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Formulation and Evaluation of Sustained Release Matrix Tablet Metformin Hydrochloride

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Abstract: ***The present study outlines a systematic approach for designing and development of Metformin Hydrochloride sustained release matrix tablets. Different formulations were formulated by wet granulation technique using Xanthan gum and HPMC K100M as polymers along with other excipients The formulations were evaluated for their physicochemical properties.***
Keywords: Floating drug delivery systems, Classification and application, Advantages and disadvantages, Factors affecting the formulation, Precompression and post compression evaluation of Metformin hydrochloride drug.

I. INTRODUCTION

Oral administration is a more common method of drug administration. The majority of medications taken orally are swallowed, however a small number are designed to dissolve in the mouth. The oral route of medication administration is the most common and has been utilized successfully for traditional drug delivery when compared to alternative routes. It is regarded as the most natural, simple, practical, safe method of giving medications. It also offers greater design flexibility for dosage forms, is inexpensive to produce, and is natural.[1] A tablet is an oral dose type used in medicine. The solid unit dosage form of a medication or medications, with or without acceptable excipients, and manufactured either by moulding or by compression, may be referred to as a tablet. It is made up of a combination of excipients and active ingredients. Typically crushed or compacted from a powder to a solid dosage. The excipients include diluents, binders,or granulating agents, glidants and lubricants to ensure efficient tablet ting; disintegrants to promote tablet break up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visuallor aid in visually appealing or aid in visually appealing or aidin visually identifying an unknown tablet.

A. Sustained Release Matrix Tablet

By delivering prolonged, regulated distribution and/or directing the drug to the targeted place, innovative drug delivery systems play a significant role in enhancing the therapeutic effectiveness of pharmaceuticals that have already been incorporated. Any drug delivery system's goal is to quickly and sustainably attain the required drug concentration by delivering a therapeutic dose of the drug to the targeted spot in the body. [1]The type of delivery system, the ailment being treated, the patient, the length of therapy, and the qualities of the drug are only a few of the linked, significant factors that affect how oral sustained release delivery systems are designed. Any drug delivery system that provides delayed drug release over an extended period of time is a sustain release system. [2]Matrix tablets are regarded as the most economically viable prolonged action dosage forms that require the fewest processing variables, work with standard equipment, and hold huge amounts of medication. There is still interest in creating innovative matrix-based formulations that enable sustained drug release utilizing easily available, affordable excipients. The interest in continuous release drug delivery systems has increased significantly during the past 20 years. This is because of a number of things, including the prohibitive cost of developing new drug entities, the ageing of existing international patients, the development of new polymeric materials useful for delaying the release of drugs, and the advancements in therapeutic effectiveness and safety that these delivery systems have made. Nowadays, veterinary products are now using the technology of sustained release. [3]

B. Mechanism of Drug Release

The diffusion or disintegration of the medication is one of the mechanisms involved in its release. Hydration of the matrix occurs when it is exposed to an aqueous solution; as a result, it swells to close off any existing pores and the contents dissolve. Gel formation results in the production of a viscous solution, which creates a positive pressure that prevents liquid entrance and leads to matrix disintegration.

The purpose of the current study was to prepare metformin hydrochloride sustained release matrix tablets using different concentrations of natural and synthetic polymers (Xanthan gum) and to analyze the stability, in-vitro release characteristics, and effects of the prepared formulations

II. MATERIALS AND EQUIPMENTS

A. List of Materials and Supplier

Metformin hydrochloride (Aarti pharmaceuticals,Mumbai). HPMC K100M (SGRS college of Pharmacy). Xanthan gum (SGRS college ofPharmacy). Sodium bicarbonate (SGRS college of Pharmacy). PVP k3 (SGRS college of Pharmacy). Microcrystalline cellulose (SGRS college of Pharmacy). Talc (SGRS college of Pharmacy).Magnesium stearate (SGRS college of Pharmacy).Aerosil (SGRS college of Pharmacy)

B. List of Equipment and Manufacturer

Electronic Weighing Balance (Shimadzu, Mumbai)(Model: AU220) Rotary tablet compression machine(Karnavati Engineers Pvt. Ltd, Mumbai) (Model: MINI PRESS- II MT). UV Spectrophotometer (Jasco, Japan) (Model: V-530 &V-630). FTIR Spectrophotometer (Shimadzu, Japan) (Model: FTIR- 8400$). Differential Scanning calorimeter (Mettler Tolendo, Mumbai) (Model: Stare SW 920). USP Tablet Dissolution Apparatus (Electro lab, Mumbai) (Model: TDT-06P). Tap density tester(Labinda, Mumbai) (Model: TD1025). Roche friability tester(Labinda, Mumbai) (Model: FT1020). Hardness tester (Labinda, Mumbai) (Model: TH 1050 M). pH Meter(Labinda, Mumbai) (Model: GMPH).

