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Design And Evaluation Of A Gastroretentive Drug Delivery System For Metformin Hcl Using Synthetic And Natural Polymers.

Jitender Singh[1], Twinkle Garg[1*]
[1] *Himalayan Institue of Pharmacy, Kala Amb, Himachal Pradesh, 173030*

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ABSTRACT
An oral anti-hyperglycemic medication called metformin hydrochloride has long been used to treat non-insulin-dependent diabetic mellitus. Metformin hydrochloride can only be absorbed in the small intestine. Additionally, traditional sustained-release dosage forms may not be as bioavailable as they once were because absorption seems to stop or decrease once the dosage forms enter the large intestine. Since metformin has poor colonic absorption, a conventional oral SR formulation necessitates that the majority of the drug content be absorbed from the colon. A SR-gastroretentive dosage form that is kept in the stomach and delivers a continual input of the drug to the sites of absorption at the upper part of the colon may provide clinical benefit in the case of poor colonic absorption.The overall objective of the present work was to develop an oral sustained-release (SR) metformin tablet prepared by the wet granulation technique, using synthetic polymer such as HPMC K100M, HPC, PVP K30 and natural polymers such as Xanthan gum, HPMC K15M, HPMC K100M and PVP K30 to increase the gastric residence time (GRT) and comparison of natural and synthetic polymer for better sustained effect. The drug polymer interaction was determined by IR spectroscopic method. The pre & post compression studies were performed by using IP standard formula and procedure. Drug release from the floating drug delivery system was studied using USP II .The release behaviour of the natural and synthetic polymer was compared according to obtained data. The weight of all formulation tablets were within the range according to IP. The hardness was in range of 4-6kg/cm$^{2.}$ Friability was found to be less than 1% for all the formulations. As friability was below 1% tablets in each formulation can withstand the mechanical shocks. Percentage drug content in all formulations were found to be in the range of 95-98 %.Natural polymer shows better sustained release properties than synthetic polymer. The formulation with HPMC K100 and xanthan gum shows better sustained release effect than others. The developed floating tablets of Metformin hydrochloride may be used in future, perspective for prolonged drug release for at least 12hrs, thereby improving the bioavailability and patient compliance.

KEYWORDS; Metformin hydrochloride, gastroretentive, floating drug delivery, sustained release, Hydroxypropylmethylcellulose (HPMC), gastric residence time (GRT).

I. INTRODUCTION

Oral dosage forms have been developed for more than 40 years due to their significant therapeutic advantages, patient consistency and ease of organization **[1]**.The development of novel frameworks for controlled drug delivery that allow for longer-term regulation of the arrival of dynamic medications is currently in vogue. However, in regulated drug delivery, the drug absorption is insufficient and extremely varied in people due to physiological fluctuations, such as gastrointestinal transit and the gastric residence time of dosages form **[1]**. This problem is overcome by gastroretentive technology that considerably extending the gastric residence time of drugs. A high pH environment makes the drugs more soluble, increases their bioavailability, reduce dose frequency & side effects of drugs and providing uniform drug delivery **[2,3]**. Optimizing blood glucose control, lowering obesity, and lowering high blood pressure are the main therapeutic objectives in patients with Type II diabetes. However, pharmaceutical therapy using insulin or oral hypoglycemic drugs is necessary **[4]**.An oral biguanide, metformin HCl, is used to treat Type II diabetes, a prevalent condition marked by abnormalities in both insulin secretion and action. Because the drug must be administered 2-3 times per day when greater dosages are needed, patient

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compliance may be affected. This is because the drug has a relatively short plasma half-life of 1.5–4.5 h and a low bioavailability of 50–60%**[5]**.The objective of the present study was to prepare oral sustained release matrix tablet of metformin hydrochloride by wet granulation using synthetic and natural polymers such as HPMC K100M, HPC, PVP K30, Xanthan gum, HPMC K15M, and to evaluate and compare the effect of concentration of polymers for the release of the drug. Such a sustained release formulation if achieved would be substantially more affordable to the patient.

II. MATERIALSANDMETHODS

SELECTED DRUG:

Molecular Formula: $C_4H_{11}N_5$
Molecular Weight: Average: 129.1636
Chemical Name: 1-Carbaimmidamido-N,N-dimethylmethanimidamide
Synonym: Dimethyl biguanide
Melting point: 223-226°C
Physical Discription: Solid
Solubility: 2gm/10ml water

Procurement of Material

Metformin HCl Besylate requested from Sigma-AldrichLimited as drug sample. Excipients used in the formulations are HPMCK100 M(Loba chemicals), HPMC K15(Loba chemicals), HPC(Loba chemicals), Xanthan Gum(Research Laboratory, HIP), PVPK30 934P (Thermofischer Scientific Pvt. Ltd.,), Magnesium stearate (Loba chemicals), Sodium Bicarbonate (Loba chemicals), Citric Acid (Loba chemicals), Talc (Merck) Distilled Water (Research Laboratory, HIP.

