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Formulation and Evaluation of Floatingtablet of Gliclazide using HPMC and Xanthan Gum

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Abstract: The objective of this study is to develop floating drug delivery system; specially floating tablet of Gliclazide. Gliclazideis a selective second generationsulphonylurea use din treatment of hyperglycemia and it absorbs rapidly and completely. However its absorption iserratic in diabetic patient due to its impaired gastric motility or gastric emptying. To overcomethese drawbacks, thepresent investigation was to develop a gastro retentive floatingtablets ofgliclazide.Certain formulations containing retardant materials such ashydroxypropyl methyl cellulose K100LVCR (HPMC)and Xanthan gum, sodium bicarbonate was used as a gasgenerating agent to reduce floating lag timeandother release promoters. Thetablets were evaluated for physicalcharacteristics like hardness, weight variation, and friability. Invitro release of drug was performedusing 7.4 pH phosphate buffer and dissolution was done for 12hrs.All the physical characters wereacceptable and within limits.
Key words – Gliclazide, HPMC, Xanthan gum, Disintegration time; drug release.

Introduction

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms.During the last decade, many studies have beenperformed concerning the sustain release dosage formsof drug, which have aimed at the prolongation of gastricemptying time (GET).

Gastric emptying of dosage forms is an extremely variable processand ability to prolong and control the emptying time is a valuableasset for dosage forms, which reside in the stomach for a longerperiod of time than conventional dosage forms. Several difficultiesare faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties isthe inability to confine the dosage form in the desired area of thegastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It iswidely acknowledged that the extent of gastrointestinal tract drugabsorption is related to contact time with the small intestinalmucosa. Thus; small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Gliclazide is an effective oral antidiabetic agent that belongs to the sulfonylureasdrug class and is widely prescribed in the management of Non insulin dependent (Type II)diabetes mellitus. It is poorly soluble inaquoes fluids and is majorly absorbed fromstomach. Gastro retentive controlled release drug delivery system are needed for gliclazide to enhance its oral bioavailability and also for better control of blood glucose levels to prevent hypoglycaemia to enhance clinical efficiency and patient compliance. Floating tablets of gliclazide were designed in the present study to enhance its bioavailability and to achieve controlled release over 24 h for once a day administration. Floating tablets of gliclazide were designed HPMC K 100 LVCR asmatrix formers, sodium bicarbonate as gas generating agent and xanthan gum as floating enhancer. Tablets prepared were evaluated for floating and drug release characteristics.

Materials and method

Materials

Gliclazide was obtained from Bal Pharma, Avicel PH 102 and Xanthan gum was obtained from Signet Chemical Corporation, Mumbai. Aerosil 200 was obtained from Evonik Mumbai and Sodium biocarbonate was procured from Junbunzlor.

Methods

Gliclazide modified release floating tablets were prepared by wet granulation method. Compositions of various formulations are shown in Table 1. Thematrix Floating tablet of gliclazide were prepared using HPMC K 100 LVCR as release modifying agent and xanthan gum as floating enhancer agent.

Gliclazide and Avicel were sifted through 40 mesh and loaded 3L RMG. Materials were mixed for 10 minutes at 600RPM. Weighed 150 g purified water in glass beaker. Weighed quantity of purified water was added in dry mixed materials at 300RPM of impeller in 3 minutes followed by kneading for 2 more minutes at 500RPM of impeller and 2800 RPM of chopper. Granulated material passed through 8# mesh. Passed materials were dried at 55◦c till % LOD was NMT 1 %. Wet granulation of all trials were done using fixed quantity of Avicel in the formulation, refer table one was showing formulation composition for all trials.

Table 1 Optimization of Betacyclodextrin quantity.

Ingredients	F1	F 2	F 3	F 4	F5	F6
Gliclazide	60	60	60	60	60	60
Avicel PH 102	60	60	60	60	60	60
Total	425	450	475	500	550	600

A granule prepared by wet granulation was milled through 2.0mm multimill screen at medium speed. HPMC K 100LVCR, Xanthan gum, Sodium bicarbonate and aerosil pharma 200 were sifted through 40 mesh manually. Further milled granules and sifted material were blended in 5L blender for 15 minutes at 10 RPM. For lubrication, magnesium stearate sifted through 40 mesh and lubricated with blended materials for 3 minutes at 15 RPM.

Table 2 Blending:

Ingredients	F 1	F 2	F 3	F 4	F5	F6
Gliclazide and Avicel granules	120	120	120	120	120	120
HPMC K 100LVCR	50	60	70	80	90	100
Xanthan gum	30	40	50	60	70	80
Aerosil Pharma 200	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total	210	230	250	270	290	310

Evaluation of pre compression parameters

Bulk and Tapped density

Before final compression of tablets, powdered mixture was subjected to pre compression parameters such as bulk density, tapped density, angle of repose, powder compressibility and Hausner ratio. All the experiments were done in triplicates and expressed as mean± SD.