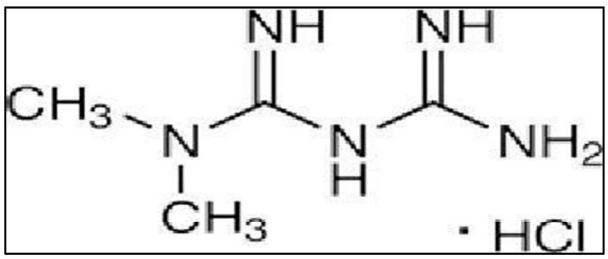
C. Diabetes Mellitus

When your blood sugar (glucose) level is too high, you develop diabetes. It happens when your body doesn't process insulin effectively or when your pancreas doesn't produce any insulin at all. All ages are impacted by diabetes. Diabetes comes in a variety of forms, the majority of which are chronic (lifelong) and treatable with medication and/or dietary modifications.

Metformin HCl

Metformin HCl helps to control the amount of glucose (sugar) in your blood. It decreases the amount of glucose you absorb from your food and the amount of glucose made by your liver. More effective than traditional delivery systems are formulations with sustained release. Especially for the treatment of chronic disorders and long-term therapeutic effect Due to this, sustained release dosage forms of metformin hydrochloride are required for the treatment of type-2 diabetes mellitus.

Structure



D. Method Of Preparation

1) Wet granulation
2) Direct compression
3) Dry granulation

III. PREFORMULATION STUDY OF METFORMIN HYDROCHLORIDE

1) *Organoleptic Properties:* The obtained sample was examined for its appearance, color and odor and observations are reported.
2) *Solubility:* The solubility of compound was determined methanol, water, pH 6.8 Phosphate buffer,HCl
3) *Melting Point:* Melting point of the metformin hydrochloride was determined by open capillary tube method using Thiele's tube. One sided closed capillary filled with drug attached to graduated thermometer and put into the Thiele's tube contains paraffin oil and constant heat was supplied to the assembly. Temperature was noted at which solid drug changed into liquid. The melting point is 224-228 reported.

4) *UV-Visible Spectroscopy:* The Metformin hydrochloride was dissolved in methanol, was scanned between 200-400 nm to determine its absorption maxima. The UV spectrum of metformin hydrochloride.
5) *Fourier Transform Infrared (FTIR) spectral Analysis:* The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by preparing KBr pellets with the help of KBr press taking 1 mg sample in 100 mg KBr. The scanning range was 400 to 4000 cm-1 and there solution was 1cm-1.
6) *Differential Scanning Calorimetry:* The DSC thermo gram of metformin hydrochloride was carried out to confirm its purity. The DSC thermo gram was recorded on Differential Scanning Calorimetry. Metformin hydrochloride was heated in crimped aluminumpan with a pierced lidat a scanning rate of 100C/min in an atmosphere of nitrogen flow (40mL/min) in the range of 40 to 200oC. DSC thermo gram ofMetformin hydrochloride are depicted.
7) *Drug-Excipient Compatibility Study:* The drug and excipient compatibility study of selected tablet of formulations performed byFTIR and DSC

A. Formulation of Sustained Release Matrix Tablet OF Metformin HCl

1) Design of Factorial Batches

A 3^2 factorial design was implemented for optimization of sustained release matrix tablet formulation of Metformin HCl. According to the model it contained 2 independent variables at 3 levels- +1, 0 and -1. According to model, total nine formulations are possible, the composition of different formulation are shown in **Table** he different independent variables were- concentration of Xanthan gum (X_1) and concentration of HPMC K100M (X_2).

Batches code	Variable level in coded form	
	X1 (Xanthan gum)	X2 (HPMC K100M)
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table No 8.2: Translation of coded value in actual unit.

Variable level	Coded Level		
	-1	0	+1
X1= Concentration of Xanthan gum(mg)	80	90	100
X2= Concentration of HPMC K100M (mg)	90	100	110

Table No 8.3: Composition of Factorial Batches.

