Solution: 100 mg of Glipizide was taken in a 100 ml volumetric flask. To that 5 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 0.1N HCl.

- From the above solution 1 ml was diluted to 10 ml with, 0.1N HCl solution to give 100 µg /ml concentration.
- From the above solution 1 ml was diluted to 10 ml with, 0.1N HCl solution to give 10 µg /ml concentration.
- The prepared solution i.e., 10 µg/ml concentration was scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer.

Evaluation of blend:[7]
Angle of Repose: The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose= $\tan^{-1}$ (h/r)
Where, h = height r = radius
Procedure: 20gms of the sample was weighed and passed through the funnel slowly to form a heap. The height of the powder heap formed was measured. The circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Bulk density: Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup. This was repeated three times for a sample.

Bulk density = M / V_0
Where M= mass of the powder; V_0=bulk volume of the powder.

Tapped density: A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 200 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed. This was repeated three times for a sample.

Tap density = M / V_r
Where M = mass of the powder, V_r = final tapping volume of the powder.

Compressibility index and Hausner ratio: The method involves measuring the unsettled apparent volume,(V_O), and the final tapped volume, (V_f), of the powder after tapping the material until no further volume changes occur. This was repeated three times for a sample. The compressibility index and the Hausner ratio are calculated as follows:
Compressibility index = $100 \times Vo\text{-}V_f/Vo$
Hausner ratio = Vo/V_f
Where, V_o = apparent volume, V_f= final tapped

volume.
Alternatively, the compressibility index and hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 ×{ tapped density - bulk density / bulk density}
Hausner ratio = tapped density / bulk density

Table1: Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio:

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	> 66	>38	>1.6

FORMULATION DEVELOPMENT

Table2: COMPOSITION OF GLIPIZIDE FLOATING TABLETS

Ingredients	Formulations				
	F1	F2	F3	F4	F5
Gglipizide	50	50	50	50	50
HPMC K15M (mg)	100	---	50	60	60
Carbopol 940 (mg)	---	100	50	40	40
MCC	52	52	52	52	52
Sodium bi carbonate (mg)	35	35	35	35	35
Magnesium stearate (mg)	2	2	2	2	2
Talc (mg)	1	1	1	1	1
Total wt (mg)	240	240	240	240	240

Preparation of Formulation:

1. Drug and polymers pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Add diluents and other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) and Lubricant (Talc) to the above blend mix it for 2min.
3. Compressed the above lubricated blend by using 8mm round punches.

Evaluation of tablets:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability, Buoyancy test and invitro-dissolution characters.

Physical Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size & Shape: It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness was measured by micro-meter or by other device.

Weight variation test: Ten tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight.

Table 3: Limits for Tablet Weight variation test:

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

Content Uniformity:

The content uniformity test was performed to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.

Method:

Randomly 30 tablets were selected. Randomly 10 of these assayed individually. The batch passes the test if 9 of the 10 tablets contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability: It was measured by Roche friabilator. 10 tablets were weighed and then placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets were weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The percentage friability was determined by the formula:

% friability = $(W_1-W_2) / W_1 X 100$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Floating lag time:

The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vesselis termed as floating lag ti me and the time for which the dosage form floats is termed as the floating or flotation time. These tests were performed in simulated gastric fluid or 0.1N HCl maintained at 37 ^{0}C, by using USP dissolution apparatus containing 900 ml of 0.1N HCl as the dis solution medium.

Drug release:

The drug release from the Glipizide tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 0.1N HCl (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and 1ml sample is diluted to 10 ml and then analyzed with UV spectrophotometry at λmax=211.5nm.

Results and Discussion:

Calibration of Standard Graph of Glipizide:

Standard graph of Glipizide in 0.1 N HCl:

The construction of standard calibration curve of Glipizide was done by using 0.1N HCl as the medium. Glipizide was found to have the maximum absorbance at 211.5nm. The standard graph of Glipizide in 0.1 N HCl was constructed by making the concentrations of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml solutions. The absorbance of solutions was examined under UV-spectrophotometer at an absorption maximum of 211.5nm. The standard graph of Glipizide was constructed by taking the absorbance on Y-axis and concentrations on X-axis.

