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FORMULATION AND EVALUATION OF EFFERVESCENT FLOATING TABLETS OF GLIPIZIDE

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Abstract:
The aim of the present research work was to develop a novel control drug delivery, to improve the solubility of poorly soluble drugs by effervescent technology.
Six formulation of effervescent floating tablets of Glipizide were prepared by direct Compression method by using HPMC 100, Eudragit R400, ethyl cellulose as a polymers and sodium bicarbonate, citric acid as an effervescent mixture. They were subjected to Various pre and post compression evaluation parameters and results found to be within I.P limits. From all formulations F4 formulation shows controlled and complete release of drug over a period of 7 hours containing polymer as HPMC 100 and Eudragit Rc100 and shows 98.24% drug release.
Key Words: *Effervescent floating tablets, Glipizide, HPMC 100, Eudragit RL100, Ethyl cellulose*

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1.INTRODUCTION:

Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. Oral controlled release drug delivery has recently has been increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in the formulation. Drugs that are easily absorbed from gastro intestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT). To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed[1,2,3,4].

Simply, Effervescence means release of CO_2 gas due to reaction of acids and bicarbonates in presence of H_2O. Some common acids used in this reaction are citric, malic, tartaric, adipic and fumaric acid and bicarbonate used in the effervescent reaction is sodium bicarbonate, potassium bicarbonate, sodium carbonate and potassium carbonate. The most common reaction for pharmaceutical purpose is the acid base reaction between sodium bicarbonate and citric acid.

$$3NaHCO_{3(aq)} + H_3C_6H_5O_{7(aq)} \longrightarrow$$

$$3Na_3C_6H_5O_{7(aq)} + 3H_2O + 3CO_2$$

This reaction occurs in presence of water, even with small amount as catalyzing agent, which increases the rate of reaction. As water act as a catalyzing agent for the reaction so all the moisture sensitive products or effervescent products is stored in moisture free environment.

Due to development of gas in effervescent floating drug delivery systems the density of the system is reduced and the dosage form remains buoyant in the stomach for a prolonged period of time which released the drug slowly at a desired rate. So it is possible to prolong the gastric residence time of drug using effervescent floating drug delivery systems or hydro dynamically balanced system.

Effervescent floating drug delivery systems requires matrices prepared with swellable polymers such as methocel polysaccharides, e.g., chitosan and effervescent components such as sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Effervescent floating tablets are prepared by compression the active ingredients with mixture of sodium bicarbonate and organic acids such as citric acid and tartaric acid. The main advantages of effervescent floating tablets are quick production of solution. Thus, it is faster and better to absorb.

On the other hand floating drug delivery systems (FDDS) is designed in such manner that it has bulk density less than gastric fluids and because of this, these systems remains buoyant for a prolonged period of time (Approx. 3-4 hours) in the stomach without affecting the gastric emptying rate. The underlying principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. The drug is released slowly at the desired rate from the system and after release of the drug; the residual system is emptied from the stomach. As a result gastric residence time is increased and fluctuations in plasma drug concentration can be better controlled[5,6,7,8].

DEFINITION:

Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow Microspheres.

Advantages of FDDS[9,10]:

1. The main advantages of this dosage form are patient compliance, increased rate of absorption, large dose can be given.

2. The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT.
3. This technique is generally employed for antacid preparations. In this preparation alkali metal bicarbonates & alkali metal carbonates like Sodium carbonate &Sodium bicarbonates are added which reacts with citric acid or tartaric acid to give effervescence.
4. The FDDS is a site-specific drug delivery system reduces undesirable effects.
5. The effervescent floating dosage form is better for drugs which get absorbed through the stomach.

Disadvantages of FDDS:
1. Plenty of water is required (Glassful of water) for effective effervesces.
2. There are certain limitations too, like it cannot be given to the children because of risk of carbon dioxide toxicity; it's shorter shelf life, chance of product deterioration if packaging is not done properly and the cost of manufacturing is high, as compared to other tablets.
3. Some drugs causes irritation to gastric mucosa this type of drug not use in floating system.
4. Some drugs not suitable for FDDS as they have solubility or stability problem in GIT and unstable in acidic environment.
5. Size-increasing drug delivery systems potentially present the hazard of permanent retention in the stomach and could lead to life-threatening effects upon multiple administrations.