PREFORMULATION STUDIES [6-10]

Physicochemical Properties The physical characterization of procured drug sample of Metformin HCl and polymers was determined as follows:

Organoleptic properties

Drug is characterized for its colour, odour and taste results were reported utilizing descriptive terminology. Colour of metformin was observed visually.

Melting Point

Melting point apparatus was used to determine the melting point of drug by open capillary method. A small amount of the sample was place in a capillary tube, attached to a thermometer, placed in a Melting point apparatus (REMI Lab. Instruments, Mumbai, India). The melting point was determined by observing the temperature where capillary tube becomes transparent (due to melting of the sample).

Solubility

The solubility was determined in different polar and nonpolar solvents. Fixed quantity of drug was added separately to a series of 10 ml solvents in test tubes at room temperature till particles get solubilises. These test tubes containing solutions were vortexed and kept for 24 hours. The observations are recorded as per I.P. 1985.

Partition Coefficient

Partition coefficient of drug was examined in n-Octanol: water system. 5 mg of drug was placed in a separating funnel having 10 ml of octanol and distilled water each. The apparatus was shaked for 2-3 hours on rotatory shaker for equilibration. The concentration of drug in octanol was estimated spectrophotometrically by preparing calibration curve in octanol. The partition coefficient of drug in phases was calculated as:

$$\textbf{The Partition Coefficient K} = \frac{\textbf{Amount of drug in organic layer}}{\textbf{Amount of drug in aqueous layer}} \textbf{..... [1]}$$

Identification

i) UV-Visible Spectroscopy [11]

An accurately weighed amount of the drug (10 mg) was dissolved in 0.1 N HCl and the volume was made up to the mark. From the stock solution, graded dilutions were made to obtain standard solution of the drug ranging from 2-10 µg/mL. This solution was then scanned between 200-400 nm in UV-Visible spectrophotometer to determine the absorption maxima. A scan was obtained by using UV visible spectrophotometer (UV-1700, Shimadzu, Japan) from which λmax was interpreted and compared with the standard literature value. After that absorbance value plotted against concentration (µg/ml) to obtain standard calibration curve.

ii) Fourier Transform infra-red spectroscopy [12]

The FTIR spectrum of the pure drug was taken on IR Spectrophotometer (Shimadzu FT/IR 8400, Japan) using KBr pellet technique. Initially, the drug was mixed with KBr and grind to a fine

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powder. The preparation of very finely grounded sample helps in reducing scattering losses and absorption band distortions. The sample was then placed in between two stainless steel disks, which upon pressure (hydraulic press) results in the formation of a thin, homogenous and transparent film. The film was placed into the IR sample holder and the spectrum was run between the range 4000-400 cm-1. The peaks obtained in the spectra were then compared with corresponding functional groups in structure of pure Metformin Hydrochloride.

iii) Differential Scanning Calorimeter (DSC) [13]

Differential Scanning Calorimetry of pure drugs and polymers used were studied to investigate any changes in melting points of the drug after combining it with the excipients. Small amount of sample (around 2 mg) was placed in the DSC aluminum pan and sealed. It was then heated under nitrogen flow at scanning rate of 10°C/ minute in the temperature range of 20 to 250°C. An empty aluminum pan was placed as a reference. The endothermic energy was derived by measuring the peak areas and hence the energy associated with various thermal events (e.g., melting, glass, transition temperature, crystallization) were evaluated.

Formulation of Metformin Hydrochloride by using various Polymers. [14]

Total four formulations were prepared and each formulation contains 500mg drug of Metformin Hydrochloride and polymer HPMC K100M, HPC, PVPK30, with other excipients like Sodium biarbonate, citric acid, talc, Magnesium Stearate. Tablets were prepared by wet granulation method. The drug was mixed with all the ingredients except magnesium stearate and Talc. Required quantity of ethanolic PVP K30 was added as a granulating agent to make a coherent mass. The coherent mass was passed through sieve no 12 mesh and the granules were then dried in a oven at a temperature of 50°C for 90 minutes. The dried granules were passed through sieve no 14 mesh sieve. The blend was lubricated with magnesium Stearate and Talc. The tablet compression process used single punch tablet machine. The formulas are given **Table 1.**

Table 1: Tablet Formulations for Metformin HCl floating tablet Using Synthetic Polymer

Composition (in mg)	FS1	FS2	FS3	FS 4
Metformin HCl	500	500	500	500
HPMC K100M	200	-	170	-
HPC	-	200	-	170
PVP K 30	20	20	40	40
Sodium bicarbonate	70	70	80	80
Citric Acid	20	20	20	20
Magnesium Stearate	10	10	10	10
Talc	10	10	10	10

Formulation of MetforminHydrochloride by using Natural Polymer. [15]

Tablets were prepared by wet granulation method by varying composition, of HPMC K15M, HPMC K100M and PVP K30 each formula as can be seen in Table 2. Granules were prepared by mixing Metformin HCl, Xanthan gum and sodium bicarbonate, Citric acid homogenously. Mix the ingredients with HPC, HPMC K100M by geometric mixing. Then, PVP K-30 in ethanol was added as the binder. The wet mass mixture was dried in an oven at 50°C for 90 minutes. The dried granules were sieved on a 12 and 14 mesh sieve. The blend was lubricated with magnesium Stearate and Talc. The mass then was compacted and compressed by using single punch tablet machine.

