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Research Article

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FORMULATION AND EVALUATION OF GASTRORETENTIVE GLIPIZIDE FLOATING TABLETS

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ABSTRACT

The objective of this research was to formulate and evaluate hydrodynamically 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 HPMC, MC and EC. The formula selected for design had a combination of Glipizide, HPMC, EC and MC. 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 buoyancy of the tablets was ranged between 10.917±0.4403hrs and 16.237±0.1217 hrs, the maximum buoyancy was seen in G8, which has a high level of drug to polymer ratio. The *in-vitro* release was found to be in the range of 59.25% to 79.50%. The Glipizide content in the formulation varied between 91–100%. The formulation G8 has an in vitro release of 59.25, showed the release of the drug in the controlled manner. The optimized formulation G8 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, hydrodynamically balanced, Glipizide.

INTRODUCTION

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[1], reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment.

Gastric retentive dosage forms are classified into:

a) Swelling systems
b) Expanding systems
c) Floating systems
d) Inflatable systems
e) Bio (muco) adhesive gastrointestinal drug delivery system.

Hydro dynamically balanced drug delivery systems

A hydro dynamically balanced gastrointestinal drug delivery system, in either capsule or tablet form, is designed to prolong GI residence time in an area of the GI tract to maximise drug reaching its absorption site in the solution state and, hence ready for absorption.

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It is solution state and, hence ready for absorption. It is prepared by incorporating a high level (20-75% w/w) of one or more gel forming hydrocolloids eg. Hydroxy ethyl cellulose, hydroxyl propyl cellulose, hydroxy propyl methyl cellulose and sodium carboxy methyl cellulose into the formulation and then compressing these granules into a tablet or encapsulating capsules.[2]

On contact with the gastric fluid, the hydrocolloid in the hydro dynamically balanced drug delivery system becomes hydrated and forms a colloidal gel barrier around its surface with thickness increasing with time. This gel barrier controls the rate of solvent penetration in to the device and the rate of the drug release from it. The mechanism of the drug release follows matrix diffusion controlled release process.[3]

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.[4]

Uses

- For treating local inflammation and stomach ulcers.
- For treating H. Pylori associated ulcers.

- In chronic disease associated with frequent medication, a prolonged medication with HBS system would be efficacious.

Glipizide is a second generation sulphonyl urea used in the treatment of type II diabetes mellitus. 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.

Oral absorption of a therapeutic dose produces a peak concentration between 1 hr to 3 hr and absolute bioavailability is estimated to be between 80 to 100%. However the bioavailability of the extended release form is 90% and co administration of food with extended release tablet has no effect on the 2-3 hr lag time in drug absorption. However if glipizide is taken before a high fat breakfast the absorption of this drug is delayed by 40%.

MATERIALS AND METHODS

Glipizide was procured from Micro labs Pvt. Ltd, Pondicherry, India; methyl cellulose was purchased from Otto Kemi, Mumbai, India. Ethyl cellulose, micro crystalline cellulose, and aerosil were obtained from Shasun drugs and chemicals, Pondicherry. Hydroxypropyl methyl cellulose was procured from SD Fine Chemicals, Boisar, Maharashtra, India, Magnesium stearate was obtained from Burgoyne Uribiges & Co, Mumbai, India and Sodium bicarbonate was obtained from Spectrum Chemicals and Reagents, Cochin, India.

Design of formulation and evaluation

The formulations were designed based on 2^3 full factorial designs for the formula. This model was found good to predict the response desired. The different factors chosen were:

A. Drug to total polymer content ratio (1:15 and 1:17)
B. Polymer mixture to ethyl cellulose ratio (4:1 and 0:1)
C. HPMC to Methyl cellulose (2:1 and 4:1)

The drug to total polymer content ratio was chosen as factor A. The drug content was calculated as 10 mg based on the biological half life and peak plasma concentration and elimination rate constant, so that the dosage form can be used. The drug to total polymer content ratio was chosen from 1:15 and 1:17. This factor signifies the role of the polymer. Polymer mixture to ethyl cellulose was chosen as factor B where polymer mixture is the combination of HPMC and MC. Ethyl cellulose is used as retardant. HPMC to MC was chosen as factor C where HPMC imparts the floating property to the dosage form and MC for binding property and also for gelation.[5]

A two level full factorial design was considered with factors. According to the model totally 8 experiments have to be conducted, one more experiment at the centre point, a total of nine experiments have to be conducted. The actual and coded levels of the factors are as follows.

