IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 4, June 2024

To Formulate and Evaluate the Metformin Hydrochloride Floating Tablet

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Abstract: *The aim of the research was to create a gastro retentive system for prolonged release of metformin HCl in the proximal part of the gastrointestinal tract (GIT) in the form of an oral floating tablet. Metformin HCl is an antidiabetic biguanide with poor bioavailability and an absorption window in the upper GIT. Floating tablets were prepared using a wet granulation method containing the natural polymers guar gum and kcarrageenan and the synthetic polymer HPMC K100 (HPMC) either alone or in combination. Sodium bicarbonate and citric acid were used as gas generators. Floating tablets were evaluated for weight variation, hardness and friability, drug content, swelling index, in vitro buoyancy and in vitro drug release. The formulation is optimized based on buoyancy, matrix integrity and in vitro drug release in simulated gastric fluid at pH 1.2. A formulation formulated with a combination of 6 wt. % k-carrageenan and 11 wt. % guar gum showed good gel strength, stable and continuous buoyancy for 12 hours, minimal buoyancy delay of 58 seconds, and good matrix integrity during dissolution period. The drug release of the optimized formulation followed the Korsmeyer- Peppas model and the mechanism was non-Fickian/divergent. PXRD and DSC studies showed partial amorphization of the drug. The mechanism of drug release appeared to be a diffusion mechanism. Stability studies have shown that the drug does not degrade when stored for 3 months at 40˚C.*

Keywords: Guar gum, K-carrageenan, HPMC K100, bioavailability, floating tablet.

I. INTRODUCTION

According to the Indian Pharmacopoeia Pharmaceutical Tablet are solid, flat or biconvex dishes unit dosage form, prepared by compressing a drugs or mixture of drugs, with or without diluent. Tablets is defined as compressed solid dosage form containing medicament with or without Excipients. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and intended mode of administration. [1, 2]
Tablet comes in classification of Solid dosage form , tablets are taken in oral form
As on the intended is Floating tablet .Gastric retention are such systems, which increase the gastric retention time of the dosage forms at the stomach and upper part of the small intestine and suitable for the drug having site-specific absorption from the above sites.

Floating Tablet:-
Floating drug delivery systems (FDDS) are invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids. The basic behind FDDS is making a dosage form less dense than the gastric fluids to make it float on them. FDDS are hydro-dynamically controlled low density systems with sufficient 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. The residual system is emptied from the stomach with the release of the drugs .This result in enhanced gastric residence time and good control over plasma drug concentration fluctuations. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. Prolonging the gastric retention of a delivery system is desirable for achieving the greater therapeutic efficacy of the drug substance under certain circumstances. For example, drug which show better absorption at the proximal part of gastrointestinal tract and drugs with low solubility and get degraded in alkaline 'PH'

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it found efficient in prolonging gastric retention. In addition, for sustained drug delivery to the stomach and proximal small intestine in treating certain ulcerative conditions, prolong gastric retention of the therapeutic moiety and hence offer numerous advantages including improve bio availability and therapeutic efficacy with reduction of dosing frequency.[3]

Stomach anatomy: -

The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir allowing a rather large meal to be consumed quickly and digest . Substantial enzymatic digestion is initiated in stomach, particularly of proteins. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing. [5]

Anatomically the stomach is divided into the 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. [6]

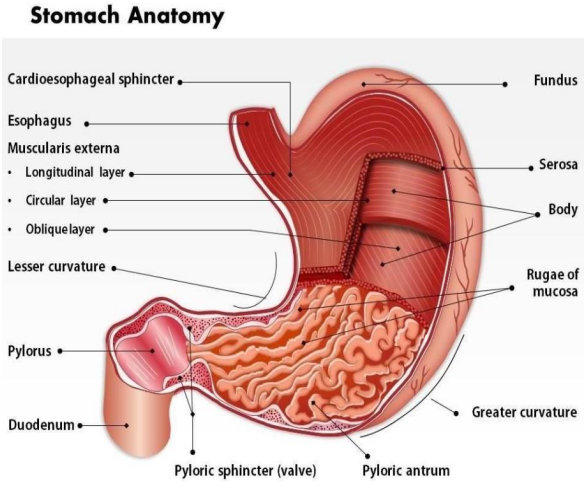

Figure 1: (Human Stomach)

It has been reported that the mean value of pH in fasted healthy subjects is 1.1± 0.15. But when food comes into the stomach, the pH may rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins. However, in fasted state, basal gastric secretion in women is slightly lower than that of men [7]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases

Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.

Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.

Phase III (burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

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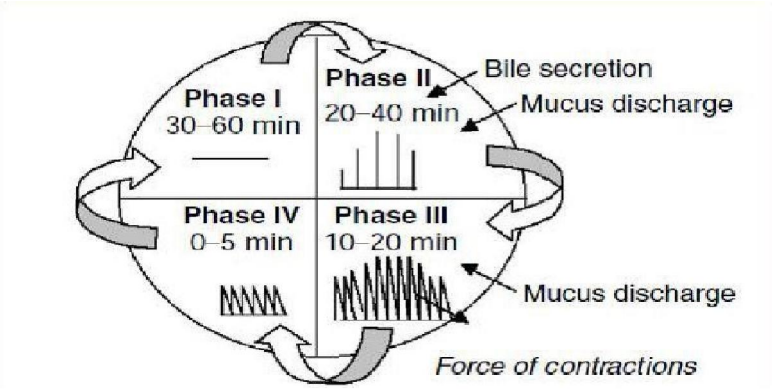


Figure 2: (Motility pattern in GIT)

II. MECHANISM OF FLOATING DRUG DELIVERY SYSTEMS

As shown in figure 3(a), the system is floating on the contents of the stomach, and the slow medication release occurs at the necessary rate during this process. After the release, the stomach's remaining system is removed. But in order to achieve the buoyancy retention principle and to keep the dosage form buoyant over the meal surface, the right level of floating force (F) must also be present, along with minimum levels of gastric contents. A novel method for calculating resultant weight (RW) has been described in the literature as a way to measure the kinetics of the floating force. Its method of operation involves measuring a force that keeps the object submerged and is equal to F (with respect to time). If RW is on the item, it floats better.

RW or F = F buoyancy – F gravity = (Df – Ds) gV Where,

F= total vertical force

Df = fluid density, Ds = object density, V = volume and g = acceleration due to gravity

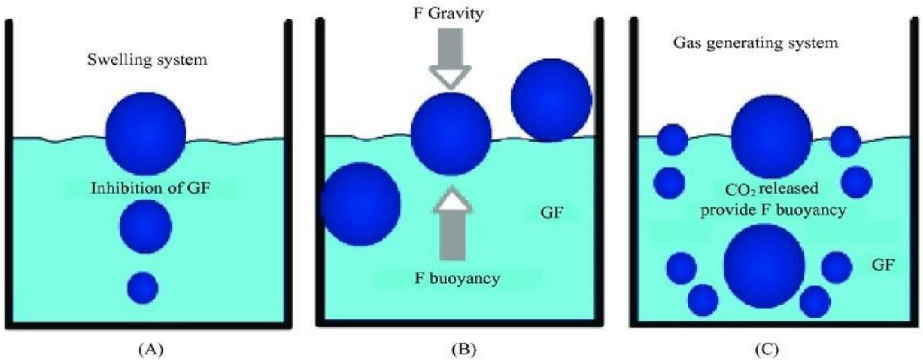
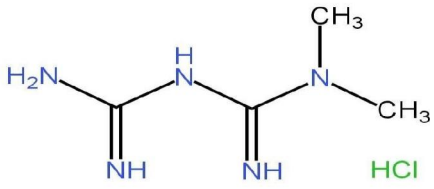


Figure 3: (Mechanism of FDDS, GF: Gastric Fluid, CO_2: Carbon Dioxide)

Drug and Excipients Profile [4]:

Drug name: Metformin Hydrochloride

Chemical structure:



Metformin Hydrochloride

Figure 4

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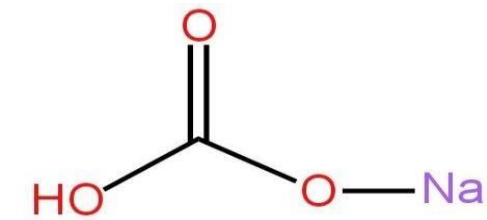
Molecular formula: $C_4H_{11}N_5$, HCl
Molecular weight: 165.6gm/mole
IUPAC name: 1, 1-Dimethyl biguainide Hydrochloride
Description: A white, odorless, crystalline powder, bitter taste, hygroscopic.
Solubility: freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone
Melting point: 225˚C
Storage: it stored in an airtight container, protected from sun light.
Therapeutic uses: It is used to treat type -2 diabetes mellitus.
Excipients:-
Sodium Bicarbonate Chemical Structure:-

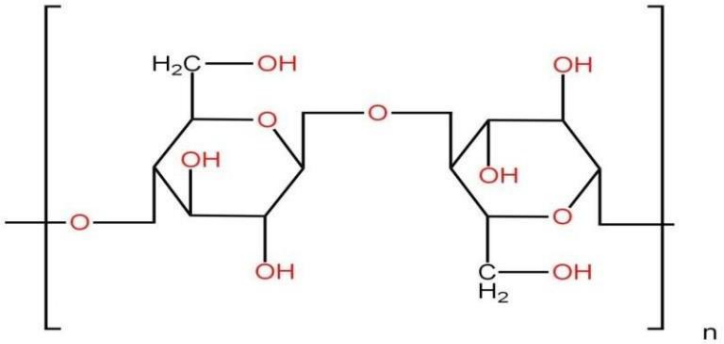


Sodium Bicarbonate

Figure 5

Molecular formula:-$NaHCO_3$ **Molecular Weight:-**84.007g/mol
IUPAC Name:-Sodium Hydrogen Carbonate.
Description:-Odorless white crystalline powder or lumps, basic in nature, non- flammable, slightly alkaline taste.
pH:-8.3
Solubility:-Sparingly soluble in water, insoluble in organic solvent.
Melting Point:-50˚C **Boiling Point:-**851˚C
Storage:-Tightly closed container and placed in a cool, dry, well-ventilated area.
Use:-to relieve heart burn. Sour stomach, or acid indigestion, antacid.

HPMC K100m
Chemical Structure



HPMC K100

Figure 6

Molecular formula:-$C_{56}H_{108}O_{30}$ **Molecular Weight:-**1261.4
IUPAC Name:-HPMC hydroxypropylmethylcellulose HYDROXY PROPYL METHYL CELLULOSE (Hydroxypropyl) methyl cellulose
Description:-White solid, ash content (‰); ≤10, odorless **pH:-**6-7

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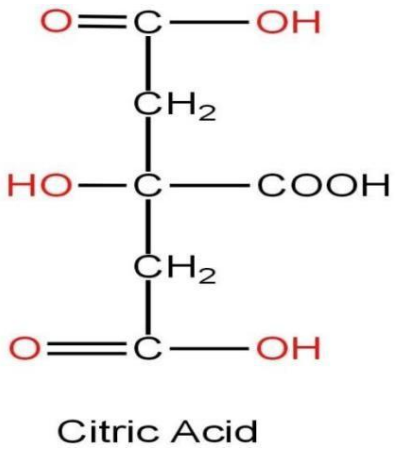
Solubility:-water soluble, practically insoluble in hot water, in acetone, in ethanol, in ether, Toluene and in chloroform
Melting Point:-225-230˚C
Boiling Point:-1101.5˚C
Storage:-Keep in a dry place, store indoors, store in closed container, store away from sources of heat and ignition.
Uses:-widely use as rate controlling polymer in hydrophilic matrices for oral ER drug delivery, emulsifier, thickening and suspending agent similar to animal gelatin.