Table 2. Tablet Formulations for Metformin HCl floating tablet Using Natural Polymer

Composition(in mg)	FN1	FN2	FN3	FN4
Metformin HCl	500	500	500	500
Xanthan Gum	50	50	70	70
HPMC K100	200	-	170	-
HPMC K15	-	200	-	170
PVP K 30	20	20	30	30

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Sodium bicarbonate	50	50	50	50
Citric Acid	15	15	15	15
Magnesium Stearate	10	10	10	10
Talc	10	10	10	10

PreprationofMetforminHydrochloride Tablets. [16-17]

By synthetic polymer

Tablets were prepared by wet granulation method. The drug metformin was mixed with all the ingredients except magnesium stearate and Talc. Required quantity of ethanolic PVP K30 was added as a granulating agent to make a coherent mass. The coherent mass was passed through sieve no 12 mesh and the granules were then dried in a oven at a temperature of 50°C for 90 minutes. The dried granules were passed through sieve no 14 mesh sieve. The blend was lubricated with magnesium Stearate and Talc.

By Naturalpolymers.

Granules were prepared by mixing Metformin Hcl, Xanthan gum and sodium bicarbonate, Citric acid homogenously. Mix the ingredients with HPC, HPMC K100M by geometric mixing.Then, PVP K-30 in ethanol was added as the binder. The wet mass mixture was dried in an oven at 50℃ for 90 minutes. The dried granules were sieved on a 12 and 14 mesh sieve. The blend was lubricated with magnesium Stearate and Talc.

Compression of Granules

The tablets were compressed using 11.0 mm round, flatpunch on 27 station, RIMEK make, Bilayer tablet press as per specification (Hardness- 16-18 kpa, Diameter- 11.10, thickness from 4.7 to 5.1mm, weight total tablet 650-700 mg).

Evaluation of granules

Determination of various important preformulation attributes such as angle of repose, bulk density, tapped density, Carr's index and Hausner ratio are essential to determine the flow property and compression property of powder/granules prior to tablet compression. The drug was mixed with all the ingredients except magnesium stearate and Talc. Ethanolic PVP K30 was added as a granulating agent to prepare granules by wet granulation method and prepared granules were evaluated for various parameters given below.

i) Bulk Density (BD) [18]

Pre-weighed powder or granule sample was sieved through 18 mesh screen, poured into a 100 mL graduated cylinder, and its volume was recorded. The same procedure was repeated three times, and the readings were averaged. Bulk density was calculated according to equation 1 and expressed in gm/mL.

Bulk Density = $\frac{\text{mass of powder}}{\text{bulk volume}}$ ---------- **equation 2**

ii) Tapped density (TD) [19]

A pre-weighed powder sample or granule was put in a 100 mL graduated cylinder and fixed onto tap densitometer . The apparatus was run for a time until it achieved a constant volume (tapped volume). Tapped density was determined according to equation 2 and expressed in gm/mL.

Tapped density = $\frac{\text{mass of powder}}{\text{tapped volume}}$---------- **equation 3**

iii) Compressibility Index (CI) [20]

CI is used to predict flow ability of powder blend prior to compression. It was calculated according to equation 3:

CI = $\frac{\text{tapped density}-\text{bulk density}}{\text{tapped density}} \times 100$-------- **equation 4**

iv) Angle of repose [21]

Powder or granule flow property at preformulation stage can be determined by this simple and quick test. Cone forming method with fixed base was applied to determine the angle of repose. Powder sample or granule, devoid of any aggregation, was poured from a fixed height of about 10 cm to a fixed base (r) through a funnel supported by stand to form a symmetrical cone of powder mass. The height of the powder mass (h) was measured in triplicate to calculate the angle of repose (Θ) according to equation 4.

$\Theta = \tan^{-1}\frac{h}{r}$---------- **equation 4**

Post-Compression Parameters [21, 22, 23]

Uniformity of Weight Test

Ten tablets were selected randomly from each formulation and weighed individually to check for weight variation. The average weight of tablet was with % deviation as per IP.

Hardness Test

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Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto Hardness Tester. The force needed to disrupt tablet by crushing in kg/cm^2 expresses it. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. The hardness of the tablets should be more than 4 kg/cm^2.

Friability Test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes (run up to 100 revolutions and tablets weight was taken (W final). The % friability was then calculated by eq. given below.

F = W initial – W final ×100

W initial = weight of tablets before friability
W final = weight of tablets after friability
% friability of tablets less than 1% are considered to be acceptable.

