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PREPARATION AND EVALUATION OF MULTIPURPOSE METFORMIN HCL GASTRO RETENTIVE DRUG DELIVERY TABLET

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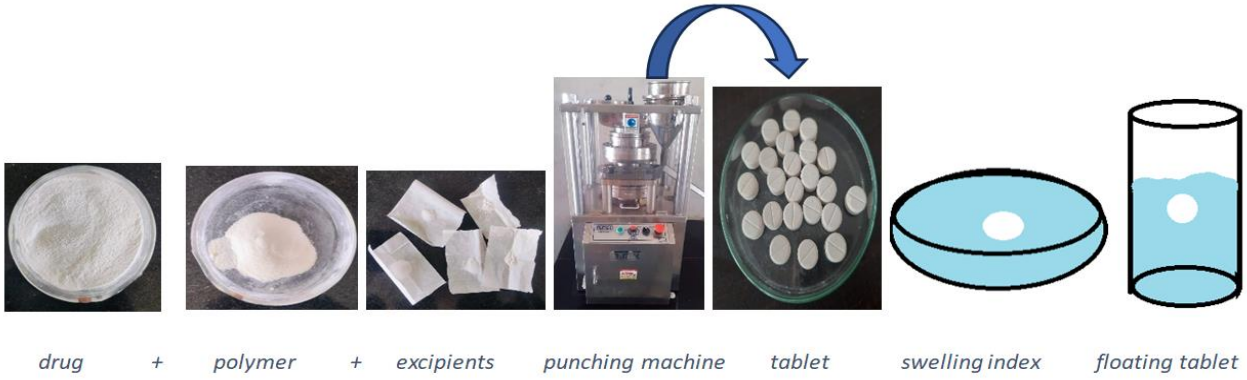
ABSTRACT

Due to its rapid intestinal transit and poor absorption in the upper gastrointestinal tract, metformin, a first-line oral treatment for Type 2 Diabetes Mellitus, has a low bioavailability (~50–60%). Using floating drug delivery system (FDDS) technology, a Gastroretentive drug delivery system (GRDDS) was developed to address these problems. To make tablets that float in stomach fluids, hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC K4M) were combined with gas-generating substances like citric acid and sodium bicarbonate. Pre-compression parameters, tablet hardness, and floating lag time were assessed for three formulations (F1–F3). F2 had the best qualities of all of them, including regulated drug release (88.2% over 12 hours), prolonged floating duration (>12 hours), and quick buoyancy (1.6 min). The study found that by keeping the medication in the stomach for a long time, floating metformin tablets present a promising strategy for enhancing therapeutic efficacy, patient compliance, and treatment outcomes for diabetes control.

KEYWORDS: Gastro retentive drug delivery system (GRDDS), floating drug delivery system (FDDS), Metformin, patient compliance, Type 2 Diabetes Mellitus.

Graphical Abstract

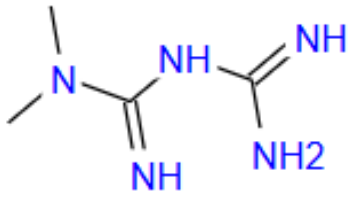


INTRODUCTION

One common oral drug for treating Type 2 Diabetes Mellitus is metformin. Its limited absorption in the upper gastrointestinal tract, which makes it extremely hydrophilic, is the main reason for its low bioavailability of about 50–60%. Due to its short half-life (about 4–6 hours) and quick passage through the small intestine, frequent dosing is required, which could have an impact on patient compliance. The development of a GRDDS is recommended as a remedy for these issues. Given that drugs can remain in the stomach region for several hours, gastro retentive mechanisms can significantly lengthen the duration of a drug's stomach residence. Long-term stomach retention improves the solubility of drugs that are less soluble in high pH settings, decreases drug waste, and boosts bioavailability.[18] Significant patient benefits and new therapeutic options will be provided by gastric retention. One drug for Type II Diabetes Mellitus that lowers blood sugar levels by acting as an antihyperglycemic is the Metformin HCL Tablet. The oral sustained-floating tablet form of metformin HCL is made by the wet granulation process. This specific tablet is made to float either inside or on top of a liquid medium. The GI (Effervescent system) comes into touch with the floating tablet with density less than 1 and the tablet with both an effervescent and non-effervescent system, where the non-effervescent system's swellable polymer, like HPMC K 100, is what makes the tablet float. There is fluid effervescence. The tablet floats and the drug's bulk are decreased. This tablet is designed to be used for extended periods of time and sustained exercise.[1,2]

❖ **Metformin Hydrochloride**

- **Molecular formula:** $C_4H_{11}N_5$
- **Molecular weight:** 165.62gm/mol
- **Melting point:** 223°c - 226°c
- **Log P Value:** 0.5



❖ **Advantages[3]**

- Enhance product safety.
- Improved Efficacy.
- Improved patient compliance.[22]
- Lower blood sugar level.
- Decrease lipid level.
- Inexpensive.

