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A Formulation and Characterization of Metformin Loaded Floating Tablet by Using Natural Polymer

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ABSTRACT: ***Diabetes is a chronic metabolic disease characterized by high glucose level in the blood. Sustain release gastro retentive dosage forms enable prolonged and continuous input of the drug to the upper parts of gastrointestinal tract and improve the bioavailability of medication that is characterized by narrow absorption window. Gastro retentive floating drug delivery system of metformin HCL, an anti-diabetic drug with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating tablet by direct compression technique, by using Guar gum as release retardant, and $NaHCo_3$ as gas generating agent to reduce floating lag time. Floating tablet were evaluated for hardness, Friability, Weight Variation, Drug content, Floating properties and In-vitro release pattern.***
Keywords: Floating Tablet, Metformin HCl, Direct compression, Guar-gum.

INTRODUCTION

Controlled release dosage form may be defined as a dosage form that releases drugs continuously either systemically or locally, in a predetermined rate for a fixed period of time, to specified target organ to obtain rapid and complete absorption of the drug.

The relatively brief gastric emptying time in humans which normally averages 2.5-3 hours through the major absorption zone, i.e. stomach & upper part of the intestine can result in incomplete drug release from the drug delivery system (DDS) leading to reduced efficacy of the administered dose. Therefore, control of the placement of a DDS in a specific region of the GIT. The CRDDS possessing the ability to be retained in the stomach are called gastro retentive drug delivery system (GRDDS). They can help in optimizing the oral controlled delivery of drug having 'absorption window' by continuously releasing drug having prior to absorption window, for a prolonged period of time thus ensuring optimal bioavailability.

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Gastroretentive techniques: The numbers of techniques have been used to increase the Gastro retentive time of dosage forms by a variety of concepts such as floating, swelling, and adhesion. These systems have been classified according to their basic principle of gastric retention.

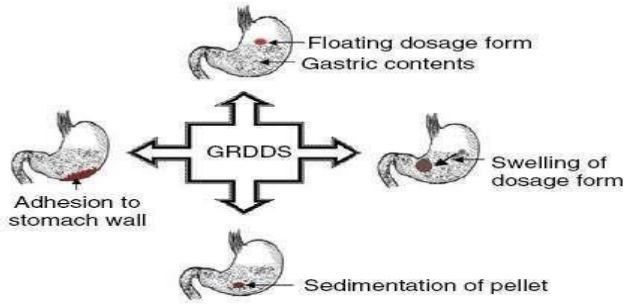

Figure no.1: Classification of GRDDS

Floating systems, first described by Sir Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents & remain in the stomach for a prolonged period. FDDS have bulk density less than gastric fluids so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

If the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time (GRT) & a better control of the fluctuations in plasma drug concentration.

The Floating drug delivery system is classified as:

1. EFFERVESCENT FLOATING DOSAGE FORMS

The effervescent floating dosage forms are matrix dosage form which is prepared by swellable polymers such as methylcellulose and chitosan and various effervescent compounds like sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when the acidic gastric contents comes in the contact with it, Co_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

2. NON-EFFERVESCENT FDDS:

The non-effervescent floating dosage forms are prepared by excipients which are gel forming cellulose like hydrocolloids, polysaccharides & matrix forming polymers such as

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polycarbonate, polyacrylate and polystyrene. One of the floating formulations is a gel-forming hydrocolloid in a capsule, which swells when it comes in the contact with gastric fluid after oral administration & maintains a relative integrity of shape & a bulk density of less than unity within the outer gelatinous barrier.

The air trapped by the swollen polymer confers buoyancy to these DFs. When such dosage forms comes in contact with an aqueous medium, the hydrocolloid starts to hydrate by forming a gel which controls the drug-out of the DF.