Table 1. Actual and coded values for the factor

Factors	Actual values		Coded values	
	Low level	High level	Low level	High level
Factor A	1:15	1:17	-1	+1
Factor B	4:1	10:1	-1	+1
Factor C	1:2	1:4	-1	+1

The coded values are calculated using the following formula:

$$Level = \frac{X - the\ average\ of\ two\ levels}{Half\ the\ difference}$$

The tablet weight was fixed to 250 mg in order to maintain tablet weight constant, microcrystalline cellulose was used as diluents, which does not interfere with the floating property of the tablet due to its low bulk density.[6]

Table 2. Quantities of ingredients per tablet and their percentage

S. no	Ingredients	Quantity/tablet (mg)	Percentage
1.	Glipizide	10 mg	10%
2.	Hydroxypropyl methyl cellulose	80-125	32-50%
3.	Ethyl cellulose	15-35	6-14%
4.	Methyl cellulose	24-52	9.6-20.8%
5.	Microcrystalline cellulose	45-65	18-26%
6.	Sodium bicarbonate	20	8%
7.	Magnesium stearate	5	2%

Table 3. Optimized formula

Ingredients	G1 (mg)	G2 (mg)	G3 (mg)	G4 (mg)	G5 (mg)	G6 (mg)	G7 (mg)	G8 (mg)	G9 (mg)
Glipizide	10	10	10	10	10	10	10	10	10
HPMC	80	96	90.92	109.10	90.66	108.8	103.4	123.64	105
EC	30	30	13.64	13.64	34	34	15.46	15.46	20
MC	40	24	45.44	27.26	45.34	27.2	51.5	30.90	35
MCC	65	65	65	65	45	45	45	45	55
Sodium bi carbonate	20	20	20	20	20	20	20	20	20
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total	250	250	250	250	250	250	250	250	250

Formulation of HBS tablets

The tablets were prepared by direct compression method. All the ingredients except glipizide were passed through # 80 mesh prior to mixing. The ingredients were weighed separately and mixed to get a uniform polymer mixture.[7] The drug was then mixed with the polymer mixture in geometric dilution for a period of 30 minutes to ensure uniform mixing of the drug. These powder mixtures were lubricated with magnesium stearate and compressed to obtain tablets.[8]

Evaluation of HBS tablets

The formulations were evaluated for the Glipizide content, duration of buoyancy and drug release rate profiles.[9]

Estimation of Glipizide in tablets

Ten tablets were selected in random and average weight was calculated. The tablets were then triturated to get a fine powder. From the resulting triturate, weight equivalent to 10 mg of the drug was transferred into 100 ml volumetric flask and add 50 ml of methanol, and placed in an ultrasonic bath for 15 mins. Diluted with buffer volume, and placed in the ultrasonic bath for an additional 15 minutes. Filtered through a solvent resistant filter.[10,11] The absorbance of the resultant solution was measured at 276 nm.[12] The same procedure was followed for all formulations.

Response evaluation

In-vitro release profile

The dissolution study was carried out in simulated gastric fluid using USP dissolution test apparatus employing paddle stirrer. In this study, one tablet containing 10 mg of Glipizide was placed inside 750 ml dissolution medium and speed of the paddle was set at 50 rpm. Samples were (5ml) withdrawn at a time interval of 1 hr and same volume of fresh medium was replaced. The samples were analyzed for the drug content against simulated gastric fluid as a blank at λmax 276 nm.[13]

Duration of buoyancy[14]

Duration of buoyancy was observed simultaneously when the dissolution has carried out. The time taken by the

tablet to rise to the surface of the media (lag time) and the time for it to sink to the bottom was noted, which gives the buoyancy of the tablets.[15]

RESULTS AND DISCUSSION

The tablets were formulated based on 2^3 full factorial design[16] and estimated for the drug content, evaluated for response like thickness, friability, hardness, weight variation, drug content, duration of buoyancy and release profile.[17]

From the results obtained, the angle of repose was in the range of 27°97" to 35°10", the formulation G8 and G9 were found to be 28°23 and 27°97 indicates good flow property. Bulk density values ranged between 0.439 ±0.0021 gm /ml and 0.4897±0.001 gm/ml and tapped density values ranged between 0.526±0.0024 g/ml and 0.591±0.0042 g/ml indicates good flow property. Hausner ratio was found to be in the range of 0.96±0.092 to 1.254±0.005. Carr's index was ranged between 13.08±0.736 % and 20.26±0.095% and these indicate the prepared granules exhibited good flow properties.[18]

Thickness of formulated tablets was arranged between 3.04±0.0163mm to 3.09 ±0.019mm and hardness for different formulations were found to be 3.13±0.170kg/cm^2 and 4.07±0.189kg/cm^2 indicating satisfactory mechanical strength. The friability was below 1% for all formulations which is an indication of good mechanical resistance of the tablets. The variations in weight were within the range of ±3% complying with pharmacopoeial specifications (±7.5%). The drug content varied between 9.127±0.1317mg and 9.923±0.0183 mg in different formulations indicating content uniformity. The buoyancy of the tablets was ranged between 10.917±0.4403 hrs and 16.237±0.1217 hrs, the maximum buoyancy was seen in G8, which has a high level of drug to polymer ratio.[19] The *in-vitro* release was found to be in the range of 59.25% to 79.50%. The formulation G8 has an *in-vitro* release of 59.25, showed that release of the drug in the controlled manner.[20]

From the results obtained the formulation G8 was found to be best among all formulation; Optimized formula[21].