❖ **Disadvantages[4]**

- Crosses the placenta.
- Stomach ache.
- Loss of appetite.[21]
- A metallic taste in mouth.

❖ **Materials**[17]

Table 1: Materials.

Ingredients	Function
Metformin HCL	API
HPMC K4M	Swelling & sustained release polymer
Sodium bicarbonate	Gas generating agent
Citric acid (anhydrous)	Gas generating agent (acidic sour
Maize starch	Disintegrant + binder
Starch (for paste)	Binder (paste form, 10% w/v)
Microcrystalline cellulose (MCC)	Diluent
Magnesium stearate	Lubricant

❖ **Formulation table**[20]

Table 2: Formulation table.

Ingredients	Qty for/tablet (mg) F1	F2	F3
Metformin HCL	500	500	500
HPMC K4M	80	70	80
Sodium bicarbonate	60	65	60
Citric acid (**anhydrous**)	10	15	10
Starch (for paste)	paste form	paste form	paste form
Microcrystalline cellulose (MCC)	35	35	35
Magnesium stearate	5	5	7.5
Talc	5	5	7.5
Total	725mg	725mg	725mg

❖ **Preparation of granules**[5]

- Weigh the necessary quantities of Metformin, HPMC K4M, Sodium bicarbonate Citric acid, MCC.
- In a mortar, evenly blend all dry ingredients.
- Make a wet granulation mixture by adding starch paste into it.
- Run a damp mixture through a 16-no. sieve to form granules.
- A hot air oven set at 40°C & dry the granules.

❖ **Preparation of Floating Tablet**[6]

- For 10 minutes, mix the dry granules.
- Add talc as glidant & magnesium stearate as a lubricant.
- Pass the mixture through 40 no. sieve to make fine powder.
- Compress the fine powder into tablet by using rotatory tablet punching machine.

❖ **Evaluation parameters**

1. Pre-Compression Parameters

➢ **Bulk Density:** It is a ratio of weight mass and Bulk Volume is known as Bulk Density.[16]

Bulk density = Mass / Volume[8]

➢ **Tapped Density**: It is a Ratio of weight Mass and Tapped Volume is known as Tapped Density. To evaluate the compressibility of powder.[19]

Tapped density = Powder weight / tapped volume of Powder[9]

- **Carr's Index:** It is a ratio of Tapped density and Bulk Density i.e. Carr's Index. To assess the granules' flow ability.[9]
- **Angle of Repose:** It defines as the Pile surface of Powder is known as Angle of Repose. To determine the flow properties.[9]

$$\text{Tan } \theta = h/r$$

Where,

- θ - Angle of repose,
- h - Height of the powder cone,
- r - Radius of the powder cone

- **Hausner ratio:** The Hausner ratio is the proportion of tapped density to bulk density.[9]

Table 3.

Formulation	F1	F2	F3
Bulk density (g/cm^3)	0.44	0.43	0.45
Tapped density (g/cm^3)	0.50	0.49	0.51
Carr's index (%)	12.00	12.2	11.8
Angle of repose (^{o})	25.4	27.7	24.9
Hausner ratio	0.8	0.8	0.8
Result	Fair	Fair	Fair

- ✓ **Bulk density:** It is important parameter for determination of flow characteristic in which the Bulk Density of Metformin HCL is reported in Table 3.
- ✓ **Tapped Density:** It is important parameter for determination of flow characteristic in which the Tapped Density of Metformin HCL is reported in Table3.
- ✓ **Carr's Index**: Values below 15% indicate good compressibility.
- ✓ **Angle of Repose:** Good flow characteristics are indicated by values less than 30°. The flow characteristics of each formulation are reasonable.

2. **Post-Compression Parameters:** The following post-compression parameters are measured[10]

- **Weight variation test:** The USP weight variation test is carried out by weighing each of the 20 tablets separately, determining the average weight, and comparing the weight of each tablet to the average. The following formula is used to calculate the weight variation percentage.[11]

$$\text{Weight variation} - [I_W - A_W / A_W] \times 100$$

Where,

- I_W - Individual weight of the tablet,
- A_W-Average weight of the tablet.

- **Thickness and Diameter:** Using a thickness gauge Vernier calliper. The diameter and thickness of the tablets were measured. Average values were computed using five pills from each batch.[11]
- **Tablet Hardness:** The hardness test involved measuring five tablets of each formulation**.** A Hardness Tester type Monsanto was used to assess the hardness. Typically, between 5-8 kg/cm² using a hardness tester.[12]
- **Friability Test**: Using a friability tester, the friability of 6 tablets was tested. Six pills from each formulation were weighed and tested for four minutes at a speed of 25 rpm. The tablets were reweighed after removal, and the friability % was measured.[23]

- **Floating Lag Time:** The time it takes for the tablet to rise to the surface of the dissolution medium.[13]
- **Total Floating Duration**: The amount of time the tablet stays afloat.[14]
- **Swelling Index:** The pill is submerged in distilled water, and the expansion is measured to get the Swelling Index.[14]
- ***In Vitro Drug Release*:** A USP Type II dissolution equipment was used in 12-hour research with Ph 6.8 Phosphate Buffer as the dissolution medium.[15]

Table 2.