Limitation of Effervescent Floating Drug Delivery System:

1. Floating drug delivery requires sufficient high level of fluids in the stomach.
2. Not suitable for the drug that have solubility or stability problem in GIT.
3. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
4. Drugs which cause irritation to gastric mucosa are not suitable for this.
5. The dose should be taken with a full glass of water.

Classification of floating system:
1) Single Unit Floating Dosage Systems
   a) Effervescent system or gas generating system
   b) Non-effervescent Systems
2) Multiple Unit Floating Dosage Systems
   a) Effervescent Systems
   b) Non-effervescent Systems

1. **EFFERVESCENT FLOATING DOSAGE FORMS**:
These are matrix type systems prepared with the help of swellable polymers such as hydroxypropyl methylcellulose or polysaccharides and chitosan and various effervescent components like sodium bicarbonate, calcium carbonate, citric acid or tartaric acid. These dosage forms are developed in such a way that, when they come in contact with gastric juice in the stomach, Carbon dioxide is liberated and is trapped in the swollen hydrocolloids. This provides buoyancy to the dosage form. The liberated carbon dioxide may intimately get mixed within the tablet matrix in case of single layered tablet.

The multiarticulate floating reservoir types of delivery systems may contain double or triple layers. The triple layered tablets may be prepared, which contains swellable gas generating layer, sustainable approach was utilized in the development of floating or pulsatile drug delivery system based on the coated effervescent core. The dosage form had two layers, first layer consisted of drug, cellulose acetate or HPMC as a sustained release core and second layer consisted of effervescent agents, PEG 4000 (4%based on the weight of the second layer) and lactose or microcrystalline cellulose as filler. Sodium bicarbonate and citric acid were used as an effervescent agent in a ratio of 1:0. in the concentration of 30-50 % of the w/w of the core. The carbon dioxide is generated upon contact with the medium and gets entrapped in the polymeric matrix, which provides buoyancy to the dosage form. It was observed that addition of 10-20% w/w of HPMC significantly retarded drug release compared to the dosage form without HPMC.
Programmable drug delivery systems for oral administration were developed. It was a new prototype model device (3 cm long and 0.9 cm internal diameter) made to comprise of a cylindrical shell in the form of oral capsule. Drug was placed in a cylindrical disc made up of slowly eroding polymer and compressed to zero porosity, a flexible rubber disc, compressible acid resistant spring and a special acid impervious nonpermeable rubber ballooning system containing bicarbonate granules. The device in the form of nondigestible oral capsule containing drug in a slowly eroding matrix was designed to utilize on automatically operated geometric obstruction that keeps the device floating in the stomach and prevents the system from passing through remainder of GIT.

