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DESIGN AND *INVITRO* CHARACTERIZATION OF GASRO RETENTIVE MUCOADHESIVE FLOATING TABLETS OF METFORMIN HCL

G.Jagadeesh[1*], Dr.Vijaya Kuchana[2]

[1]Research scholar, Department of Pharmaceutics, Norh East Frontier Technology University, Aalo (P.O), West Siang (Dist.), Arunachal Pradesh, India - 791001.

[2]Research Guide, Department of Pharmaceutics, Norh East Frontier Technology University, Aalo (P.O), West Siang (Dist.), Arunachal Pradesh, India - 791001.

Abstract:

In the present research work gastro retentive mucoadhesive floating formulation of Metformin was developed by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent accrual and bioadhesive polymer carbopol concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various polymers. 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 with HPMC K15M retarded the drug release up to 12 hours in the concentration of 220mg (F10).The formulations prepared with HPMC K4M and HPMC K100M released drug less than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order kinetics of drug release.

***Key words**: Gastro retentive, Mucoadhesive, Floating, HPMC etc.*

Corresponding Author:

G.Jagadeesh

Research scholar,
Department of Pharmaceutics,
Norh East Frontier Technology University,
Aalo (P.O), West Siang (Dist.),
Arunachal Pradesh, India - 791001.
Email ID: gjagadish04@gmail.com

QR code

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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 systems [1-5].

Significance of Floating Bioadhesive Dosage Form (FBDF) [6-10]:

Individual disadvantages of Floating dosage form & bioadhesive can be avoided if used a combination of both approaches as a Floating with bioadhesion at the time available the full gastric media in stomach will be dosage form float over the surface when stomach is empty at the time dosage form is adhere to the stomach mucosa prevent the passage of the stomach and dosage form is retained in stomach prolong period of time get the drug release in sustained manner.

Merits of FBDF:

1) It avoids disadvantages of the single gastroretentive drug delivery system by using the Combinational approach of floating with bioadhesive.
2) Decrease the frequency of drug administration.
3) Increase the desired residence of drug at the site of action mainly in the stomach.
3) Minimize the side effects.
4) Minimize the cost of treatment.
5) Improvement of patient compliance.

Demerits of FBDF:

Following of category of drug are unsuitable for FBDF

1) Drugs that cause gastric lesions like NSAID & Aspirin.
2) Drugs that have very limited acid solubility like Phenytoin.
3) Bioadhesion in the acidic environment and high turnover of mucus may raise doubts about the usefulness of Floating with bioadhesion

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoetin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, we areas close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

Materials Used:

Metformin-Natco LABS, HPMC K4M-Merck Specialities Pvt Ltd, Mumbai, India, HPMC K15M-SD fine chemical, Mumbai, India, HPMC K100M-SD fine chemical, Mumbai, India, Carbopol 934P-SD fine chemical, Mumbai, India, Carbopol 971P-SD fine chemical, Mumbai, India, Accural-Merck Specialities Pvt Ltd, Mumbai, India, Magnesium stearate-Merck Specialities Pvt Ltd, Mumbai, India, Micro crystalline cellulose- Heligent pharma, Mumbai, India, Talc-SD fine chemical, Mumbai, India.

METHODS:

Analytical method development:

a)Determination of absorption maxima:

A 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.

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.

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.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compression of different formulations is given in Table 6.3.The tablets were prepared as per the procedure given below and aim is

to prolong the release of Metformin. Total weight of the tablet was considered as 1150mg.

Procedure:

1.Metformin 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.

Optimization of Accural concentration:

Accural was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of accural were employed; floating lag time and floating duration were observed. Based on that the concentration of accural was finalized and preceded for further formulations.

Table 1: Optimization accural concentration

S.No	Excipient Name	EF1	EF2	EF3
1	Metformin	500	500	500
2	HPMCK 4M	180	180	180
4	CARBOPOL 934P	100	100	100
5	Accrual	60	120	180
5	Mg.Stearate	12	12	12
7	Talc	12	12	12
8	MCC pH 102	Q.S	Q.S	Q.S
Total weight		1150	1150	1150

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of accural was optimised.

Table 2: Formulation composition for floating tablets

Formulation No.	Metformin	HPMC K4M	HPMC K15M	HPMC K100M	Accural	Carbopol 934P	Carbopol 971P	Mag. Stearate	Talc	MCC pH 102
F1	500	80	-----	-----	120	100	100	12	12	QS
F2	500	120	-----	-----	120	100	100	12	12	QS
F3	500	180	-----	-----	120	100	100	12	12	QS
F4	500	-----	80	-----	120	100	100	12	12	QS
F5	500	-----	120	-----	120	100	100	12	12	QS
F6	500	-----	180	-----	120	100	100	12	12	QS
F7	500	-----	-----	80	120	100	100	12	12	QS
F8	500	-----	-----	120	120	100	100	12	12	QS
F9	500	-----	-----	180	120	100	100	12	12	QS
F10	500	220	-----	-----	120	100	100	12	12	QS
F11	500	-----	220	-----	120	100	100	12	12	QS
F12	500	-----	-----	220	120	100	100	12	12	QS

All the quantities were in mg, Total weight is 1150 mg.