Formulation code / INGREDIENTS (mg)/tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCl	500	500	500	500	500	500	500	500	500
Xanthan gum	80	80	80	90	90	90	100	100	100
HPMC K100M	90	100	110	90	100	110	90	100	110
MCC	140	140	140	140	140	140	140	140	140
PVPK30	20	20	20	20	20	20	20	20	20
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5
Total weight (mg)	850	850	850	850	850	850	850	850	850

2) Preparation of Factorial Batches

Sustained release matrix tablets containing Metformin hydrochloride are prepared by Wet granulation technique using varying concentrations of different grades of polymers. All the ingredients are accurately weighed and passed through different mesh sieves accordingly. After mixing of drug as well as other components, magnesium stearate, talc and aerosil is added, as post lubricant, and further mixed for additional 2-3 minutes. Powder blend was evaluated for pre- compression properties. 850 mg of powder blend is weighed and compressed into 12 mmsize punches by using a rotary punch tablet compression machine.

IV. EVALUATION OF FACTORIAL DESIGN FORMULATIONS

A. Evaluation of Pre-compression Parameters of Powder Blend-

1) Bulk Density
2) Tapped Density
3) Hausner's Ratio
4) Compressibility Index
5) Angle of Repose

B. Evaluation of Post-compression Parameters of Formulated Batches-

1) Weight Variation Test
2) Hardness Test
3) Tablet Thickness
4) Friability Test
5) Drug Content Determination
6) In-vitro Dissolution Study

V. RESULTS AND DISCUSSIONS

A. Pre-Formulation Studies Of Drug

1) Organoleptic Properties: The obtained sample of Metformin hydrochloride was studied for organoleptic properties such appearance,color and odor. Results of organoleptic properties of Metformin hydrochloride were found to be complies with Indian pharmacopoeia as shown inTable 5

Identification	Observation	Inference
Appearance	CrystallinePowder	Complies with IP
Color	White	Complies with IP
Odor	Odorless	Complies with IP

a) Melting point

Sr No	Method	ReportedMeltingpointasperIP	ObservedMeltingPoint	Inference
1	Open capillarytube method	222-226	224-228	Complies with IP

The melting point of Metformin Hydrochloride was determined and temperature was noted at which soliddrugchanges into liquid and observed melting point of Metformin Hydrochloride was in the range of reportedmeltingpoint range as per Indian Pharmacopoeia as shown in **Table 9.2.** Therefore it was confirmed thatthe givensamplewasinpureform

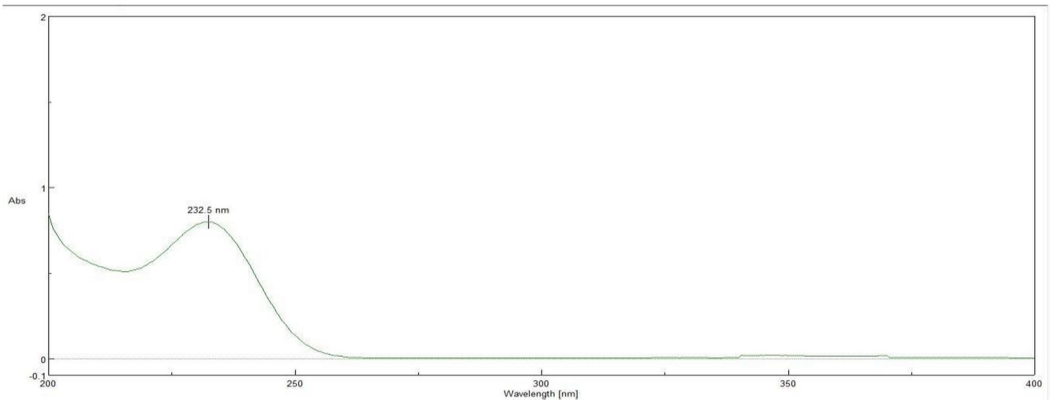
b) Solubility

1	pH 6.8 Phosphatebuffer	soluble	Complies withIP
2	HCl	Freely Soluble	Complies withIP

c) UV Spectroscopy

The λ_{max} of Metformin HCl was recorded by scanning the 10 µg/ml of the drug solution in 0.1 N HCl. It showed the λ_{max} at 232.5 nm in 0.1 N HCl and reportedλ_{max} of Metformin HCl is 233. It indicates that procured Metformin HCl complies with standard. TheUV spectrumof MetforminHClisshown inFigure8.1.