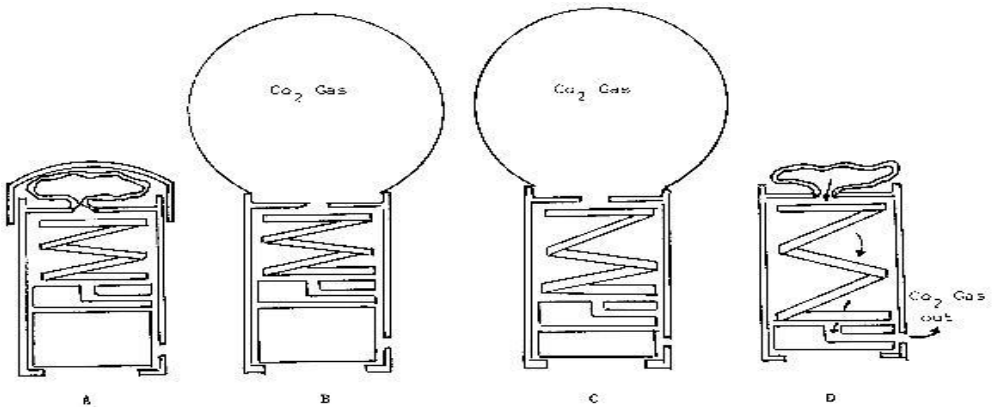


Fig no: Mechanism of Effervescent systems

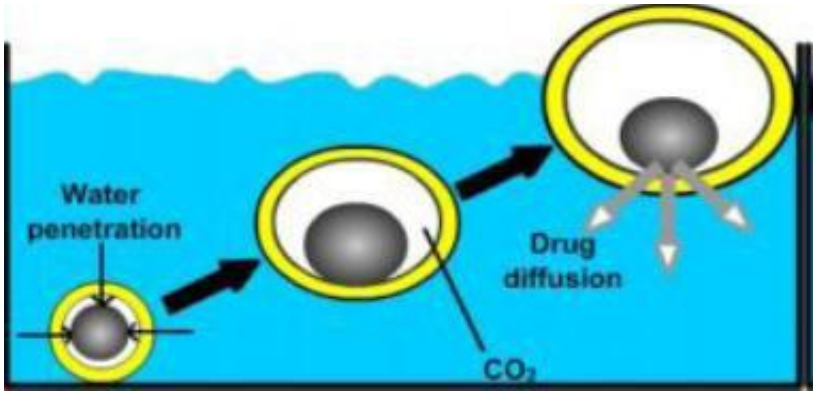
2. NON-EFFERVESCENT FDDS:

The non-effervescent FDDS works on the mechanism of polymer swelling, bio adhesion of the polymer to mucosal layer of GI tract. The most commonly used excipients for the preparations of non-effervescent FDDS are gel forming or swellable type hydrocolloids, polysaccharides and matrix forming polymers like polymethacrylates, polycarbonates, polyacrylates polystyrenes and bio adhesion polymers like chitosan and carbopols. One of the approaches in the development of such floating dosage forms involves thorough mixing of drug and gel forming hydrocolloids. After oral administration, the dosage form comes in contact with gastric fluids and gets swollen, form a gelatinous barrier at the surface. The swollen dosage form maintains a relative integrity of shapes and bulk density less than 1.0. The air entrapped within the swollen polymer matrix imparts buoyancy to the dosage forms.

Novel levodopa gastro retentive dosage form based on unfolding polymeric membranes, that combines extended dimensions with high rigidity. It was folded into a large size gelatin capsules. In vitro studies showed that unfolded form reached within 15 minutes after administration and it was confirmed in vivo in beagle dogs. The unfolded form was maintained for at least 2 hours. It was concluded that this dosage form could improve therapy of different narrow absorption window drugs. However, there are possibilities of the polymeric films to get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries and repeated administration of rigid dosage form may result in gastric obstruction[12].

Mechanism of Floating Effervescent[13]:

After administration of effervescent floating dosage form coming in contact with the gastric fluid the dosage form get swells up and the slowly release of the drug without disintegration of the tablet takes place. When the tablet comes in the contact of gastric fluid, it produces effervescence by releasing CO2 gas. When the fluid penetrates into the tablet, tablet starts to float.



Mechanism of floatation via CO2 liberation

MATERIALS AND METHODS:

Materials:

Table 1: List of materials

MATERIALS	VENDOR
Glipizide	Chandra analytical lab, Hyderabad
HPMC	S.D. Fine Chem.Ltd, Mumbai, India
Eudragit RL 100	S.D. Fine Chem.Ltd, Mumbai, India
Ethyl cellulose	MYL Chem Mumbai
Lactose	S.D. Fine Chem.Ltd, Mumbai, India
Sodium bicarbonate	S.D. Fine Chem.Ltd, Mumbai, India
Citric acid	MYL Chem Mumbai
Talc	Himedia laboratory Pvt Ltd
Magnesium stearate	S.D. Fine Chem.Ltd, Mumbai, India

Equipment's:

Table 2: list of equipment

Equipment	Model/Company
Electronic balance	Citizen , India
Tablet compression machine	Cadmach single punch machine
Hardness tester	Monsanto hardness tester
Dissolution test apparatus	Lab India
Disintegration test apparatus	Campbell Electronics
Friability test apparatus	Riche Rich
U.V visible spectrophotometer	Schimadzu UV-1601, Japan
FTIR	Bruker (Tensor 27)
pH meter	Citizen, India

STANDARD CALIBRATION CURVE OF GLIPIZIDE

Preparation of standard calibration curve of glipizide:

The standard calibration curve of glipizide was prepared using 0.1N HCL (PH 1.2).

Standard solution:

10 mg of glipizide tablets were dissolved in 100ml 0.1N HCL (pH 1.2) to give concentration of 1µg/ml.