Drug Content Uniformity Test [24]

The uncoated tablets were tested for their drug content. Ten tablets were randomly selected, accurately weighed and average weight per tablet calculated. Tablets were ground individually to fine powder. Accurately weighed tablet powder, equivalent to 500mg of Metformin was separately transferred to 100 mL volumetric flask. These powders were dissolved in 85 mL of 0.1 N Sodium Hydroxide and sonicated well to ensure complete solubility of the drugs. Then the volume was made up to 100 mL with 0.1N sodium hydroxide. Applying vacuum later filtered this solution. From this 1 mL of solution was withdrawn and volume made up to 100 mL by using 0.1 N sodium hydroxide solution. Absorbance of the sample solution was measured at 234 nm respectively and concentration of drug in sample was calculated using standard calibration curve.

In Vitro Buoyancy Studies [25]

In vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing 0.1 N HCL (pH 1.2). The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

Swelling Index [26]

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behaviors of all matrix tablet formulations were studied. One tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 5 hours. The % weight gain by the tablet was calculated by the formula

S.I = {(Mt-M0) / M0} X 100

Where, S.I = swelling index,
Mt = weight of tablet at time (t)
Mo = weight of tablet at time t = 0.

In-vitro dissolution studies [27]

In vitro release study of Metformin Hydrochloride from the tablets equivalent to 500 mg of drug was determined using the USP paddle apparatus type II with containing 900 ml of 0.1 N Hydrochloric acid, pH 1.2 as dissolution medium in which the dosage form was fully submerged. The paddle rotation speed was kept at 50 rpm, and a temperature of 37±0.5 ^{0}C was maintained. Five ml samples were withdrawn at predetermined intervals (0, 2, 4, 6, 8, 10, 12 hours). The samples were replaced by its equivalent volume of fresh dissolution medium. Absorbance of these solutions was analyzed at 234 nm using double beam UV/Visible spectrophotometer. The content of drug was calculated using calibration curve. The percentage drug release was plotted against time to determine the release profile.

III. RESULTS AND DISCUSSION

Preformulation studies

The preformulation studies shown that, Metformin HCl was observed visually white in colour. Taste is tasteless and odour was found to be odourless. It is freely soluble in water and 95% alcohol and is practically insoluble in acetone, ether and chloroform. It was also freely soluble as HCl salt. 6.68 pH of the drug was evaluated in 1% aqueous solution of HCl. Its melting point was found to be 221^{0}C to 227^{0}C and Partition coefficient was found to be 0.063±0.0022.

Identification of pure drug

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i) UV-Visible Spectroscopy

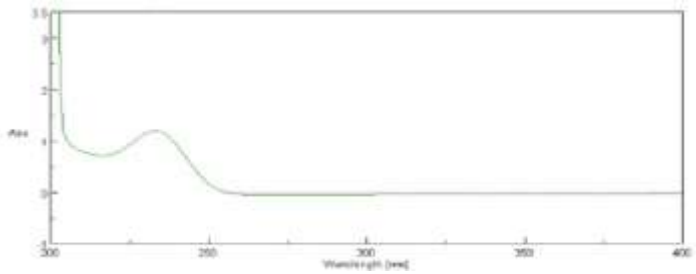

Figure 1: UV -spectra of Metformin HCl

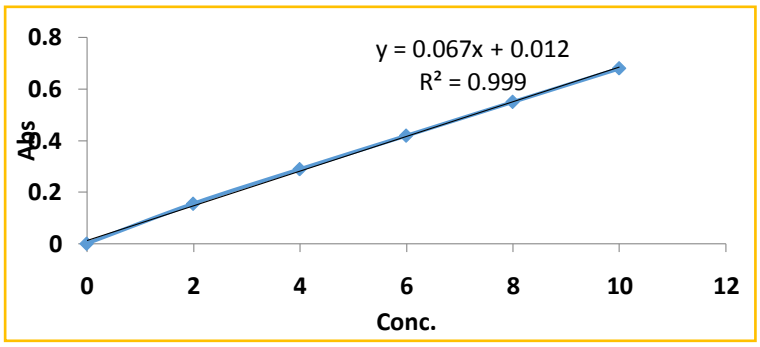

Figure 2: Standard curve of Metformin HCl

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II. FTIR

FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. FTIR spectra of Metformin HCl and polymers (HPMC K100, HPC,PVPK30, and Xanthan gum) were obtained and shown in **Figure3-8.** The observed peaks were identified and were similar to reported reference FTIR spectra. Characteristic peaks are summarized given below.

The FTIR spectra for different polymers (HPMC K100, HPC,PVPK30, and Xanthan gum) are shown in **Table7-11.**On the basis of physicochemical characteristics drug and polymers were selected.