Advantages of Floating Drug Delivery Systems FDDS:

- Enhanced bioavailability of the drug.
- Decreased adverse activity at the colon.
- Site specific drug delivery.
- Reduced frequency of dosing.
- Avoidance of gastric irritation.
- Enhanced absorption of drugs.

Limitations of FDDS:

- One of the major disadvantages of floating systems is the requirement of high levels of fluids in the stomach for the delivery system to float & work efficiently.
- These systems also require the presence of food to delay their gastric empting.
- Drugs which are irritant to gastric mucosa are also not suitable for such dosage forms.
- Drugs that may cause gastric lesions are not suitable. E.g. Non-steroidal anti-inflammatory drugs.

Applications of Floating Drug Delivery System:

- Sustained delivery of the drug.
- Site-specific drug delivery.
- Absorption enhancement.
- Enhanced bioavailability.
- Reduced frequency of dosing.
- Reduced fluctuations of drug concentration.

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MATERIAL AND METHOD

The polymer (Guar-gum) was procured from BRD pvt ltd and other excipients were procured form different sources like HPMC K15 M (Rankem Laboratory, New Delhi), Guar Gum from (Chemdyes Corporation, Rajkot), Sodium bicarbonate from (Rankem Private Limited, Mumbai), Tartaric acid from (Oxford Laboratory Private Limited, Mumbai), Di calcium phosphate, talc, magnesium stearate from (Oxford Laboratory Private Limited, Mumbai).

THE METHOD OF PREPRATION OF METFORMIN LOADED FLOATING TABLETS

Sustained release floating tablets were prepared by direct compression method. For the preparation of tablets, all the ingredients were weighed accurately and were screened through sieve #40. Metformin and other polymers were mixed in a poly bag for 15 minutes, followed by the addition of diluent and further mixed for 5-10 minutes. Finally talc and magnesium stearate were added to the previous blend and mixed it again, for uniform distribution. Then the tablets were compressed by using 6-station Rotary tablet punching machine with 14 mm oval shape punches. Each tablet contains 500 mg of Metformin and the weight of the tablet is 700 mg.

In-vitro characterization

- **Weight variation:** The USP weight variation test is perform by weighing 20 tablets collectively and individually, calculating the average weight.
- **Tablet Hardness:** The hardness of the tablet is calculated by Monsanto hardness tester. The hardness was calculated in unit of kg/cm^2.
- **Friability:** Friability is the measurement of mechanical strength of Tablets. Roche friabilator was used for friability with the following steps. The pre-weighed 20 Tablets revolved at 25 rpm speed for 4 minutes. Further dropped from the distance of 6 inches. The Tablets are dusted and reweighed, & calculated as

$$\% \text{ Friability} = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 100$$

- **Drug Content:** The drug content was carried by weighing 20 tablets and calculated the average weight. The ten tablets were triturated to get a fine powder. From the resulting weighed accurately about 100 mg of the powder metformin HCl was taken, shake with 70 ml of water for 15 minutes, dilute to 100 ml with water and filter. Taken 10 ml of the filtrates and dilute to 100 ml with water. Further dilute 10 ml to 100 ml with water and measure the absorbance at the maximum at about 233 nm.
- **Buoyancy Determination:** The buoyancy was determined by one tablet from each formulation batch was placed in USP type II dissolution apparatus containing 900 ml

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0.1N HCl dissolution medium using paddle at a rotational speed of 75 rpm. The temperature of medium was maintained at 37℃ ±2℃. The time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remain on the surface of medium was noted.