Bulk Density

Bulk density was determined by measuring the volume of the predetermined or preweighed mass of the powder blend according to the protocol described.

Bulk Density (Db) = (M) / (Vo) [1, 2]

Where,
M = Mass or weight of the powder blend
Vo = Apparent volume of the powder blend into the cylinder

Tapped Density

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed. The mechanical tapping was achieved by raising the cylinder and allowing it to drop under its own weight from a specified distance

Tapped density (Dt) = (M) / (Vf) [3]
Where,
M = Mass or weight of the powder blend
Vf = Final volume of the powder blend into the cylinder.

Carr's Index or Compressibility Index (I)

This was calculated by the formula and expressed as percentage (%)

I = Dt -Db / Dt ×100% [4]
Where
Db = Bulk density,
Dt = Tapped density.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula-

Hausner Ratio = Dt/Db [5]
Where,
Db = Bulk density,
Dt = Tapped density.

Angle of Repose

The determination of angle of repose of powder blend was carried out by employing fixed funnel method

Angle of Repose = $\tan^{-1}$ (H/R), [6]
Where,
H = height of the pile,
R = radius of the pile.

Evaluation of post compression

These tests are as following:-

- Appearance
- Thickness
- Hardness
- Weight variation
- Friability
- Dissolution
- Drug content
- Stability studies

Appearance

The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance. Tablets have smooth, clean surface, round concave shaped, white color tablet with pleasant taste.

Thickness:

The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected were used for determination of thickness that expressed in Mean± SD and unit is mm.

Weight variation:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated [6,7].

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator is rotated at 25rpm for 4 minutes for 100rounds. The tablets were dedusted and weighed again. The percentage weight loss was calculated using the formula [6, 7].

$$\% f = \frac{W0 - W1}{W0} \times 100$$

Here, %f = Percentage friability
W0 = Initial weight (Before test)
W1 = Final weight (After test)

Drug content:

10 tablets were powdered and 100mg drug equivalent powder dissolved in suitable media 0.1N HCl. Volume of the solution made up to 100ml by that media. Solution was filtered and diluted 100times and analyzed spectrophotometrically and further calculation carried out to determine drug content in one tablet [6, 7].

In vitro dissolution studies

The drug release study was performed using USP I basket apparatus at 37◦c C±1◦C and 100 rpm using 900 ml of is phosphate buffer (pH 7.4) Sample of 5 ml were withdrawn at predetermined time interval andfilter through 0.45 micron membrane filter, diluted suitable and analyzed at 225nm.Percentage drug dissolved at different time intervals was calculated using BeersLambert's law equation. [7,8].

Stability Study:

The stability of samples was monitored upto 3-month at ambient temperature and relative humidity(30°C/65% RH). Periodically samples were removed andcharacterized for disintegration time, hardness, drug-content and dispersion time.

Results and Discussion

Flow Properties of Granules:

Angle of Repose of Granules: All batches were evaluated for flow property. The results of all the batches were shown in table 3.

Table 3: Angle of repose of granules of batch F1 to F6

Batch No.	Angle of Repose(θ)	Carr's Index (%)	Hausner's Ratio(%)
F1	28.56	14.2	1.16
F2	29.25	15.6	1.18
F3	28.10	12.8	1.17
F4	27.90	12.6	1.18
F5	29.36	16.6	1.24
F6	28.56	17.1	1.25

From the results of flow properties of the all batches, it is concluded that all batches had good flow property.

Post compression parameters

The powder blend was compressed using 4 station compression machine. Tablets prepared by using mentioned formula have found to be good without any chipping, capping and sticking. Various physical parameters like thickness, hardness, weight variation, friability, hardness, dissolution were measured to evaluate tablets. All the formulations have therefore thought to show the acceptable physical parameters of tablets.