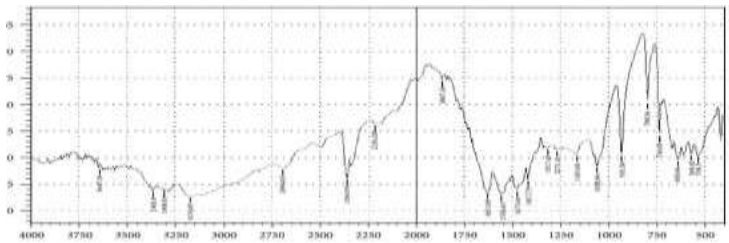

Figure 3:FTIR spectra of Metformin HCl

FTIR spectra of Metformin HCl many peaks were observed shown in figure 3. C-H Stretching was observed at the IR rang of 3372cm^{-1}. Another peak was observed at 3176 cm^{-1}which was associated with Symmetric N-H stretching. The secondary amine $(CH_3)_2N$ absorption was observed at 2619 cm^{-1}. The three peaks were observed at 1626 cm^{-1}, 1583 cm^{-1}, 1417 cm^{-1}due to the N-H deformation. The two peaks of C-N stretching were observed at 1170 cm^{-1}, 1061 cm^{-1}. peak observed at 1707 cm-1. The two peaks were observed at 933 cm^{-1} and750 cm^{-1} due to the N-H out of plane bending& N-H wagging.

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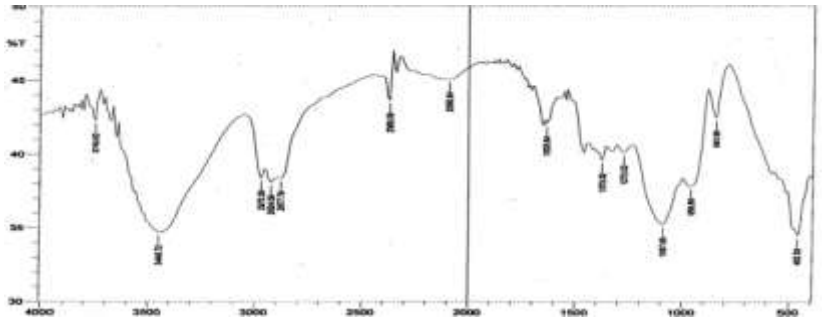

Figure 4:FTIR spectra of HPC

FTIR spectra of HPC many peaks were observed shown in **(figure 4)**. In the pyranose stretching OHgroup shown IR rang at 3431 cm^{-1}. the CH_2 stretching vibration&C-H stretching vibration observed at 2967 cm^{-1} &2932 cm^{-1}. Another peak was observed at 1533 cm^{-1}which was associated with C=C stretching. Stretching vibration of C-O-C was observed at 1069 cm^{-1}. CH_2 group shows rocking mode peak at 750 cm^{-1}**.**

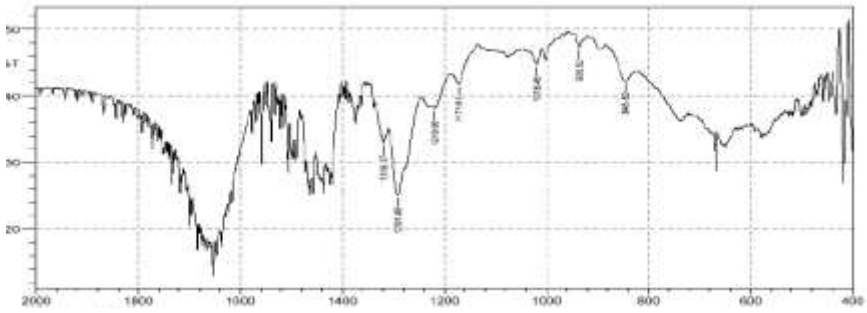

Figure 5: FTIR spectra of PVP K 30

In IR spectrum **of PVP K 30 c**ontain many peaks **(Figure 5).** The acid C=Ostretching vibration observed at1646 cm^{-1}. The alkane C-C stretching vibration were observed at 1935 cm^{-1}Two peaks at 1018.45 cm^{-1} and1018.45 cm^{-1} were recorded for aromatic C-C stretching CH_2 rocking vibration. The N atom adjacent to carbonyl group (N-C=O) peak was observed at 572 cm^{-1}.

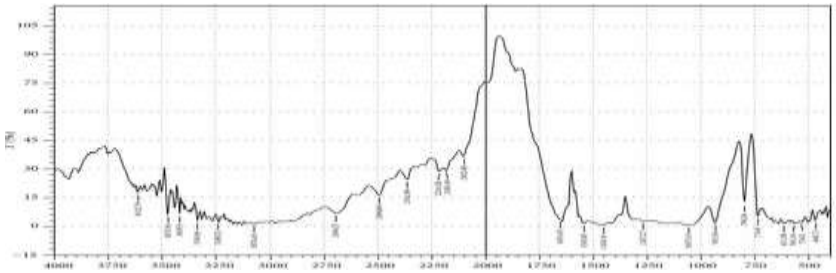

Figure 6:FTIR spectra of HPMC

In IR spectrum **of** HPMC **c**ontain many peaks **(Figure 6)**. The bands of Stretching vibration of C-O-C group observed at 1100 cm^{-1}. The peaks at 3472 cm^{-1} and 2650 cm^{-1} resulted from O-H stretching vibration. Other peaks was identified at 1458 and 1378 cm−1 as methyl and propyl C H vibrations. The rocking mode of CH_2 group observed at 750 cm^{-1}**.**