- **In vitro drug release studies:** The release rate of metformin from floating tablets was determined using USP dissolution test apparatus II (Paddle type).
  The dissolution test was performed using 900 ml 0.1N HCl, at 37℃ ±2℃. One tablet was placed in each dissolution vessel and the rotational speed of the paddle was set at 50 rpm. After regular interval 10 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced. The sample were analysed for drug content against dissolution media as a blank at 233 nm using UV visible spectrophotometer.
- **Quantitative estimation of drug:** Accurately weighed quantity of metformin hydrochloride (50 mg) was dissolved in little quantity of 0.1 N HCl solution and volume was made up to 100 ml. Appropriate aliquots were taken into different volumetric flasks and volume was made with 0.1 N HCl solution so as to get drug concentrations of 5, 10, 15, 20, 25 µg/ml. The absorbances of these drug solutions were estimated at λ max 233 nm.
- **Drug-excipient interaction study by FTIR:** (Fourier Transform Infrared Absorption Spectroscopy) The successful formulation of a suitable and effective solid dosage form depends upon the careful selection of the excipients.
  It's necessary to study the compatibility of excipients with drug. Here FTIR spectroscopy was used to investigate and predict any physicochemical interaction between components in a formulation and to the selection of suitable compatible Excipients. FTIR studies were conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}.
  The procedure consisted of, dispersing a sample (drug alone, and mixture of drug and polymers in KBr and compressing into discs by applying a pressure of 7 tons for 5 min in a KBr press. The pellet was placed in the light path and the spectrum was obtained.

RESULTS AND DISCUSSION

The Tablets provide greater benefits floating in the upper part of the GI Tract, shows sustain drug release, reduce side effects, and reduces dosage frequency.

In the current study the attempts were made to provide sustain release the drug Metformin hydrochloride using natural polymer guar gum, the tablets were prepared with guar-gum.

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The preformulation studies of the drug were carried out for that the natural guar gum was taken to prepare the floating tablet of metformin with the other excipients like HPMC, sodium bicarbonate, tartaric acid, talc, and magnesium stearate. Batches were prepared by direct compression method.

These formulations were subjected to preformulation studies and various evaluation parameters like hardness, friability, tablet density, floating test, drug content and in vitro release studies.

Evaluation parameters viz. tablet dimensions, hardness, weight variation, friability and drug content were within acceptable limits for all formulations.

Buoyancy lag time, total floating time showed satisfactory results for batch F1 and F3. The F3 was optimized & selected for further studies. Since it had sustain activity good buoyancy leg time.

Results showed that 50mg guar gum provides a better option for control release action.

The formulation F1 containing Drug: HPMC shown cumulative percentage release of 98.55% at 8^{th} hr. But the objective of the formulation is to develop metformin tablet which sustain the release up to 12 hrs. Formulation F2 containing Drug: HPMC was increased showed 98.6% cumulative release at the end of 10^{th} hr. In the formulation F3 and F4 attempt was made to achieve the objective by incorporating Guar gum instead of HPMC. The formulation F3 containing Drug: Guar gum shown cumulative percentage release of 98.33% at 12^{th} hr. F4 formulation containing Drug: Guar gum, showed 98.3% cumulative release at the end of 11^{th} hrs. An attempt was made to optimize the release by using mixture of HPMC and Guar gum in different ratio. Formulation F5 containing combination of HPMC: Guar gum (2:1) showed cumulative percentage release of 98.47 % at 10^{th} hrs. Formulation F6 containing HPMC: Guar gum (1:2) showed 98.38% cumulative release at the end of 9^{th} hrs. Formulation F3 was found to achieve the objective. F3 had good sustained activity and optimized formulation F3 had better control release action and improve bioavailability.

SUMMARY

In the present work, an attempt has been made to formulate controlled release floating tablet of metformin HCl by using natural polymer which is used in the treatment of diabetes. FDDS were prepared using polymer guar-gum and drug by direct compression method. Guar gum meets all ideal characteristics to formulate the floating tablet. All the formulation were characterized on the basis of their evaluation studies. The drug excipients compatibility study were performed by FTIR spectroscopy. There was no interaction found between drug and excipient.