Table 4: Standard graph of Glipizide in 0.1 N HCl at λ_{max}= 211.5nm

S. no.	CONCENTRATION (µg/ml)	ABSORBANCE
1	0	0
2	2	0.215
3	4	0.396
4	6	0.595
5	8	0.773
6	10	0.987

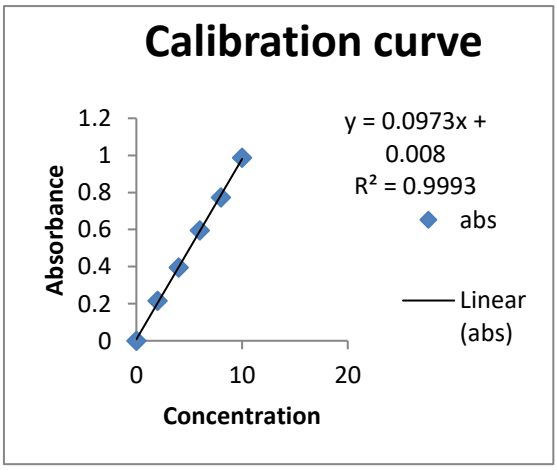

Figure 1: Standard graph of Glipizide

Evaluation of Preformulation parameters:

The properties like compressibility index, angle of repose and hausner ratio were calculated.

Table 5: Micromeritic properties of Active Pharmaceutical Ingredient:

S.No	**Parameter** (n=3)	**Results**
1	Angle of repose	26.45± 0.1
2	Bulk Density	0.95±0.3 gm/ml
3	Tapped Density	1.02±0.2gm/ml
4	Compressibility Index	7.36±0.5%
5	Hausner's ratio	1.07±0.29

based on the above pre-formulation results it was observed that the flow was good.

Table 6: List of Micromeritic properties of directly compressible powder:

Parameter (n=3)	F1	F2	F3	F4	F5
Angle of repose	25.43±0.1	26.46±0.2	23.31±0.17	27.29±0.17	29.14±0.13
Bulk density	0.725±0.3	0.734±0.4	0.717±0.22	0.724±0.28	0.96±0.24
Tapped density	0.829±0.18	0.854±0.23	0.832±0.16	0.843±0.21	1.03±0.27
%Compressibility	12.54	14.05	13.82	13.63	7.29
Hausner's ratio	1.14	1.16	1.16	1.16	1.07

Evaluation of the Prepared Tablets for Physical Parameters: All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 7: Results for post compression evaluation parameters of all formulations

Parameter	**F1**	**F2**	**F3**	**F4**	**F5**
Weight Variation (N=10)	260.9±2	260.1±2	260.8±2	260.7±2	260.1±2
Thickness (mm)	5.5±0.4	5.9±0.4	5.3±0.4	5.6±0.4	5.5±0.4
Hardness (kg/cm^2)	8.9±1.4	7.4±1.2	8.2±1.2	6.9±0.9	8.4±1.9
Friability (N=10)	0.12%±0.2	0.16%±0.23	0.15%±0.19	0.15%±0.26	0.15%±0.22
Content Uniformity (N=10)	95.01%±0.2	96.4%±0.4	98.7%±0.3	98.8%±0.2	99.8%±0.3
Floating lag time(min)	15	12	13	11	<1

Data is represented as mean±SD

Floating lag time: The floating tablets of Glipizide were prepared by using HPMC K15M and Carbopol 940. five different formulations were prepared using different ratios of polymers. The prepared formulations were evaluated for floating lag time and buoyancy time. Sodium bicarbonate released carbon dioxide in the presence of dissolution medium (0.1 N HCl). It was observed that the gas generated was trapped and protected within the matrix, formed by polymers, thus density of the tablet decreased and it started floating. The floating lag time of the optimized formulation f5 was 29 sec.

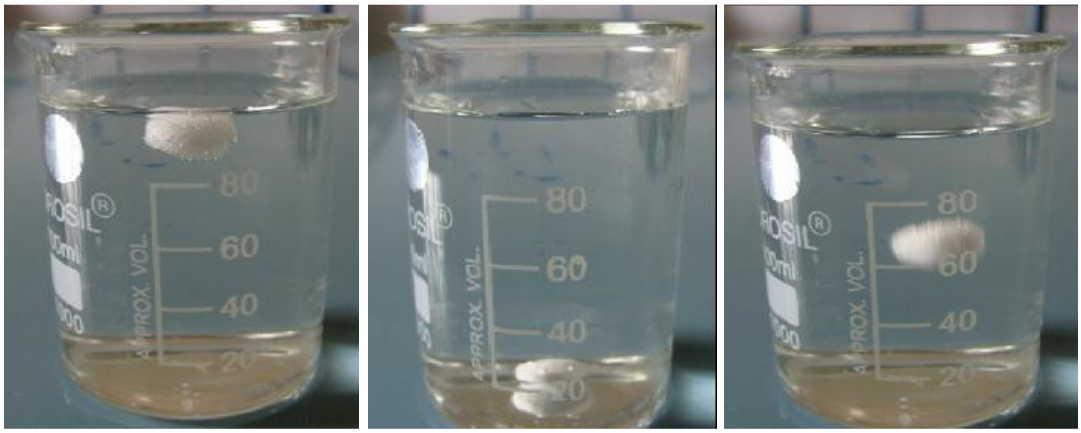

Figure 2: representation of floating lag time for optimiztion formulation

In vitro Dissolution studies:

The dissolution conditions used for studying the drug release from tablet of Glipizide are:

Apparatus : USP apparatus II (Paddle)
Agitation speed (rpm) : 50rpm
Medium : 0.1N HCl
Volume : 900 ml
Temperature : 37.0 ± 0.5 C
Time : 30, 60, 120, 240, 360, and 600min.
Wavelength : 211.5nm

The samples were withdrawn at predetermined time points, and were analyzed spectrophotometrically at 211.5nm.

Table 8: Results of Dissolution profile for F1-F5:

%Drug Release					
Time	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
30	12.45	21.36	14.67	15.67	18.95
60	27.94	34.92	26.91	23.68	35.78
120	54.68	67.93	51.24	56.98	46.48
240	74.98	84.72	73.97	79.97	73.18
360	96.59	95.92	89.92	92.15	82.94
600	98.95	97.83	99.13	98.99	94.56

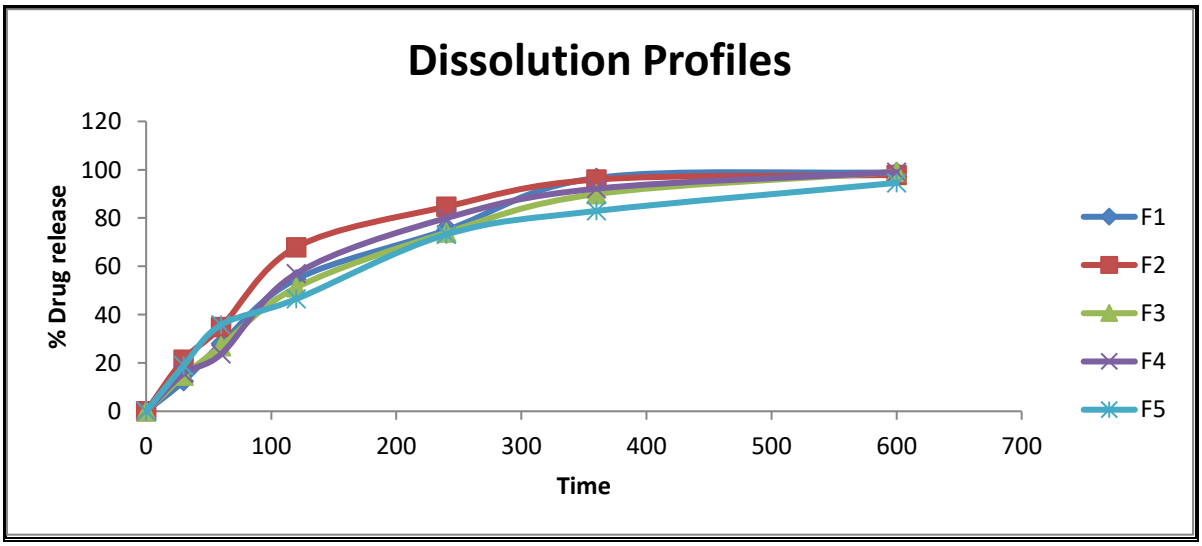

Figure 3: dissolution profile of formulations F1 to F5

CONCLUSION:

The present was performed with an aim to develop a Floating tablet of Glipizide. Systematic studies were conducted using different concentration of rate releasing polymer HPMC and Sodium carboxy methyl cellulose for extending the drug release in upper GIT. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies were carried out to assess flowability, compressibility properties, solubility studies and the results were satisfactory. Later the powder blend was compressed into a tablet and evaluated for various parameters like tablet dimensions, hardness, friability, weight variation, buoyancy, content uniformity, all the formulations were found within the permissible range. The results of the present research work demonstrates that among all five formulations The F5 formulation was found to be best of all the trials because it gave good results in terms of the required in vitro buoyancy study, good floating integrity and drug released in sustained manner.

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