Figure8.1: UV Spectrum of Metformin HCl

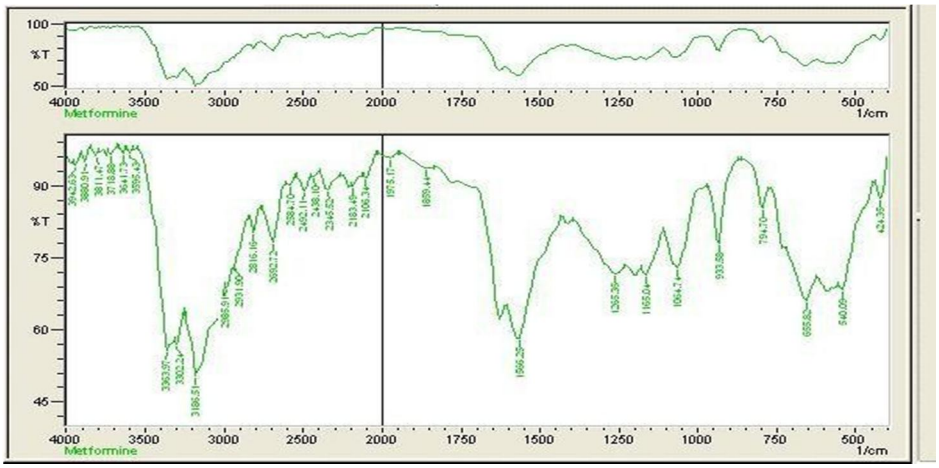


d) FT-IR Spectroscopy

The observed IR peaks of Metformin HCl matches with the reported peaks which are shown in the Table 8.1.

Table 8.1:Reported&Observed IR peaks of Metformin HCl

Functional groups	Reported frequency (cm^{-1})	Observed frequency(cm^{-1})
Aromatic C-H Stretching	3000-3100	3248.23
C=C Stretching	1450-1600	1473.66
Aliphatic C-H	2700-3300	2839.31
C=O Stretching	1670-1820	1604.83
O-H Stretching	2500-3100	2962.76
C-O Stretching	1210-1320	1273.06



Resemblance of observed IR peaks and reported peaks indicated purity o f Metformin HCl.

B. standard Calibration Curve for Metformin Hcl

Preparation of dissolution medium(0.1NHydrochloricAcid):

The preparation of dissolution medium was prepared by using 0.1NHCl.Preparation of standard calibration curve for Metformin HCl: Linear correlation coefficient was obtained for calibration of Metformin HCl in0.1N HCl. Metformin HCl obeys the Beer's law within the concentration range10 to 50 µg/ml. The regression coefficient was found to be 0.998.Calibration plot of Metformin HCl in 0.1N HCl was shown in Table8.2&Figure8.4.

Table8.2:Data for calibration curve of Metforin HCl in 0.1NHCl

SR NO.	CONC(µg/ml)	ABSORBANCE
1	2	0.0733
2	4	0.1176
3	6	0.1703
4	8	0.2161
5	10	0.2783
6	12	0.3356
7	14	0.4013
8	16	0.4547
9	18	0.4983
10	20	0.5644

C. Compatibility Study Of Drug With Polymers

The drug-excipients compatibility studies were performed in order to confirm the compatibility of drug with the used excipients in the formulation. These studies mainly include FTIR.

1) FT-IR Spectroscopy Study

FT-IR studies were carried out to confirm the compatibility between pure drug and polymers.The spectra obtained from the FT- IR studies from 4000-400 cm-1. The FT-IR spectrum of the drug & polymers were shown in the Figure 8.5 &8.6. The comparison of IR spectrum of pure drug with IR spectra of polymers showed no appreciable change in the positions of characteristic absorption band.