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.

RESULTS AND DISCUSSION:

Preformulation parameters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Optimization of Accural concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 50mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

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 3: quality control parameters for tablets

Formulation code	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	1155	3.5	0.52	4.8	99.76	4.0
F2	1143	3.2	0.54	4.9	99.45	4.2
F3	1149	3.4	0.51	4.9	99.34	4.5
F4	1152	3.5	0.55	4.9	99.87	4.1
F5	1150	3.4	0.56	4.7	99.14	4.0
F6	1148	3.2	0.45	4.5	98.56	4.4
F7	1147	3.1	0.51	4.4	98.42	4.5
F8	1151	3.3	0.49	4.7	99.65	4.6
F9	1153	3.5	0.55	4.6	99.12	4.7
F10	1145	3.5	0.45	4.5	98.42	4.5
F11	1146	3.4	0.51	4.4	99.65	4.6
F12	1149	3.2	0.49	4.7	99.12	4.7

Table 4: Detachment forces of different formulations.(bioadhesive strength)

S. number	Formulation code (F)	Detachment force (dynes/cm2)
1	F1	133.45
2	F2	141.74
3	F3	137.53
4	F4	146.72
5	F5	130.42
6	F6	149.65
7	F7	147.80
8	F8	132.18
9	F9	130.21
10	F10	146.24
11	F11	153.78
12	F12	155.26

