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FORMULATION AND *IN VITRO* EVALUATION OF GLIPIZIDE AS FLOATING DRUG DELIVERY SYSTEM WITH NATURAL POLYMER (GUAR-GUM)

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ABSTRACT
The purpose of this investigation was to prepare a gastro retentive drug delivery system of Glipizide. Floating tablets of Glipizide were prepared employing different polymers like HPMC K15M, Guar-Gum, Carbopol 934p and Magnesium Stearate by effervescent technique. Sodium bicarbonate and citric acid were incorporated as a gas generating agent. The Floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in- vitro* buoyancy, swelling study, dissolution studies and stability studies. The drug release profile and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good *in vitro* buoyancy. It was aimed to prepare for prolonged residence in the stomach over conventional Gastroretentive approaches. The tablets are produced by direct compression method.
The release of the drug is concern from the nine formulations. F5 is a best formulation to determine the mode of release the data was subjected to Zero Order model. F5 optimized formulation released approximately 98.15% drug in 12 hours *in vitro*.
Key words: Floating drug delivery system, Glipizide, Guar-Gum, buoyancy studies, swelling studies.

INTRODUCTION:

Oral route of administration is the most important and convenient route for drug delivery. The benefits of long term delivery technology have not been fully realized for dosage forms designed for oral administration. This is mainly due to the fact that the extent of drug absorption from gastrointestinal tract is determined by gastrointestinal physiology irrespective of the control release properties of the device prolonged gastric retention improves bioavailability.[1]

Gastric retentive dosage forms are designed to be retained in the stomach and prolong the gastric residence time of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Based on the mechanism of flotation, delivery systems can be classified in two types. Effervescent floating drug delivery system and non-effervescent floating drug delivery

System it release the drug from floating drug delivery system. These systems when reached to stomach, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the jellified Hydrocolloid.[2]

This is prepared by swellable polymers such as HPMC, Guar-Gum, Carbopol 940 and various effervescent components like sodium bicarbonate and citric acid mixtures may be used. Glipizide is a second generation sulfonylurea used in the treatment of hyperglycemia. It's poorly soluble in acidic acid it absorbs rapidly and completely. However its absorption is erratic in diabetic patients due to the impaired gastric motility or gastric emptying to overcome the presence study gastric retentive controlled release dosage form of the drug in the form tablet was formulated with different polymers. The object of the present work is preparing floating tablets in controlled fashion. The gas generating agent sodium bicarbonate and citric acid were added in different concentrations with varying amount of retardation and investigated the release profile following USP type-II *in vitro* dissolution model.[3]

MATERIALS AND METHODS:

Glipizide was procured from Micro labs Pvt. Ltd, Pondicherry, Hydroxypropyl methyl cellulose was procured from SD Fine Chemicals, Boisar, Maharashtra, and all other chemicals were of analytical grade.

METHODS:

Preparation of gastro Retentive floating tablets of Glipizide:

Floating tablets containing Glipizide were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and citric acid. Gastro retentive floating tablets of Glipizide were prepared by direct compression method. Accurately weighed quantities of hydrophilic polymers, Bioadhesive polymer were taken in a mortar and mixed geometrically. To this mixture required quantity of Glipizide was added and mixed slightly with pestle. This mixture was passed through 40# and later collected in a plastic bag and blended for 5 min. To this required amount of sodium bi- carbonate was added and again mixed for 5 min. Later sufficient quantity of Magnesium Stearate and Talc were added and the final blend was again passed through 40#. Thus obtained blend was mixed thoroughly for 10 min and compressed into tablets with 8.5 concave Punches and corresponding dies at a hardness of 6 kg/ cm single station tablet punching machine.[4]

Table-1: Formulation of floating tablets containing Glipizide

Formulation code	Glipizide (mg)	Guar-gum (mg)	HPMC K15 M (mg)	Carbopol 934p (mg)	$NaHCO_3$ (mg)	Citric Acid (mg)	Mg.Stearate (mg)	Talc (mg)
F1	10	65	40	25	35	20	3	2
F2	10	55	50	25	35	20	3	2
F3	10	45	60	25	35	20	3	2
F4	10	65	40	25	35	20	3	2
F5	10	55	40	35	35	20	3	2
F6	10	45	40	45	35	20	3	2
F7	10	65	40	25	35	20	3	2
F8	10	55	45	30	35	20	3	2
F9	10	45	50	35	35	20	3	2

Evaluation of Granules:

Angle of repose:

Flow properties of the granules were evaluated by determining the angle of repose was measured according to the fixed funnel and free standing cone method of Banker & Anderson. Angle of repose was calculated by using the equation.[5]

$$\tan\Theta = h/r$$

Where Θ- angle of repose, h- Height of the pile

r- Radius of the pile

Table-2: Effect of Angle of repose (ϕ) on Flow property:

Angle of Repose (Φ)	Type of Flow
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density:

Both loose bulk density (LBD) and Tapped bulk density were determined. Powder was taken in a 10ml measuring cylinder and initial volume was noted and tapped at height of 2.5cm at 2 second intervals until no further change in volume was noted. LBD and TBD were calculated using the following formula.[5]

LBD = Weight of the powder/volume of the packing

TBD= Weight of the powder/Tapped volume of the packing

Compressibility index:

Compressibility index of the powder was determined by Carr's Compressibility index

Carr's index (%) = (TBD-LBD) x100/TBD

Table-3: Pre-Compression Parameters of designed formulations (F1 to F9):

Pre-compression evaluation parameter					
Formulations	Bulk density(gm/ml)	Tapped density(gm/ml)	Angle of repose	Carr's Index (%)	Hausner Ratio
F1	0.4731	0.5893	$27^0 60'$	19.71	1.2456
F2	0.4995	0.6152	$29^0 36'$	18.80	1.2316
F3	0.4658	0.5942	$28^0 76'$	21.60	1.2756
F4	0.4832	0.5956	$26^0 74'$	18.87	1.2326
F5	0.4925	0.6012	$27^0 82'$	18.08	1.2207
F6	0.4636	0.5836	$27^0 64'$	20.56	1.2588
F7	0.4857	0.5751	$29^0 32'$	15.54	1.1840
F8	0.4852	0.5963	$28^0 10'$	18.63	1.2289
F9	0.4635	0.5785	$28^0 70'$	19.87	1.2481

Evaluation of tablet properties:

Determination of pre-compression parameters:

As per standard procedures, the Preformulation studies including Bulk density, Tapped density, Compatibility study, Hausner's ratio and Angle of repose was performed of the powder.

Determination of post-compression parameters:

Hardness:

For each formulation, the hardness of 6 tablets was determined using the Monsanto Hardness Tester and the average was calculated and presented with standard deviation.[6]

Friability:

Twenty tablets were accurately weighed and placed in the friabilator (Roche's Friabilator) and operated for 100 revolutions. The tablets were dedusted and reweighed. The tablets that loose less than 1% weight were considered to be compliant.[6]

The % friability was then calculated by,

$$F = \left[\frac{W_{Initial} - W_{Final}}{W_{Initial}}\right] \times 100$$

Weight variation:

20 tablets were selected randomly from the lot and weighed individually to check for weight variation using an electronic balance and the test was performed according to the official method. Weight Variation limits as per USP.[7]

Table no-4: Tablet weight variation:

Sr. No.	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	324<	5

Content uniformity test:

The Glipizide floating tablets were tested for their drug content. Five tablets were finely powdered quantities of the powder equivalent to 15mg of Glipizide were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with 0.1N HCl (pH 1.2 buffers) solution and mixed thoroughly. The solution was made up to volume 100ml and filtered. Dilute 1 ml of the resulting solution to 10 ml with 0.1N HCl. The absorbance of the resulting solution was measured at 276 nm using a Shimadzu UV-visible

spectrophotometer. The linearity equation obtained from calibration curve was used for estimation of Glipizide in the tablet formulations.[8]

In-vitro buoyancy study:

The in-vitro buoyancy study was characterized by floating lag time and total floating time. The test was performed using a USP type-Π paddle apparatus.(electro lab)using 900ml of 0.1N HCl at paddle rotation of 50rpm at 37o ±0.5o. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium were noted as floating lag time and total floating time.[9]

Swelling Study:

The floating tablets were weighed individually (designated as W0) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1-h time intervals until 24 h, the floating tablets were removed from beaker, and the excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then re-weighed (Wt), and % swelling index (SI) was calculated using the following formula.[10, 11]

SI (%) = (Wt – W0/ W0) x 100

In vitro Dissolution Studies:

The *In vitro* dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at 37oC ± 0.5oC. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 24 h and the same volume was replaced with pre -warmed fresh dissolution media. The samples were diluted to suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 276nm using a UV spectrophotometer.[12]

Curve fitting analysis:

The mechanism of Glipizide release from the floating tablets was studied by fitting the dissolution data of optimized formulation in following models

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

Based on the slope and the R2 values obtained from the above models the mechanism of drug release was decided.