Citric acid Chemical Structure:

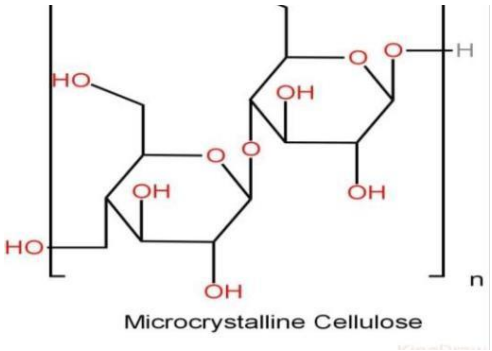


Citric Acid

Figure 7

Molecular formula:-$C_6H_8O_7$ **Molecular Weight:-**192.124g/mol
IUPAC Name: - 2-hydroxypropane-1, 2, 3- tricarboxylic acid
Description:-odorless, sour in test, appear as white crystalline solid **pH:-**3-6
Solubility:-soluble in water, acetone, dimethyl sulfoxide, ethyl acetate, insoluble in alcohol
Melting Point:-153˚C
Boiling Point:-310˚C
Storage:-store in tightly closed original container in a dry, cool and well ventilated place .
Uses:-As flavoring and antioxidant. And also used as preservatives.

Microcrystalline Cellulose Chemical Structure:



Microcrystalline Cellulose

Figure 8

Molecular formula :-$(C_6H_{10}O_5)$ n
Molecular Weight:-370.35
IUPAC Name: - 4-0-[(1S)-hexopyranosyl]-D-glcero- hexopyranose
Description:-fine, white or almost white, odorless, free flowing powder

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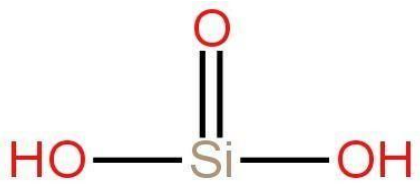
pH:-5.0-7.5
Solubility:-Practically insoluble in water, in acetone, in anhydrous ethanol, in toluene, in dilute acids and in a 50g/L solution of Sodium hydroxide.
Melting Point:-76-78˚C **Boiling Point:-**667.9˚C
Storage:-store in dry, cool and well-ventilated area and away from incompatible material and keep in well closed container, protected against physical damage
Uses:-Emulsifier stabilizer and anticaking .

Talc
Chemical Structure



Talc
Figure 9

Molecular formula: - $H_2Mg_3O_{12}Si_4$
Molecular Weight:-379.29g/mol
IUPAC Name:-tries (Oxo magnesium) tetrakis (silanedione) hydrate **Description:-**Translucent to opaque, with colors ranging from whitish Grey to green with a vitreous and pearly luster **pH:-8**.5-10.5
Solubility:-Insoluble in water and slightly soluble in dilute mineral acid
Melting Point:-1500˚C **Boiling Point:-**900˚C
Storage:-keep the product dry and in closed containers and store in a cool and well ventilated place **Uses:-**To absorb moisture, prevent caking, and improve it's consistency . And also used as lubricant for opaque .

III. MATERIAL AND METHODOLOGY

Materials:-
Metformin HCL was supplied by research lab Scientific, HPMC K100m, Citric acid, Nacho, Microcrystalline cellulose, Talc are supplied by AG Trader.

Sr. No	Ingredient	Quantity Taken
1.	Metformin HCL	500mg
2.	HPMC K100m	166mg
3.	NaHCO3	230mg
4.	Citric Acid	10mg
5.	Microcrystalline Cellulose	7mg
6.	Talc	7mg

Table 1

Wet granulation method [5]**:-**
Wet granulation form the granule by binding the powders together with an adhesive, instead of compaction. Wet granulation technique employs a solution, suspension or slurry containing a binder which is usually added to powder mixture however the binder may be incorporated dry into the powder mixture; however binder may be incorporated dry into powder mix and liquid may be added by itself.
Since in general, the mass should merely be moist rather than weight or pasty, there is a limit to amount of solvent that may be employed.

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When a large quantity is required, the binder is usually dissolved in liquid. The solubility of binder also has an influence of on the choice of methods, since the solution should be fluid enough to disperse readily in the mass.

If the ball crumbles under moderate pressure, the mixture is ready for the next stage in processing, which is wet screening.

The wet screening process involves converting the moist mass into coarse, granular aggregates by passage through hammer mill or oscillating granulate, equipped with screens having large perforations. Overly wet material dries slowly and forms hard aggregates, which tend to turn to powder during subsequent dry milling . Wet granulation is very important when we are making tablet , it is very

.used technique for tablets .And also on the time when the granules reach the desired properties such as granule size distribution , or bulk density , as stipulated by the formulator . A drying process is required in all wet granulation procedures to remove the solvent that was used in forming the aggregates and to reduce the moisture content to an optimum level of concentration within the granules. During drying, inter particulate bonds result from fusion or re-crystallization and curing of binding agent. After drying, the granulation is screened again. The size of screen depends upon the grinding equipment used and the size of tablet to be made.