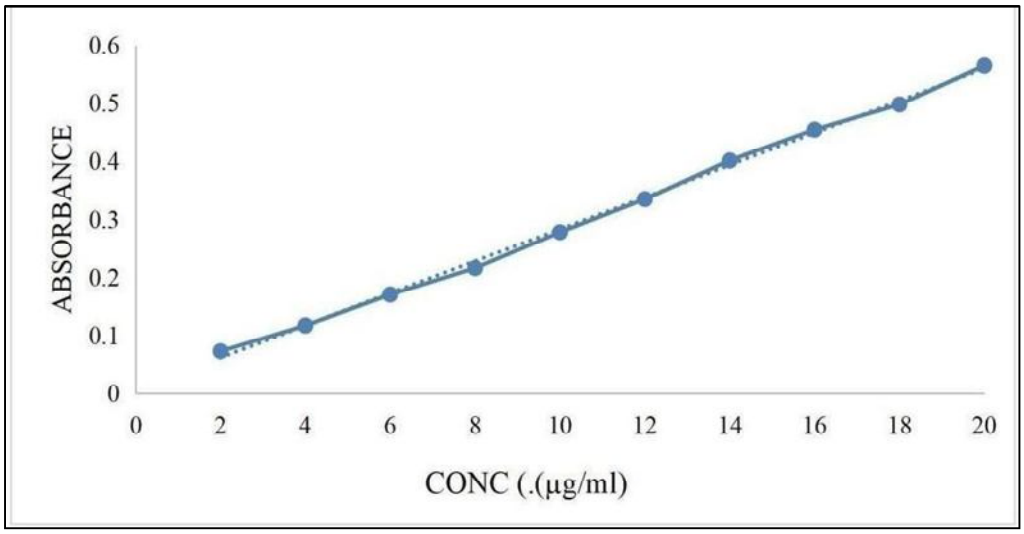
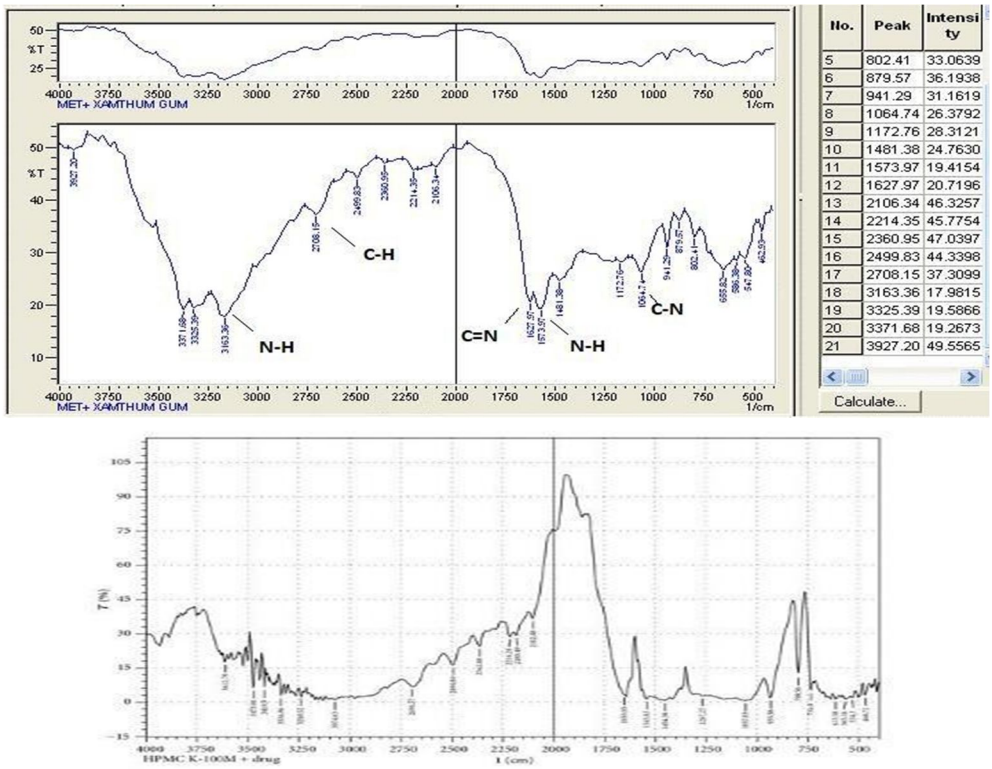