Stability studies:

The optimized formulation of Glipizide were packed in amber colour bottle and aluminium foil laminated on the upper part of the bottle and these packed formulation was stored in ICH certified stability chambers maintained at 40 ^{0}C and 75% RH (zone III conditions as per ICH Q1 guidelines) for 3 months. The samples were withdrawn periodically and evaluated for their content uniformity, *in-vitro* buoyancy studies and for *in-vitro* drug release.[13]

Table 5: Post-compression parameters

Formulations	Weight (mg)	Hardness (kgs)	Friability (%)	Thickness (mm)	Drug Content (%)	Floating Lag Time (sec)	Floating Time (hours)
F1	200.8±0.74	5.4±0.4	0.69±0.14	4.46±0.01	101.02±3.2	117	12
F2	205.9±0.28	5.8±0.3	0.81±0.21	4.48±0.03	97.28±3.1	115	10
F3	207.6±0.85	5.4±0.2	0.65±0.11	4.38±0.06	99.01±0.8	119	9
F4	201.4±1.01	6.1±0.3	0.89±0.21	4.55±0.09	101.2±2.4	116	11
F5	195.1±0.52	6.1±0.7	0.71±0.21	3.48±0.05	98.2±2.5	128	8
F6	201.7±0.14	5.9±0.1	0.54±0.12	4.62±0.06	100.07±3.5	118	12
F7	197.3±1.14	5.5±0.2	0.91±0.10	4.60±0.03	100.06±0.9	119	10
F8	198.2±0.34	5.1±0.6	0.71±0.15	4.58±0.02	99.12±0.5	121	10
F9	202.1±0.48	5.6±0.2	0.63V0.11	4.45±0.05	98.2±2.5	116	9

Table 6: *In-VITRO* Dissolution Data for Formulation F1 to F9

Cumulative % drug release of formulation F1 to F9 mean ±SD (n=3)									
Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	13.52±0.263	14.21±0.894	15.02±0.723	8.73±0.251	8.79±0.215	14.62±0.621	12.52±0.801	17.13±0.261	14.01±0.231
2	20.65±0.352	18.90±0.923	19.32±0.821	11.58±1.010	13.58±1.010	17.81±0.613	17.27±0.421	22.61±1.251	17.61±0.615
3	26.52±0.623	22.84±0.763	23.35±0.652	14.25±1.025	19.52±1.091	23.83±0.618	23.20±1.761	29.84±0.814	26.31±1.263
4	36.76±0.793	27.02±1.388	28.27±1.225	19.11±1.072	26.95±1.042	28.96±0.425	28.62±2.581	35.09±1.251	33.16±1.521
5	43.62±0.238	32..76±1.321	35.71±1.352	23.35±1.492	38.61±1.092	36.56±0.082	36.34±2.621	43.09±1.065	39.25±2.512
6	50.26±0.697	40.42±2.034	42.16±1.351	30.31±1.648	45.41±1.252	42.52±0.615	43.25±1.251	51.32±0.810	48.18±2.530
7	69.12±1.412	48.91±1.961	49.11±1.381	38.79±1.212	58.96±1.908	52.65±0.803	58.82±2.526	60.49±0.761	56.15±1.231
8	76.63±2.215	57.14±1.241	65.92±1.521	47.44±1.418	73.95±1.252	65.49±0.821	66.49±0.815	69.65±1.231	65.27±1.561
9	88.67±2.114	71.91±1.923	74.72±1.761	59.24±1.523	88.06±1.725	77.03±1.011	76.03±0.455	78.21±0.231	72.18±2.131
10	92.17±1.921	76.21±1.984	88.23±1.984	85.21±1.621	94.26±1.721	82.96±0.612	83.26±0.125	83.61±0.156	79.15±1.013
11	93.23±1.231	85.81±1.723	-	90.67±1.234	96.12±1.523	-	-	92.13±1.261	85.12±1.021
12	95.12±1.631	-	-	-	98.15±1.251	-	-	-	-

RESULT AND DISCUSSION:

The main of this work was to formulate Glipizide Gastric oral floating tablet and to improve the release of drug in controlled fashion in the acidic pH, polymer used in the formulation for control release as well as to make the formulation buoyant. Nine formulations were formulated by using two different polymers HPMC K15 and Guar-Gum. The tablets were prepared by direct compression method.

The 9 formulation granules evaluated were to as for angle of repose.LBD, TBD, compressibility index and in process parameters evaluation for tablets. Such as physical appearance, thickness, diameter, content uniformity, weight variation, hardness, friability test.