Table 4: Post Compression parameters

Batch No.	Weight variation	Thickness	Hardness	Friability
F1	210±0.74	3.10± 0.09	80±0.4	0.001
F2	230±0.33	3.20±0.11	88±0.15	0.241
F3	250±0.28	3.35±0.21	85±0.42	0.199
F4	270±0.30	3.50±0.19	90±0.60	0.185
F5	290±0.85	3.60±0.15	90±0.56	0.248
F6	310±1.18	3.80±0.18	95±0.29	0.126

Table 5: Post Compression Evaluation

Batch No.	Floating lag time	Floating time (hours)	% drug content
F1	18	12	99.5
F2	19	12	100
F3	16	12	99.9
F4	14	12	99.8
F5	20	>15	100.2
F6	19	>15	99.8

In-vitro drug release:

Dissolution parameter: Medium: pH 7.4 Phosphate buffer
Volume: 900 ml
Apparatus: USP Type I
Speed: 50 rpm
Time Point: 1,2,4,8 and 12 hours.
Temperature: 37oC
Identification: At 225.1 nm in UV-Visible spectrophotometer

Table 6: In-vitro drug release profile of batches F1 to F6

Time in min	**Cumulative % drug release**					
Batch no	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	18	15	13	12	9	7
2	32	25	23	20	19	14
4	70	62	58	52	42	35
8	85	79	71	68	61	55
12	100	98	99	100	99	95

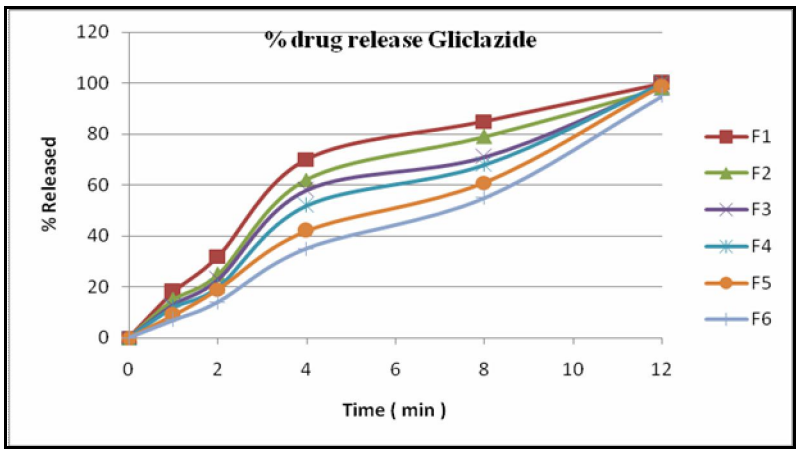

Figure 1 In-vitro drug release of Gliclazide batches F1 to F6

Discussion

The present study was aimed at not only to improve therelease of drug,gliclazide, in the acidic pH, but also torelease the drug in controlled fashion. Also, to make theformulation remain in the stomach for longer period oftime, gastro retentive dosage form was designed, to makethe therapy more effective as the drug is known forincomplete absorption in diabetic patients as explainedbefore. The polymers used in the formulation are wellestablished polymers for the said dosage form. The rolesof polymers are to control the release as well as to makethe formulation buoyant. The tablets were prepared bydirect compression method after mixing the ingredientswith the help of mortar and pestle. The granules ofdifferent formulations were evaluated for angle ofrepose, compressibility index, and drug content. Theresults of angle of repose indicate reasonablygood flow property of granules.The compressibilityindex values in the range of 12.7 to17.1 (<25), furthersupport flow property of granules. The drug content ofall the formulations was found to be more or lessuniform. Tablets of all the formulations weresubjected to many inprocess parameters evaluation suchas physical appearance, thickness, content uniformity,weight variation, hardness, and friability tests. Also the tablets were circular in shape withno visible cracks with smooth appearance. Weightvariation test revealed that the tablets were within therange of pharmacopoeial limit. Good uniformity indrugcontent was found among different formulations of thetablets, and the percentage drug content was more than. All the formulations showedreasonably goodhardness value.Further, tostrengthen these values, friability test values are alsoconsidered.The weight loss of less than 1% in friabilitytest is considered as acceptable value for conventionaltablet. This indicates that the tablets can withstand themechanical shocks reasonably well during handling.Formulations were prepared by different concentrationsHPMC K100LVCR and xanthan gum polymers. All thepolymers were chosen as they are wellestablished in the similar studies and have good swellingproperties.The rate of swelling of polymer depends uponthe amount of water taken up bypolymer. Sodiumbicarbonate is added in the formulation which uponcontact with carbon dioxide and expelsfrom the dosage form creating pores through whichwater can penetrate in to dosage form and increasewetting. Formulations F5 has been selected asbest formulation among all the other formulations. Formulation F5 providesbetter invitro release.Thedata obtained from invitro release studywere fitted to various mathematical models likeHiguchi,Peppas model, first order, the best fitmodel in all the cases. The release was foundto be non–fickianas the n value for m3 andg3 was found to be 0.52, 0.51. The formulationwas found to follow first order.

Stability study:

Three months stability study at ambient temperature and relativehumidity (30 °C / 65% RH) of formulation F5 revealed that theformulation was stable and there were no significant changesobserved for hardness, drug content and disintegration time.Hence, the results of stability studies reveal that the developedformulation has good stability.

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