Procedure:

Floating tablets were prepared by effervescent technology. Each floating tablet containing metformin HCl 500mg was prepared by conventional wet granulation method employing sodium bicarbonate and citric acid as gas generating agent.

Weighed quantities of all the ingredients were sifted through stainless steel sieve no 40 .

Sifted materials were dry mixed in geometric dilution by spatulation without addition of magnesium stearate and talc.

Distilled water was added to dry -mixed blend of drug and excipients, slowly add the wet mass was mixed to get desired doughy consistency.

The doughy mass passed through stainless steel sieve no 16 to form granules .

Granules were dried in hot air oven at 50 degree celsius (it is intense heat) for 30 minute and mixed with lubricant magnesium stearate and glidant talc.

The lubricated granules were compressed on a 10 station tablet mini press using a 13 mm flat punch.

Compression force adjusted to obtained hardness in the range of 3 -5 kg/cm² .

Figure no : 10 Direct Compression (Tablet Punching Machine)

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Experimental Work:-

Preformulation:-

The angle of repose of the granules was determined by using funnel method. Bulk density (BD) and tapped density (TD) were calculated by formula

Angle of Repose:-In this method of determination of angle of repose in which the angle of repose is to pour water the powder a conical on a level, flat surface and measure the included angle.

$$\tan\theta = \frac{h}{r}$$

Where, θ- Angle of Repose h-Height of the powder cone

r-Radius of the powder

= 21.13

Bulk Density[7]**:-** In this method Amount of is weighed separately and transferred into 100 ml of measured cylinder, initial volume of Powder material is measured and calculated bulk density according to the following formula,

$$\text{Bulk Density} = \frac{Weight\ of\ the\ powder}{Bulk\ Volume\ of\ powder}$$

= 0.61 gm/cm3

Tapped Density[8]**:-**Tapped Density is important evaluation parameter is determined by placing a graduated cylinder containing a known mass of powder undergoes tapping in manually (100 tapes) as well as using a Mechanical apparatus under powder bed volume has reached a minimum volume

.Tapped Density is calculated by formula $\text{Tapped Density} = \frac{weight\ of\ the\ powder}{Tapped\ Volume\ of\ powder}$

= 0.78 gm/cm3

Compressibility index and Hausner's ratio of the granules was determined by using the formula:

Compressibility Index [9, 10]**: -**It's calculation is based on the Tapped Density and Bulk density. It is a ratio of Tapped density and bulk Density i.e., Compressibility Index

$$\text{Compressibility Index} = \frac{\rho t - \rho 0}{\rho t} \times 100$$

= 4.91 %

Where ρ0=bulk density g/ml

ρt=tapped density g/ml

Hausner's ratio: $= \frac{tapped\ densit}{bulk\ density}$

= 1.27

Evaluation parameters:-

Non official test [6]

Hardness test:-

A tablet was placed vertically on the Monsanto hardness tester and then load was then applied along the radial access of tablet.

The load required for breaking the tablet was noted down

Result

:- 8 kg

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Figure no : 11 (Monsanto hardness tester)

Friability test: - it was performed by using Roche friabilator. 10 tablets were weight and placed in apparatus then apparatus was roated at 25 rpm as (Revolution per minute) . Friability test show us hardness of tablets , it is very necessary , when tablet is formulated and completely ready , then this test show us our raw material quality and tablet survival chance in certain cases , this test show us tablet durability.

Result :- 0.5 %

Figure 12

Roche friabilator
Thickness:-
Result :- 0.5 cm
Official test
Weight variation: - 20 tablet were taken and were weight using high precision weighing machine **Weight variation = (IW - AW)/AW ×100**
Where,
IW: Individual weight AW: average weight
Result :-0.50

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Disintegration test:-

Introduce one tablet in each tube operate the apparatus using the water as immersion fluid maintained at 37±2℃.

