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FORMULATION DESIGN AND EVALUATION OF NON EFFERVACENT FLOATING TABLETS OF GLICLAZIDE

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Abstarct:

The aim of the present study was to develop non effervescent floating tablet formulation of Gliclazide to maintain constant therapeutic levels of the drug for over 9 hrs for the treatment of diabetis. Various grades of poly methacrylate polymers and accural was employed as polymers. Gliclazide dose was fixed as 80 mg. Total weight of the tablet was considered as 500 mg for Gliclazide. Polymers were used in the concentration of 10, 20 and 30 mg concentration and accrual concentration used in the formulations were optimised according to the floating properties of the formulations. All the formulations were passed various physicochemical evaluation parameters like hardness,bulk density, friability, weight variation etc.and they were found to be within limits.and also the drug and excipient studies showed that there is no incompatability between pure drug and excipient. Whereas from the dissolution studies it was evident that the optimized formulation (F6) showed better and desired drug release pattern i.e.,91.17 % in 9 hours. It followed higuchi release kinetics mechanism.

Keywords: *Gliclazide, Floating tablets, HPMC K 100M, HPMC K15M, HPMC K4M, Accural.*

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INTRODUCTION:

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50%of the drug delivery systems available in the market are oral drug delivery systems1. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances.

The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.

1. The physiochemical characteristics of the drug
2. Anatomy and physiology of GIT and Characteristics of Dosage forms

Gastro intestinal retention

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

To successfully modulate the gastro intestinal transit time of a drug delivery system through floating drug delivery system(FDDS)For maximal gastro intestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT.

Advantages of FDDS

1.The gastro retentive systems are advantageous for drugs absorbed through the stomach, e.g. ferrous salts, antacids.

2.Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence, HBS formulation may be useful for the administration of aspirin and other similar drugs.

3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

4. The gastro retentive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.

5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

6.FDDS improves patient compliance by decreasing dosing frequency.

7.Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.

8.Better therapeutic effect of short half-life drugs can be achieved.

9.Gastric retention time is increased because of buoyancy.

10.Enhanced absorption of drugs which solubilize only in stomach.

11.Superior to single unit floating dosage forms as Such microspheres releases drug uniformly and there is no risk of dose dumping.

12. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.

MATERIALS AND METHODS:

Gliclazide, HPMC K4M, HPMC K15M, HPMC K100M, Accural, Magnesium stearate, Micro crystalline cellulose, Talc.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be

measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\mathbf{Tan\ \theta = h / r}$$ Tan θ = Angle of repose

h = Height of the cone,

r = Radius of the cone base

Bulk density:
Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\mathbf{Bulk\ Density = M / V_o}$$

Where, M = weight of sampleA solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

V_o = apparent volume of powder

Tapped density:
After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\mathbf{Tap = M / V}$$

Where, Tap= Tapped Density

M = Weight of sample
V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\mathbf{Carr's\ Index = [(tap - b) / tap] \times 100}$$

Where, b = Bulk Density
Tap = Tapped Density

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:
The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Formulation development of Tablets:
Gliclazide
All the formulations were prepared by direct compression. The compression of different formulations is given in Table 3.6.The tablets were prepared as per the procedure given below and aim is to prolong the release of Gliclazide. Total weight of the tablet was considered as 500mg.

Procedure:

1) Gliclazide and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

RESULTS AND DISCUSSION:

Preformulation parameters of powder blend for Gliclazide

Table1: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02
F10	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F11	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F12	26.13	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F13	26.09	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F14	24.02	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F15	27.23	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

Table 2: quality control parameters for tablets

Formulation code	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	302.5	4.5	0.52	4.8	99.76	4.0
F2	305.4	4.2	0.54	4.9	99.45	4.2
F3	298.6	4.4	0.51	4.9	99.34	4.5
F4	300.6	4.5	0.55	4.9	99.87	4.1
F5	299.4	4.4	0.56	4.7	99.14	4.0
F6	300.7	4.2	0.45	4.5	98.56	4.4
F7	302.3	4.1	0.51	4.4	98.42	4.5
F8	301.2	4.3	0.49	4.7	99.65	4.6
F9	308.3	4.5	0.55	4.6	99.12	4.7
F10	302.5	4.5	0.51	4.7	99.76	4.0
F11	305.4	4.2	0.45	4.5	99.45	4.2
F12	298.6	4.4	0.51	4.4	99.34	4.5
F13	300.6	4.5	0.49	4.7	99.87	4.1
F14	299.4	4.4	0.55	4.7	99.14	4.0
F15	300.7	4.2	0.45	4.9	98.56	4.4

***In-Vitro* Drug Release Studies**

Table 3: Dissolution Data of Gliclazide Tablets

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	30.22	33.26	25.02	59.21	24.66	15.12	51.10	19.80	14.54
2	69.88	70.65	75.55	97.52	38.44	22.05	97.73	31.58	32.23
3	96.25	94.82	98.69		72.85	31.29		59.28	44.85
4					96.66	42.83		71.01	51.31
5						59.21		98.06	60.86
6						61.70			78.98
7						74.33			94.26
8						87.26			
9						91.17			