S. No	Evaluation tests	F1	F2	F3
1	Weight variation (%)	±2.1	±2.2	±2.4
2	Thickness(mm)	±9.55	±9.61	±9.56
3	Tablet Hardness (kg/cm²)	8.2	9.8	9.9
4	Friability (%)	0.66	0.22	0.88
5	Floating Lag Time (min)	1.8	1.6	2.00
6	Total Floating Duration (hours)	>12	>12	>12
7	Swelling Index (%)	152	135	150

- ✓ **Weight Variation:** Ensures uniformity in weight. Variations ranged between ±2.1% to ±2.4%, which is within the acceptable limits. The Weight Variation of tablet is reported in table4.
- ✓ **Tablet Hardness:** Indicates how strong the tablets are. Good mechanical integrity was indicated by the excellent hardness of all formulations, which ranged from 6.5 to 7.1 kg/cm². The hardness of tablet is reported in table 4.
- ✓ **Friability:** The Friability of tablet is always less than 1% and the friability of Metformin HCL is reported in Table 4.
- ✓ **Floating Lag Time:** The amount of time needed for the tablet to begin floating is known as the "floating lag time." F3 had the longest lag time (2 min), whereas F2 had the smallest (1.6 min), suggesting quick buoyancy.
- ✓ **Total Floating Duration:** Every formulation showed good floating behaviour, remaining buoyant for over 12 hours.
- ✓ **Swelling Index:** This measures the expansion of the tablet. F3 had the highest swelling index (150%), while F1 had the lowest (125%).
- ✓ ***In Vitro Drug Release*:** The In vitro drug release studies of Metformin HCL Floating tablet is determined in Ph 6.8 phosphate buffer, in which Avg.97.74% drug releases at the end of 12 hours. And the in vitro drug released of Metformin HCL is reported in Table 5 and the in vitro drug released shown in Figure 1.

Table 3: In vitro drug release.

Time (hour)	F1	F2	F3
1	16.5	17.5	15.3
2	20.23	22.3	24.61
3	35.23	40.52	38.56
4	45.52	50.12	48.56
5	55.89	57.65	59.61
6	62.52	64.52	68.23
8	84.56	86.80	88.59
12	95.56	99.25	98.42

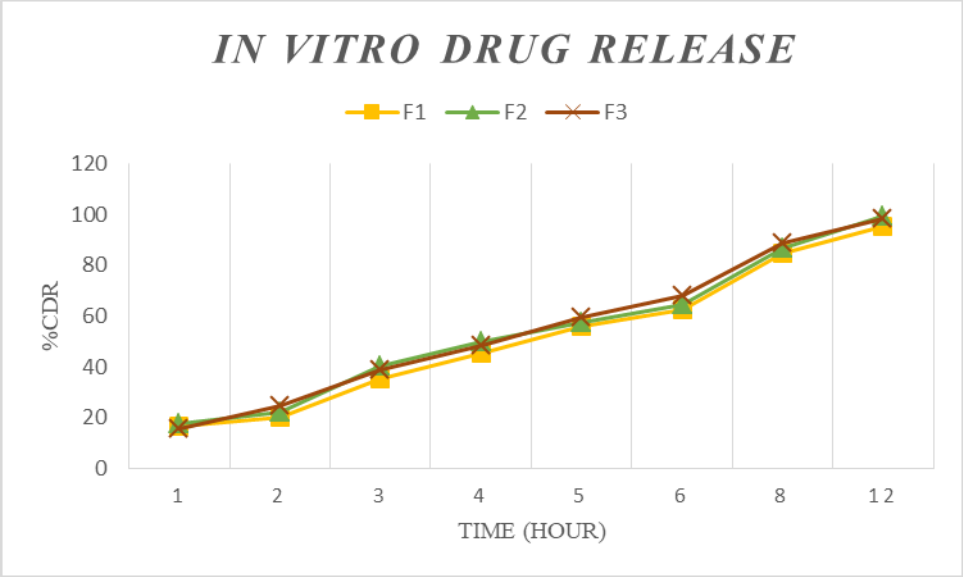


Figure 1: In vitro drug release.

CONCLUSION

The formulation and assessment of metformin HCl tablets with an emphasis on attaining ideal physicochemical characteristics, regulated drug release, and improved stomach retention were successfully demonstrated in this work. The final formulation demonstrated desirable properties such as acceptable hardness, low friability, short floating lag time, prolonged floating duration, and a sustained drug release profile that complied with pharmacopeial standards, all of which were achieved through systematic optimization of excipients, especially polymers like HPMC and effervescent agents. The resilience of the formulation under accelerated settings was confirmed by the stability data. According to these results, the proposed formulation may be a promising gastro-retentive delivery strategy for metformin HCl, which could enhance glycaemic control and patient compliance in the treatment of type 2 diabetes.

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