At the end of disintegration time lift the basket and observe the tablet. **Result**:-15min

Figure no : 13 (Disintegration apparatus)

Dissolution test [11]**:-**

Procedure: Add medium 900ml 0.1N HCL buffer pH 1 in a vessel and maintain temp. Of medium up to 37±0.5˚C.

Speed and time 50rpm and 30minute .

Withdraw 1ml sample and add 1ml fresh HCL buffer to maintain sink condition. Filter and dilute a suitable volume of filtrate with same solvent.

Measure the absorbance of the resulting solution at the maximum at about 233nm. About 93-99% of the drug was released in 8 hours .

Figure no : 14 (Dissolution apparatus)

Total Floating Time (Floating Lag Time):-The one tablet is added into 100 ml of pH 1 Acidic buffer in beaker (The Tablet is float in pH acidic buffer) and calculated total floating time of the tablet. In case **Metformin HCL tablets Total Floating Time is 10 minute .**

Figure no : 15 (Floating Lag Time)

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Result:- A) Preformulation Data:-

1.	Angle of Repose	21.13
2.	Bulk Density	0.61gm/cm³
3.	Tapped Density	0.78gm/cm³
4.	Compressibility Index	4.91%
5.	Hausner Ratio	1.27

Table No:-2

Non-official Test:-

1.	Hardness	8 Kg
2.	Friability	0.5 %
3.	Thickness	0.5 cm

Table No:-3

Official Test:-

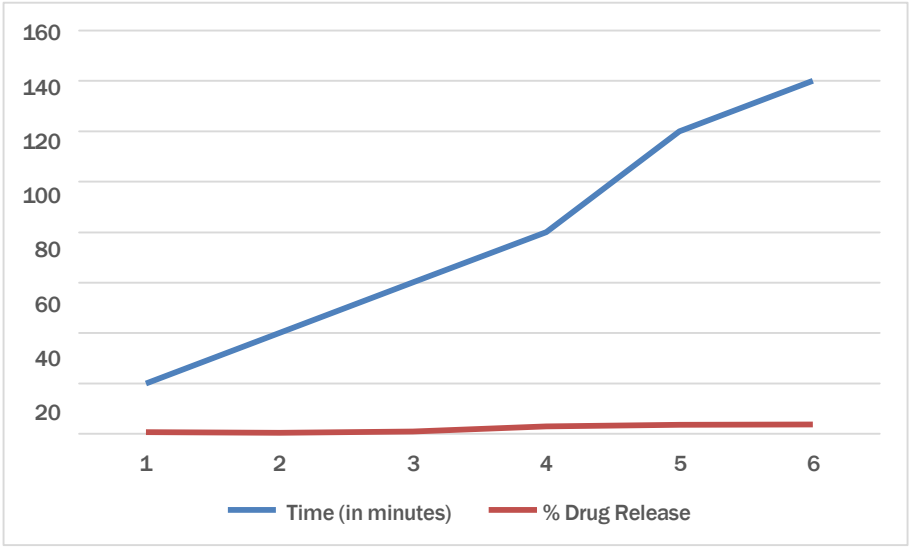
1.	Weight Variation	0.50
2.	Disintegration Test	15 min

Table No:-4

Dissolution Test:

Sr. No.	Time (in minutes)	% Drug Release
1.	20	0.715
2.	40	0.374
3.	60	0.883
4.	80	3.092
5.	120	3.627
6.	140	3.735

Table No:-5



GRAPH:-1 (Time vs % Drug Release)

Figure no : 16 (Dissolution Profile of Metformin Hydrochloride Tablets)

Above graph Time vs % Drug Release shows linearity.

The % Drug Release is increase with respect to time. About 93-99% of the drug was released within 8 hours.

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Total Floating Time (Floating Lag Time):-

Metformin Hydrochloride Tablet show Total floating Time is get 10 minutes

IV. CONCLUSION

The wet granulation method is used to create the Metformin HCL floating Tablet, which has density below 1.The Tablet as both effervescent and non-effervescent mechanism and is gastro retentive floating sustained releasing. The floating (non effervescent system) is caused by the HPMC K100m swellable polymer, the effervescent system is caused by Sodium bicarbonate and Citric acid. The outcome shows, weight variation and friability parameters. The In-vitro dissolution studies show demonstrate of the drug highest percentage of release.

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