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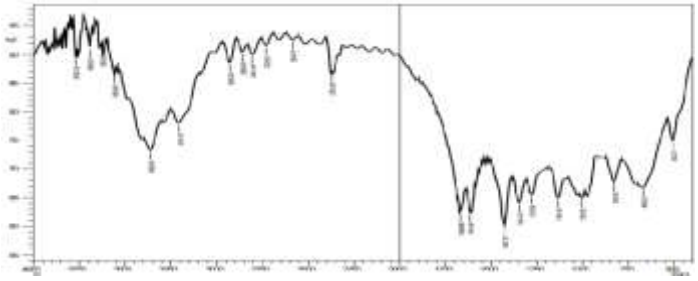

Figure 7:FTIR spectra of Xanthan gum

The spectrum of xanthan gum exhibits a prominent broad band at 3547.21 cm−1, a typical stretch for the OH groups and same hydrogen-bonded OH groups are responsible for interacting with water molecules**(Figure 7)**.Two more peaks were observed at 2928.04 cm^{-1} , 1668.48cm^{-1} due to the presence of alkane C-H stretching. The C=O (Ester of acetyl group) observed at 1614.47 cm^{-1}. The methyl -CH3 (Angular) vibration was observed at 1427.37 cm^{-1}. Two peaks at 1451 cm-1 and 1415 cm-1 were recorded for aromatic C=C stretching.

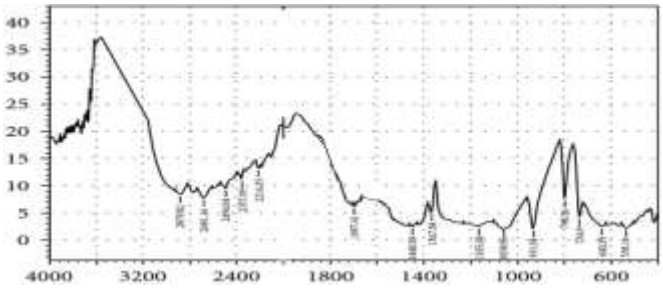

Figure 8:FTIR spectra of Physical Mixture

Drug and polymers were identified by physical characterization and FTIR analysis**(Figure 8)** Compatibility of drug-polymer was studied by physical observation and FTIR analysis. No sign of interactions between drug with any of the polymer was observed during the study. Thus, selected drug and polymers were suitable for formulation of floating tablet.

iii) Diffrential Scanning Colorometry

The DSC thermograms of pure Metformin HCl is shown in **Figure 9** Thermogram exhibits a sharp endothermic peak at 226.91°C which corresponds to melting point of Metformin HCl.. This was further confirmed by comparing the DSC thermograms of standard. . From the DSC and the FTIR studies, it can be concluded that MTH is highly compatible with other excipients used in the formulation.

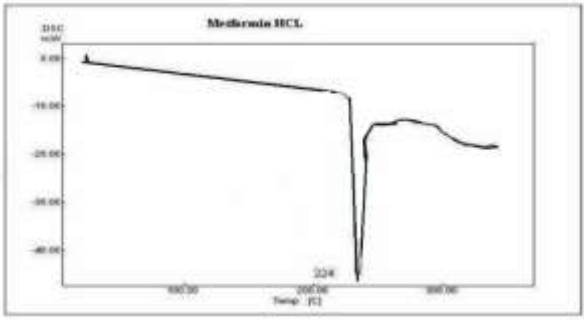

Figure 9: DSC of pure Metformin HCl

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Pre-compression evaluation

Powder prepared for direct compression method of synthetic and natural polymers was evaluated by measuring all the parameters such as; bulk density (BD), tapped density (TD), compressibility (Carr's), angle of repose and Hausner's Ratio. The results are shown in table 3 & table 4.The result shows that angles of repose for all formulations were found to be in the range of 20-25 ° indicating excellent flow properties. The values for BD and TD were found to be in the range of 0.24 to 0.42 gm/ml and 0.28 to 0.49 gm/ml in case of blend of synthetic polymers and 0.61 to 0.65 gm/ml and 0.72 to 0.85 gm/ml for the blend of natural polymer indicating good packing capacity. Carr's indexes for all formulations were found to be in the range of 12 to 25% and Hausner ratio <1.25 indicating excellent flow properties, cohesiveness of powder blend was fair to facilitate smooth operation of tableting.