Figure8.5:FTIR spectra of mixture of Metformin HCl and Xanthan Gum



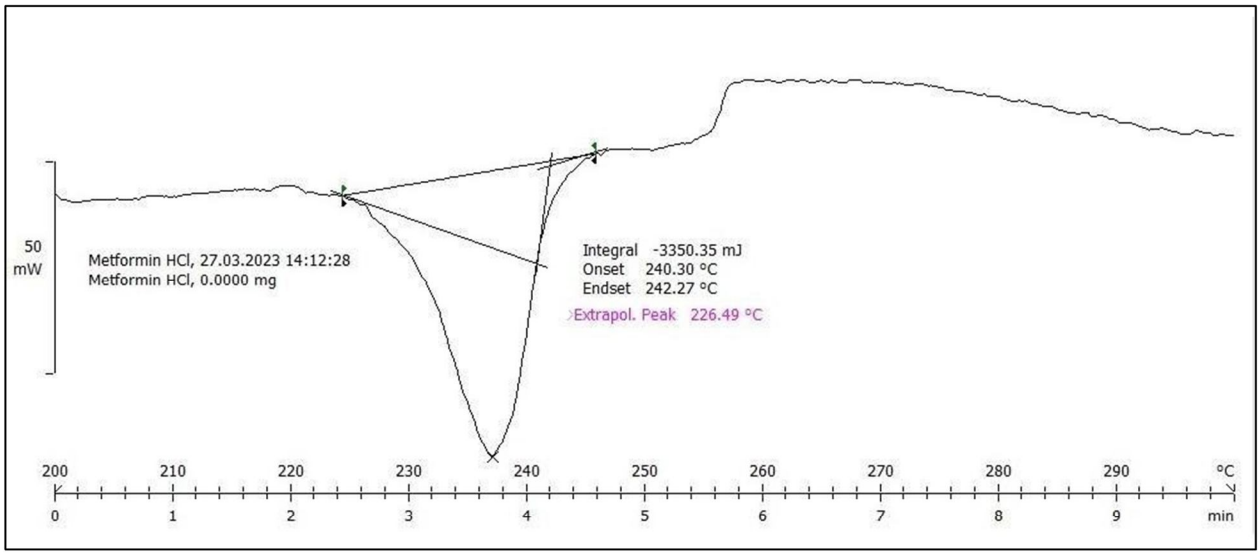
No.	Peak	Intensity
5	802.41	33.0639
6	879.57	36.1938
7	941.29	31.1619
8	1064.74	26.3792
9	1172.76	28.3121
10	1481.38	24.7630
11	1573.97	19.4154
12	1627.97	20.7196
13	2106.34	46.3257
14	2214.35	45.7754
15	2360.95	47.0397
16	2499.83	44.3398
17	2708.15	37.3099
18	3163.36	17.9815
19	3325.39	19.5866
20	3371.68	19.2673
21	3927.20	49.5565

Figure8.6:FTIR spectra of mixture of Metformin HCl and HPMC K100

Functional groups	Reported frequency (cm^{-1})	Observed frequency(cm^{-1})
Hydroxyl group	3500-3400	3416.83
Hydroxyl group	3000-2600	2648.48
C-F group	1100-1000	1076
C=OStretching	1650-1600	1601
Ester group	1400-1350	1372.70
C=OStretching	1500-1450	1438.40
Pyranose ring	1000-950	968.30
Methoxy group	1400-1350	1370.70

Major bands present in the spectrum of the pure drug are clearly observed in the spectrum of polymers with negligible changes in their position. This study clearly suggests that the pure drug remains in its normal form and hence there was no interaction between the drug and polymer.

2) Differential Scanning Calorimetry



D. Evaluation Of Factorial Design FormulationsPre-Compressionalevaluationofpowderblend

1) Bulk Density
2) Tapped density
3) Compressibility index(CI)
4) Hausner'sratio
5) Angle of repose

Table8.3:Results of pre-compressional evaluation of powder blend

Batch	Bulk Density(gm/ml)	Tapped Density(gm/ml)	Angle of Repose (θ)	Hausner's Ratio	Carr's Index (%)
F1	0.781±0.1	0.822±0.4	20.26±0.6	1.05±0.01	11.8±0.88
F2	0.793±0.15	0.818±0.5	21.00±0.5	1.03±0.01	10.86±0.5
F3	0.673±0.2	0.815±0.4	20.55±0.9	1.21±0.02	9.75±0.15
F4	0.791±0.225	0.822±0.2	20.26±0.7	1.03±0.01	15.69±0.76
F5	0.783±0.2	0.818±0.3	21.00±1	1.04±0.02	13.47±0.19
F6	0.773±0.2	0.815±0.4	20.55±0.5	1.05±0.02	8.64±0.18
F7	0.783±0.025	0.810±0.3	23.25±0.5	1.03±0.01	10.66±0.2
F8	0.785±0.4	0.812±0.4	24.28±0.1	1.03±0.02	1.86±0.89
F9	0.781±0.5	0.808±0.6	23.51±0.2	1.03±1.02	13.87±1

(All values are in SD±n=3)