IR Data for pure Glipizide

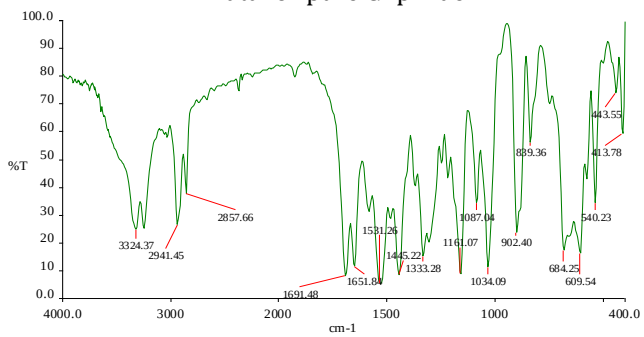


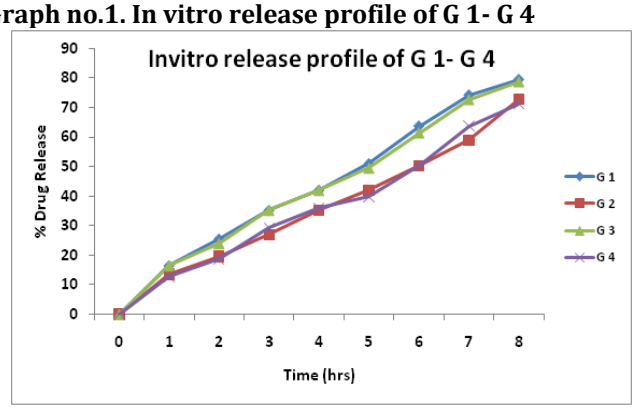
Table no. 4. Evaluation of the formulation G8

Parameters	Trial 1	Trial 2	Trial 3	Average ±S.D
Angle of Repose(^{0})	28^{0}34	28^{0}79	27^{0}55	28^{0}23
Bulk Density(g/ml)	0.450	0.448	0.452	0450±0.0016
Tapped Density (g/ml)	0.559	0.552	0.562	0.558±0.0048
Carr's index (%)	19.49	18.84	19.57	19.29±0.327
Hausner ratio	1.24	1.23	1.24	1.237±0.005
Thickness (mm)	3.06	3.062	3.08	3.067±0.009
Hardness (kg/cm^2)	3.8	4.2	4.2	4.067±0.188
Friability (%)	0.513	0.514	0.630	0.552±0.055
Buoyancy (hrs)	16.22	16.09	16.40	16.237±0.1271
Drug Content (mg)	9.566	9.587	9.577	9.576±0.0088

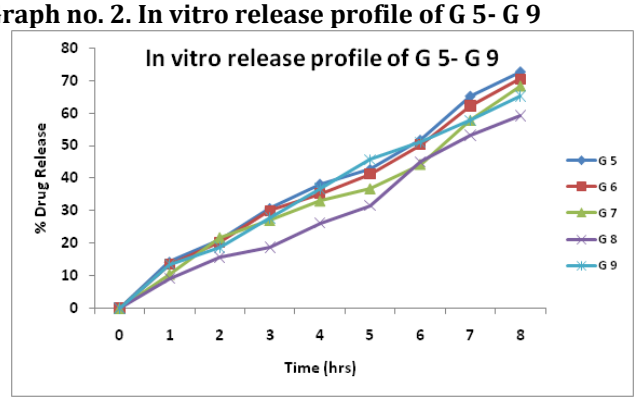
Table no. 5. *In-vitro* Release Profile Of Glipizide HBS Tablets (G8)

Time (hrs)	Absorbance	Conc. (µg/ml)	Conc.in 750 ml (mg)	% Drug release
1	0.022	1.2	0.912	9.12
2	0.036	2.1	1.575	15.75
3	0.043	2.5	1.875	18.75
4	0.061	3.5	2.625	26.25
5	0.082	4.2	3.150	31.50
6	0.104	6.0	4.503	45.03
7	0.121	7.1	5.325	53.25
8	0.138	7.9	5.925	59.25

Graph no.1. In vitro release profile of G 1- G 4



Graph no. 2. In vitro release profile of G 5- G 9



CONCLUSION

The principle of hydrodynamically balanced controlled drug delivery systems offers a suitable and practical approach to obtain controlled release of Glipizide with enhanced bioavailability and reduced dosing frequency.

The methodology of factorial design helps in determining the relationship between the factors acting on the system and the response or properties of the system.

The optimized formulation G8 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.

Hence the technique of optimization is a reliable means to reach the objectives of the experimentation as quickly as possible with the best possible precision, while still respecting the various restrictions that are imposed.

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