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Table no.1: Standard curve of Metformin HCl

Concentration (µg/ml)	Absorbance at 233 nm
0	0.000
5	0.112
10	0.211
15	0.321
20	0.435
25	0.535

Figure no.1: Calibration curve of Metformin HCl

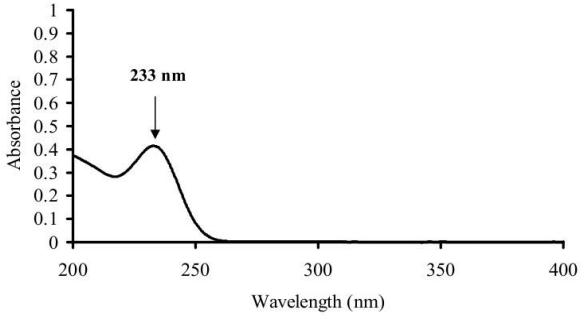

Table no.2: Different formulations containing varying proportions of excipients

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6
Metformin	500	500	500	500	500	500
HPMC K 15 M	50	75	-	-	25	50
Guar gum	-	-	50	75	50	25
Sodium bicarbonate	20	20	20	20	20	20
Tartaric acid	10	10	10	10	10	10
PVP-K-30	10	10	10	10	10	10

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Di calcium phosphate	100	75	100	75	75	75
Magnesium Stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total weight	700	700	700	700	700	700

Table no.3: Weight variation, Thickness, Hardness and friability

Formulation Code	Thickness ± SD (mm)	Hardness ± SD (kg/cm^2)	Friability (%) ± SD	Average weight variation ± SD
F1	4.30 ± 0.021	5.14 ± 0.041	0.513 ± 0.090	2.655 ± 0.124
F2	4.42 ± 0.034	5.28 ± 0.096	0.380 ± 0.044	4.516 ± 0.214
F3	4.51 ± 0.012	5.18 ± 0.013	0.485 ± 0.086	3.311 ± 0.154
F4	4.55 ± 0.001	5.11 ± 0.038	0.266 ± 0.027	2.963 ± 0.413
F5	4.23 ± 0.005	5.51 ± 0.052	0.385 ± 0.020	1.051 ± 0.622
F6	4.10 ± 0.011	5.27 ± 0.016	0.578 ± 0.04	2.922 ± 0.266

Table no.4: Drug content uniformity of metformin floating tablets

Formulation Code	Amount of Metformin HCl (mg)	%Drug content ± SD
F1	500	96.18 ± 0.005
F2	500	95.25 ± 0.003
F3	500	96.71 ± 0.004
F4	500	95.36 ± 0.005
F5	500	95.27 ± 0.004
F6	500	96.33 ± 0.005

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Table no.5: Floating lag time and total floating time

Formulation code	Floating lag time (min)	Total floating time (h)
F1	24.13 ± 1.12	7.35
F2	45.0 ± 1.03	8.10
F3	72.76 ± 2.18	12.17
F4	63.46 ± 0.27	10.30
F5	51.04 ± 2.05	11.11
F6	64.09 ± 1.1	10.08

Table no.6: In vitro drug release data of metformin floating tablets

S.No.	Time (hr)	% Cum. drug release					
		F1± SD	F2± SD	F3± SD	F4± SD	F5± SD	F6± SD
1	0	0	0	0	0	0	0
2	1	32.58±0.47	28.52±0.41	31.48±0.43	27.60±0.46	28.45±0.42	25.43±0.48
3	2	44.77±0.32	41.34±0.51	48.23±0.42	38.40±0.45	39.38±0.29	42.47±0.45
4	3	55.58±0.37	56.46±0.40	52.43±0.47	47.48±0.37	49.48±0.35	52.52±0.40
5	4	66.38±0.46	68.22±0.17	67.41±0.41	57.46±0.40	58.56±0.44	59.58±0.42
6	5	77.65±0.34	75.32±0.49	77.36±0.47	65.4±0.42	67.3±0.20	65.23±0.13
7	6	88.56±0.40	81.52±0.39	85.31±0.52	72.44±0.41	76.62±0.44	70.52±0.45
8	7	93.44±0.29	86.5±0.42	91.31±0.38	78.53±0.42	84.57±0.35	76.43±0.38
9	8	98.55±0.40	90.62±0.3	95.22±0.12	83.84±0.7	89.39±0.43	83.54±0.38
10	9	-	94.34±0.35	98.33±0.35	89.17±0.22	94.45±0.38	98.38±0.36
11	10	-	98.6±0.43	-	94.43±0.42	98.47±0.40	-
12	11	-	-	-	98.35±0.31	-	-
13	12	-	-	-	-	-	-

