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Formulation and *in vitro* Evaluation of Gastro Retentive Floating Tablets of Glipizide

M. Sampath Kumar*, R. Senthil Selvi, P. Perumal, Chandra Sekhar. Y and Zakir
[*]J.K.K. Natraja College of pharmacy, Komarapalayam, Namakkal (DT), Tamil Nadu, India-638183.

ABSTRACT

The objective of this research was to formulate and evaluate hydro dynamically balanced controlled drug delivery system of Glipizide. This dosage form is associated with many advantages especially increased bioavailability and reduction in dosing frequency. The formulation was designed adopting optimization technique, which helps in setting up experiments in such a manner that the information is obtained as efficiently and precisely as possible. Initially, considering buoyancy as the main criteria, blank tablets were compressed for different formulae with various polymers like Carbopol-940p, HPMC, Citric acid and sodium bi carbonate. The formula selected for design had a combination of Glipizide, Carbopol-940p, HPMC, Citric acid. The tablets were prepared by direct compression method and evaluated for Glipizide content, in vitro release profile and buoyancy. The dissolution study was carried out in simulated gastric fluid using USP dissolution test apparatus employing paddle stirrer. Duration of buoyancy was observed simultaneously when the dissolution has carried out. The variation in weight was within the range of ±3% complying with pharmacopoeial specifications (±7.5%). The drug content varied between 9.127±0.1317mg and 9.923±0.0183mg in different formulations indicating content uniformity.. The in-vitro release was found to be in the range of 50.28% to 99.65%. The Glipizide content in the formulation varied between 91–100%. The optimized formulation F9 exhibited responses that were comparable with that of the predicted values of the design in optimization technique. This indicates the suitability of the technique chosen for the present dosage form.

Keywords: Gastro retentive, floating tablet, optimization, Glipizide.

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 GIT is determined by GI physiology, irrespective of the control release properties of the device Prolonged gastric retention improves bioavailability (Kathleen JW, 1996). Although differential absorption from various regions of GI has been known for decades, only recently drug delivery systems have been designed to target drugs to differential regions of GIT. These include gastro retentive systems, delayed release systems and colon targeting.

HYDRODYNAMICALLY BALANCED SYSTEM (FDDS)

Floating dosage form is also known as hydro dynamically balanced system (HBS). It is an oral dosage form (capsule or tablet) that is designed to prolong the residence time of the dosage form within the GI tract.

***Corrosponding author**

M. Sampath Kumar
Email id: sampathkumar_varma@yahoo.com

This not only prolongs GI residence time but also does so in an area of the GI tract that would maximize drug reaching its absorption site in solution and hence ready for absorption. Drug dissolution and release from the capsule retained in stomach fluids occur at the stomach, under fairly controlled condition. The retentive characteristics of the dosage form in gastric content are most significant for drugs (Srivastava A K *et al*., 2005).

1. Insoluble in intestinal fluid.
2. That acts locally.
3. That exhibits site-specific absorption.

Gastric retention systems are important for drugs that are degraded in the intestine, drugs with local action in the stomach, drugs with poor solubility in intestine due to alkaline pH, drugs with rapid absorption from gastrointestinal tract to produce transient peaks in serum drug levels (Burns SJ *et al*., 1995).

Glipizide is a second generation sulphonyl urea used in the treatment of type II diabetes mellitus. From gastrointestinal tract to produce transient peaks in serum drug levels (Mishra B *et al*., 2007). It lowers blood glucose by stimulating pancreatic beta cells to release insulin, reduces glucose output from the liver and increase insulin sensitivity at peripheral stage sites. Bioavailability -100% (regular formulation),

90% Extended release and half life is Half-life – 3.4 ± 0.7 h.

MATERIALS AND METHODS

Glipizide was procured from Micro labs Pvt. Ltd, Carbopol 940P was produced from Ranikem Ltd, Mumbai, India. Hydroxy propyl methyl cellulose was procured from CDH, New Delhi India. Sodium bicarbonate and Citric acid were produced from Loba chemie, Mumbai India. Magnesium Stearate Poly vinyl pyrollidine K 30 and Micro crystalline cellulose were obtained from CDH, New Delhi.

DRUG POLYMER INTERACTION STUDY BY IR

Glipizide discs were prepared by pressing the Glipizide with potassium bromide and the spectra between 4000^{-1}cm -400^{-1}cm was obtained under the operational conditions. The absorption maxima in spectrum obtained with the substance being examined.