The formulation F1-F 9 exhibited good flow property and compressibility index shown in Table: 3.The angle of repose ranged from 26^0 74' to 29^0 36' and compressibility index (%) ranged from 15.54 to 21.60. The shape of the tablet of all ten formulations was circular with no visible cracks. The thickness of all 9 formulations was range from 3.48±0.05 to 4.62±0.06 mm. The percentage friability of the tablets of all the batches remained in the range of 0.54±0.12 to 0.91±0.10. Hardness of the formulations was range of 5.1±0.6 to 6.1±0.7 kg/cm^2. Drug content was ranged from 97.28±3.1 to 101.02±3.2%. In-vitro buoyancy studies conducted the gas generated id trapped and protected within the gel formed by hydration of polymer. The floating lag time was in range 115 to 121 sec also tablets remained buoyant for a period of 12 hours. . The release profiles of various formulations are
Formulation F1 released 95.12% of the drug in 12 hours.
Formulation F2 released 85.81% of the drug in 11 hours.
Formulation F3 released 88.23% of the drug in 10 hours.
Formulation F4 released 90.67% of the drug in 11hours.
Formulation F5 released 98.15% of the drug in 12 hours.
Formulation F6 released 82.96% of the drug in 10hours.
Formulation F7 released 83.26% of the drug in 10 hours.
Formulation F8 released 92.13% of the drug in 11 hours.
Formulation F9 released 85.12% of the drug in 11 hours.
Thus F5 formulation was said to be optimized formulation.
Optimized formulation F5 was subjected to curve fitting analysis, zero order, and first order, Higuhi Kinetics, Korsmeyer and Peppas model. The slope and R^2 are shown in Table 9 and graphs in Figure 3. Optimized formulation 5 fitted best for Zero order equation with R2 value of 0.9783**.**
It is, thus concluded that effervescent floating tablet containing Glipizide (F5 formulation) gave slow and complete drug release spread over 12hours.

Figure-1: In-vitro dissolution profile of formulations F 1 to F 9

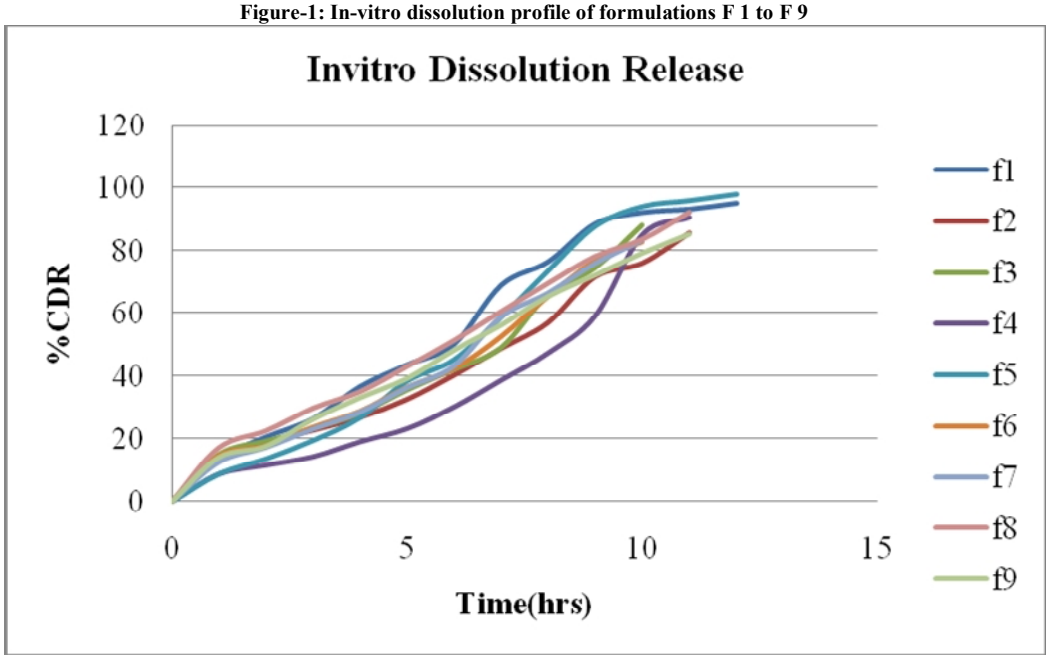


Figure-2: In-vitro dissolution profile of optimized formulation (F 5)