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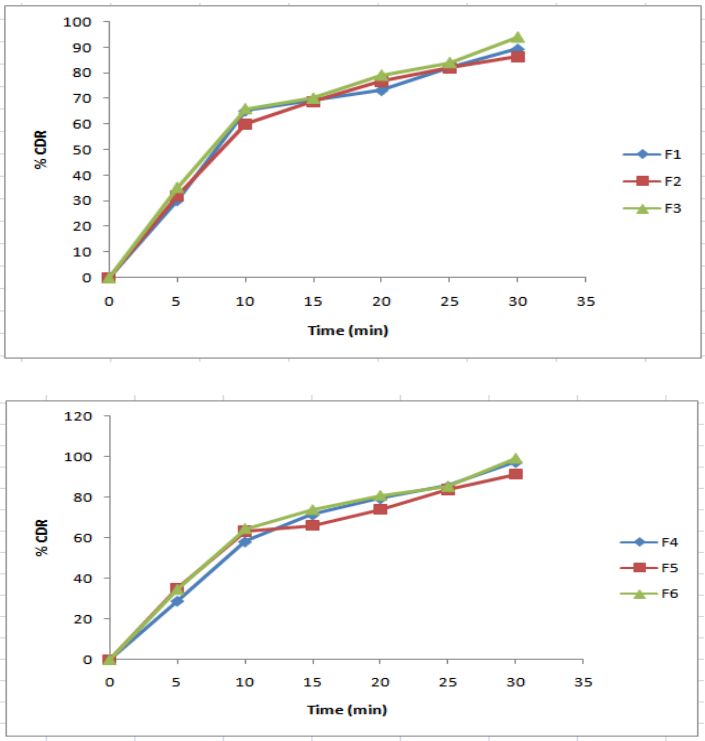
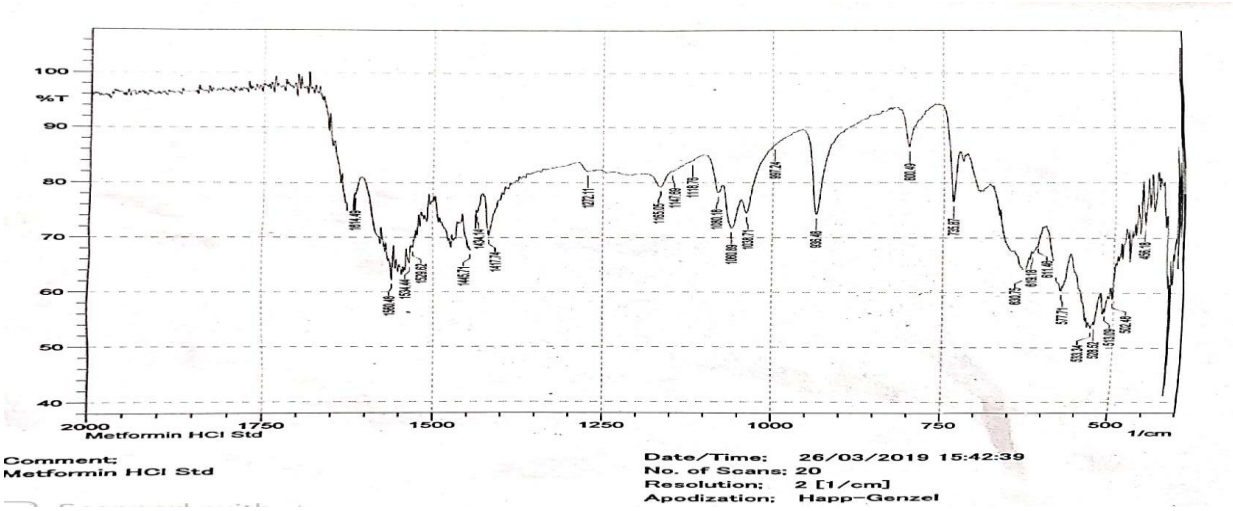
Figure no.3: Comparative In-vitro % Drug release profile for all the prepared formulation