Table 3: Evaluation of blend of Synthetic Polymers

Batch No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner Ratio	Angle of Repose(^{0})
FS1	0.42 ± 0. 01	0.49 ± 0.01	16.49 ± 0.31	1.16 ± 0.01	21.33 ± 0.73
FS2	0.25 ± 0.01	0.28 ±0.01	12.66 ± 1.17	1.13 ± 0.01	26.13 ± 0.35
FS3	0.36 ± 0.02	0.41±0.01	15.06 ± 2.24	1.15 ± 0.02	24.16 ± 0.45
FS4	0.24± 0.03	0.29±0.01	13.41± 1.13	1.14 ± 0.01	22.76 ± 0.13

Table 4: Evaluation of blend of Natural Polymers

Batch No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner Ratio	Angle of Repose(^{0})
FN1	0.61± 0.02	0.72± 0.03	15.2± 1.15	1.25± 0.03	25.12± 0.53
FN2	0.66± 0.03	0.89± 0.01	25.8± 1.23	1.43± 0.02	21. 21± 0.38
FN3	0.62± 0.02	0.73± 0.01	15.06± 2.13	1.08± 0.01	20.32± 0.03
FN4	0.65± 0.01	0.85± 0.02	23.5± 1.35	1.11± 0.02	22.17± 0.16

POST COMPRESSION EVALUATION

Tablets formulation made by using both natural and synthetic polymers type were evaluated for parameters such as weight variation, hardness, thickness, drug content, and friability given in Table 5& 6. The weight of all formulation tablets were within the range according to IP. The hardness was in range of 4-6kg/cm^2. Friability was found to be less than 1% for all the formulations. As friability was below 1% tablets in each formulation can withstand the mechanical shocks. Percentage drug content in formulations F1 to F4 were found to be in the range of 95-98 %. It showed uniform distribution of drug.

Table 5: Evaluation of Tablet of Synthetic Polymers

Batch No.	Weight Variation (n =20)	Hardness (kg/cm^2) (n =3)	Thickness (%) (n =5)	Friability (n =10)	Content Uniformity (%)
FS1	832 ±1.21	5.05	6.9	0.21	98.2±1.2
FS2	829 ±1.31	5.01	6.8	0.32	96.1 ±2.4
FS3	833±1.11	4.31	6.9	0.42	97.02±1.7
FS4	827±1.32	4.52	6.9	0.39	97.07±4.2

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Table 6: Evaluation of Tablet of Natural Polymers

Batch No.	Weight Variation (n =20)	Hardness (gm/ml) (n =3)	Thickness (%) (n =5)	Friability (n =10)	Content Uniformity (%)
FN1	856±1.41	`6.05	6.10	0.32	98.5±1.1
FN2	852±1.32	5.50	6.11	0.30	97.6±1.3
FN3	851±1.18	5.02	6.10	0.22	98.9±1.5
FN4	857±1.31	5.57	6.10	0.26	95.7±1.2

RELEASE CHARACTERISTICS

Floating Behavior of the Tablets

The floating tablets (FS1, FS2) of Metformin HCl with the synthetic polymer (HPMC) (Table7 & Table 8) shows better floating lag time and it was floated up to 12 hrs, and formulation with natural polymers shows more floating lag time (100, 105 second FN1 and FN2 respectively) but it was floated more than 12 hrs.

Overall all the formulation shows better floating time. Formulations with the synthetic polymers shows the floating time between 10-12 hrs and the formulations with the natural polymers showed the floating time 12 or more than 12 hours.

Table 7: In Vitro Buoyancy Studies by Using Synthetic Polymer

Batch Code	Buoyancy lag time (Sec)	Total Floating time (hrs)
FS1	45	12
FS2	50	12
FS3	15	10
FS4	20	10

Table 8: In Vitro Buoyancy Studies By Using Natural Polymer

Batch Code	Buoyancy lag time (Sec)	Total Floating time (hrs)
FN1	100	≥12
FN2	105	≥12
FN3	85	12
FN4	95	12

Table 9:Swelling Index of the all Formulations

Time (hrs)	Swelling Index (%)							
	FS1	**FS2**	**FS3**	**FS4**	**FN1**	**FN2**	**FN3**	**FN4**
1	**34**	64	**40**	**39**	82	65	53	56
2	56	82	52	46	96	84	68	0
3	63	99	63	54	114	85	91	76
4	83	106	69	59	123	113	103	105
5	101	120	74	65	145	130	107	111

The floating behavior of all the tablet of metformin HCl i.e. of floating lag time and floating time of each formula can be seen in Tables 7&8 respectively. The main requirement for preparation can float is the system must continue to have a specific gravity lower than the overall specific gravity of the specific contents of the stomach. When the density of tablets was less than 1, the tablet becomes floating. Differences floating lag time can be influenced by the molecular weight of each polymer. The smaller the value of the molecular weight of a polymer, the faster the tablet floats to the surface of the medium. Floating time is also affected by the solubility of the polymer used as a matrix. The longer the matrix is dissolved in the medium, the longer the matrix floats on the surface of the medium. The swelling Index of all the formulations including natural and synthetic polymers were shown above in table 9.