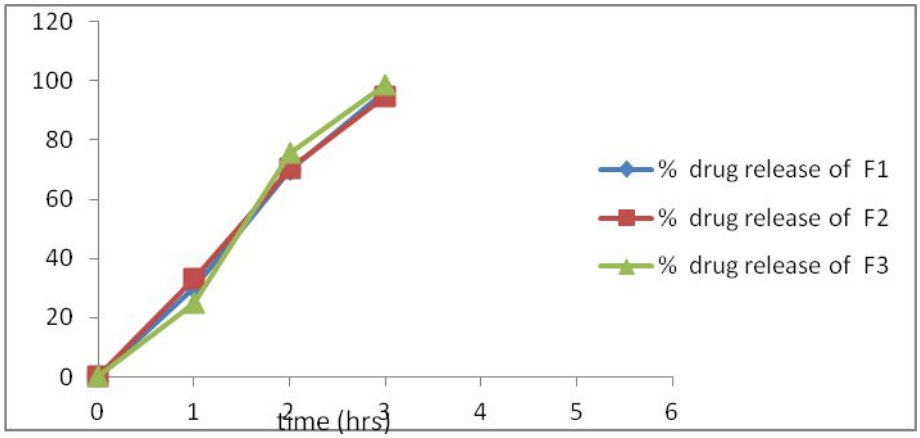

Fig :1dissolution profiles of formulations F1-F3

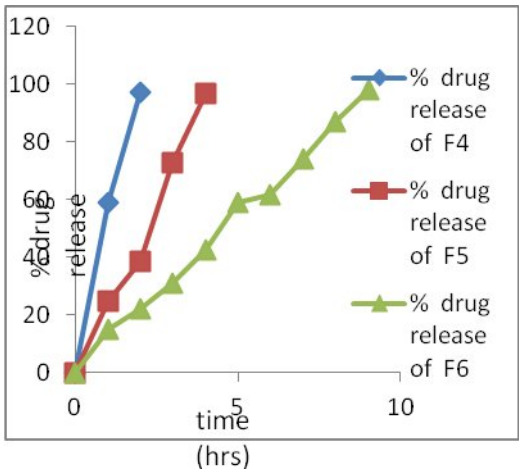

Fig 2 : dissolution profiles of formulations F4-F6

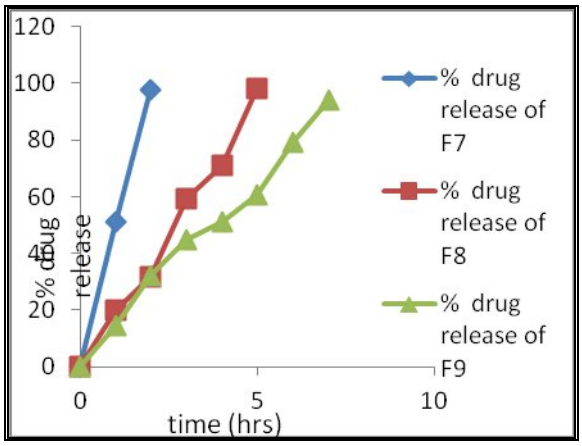

Fig 3: dissolution profiles of formulations F7-F9

Table 4 : dissolution profile of formulations F10-F15

Time(hrs)	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0
1	22.52	25.09	13.26	50.21	24.66	25.12
2	49.88	75.25	20.65	97.82	38.44	52.05
3	69.25	92.65	34.82		72.85	92.29
4	80.10		44.59		96.26	
5	95.15		50.10			
6			59.89			
7			72.29			
8			81.02			
9			89.87			

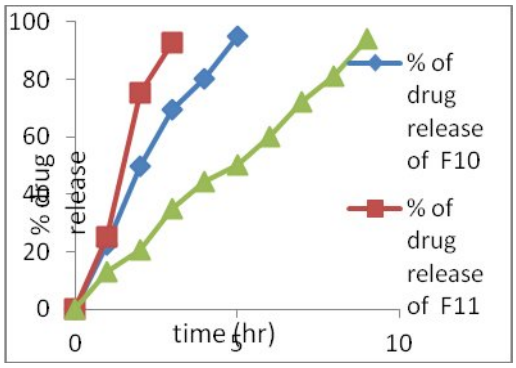

Fig 4 : dissolution profile of formulations F10-F12

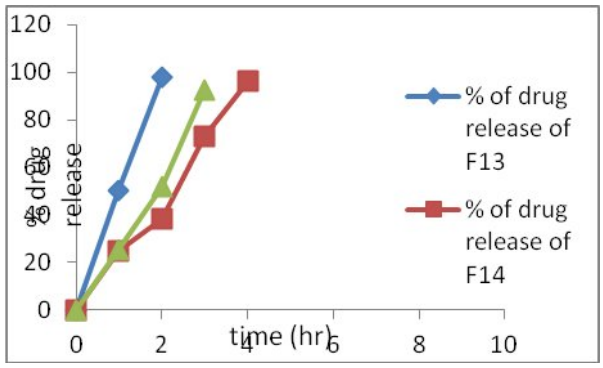

Fig 5 : dissolution profile of formulations F13-F15

CONCLUSION:

In the present research work gastro retentive non effevescent floating matrix formulation of Gliclazide were formulated by using various hydrophilic polymers. Initially analytical method development was done for the drug molecules. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Then the formulation was developed by using different concentrations of polymers of various grades of HPMC. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using HPMC K100M were unable to produce desired drug release, they were unable to retard drug release up to 9 hours. The formulations F6 prepared with HPMC K15M retarded the drug release up to 9 hours in the concentration of 30 mg. Hence they were considered. The optimized formulations (F6) dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

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