E. Post-Compressional Evaluation Of Sustained Release Matrix Tablets OfmetforminHydrochloride

Batch	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	DrugContent(%)
F1	5.9±0.3	5.80±0.8	0.20±0.1	850.2±1.5	98.5±0.4
F2	5.9±0.2	5.24±0.1	0.26±0.2	850.3±2	98.96±0.1
F3	5.8±0.2	6.20±0.1	0.31±0.2	850.4±1.2	98.4 ±0.2
F4	5.9±0.1	6.32±0.1	0.27±0.1	850.3±1.9	99.4±0.1
F5	5.9±0.5	5.06±0.6	0.46±0.2	850.1±0.4	98.5±0.4
F6	5.9±0.5	5.10±0.4	0.34±0.3	850.5±1.4	100.2±0.9
F7	5.8±0.2	5.06±0.1	0.46±0.2	850.8±1.6	98.5±0.1
F8	5.9±0.2	5.12±0.6	0.31±0.1	850.4±1.6	96.5±0.2
F9	5.9±0.2	5.01±0.2	0.46±0.2	850.9±1.9	101.5±0.1

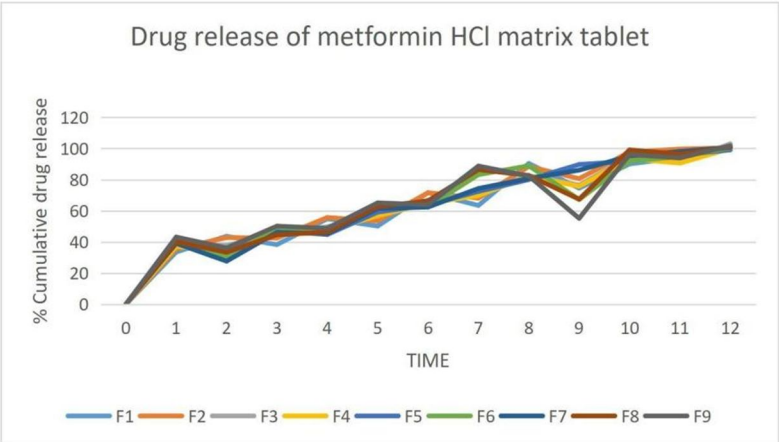
(All values are in SD±n=3)

1) In vitro Drug Release Studies

Table8.11:Drug release(%)of formulation F1-F9

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	33.57	35.66	38.77	37.14	39.53	42.57	39.11	40.20	43.19
2	43.68	42.84	37.80	33.88	33.32	30.24	27.70	33.40	36.20
3	38.32	42.50	45.20	45.89	47.26	49.53	46.22	44.60	50.20
4	54.88	55.72	49.82	47.32	44.8	46.20	45.36	46.40	48.80
5	50.23	53.520	57.84	56.76	59.18	62.35	61.45	62.67	65.17
6	71.68	71.68	66.92	64.92	63.84	62.72	62.44	66.40	63.90
7	63.48	68.14	71.31	69.80	72.45	83.24	74.36	86.50	88.80
8	90.44	88.48	82.60	82.32	80.08	88.96	80.84	82..72	82.40
9	74.55	80.68	76.55	75.77	89.79	67.26	86.13	67.46	55.18
10	90.12	97.72	94.64	93.52	91.84	91.84	95.20	99.12	96.16
11	94.26	99.68	91.19	90.67	95.72	94.83	98.13	96.46	93.99
12	101.36	100.52	103.04	99.96	99.12	100.52	100.80	100.92	101.82

Figno-8.11 Drug release profile of Sustained release matrixtablet of Metformin Hydrochloride(F1toF9).



VI. CONCLUSION

1) Metformin hydrochloride is mostly used in the treatment of Type 2 Diabetes, it lowers the blood sugar by causing the pancreas to produce insulin.

2) In this study the attempt was made to develop once a day sustain release tablet of metformin hydrochloride by using different polymersXanthan gum and HPMC K100 as a polymer, magnesium sterate as lubricant, talc as anti-adherent, MCC as filler and PVPK30 as a binder, Aerosil as glidant. In this study attempt was made to findout the effect of natural and synthetic polymer on drug release.

3) To confirm compatibility of natural and synthetic Polymer. To study the effect of various excipient in formulation of sustain release tablet. Metformin hydrochloride is first considered for their purity by performing several tests.

4) It was found that the tablets showed more than 98% drug released in 12 hrs .The release data indicated zeroorder release pattern. The release rate and the pattern indicated the suitability of the dosage form.