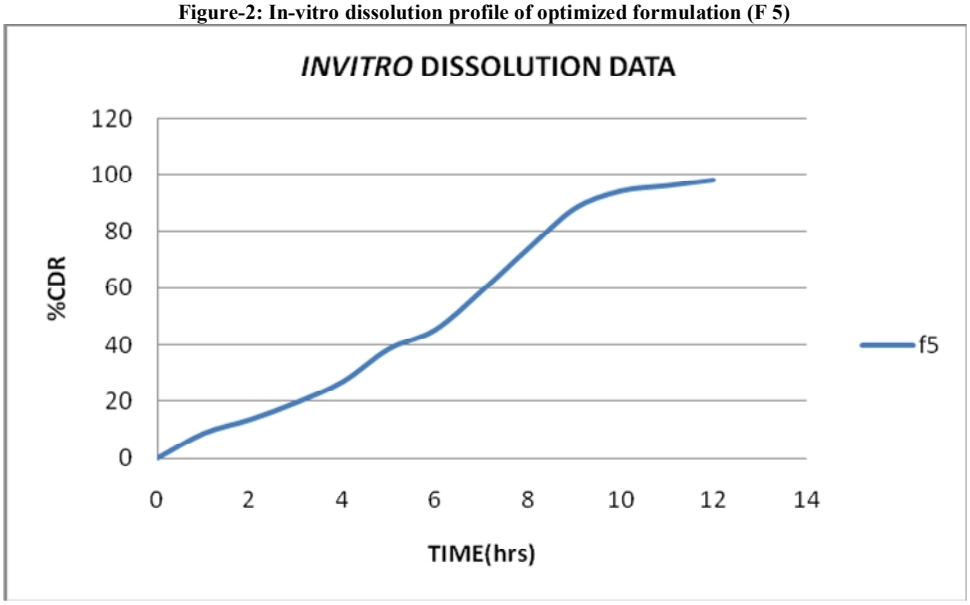
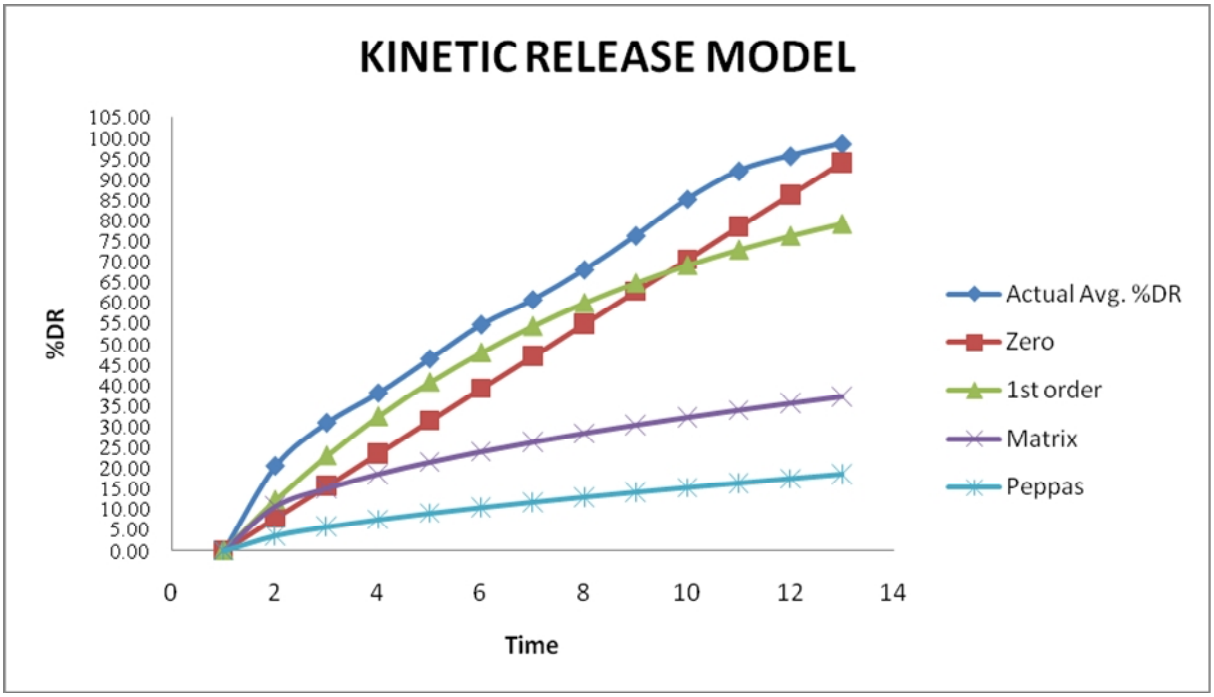


Table-7: Kinetic Release Data of Different Model for Optimized Formulation (F5)

Model	R^2 VALUE	Slope
Zero order	0.9783	9.1662
1st order	0.8603	-0.3229
Higuchi Matrix	0.9312	11.2122
Peppas	0.9781	2.3320
Hix.Crow.	0.9285	0.0647

Figure 3: Kinetic Model Fitting Graph OF Formulation (F 5)



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