Stock solution preparation:

From the standard solution pipette out 0.2, 0.4, 0.6, 0.8, 1.0ml of solution into 10 ml of volumetric flask. The volume was made up to the mark with 0.1N HCL (pH 1.2) to produce various concentrations such as 2,4,6,8,10 microgram/ml of glipizide respectively. The absorbance of prepared solution o glipizide was measured at 274nm in Schimadzu UV/visible spectrophotometer against 0.1N HCL as a blank.

Preparation of floating effervescent tablets of glipizide by direct compression method:

All the ingredients were weighed and the drug along with required quantities of HPMC is taken in mortar and pestle then mix well. To that add $NaHCO_3$ and lactose mix well and pass the entire mixture through a sieve no. 40. After that add citric acid, then above mixture is passed through sieve no. 10 add required quantities of magnesium stearate and talc. It is then compressed to form tablets.

SOLUBILITY PROFILE:

The solubility study of glipizide was performed using different organic solvents and water.

EVALUATION PARAMETERS FOR FLOATING TABLETS OF GLIPIZIDE:

Active pharmaceutical ingredient:

Organoleptic evaluation: These are preliminary characteristics of any substance which is useful in identification of specific material. Following physical properties of API were studied.

a) color

b) odour

c) taste

Table 3: Organoleptic Evaluation

PARAMETER	GLIPIZIDE
Organoleptic evaluation	White to off white powder.
Solubility analysis	Insoluble in water & ethanol &soluble in 0.1N NaOH, HCL

PRECOMPRESSION PARAMETERS:

Bulk density:

Bulk density of powdered blend was determined by pouring gently through a glass funnel into 50ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density= weight of sample in grams/volume occupied by the sample

Bulk density= weight of sample in grams ÷ volume occupied by the sample

Tappared density:

Tappared density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or percentage of difference is not more than 2%

Tappared density= weight of sample in gram/ tappared volume

.

A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and tappared density is calculated using following formula.

Compressibility Index and Hausner's ratio:

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast and popular methods of predicting powder flow characteristics. Both the compressibility index and Hausner's ratio were determined by using bulk density and tappared density of powder.

Carr's index= tappared density-bulk density /100

Hausner's ratio= Tappared density / bulk density

Relation of flow property with HR & CI:

Table 4: **Relation of flow property**

Compressibility index (%)	Flow Character	Hausner's Ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Possible	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Angle of repose: (USP29-NF-24)

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane.

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

$$\Theta = \tan^{-1} h/r$$

Where, = angle of repose, h = height, r = radius

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of powder formed. Determine the angle of repose by measuring the height of cone of powder and radius of heap of powder.

Flow properties and corresponding angle of repose:

Table 5: flow properties and corresponding angle of repose

Flow property	Angle of repose
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Possible – may hang up	41-45
Poor- must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

Post compression parameters:
The quantitative evaluation and assessment of tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. These are various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, disintegration and dissolution characters.

Physical appearance:
The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence of odor, taste etc.

Size & shape:
It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by another device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Drug content:
An accurately weighed quantity of tablets of glipizide was taken into 100 ml volumetric flask, dissolved in 1.2pH (0.1N HCL). The content of glipizide was determined spectrophotometrically at 274 nm against suitable blank using UV- visible spectrophotometer.

Weight variation test:
This is an in-process quality control test to ensure that the manufactures control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on comparison of the weight of individual tablets of a sample of tablets with an upper and lower percentage limit of the observed sample average. The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50 mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method:
Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in the average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table 6: Limits for tablet weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10%
From 130 to 324	7.5%
>324	5%

Thickness and diameter:
The thickness and diameter of 10 tablets were recorded during the process of compression using Vernier callipers.

Friability:
Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method:
A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\%\text{Friability} = \frac{W1-W2}{W1}$$