5) The results of accelerated stability studies carried out according to ICH guidelines indicated that the tablets did not show any physical changes (color change. friability and hardness), assay and dissolution characteristics during the study period.

6) The study was undertaken with the aim to formulate and evaluate matrix tablets of Metformin hydrochloride using various concentrations of polymers. From the above results and discussion, it is concluded that F-9 formulation of tablet of Metformin hydrochloride containing Xanthan gum and HPMC k100 showed desired drug release. Therefore batch F-9 was considered as optimized formula for preparation of Metformin HCl sustained release matrix tablet using wet granulation method.

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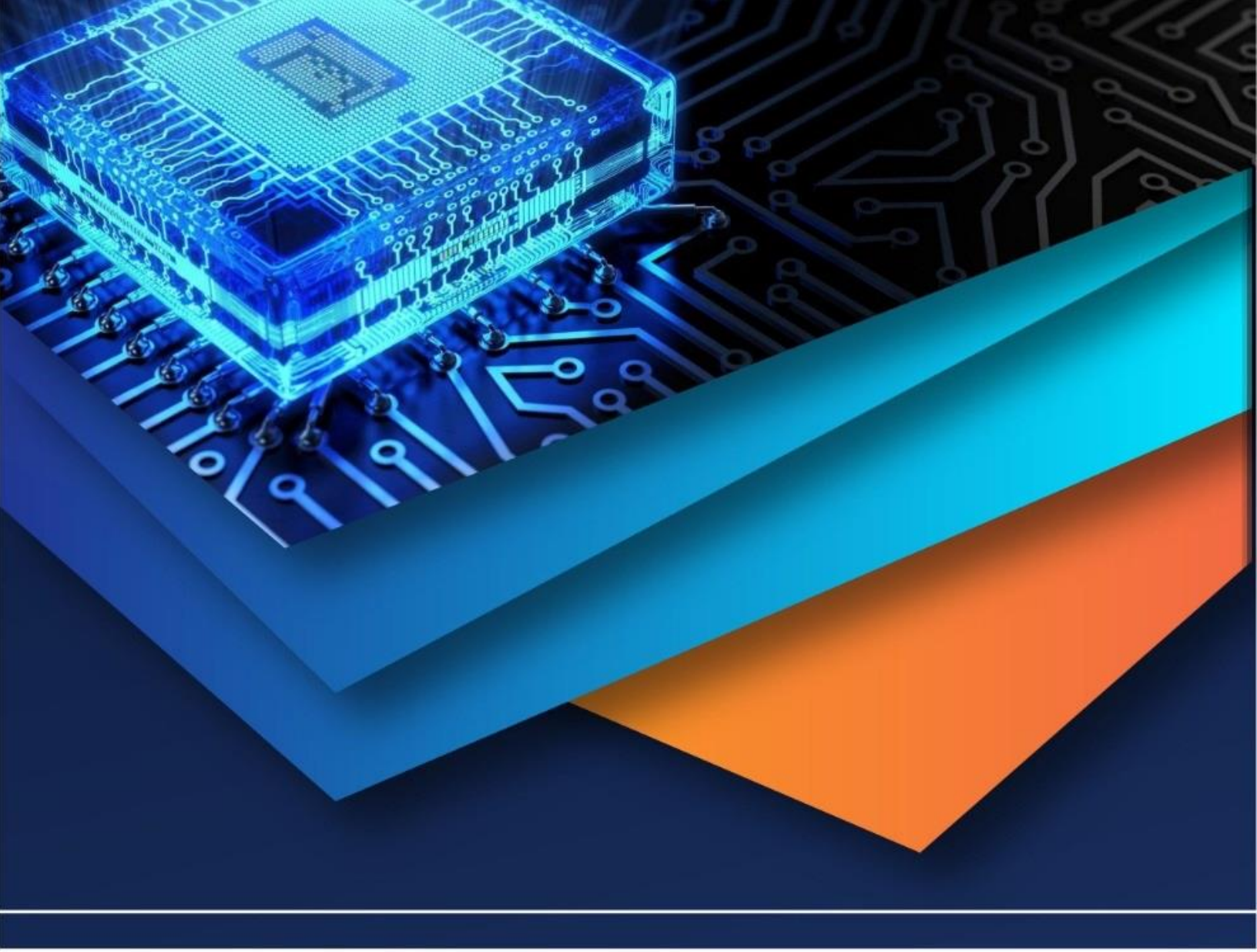

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