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

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

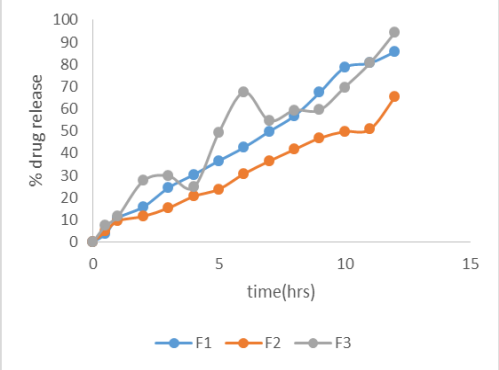

Fig 1:dissolution profiles of formulations F1-F3

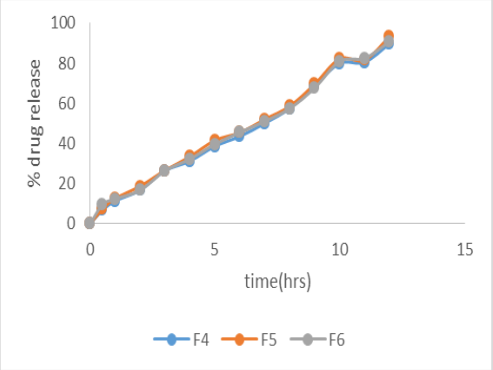

Fig 2: dissolution profiles of formulations F5-F6

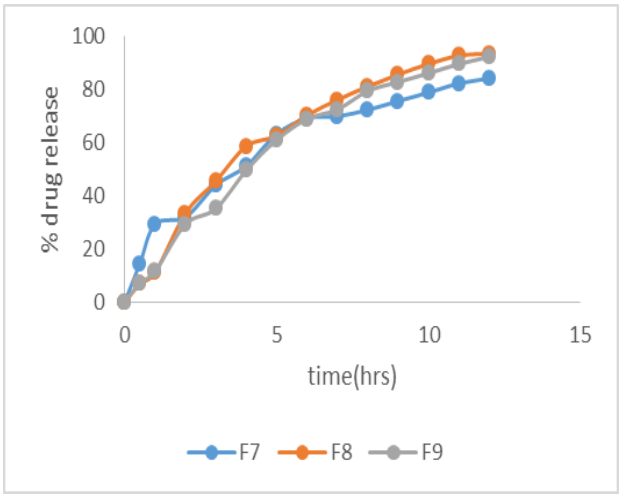

Fig 3:dissolution profiles of formulations F7-F9

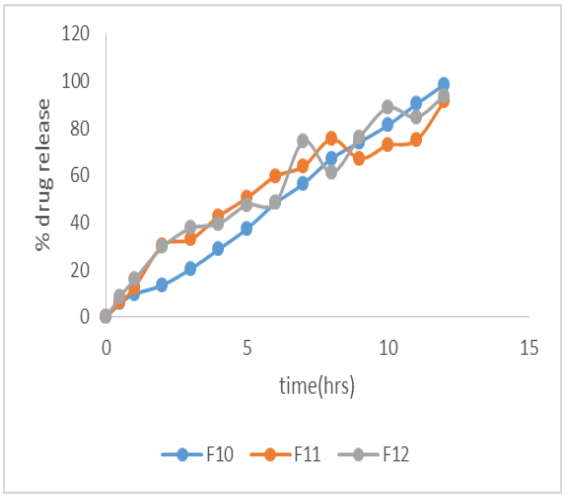

Fig 4: dissolution profiles of formulations F10-F12

Table 5: Determination of swelling index

S. number	Formulation code (F)	swelling index(%)
1	F1	95.23
2	F2	101.42
3	F3	110.36
4	F4	104.87
5	F5	110.25
6	F6	115.78
7	F7	99.45
8	F8	105.55
9	F9	109.63
10	F10	124.5
11	F11	119.35
12	F12	118.53

From the data observed from graphs it was evident that the formulation F3 was followed Zero order kinetics.

Fourier Transform-Infrared Spectroscopy:

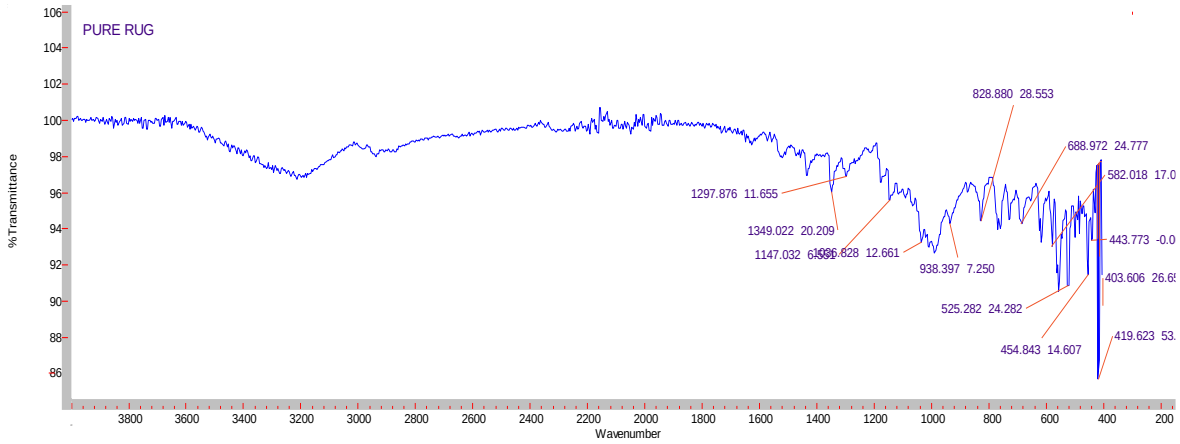

Fig 5: FT-TR Spectrum of Metformin pure drug.

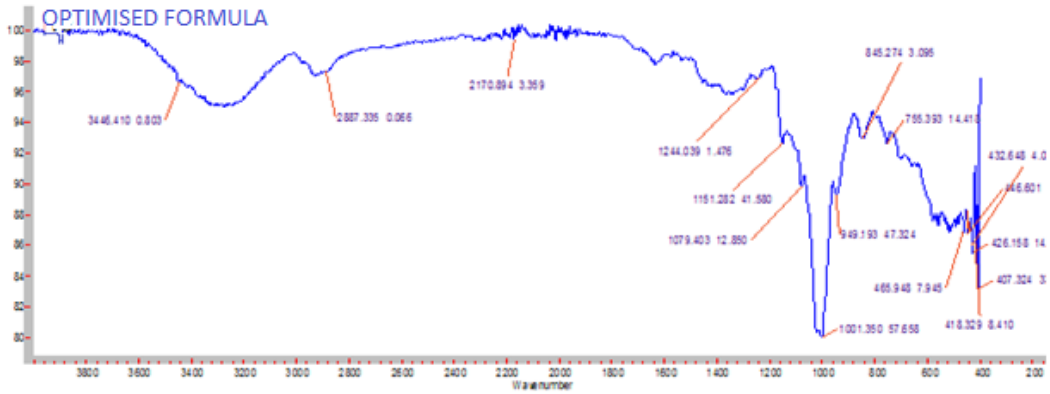

Fig 6: FT-IR Spectrum of Optimized Formulation

CONCLUSION:

- In the present research work gastro retentive mucoadhesive floating formulation of Metformin by using various hydrophilic polymers.
- Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent accrual and bioadhesive polymer carbopol concentration was optimized.
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