6.3.2 Dissolution Profile of the All Formulations

The in vitro release of all batches of floating tablets prepared from synthetic and natural polymers showed the release with an initial effect. In the first 2 hours % drug released were 20.1±1.11, 21±1.01, 20±1.03, 21±1.41, for FS1, FS2, FS3 and FS4 r and 20±1.07,15±1.01, 13±1.23, 12±1.06 for FN1, FN2, FN3 and FN4 respectively .After 12

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hours both synthetic and natural polymers formlations showed the significant results I the range of 91%-98%. Although if comparison is done than the natural polymers showed more sustained effects as compared to synthetic polymers. The results of in-vitro release were depicted in figure10 and 11.

Table 10:Invitro Release by using Synthetic Polymers

TIME	FS1	FS2	FS3	FS4
0	0	0	0	0
2	20.1±1.11	21±1.01	20±1.03	21±1.41
4	41.2±1.21	38±2.02	45±1.10	34±1.11
6	55±1.32	54±3.01	59±2.01	49±1.01
8	68±2.31	64±2.13	71±1.32	60±1.04
10	86±1.01	81±2.01	90±1.30	78±1.41
12	94±2.05	93±1.51	96±1.01	91±1.01

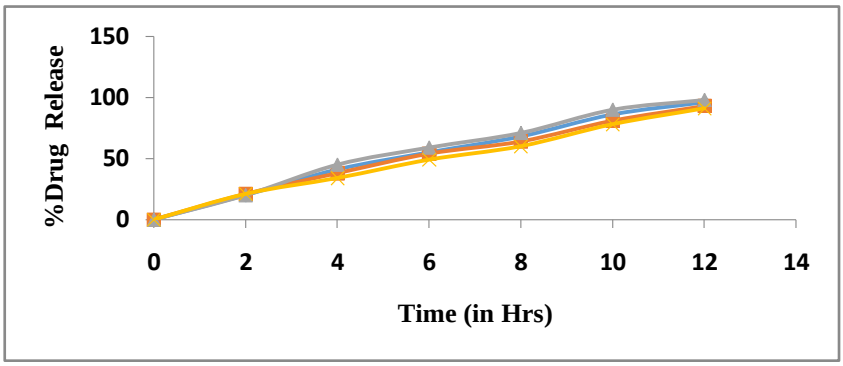

Figure 10 : In-vitro Release graph by using Synthetic Polymer

Table 11:In-vitro Release by using Natural Polymers

TIME	FN1	FN2	FN3	FN4
0	0	0	0	0
2	20±1.07	15±1.01	13±1.23	12±1.06
4	39±1.17	31±1.06	29±1.34	26±2.03
6	59±1.08	51±1.05	49±1.25	44±2.05
8	76±1.62	69±1.08	64±1.01	59±1.21
10	87±1.10	84±1.03	79±1.12	72±1.31
12	98±1.41	95±1.02	92±1.01	89±1.21

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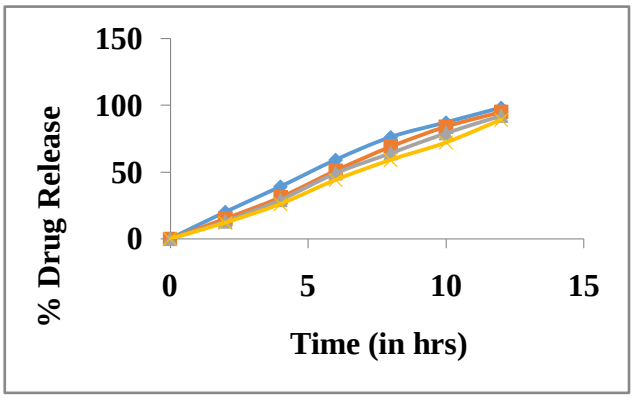

Figure 11:In-vitro Release graph by using Natural Polymers

This study discusses the preparation of floating tablets of Metformin HCl by using synthetic and natural polymers. The based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel-forming polymer HPMC K100M, natural polymer and gas-generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release .The release of the formulation FN1and FN2 shows more release as compare to FS1 and FS3.Natural polymer shows better sustained release properties than synthetic polymers.

IV. CONCLUSION

The current work was carried out to develop the sustained delivery of Metformin hydrochloride for an effective and safe therapy using synthetic and natural polymers such as HPMC K100M, HPC, PVP K30, Xanthan gum, HPMC K15M. Drug is highly compatible with other excipients used in the formulation that checked by DSC and FTIR. The post compression studies hardness, friability, thickness, weight variation etc. values have within the acceptable range. The floating behavior of all the tablet of Metformin HCl, Polymer grade of hydroxyl propyl methyl cellulose alone and those combinations of Xanthan gum, was found to have floating characters for a longer period. From the in-vitro dissolution data shows that after 12 hours both synthetic and natural polymers formulations showed the significant results the range of 91% - 98%. Although if comparison is done than the natural polymers showed more sustained effects as compared to synthetic polymers.

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