Where W_1 = weight of tablets before test
W_2 = weight of tablets after test

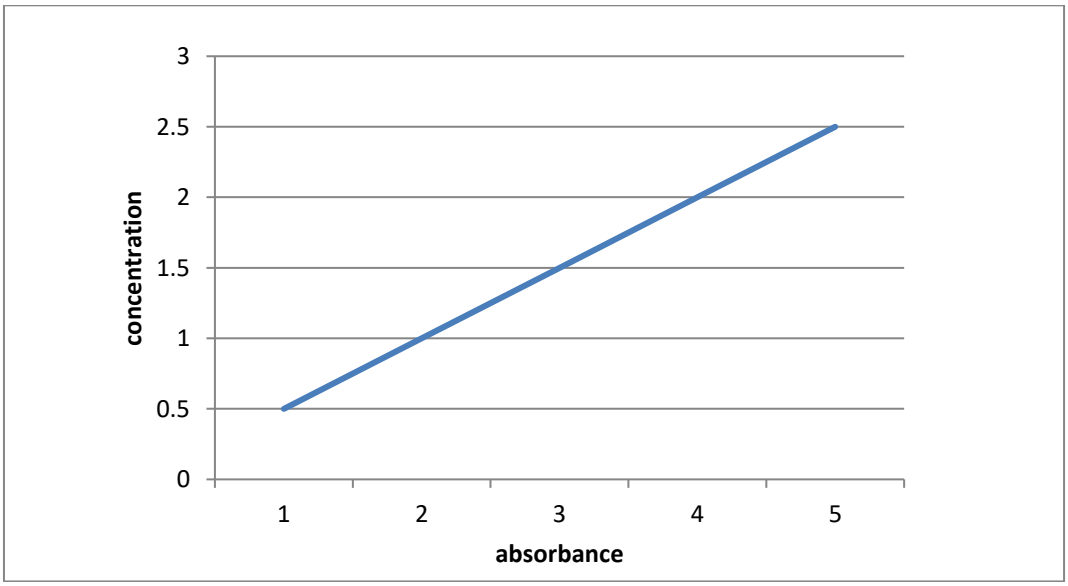
***In vitro* Dissolution Studies**:
The In vitro dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 50 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at $37^0C \pm 0.5^0C$. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 24 hrs and the same volume was replaced with pre -warmed fresh dissolution media. The samples were filtered through a whatman filter paper and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 274 nm using a UV spectrophotometer.

RESULTS AND DISCUSSION:

ANALYTICAL METHOD:
Graph of glipizide was taken in simulated gastric fluid

Table 7: Observations for graph of glipizide in the 0.1 N NaOH medium at 274 nm:

Conc	Absorbance
0.5	1.903
1.0	2.011
1.5	2.348
2.0	2.470
2.5	2.730



Standard graph of glipizide in 0.1N NaOH

Table 8: Preformulation parameters of powder blend:

formulation	Bulk density (gm/ml)	Tappared density (gm/ml)	Carr's index (%)	Angle of repose	Hausner's ratio
F1	0.637	0.85	25	36	1.33
F2	0.559	0.768	23.3	38	1.30
F3	0.606	0.833	27	41	1.37
F4	0.725	0.831	12.75	26	1.14
F5	0.832	1.011	17	28	1.21
F6	0.761	0.983	22.5	34	1.29

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 9: Quality Control Parameters For tablets

Formulation	Weight variation(mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	238.89	3.32	0.58	2.1	99.67	2.8
F2	237.67	3.29	0.59	2.3	99.56	3.0
F3	236.24	3.23	0.61	2.2	99.45	3.3
F4	242.38	3.58	0.50	2.7	99.89	2.2
F5	240.12	3.45	0.52	2.6	99.82	2.4
F6	239.65	3.42	0.55	2.5	99.74	2.6

Invitro quality control parameters for tablets

Table 10: *In-Vitro* Drug Release Studies:

Time	F1	F2	F3
0.5	22.40	23.42	19.46
1	28.89	29.76	27.92
2	39.62	41.12	38.06
3	48.89	47.65	46.42
4	57.56	59.31	55.89
5	63.73	64.52	62.12
6	71.34	72.81	69.08
7	78.85	79.23	75.89