FORMULATION AND EVALUATION OF FLOATING TABLETS OF GLIPIZIDE

Preparation of Glipizide Floating Tablets:

Nine formulations (F_1, F_2, F_3, F_4, F_5, F_6, F_7, F_8, F_9) of varying constituents were prepared. Nine floating matrix formulations of Glipizide based on gas forming agent were prepared. HPMC 5cps and Carbopol 940P were used in formulating the Matrix system. Incorporation of sodium bicarbonate into matrix resulted in the tablet floating over simulated gastric fluid for sustained release.

Table.1 Formulation of floating matrix tablets of Glipizide

INGREDIENT	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Glipizide	10	10	10	10	10	10	10	10	10
HPMC 5cps	30	40	50	-	-	-	50	50	50
Carbopol 940	-	-	-	30	40	50	10	20	30
Sodium bicorbonae	20	20	20	20	20	20	20	20	20
Citric acid	5	5	5	5	5	5	5	5	5
PVP-K 30	5	5	5	5	5	5	5	5	5
MCC	175	165	155	175	165	155	145	135	125
Magnesium stearate	5	5	5	5	5	5	5	5	5

EVALUATION CHARACTERISTICS GLIPIZIDE FLOATING TABLETS

Tablet Size

Thickness of the tablet was measured by using Vernier caliper in mm.

Hardness test

Hardness test was carried out by using Monsanto hardness tester.

Friability test

Friability of the tablets was tested using Roche friabilator. Loss of less than 1% in weight is considered to be acceptable. The weight of 10 tablets was noted initially (W1) and placed in the friabilator for 5 min / 100 rpm. The tablets were reweighed and noted as (W2). The difference in the weight is noted and expressed as percentage.

Percentage Friability = (*W1 – W2)/W1 * 100*

Official Limit not more than 1%

Weight variation test

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight

Average weight of tablet	Percentage
80 gm or less	+/- 10 %
More than 80 mg and less than 250 gm	+/- 7.5 %
250 mg or more	+/- 5 %

by more than the percentage shown in table and none deviates by more than twice the percentage.

Official limit (V. Mallikarjun *et al*., 2009) of Glipizide Floating formulations (F_1-F_9) percentage deviation is ±7.5%.

Uniformity of content

This test was applicable to tablets that contain less than 10 mg or less than 10 % w/w of active ingredient. Content of active ingredient in tablets and capsules, taken at random, was determined. Crush tablets and powder equivalent to weight of tablet dissolved in 0.1 N HCL. In case of capsules remove the hard gelatin shells and powder equivalent to 15.2348 mg of drug and dissolved it in hot 0.1 N HCL. Drug content was calculated by measuring absorbance at wavelength 318.5 nm.

The tablet/capsule comply with the test if not more than one of the individual values thus obtained was outside the limits 85 to 115 % of the average value and none is outside the limits 75 to 125 % of the average value. If two or three of the individual values are outside the limits 85 to 115 % of the average value and none is outside the limits 75 to 125 %, repeat the determination using another 20 tablets. The tablet/capsule comply with the test if in the total sample of 30 tablets not more than three of the individual values are outside the limits 85 to 115 % and none is outside the limits 75 to 125 % of the average value.

Buoyancy determination

In practice floating time and buoyancy lag time was determined by using beaker containing 100 ml of 0.1N

HCl, maintained at 37ºC. The time required for the tablet to rise to the surface of the medium was determined as Buoyancy Lag time and the duration of which the tablet floats on the surface of the medium was noted as the Buoyancy floating time.

Drug content

Drug content (Ponchel G *et al*., 1998) of the tablets were determined by using UV visible spectrophotometer.10 tablets were taken and powdered. The tablet powder equivalent 100 mg of Glipizide was accurately weighted and transferred to 100 ml volumetric flask and the volume was made up to 100 ml with 0.1N HCL of pH1.2, 1ml of the aliquot was further diluted to 100 ml with 0.1N Hcl pH1.2. The absorbance was measured at 276 nm.

***In vitro* Dissolution of Fabricated Tablets**

Tablet's dissolution was assessed using standard USP Dissolution apparatus (paddle) equipment in 900 ml of 0.1N HCL of pH1.2. The stirring speed of 100 rpm for the basket was used. The Glipizide tablets were subjected to dissolution testing in 900 ml dissolution medium. Three tablets were taken in each batch and a temperature of 37 ºC was maintained throughout the experiment. Dissolution studies were carried out for 24 h. 5ml of the Aliquot was taken at intervals of 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h. After collecting the sample, the dissolution medium was replenished with the same volume of fresh medium, and the sample was filtered 1ml of the filtrate was diluted to 10ml with the phosphate buffer and analyzed spectrometrically (Reddy K R *et al*., 2003) at 275 nm.