FTIR Studies:

Figure no.4: FTIR Spectra of Metformin HCl



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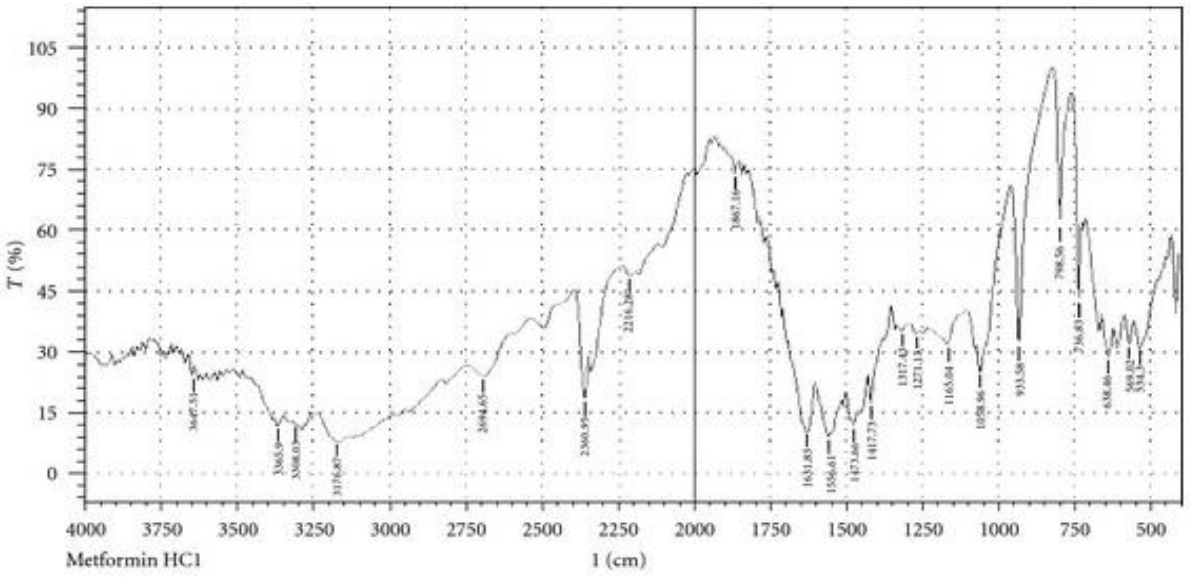
Sr. No.	Mode of bond vibration	Wave no. range (cm^{-1})
1	(CH3) 2N absorption	3000–3700
2	N–H bending	1500–1700
3	N-H deformation	1200–1500
4	C-N stretching	900–1300

Figure no.5: FTIR Spectra of Metformin HCl and Guar-gum



The drug-excipient compatibility and interaction was checked by the FTIR.

The drug with the various excipients were showed to be compatible with each other. This helps to know that there was no chemical interaction between the drug and excipients and are compatible in the formulation and characterization.

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CONCLUSION

In the current study the attempts were made to provide sustain release the drug Metformin hydrochloride using natural polymer guar gum, the tablets were prepared with guar-gum.

F3 had good sustained activity and optimized formulation F3 had better control release action and improve bioavailability.