Dissolution formulations of drug F1-F3

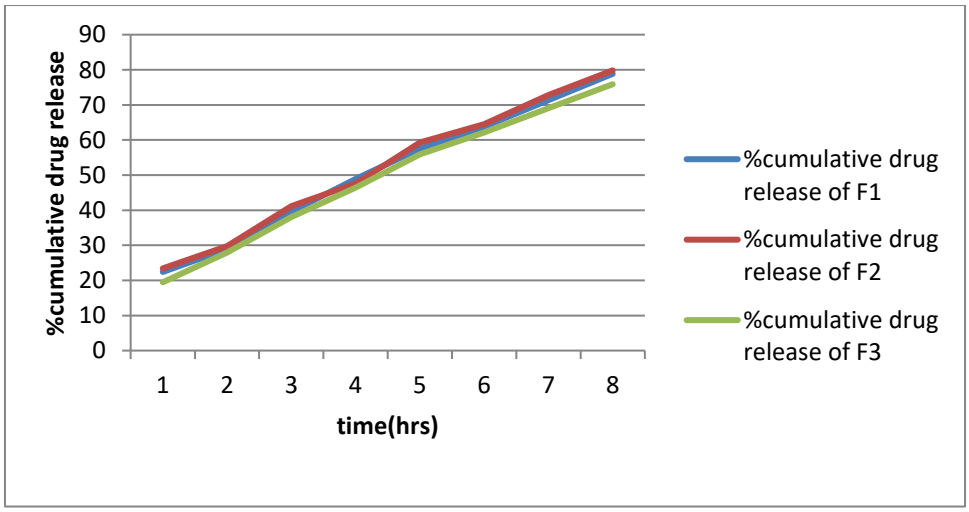
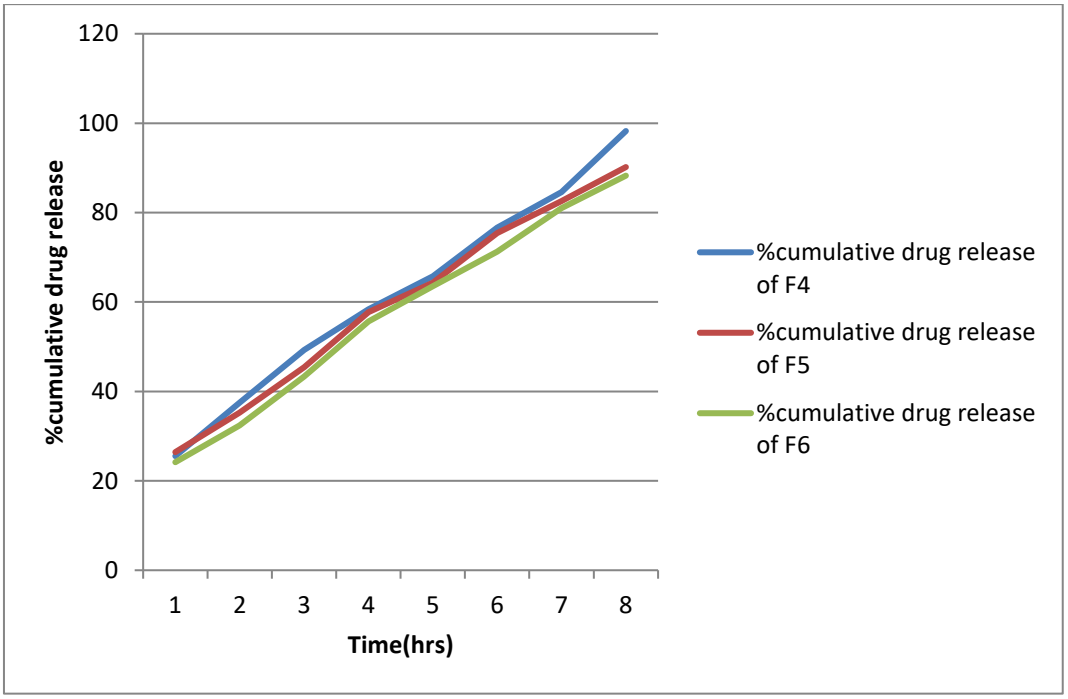


Table 11: Dissolution profiles of formulations F1-F3

Time	F4	F5	F6
0.5	25.54	26.42	24.17
1	37.47	35.27	32.41
2	49.29	45.41	43.32
3	58.37	57.76	55.63
4	65.74	64.34	63.50
5	76.65	75.43	71.26
6	84.56	82.61	80.97
7	98.24	90.18	88.26

Dissolutions formulations of drug F4-F6



Dissolution profiles of formulations F4-F6

CONCLUSION:

To develop controlled drug delivery and improve solubility of poorly soluble drug i.e., Glipizide we prepared six different formulations of effervescent floating tablets.

In this study HPMC 100, Eudragit RL 100 and ethyl cellulose used as polymer and $NaHCO_3$, citric acid as aneffervescent mixture.

All six formulations were subjected to various pre and post compression evaluation parameter and concluded that all passed the test within I.P limits.

Finally, we concluded that F4 formulation as a best formulation because it released drug controlled and completely over a period 7 hours and 98.24% drug release among the all formulations of effervescent floating tablets of Glipizide.

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