Release Kinetic Study

Figure.1 IR spectroscopy of Glipizide

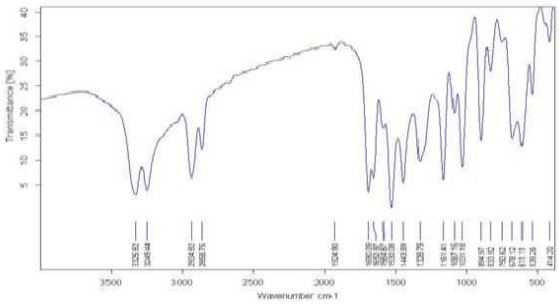
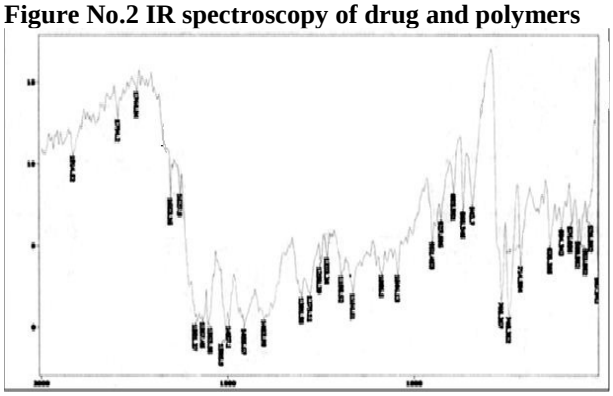


Figure No.2 IR spectroscopy of drug and polymers



The rate and mechanism of release of Glipizide through the prepared Floating matrix tablets were analyzed by fitting the drug release data into zero order, first order, higuchi and peppas equation.

RESULTS AND DISCUSSION

The major IR peaks observed in GLIPIZIDE were 1640 (CONH stretching), 1370 (SO_2NH Stretching), 1142 (cyclo hexyl stretching) the crystal behaviors was not observed in the physical mixture which can be confirmed by the FTIR study. In FTIR study of drug and polymers they show all prominent peaks. The preliminary identification tests were also carried out according to USP which complies with the same.

Evaluation of floating tablets

The physical properties of the tablets (F_1 – F_9) obtained by compressing the blend using Cadmach eight punches tablet machine .The physical properties of Glipizide (F_1 – F_9) such as tablet size, hardness, friability and weight variation were determined and results of the formulations (F_1 – F_9) found to be within the limits specified in Pharmacopoeia.

Buoyancy and floating time of Glipizide Floating Tablets (F_1 – F_9)

Buoyancy lag time and duration of floating were determined using USP dissolution test apparatus in 0.1N HCl Maintained at 37ºC. Buoyancy lag time of F_1- F_9 was in the range of 45-90secs.The Floating time was found to be 24 hours for F_9. Based upon the floatation time, the formulation F_9 was selected as the best formulation.

S.No	Peaks (cm^{-1})	Groups
1	1640	CONH Stretching
2	1370	SO_2NH Stretching
3	1142	Cyclo hexyl stretching

KINETIC DATA ANALYSIS

Figure.4 Zero order release plot

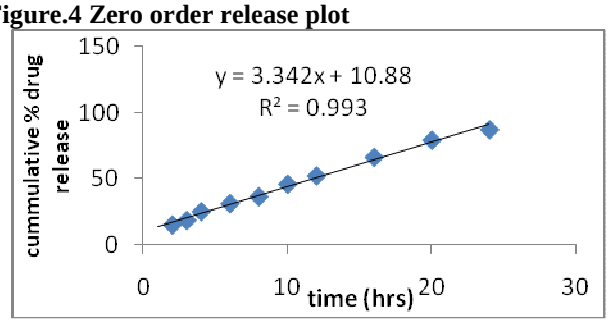


Figure.5 First order plot

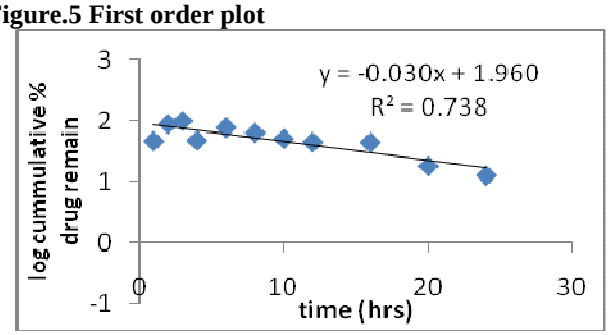


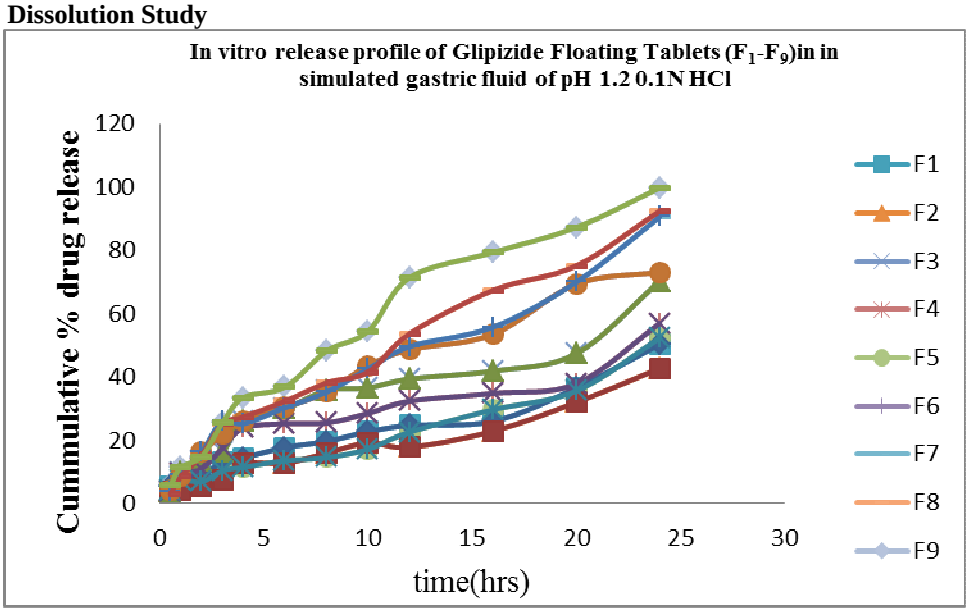
Table.2 Physical Characteristics of Glipizide Floating Tablets ($F_1 – F_9$)

Batch No	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)	Weight Variation (mg±SD)	Percentage Content
F_1	3.4±0.12	0.47	5.5±0.34	202±2.99	93.76±0.19
F_2	3.2±0.21	0.68	5.2±0.73	205±1.98	98.16±0.27
F_3	3.4±0.53	0.47	5.4±1.92	202. 5±3.7	89.87±0.41
F_4	3.2±0.16	0.46	5.3±0.34	198±6.5	97.28±0.33
F_5	3.3±0.42	0.72	5.6±0.28	204±1.3	91.48±0.26
F_6	3.1±0.53	0.74	5.5±0.37	199±6.59	95.67±0.17
F_7	3.3±0.24	0.63	5.4±0.89	204±1.6	93.87±0.32
F_8	3.2±0.16	0.83	5.3±0.42	194±3.06	88.92±0.21
F_9	3.4±0.29	0.45	5.8±0.56	207±3.9	97.87±0.16

Table.3 Buoyancy and floating time of Glipizide Floating Tablets (F_1-F_9)

S.No	Batch No	Buoyancy lag time (sec)	Floating duration (hrs)
1	F_1	45	16
2	F_2	60	20
3	F_3	50	22
4	F_4	65	18
5	F_5	70	19
6	F_6	90	21
7	F_7	45	22
8	F_8	50	24
9	F_9	55	24

Figure.3 Invitro Dissolution Study



From The Above Data It Was Found That F9 Obtained As The Best Formulation Because It Releases Drug Up To 24 Hrs With 99.65% Of Drug Release.

Figure.6 Higuchi plot

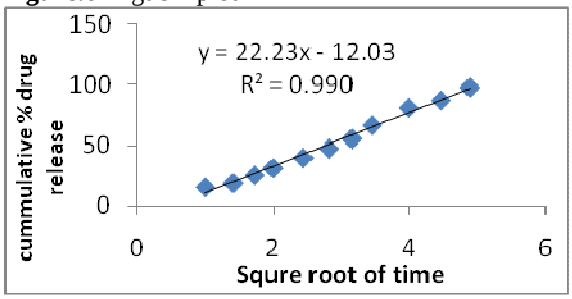
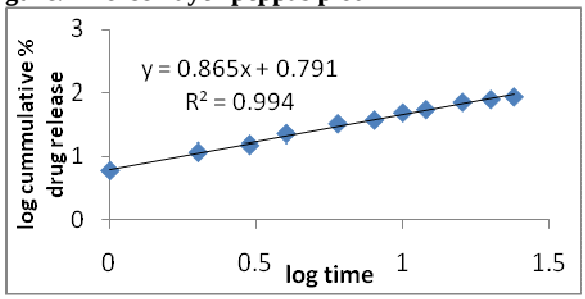


Figure.7 Korsemayer peppas plot



To know the mechanism of drug release from these formulations, the data were treated according to zero order (cumulative amount of drug released vs. time), first-order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), and Korsmeyer (log cumulative percentage of drug released vs log time) equations.

From the kinetic data analysis it was found that the release of the drug from the formulation follows the zero order and non-fickian transport of diffusion.

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