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The Use of Natural and Semi-synthetic Polymers in the Formulation and Evaluation of Metformin HCl Sustained Release Matrix Tablets

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ABSTRACT—
The main objective was to use of natural and synthetic polymers in the formulation and assessment of Metformin HCL sustained release matrix Tablets. In the present study, Metformin HCL 800 mg sustained release matrix tablets were prepared by direct compression and in vitro drug dissolution studies were performed to find out the drug release rate and patterns. gum was used as a natural polymer and HPMC (Hydroxypropylmethylcellulose) were used as synthetic polymers. Tablets were formulated using natural polymer and semi synthetic polymer content as 12.5, 18.7 and 25 percent. In-vitro drug release was carried out using USP Type II dissolution test apparatus 37 ℃ ± 5 ℃ and 50 rpm in 900 ml of phosphate buffer pH 6.8 for 12 hours, 10 ml of sample was withdrawn at different time intervals and diluted suitably, then drug release percentage was estimated by spectrophotometer at 232.60 nm, using phosphate buffer as blank. Drug excipients compatibility was checked with the help of Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). The drug content of all the formulations ranged from 91.7% to 94.8%. All formulations showed release up to 12 h. It was observed that as per increase in the polymer concentration, the release rate also increased. F3 formulation was found to be the optimized formulation.

Keywords— Sustained release, Matrix tablet, Natural polymer, Semi synthetic polymer, Metformin HCl, Diabetes

I. INTRODUCTION

Oral drug administration is the quickest and most common method of drug administration, as well as the largest and oldest component of the entire drug delivery industry. There are several types of drug delivery systems available to improve pharmacological therapeutic action, with rapid release drug delivery systems gaining popularity due to their numerous advantages over others, such as simplicity of administration, convenience, and non-invasiveness.[1]

Sustained release oral drug delivery system

Sustained release oral drug delivery system are the types of controlled drug delivery systems that release the medication in a continuous way using both dissolution and diffusion controlled processes. To manage the release of medications with varying solubility qualities, the pharmaceuticals are disseminated in swellable hydrophilic substances, an insoluble matrix of hard non-swellable hydrophobic materials, or plastic materials.[2]

Direct compression of a combination of medication, retardant material, and additives to make a tablet in which the drug is embedded in a retardant matrix is one of the least difficult techniques to the fabrication of sustained release dosage forms. Alternatively, the medication and retardant mixture might be granulated before compression. Hydrophilic and hydrophobic polymers are the most often employed materials in the preparation of matrix systems.

Characteristics of drug appropriate for sustained release tablet [3],[4]

The optimum physicochemical and pharmacokinetic properties of drugs classified as extended release tablets are as follows:

1. Atomic size should be less than 1000 Dalton.
2. Aqueous solvency should be more than 0.1 mg/ml for pH 1 to pH 7.8.
3. The partition coefficient should have been large.
4. The absorption method should be diffusion, and the overall absorbability from all GI pieces discharge should not be affected by pH or catalysts.
5. The elimination half-life should be between 2 and 8 hours.
6. Drugs should not be metabolised before to absorption because this reduces bioavailability.

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7. Absolute bioavailability should be at least 75% or higher.
8. The absorption rate constant (Ka) should be greater than the discharge rate. The apparent volume of dispersion (Vd) should be significant.
9. Total clearance should not be based on dose.

Advantages of sustained release dosage form: [1],[5]

- Reduced see-saw fluctuations.
- Total amount of dose decreases.
- Improved patient compliance.
- Increased safety of drugs
- Can provide zero order drug release.
- Easy to formulate
- Improvement of deficiency in treatment

Disadvantages of sustained release dosage form: [1],[2],[6]

- Reduced potential for dose adjustment.
- Cost is more than conventional dosage form.
- Increase potential for first pass metabolism.
- For proper medication patient education is necessary.
- Possible reduction in systemic availability.
- Poor in vivo and in vitro correlations.

Natural Polymers in Drug Delivery [7],[8]

Natural polymers are biodegradable, biocompatible, and considerably safer. Natural polymers have emerged as one of the most extensively studied materials for improving the therapeutic benefits of current medication compounds. Carbohydrate polymers are being researched intensively for biological and pharmacological uses. Plants, animals, and microorganisms such as bacteria and fungus are all sources of natural polymers. Carbohydrates, in different forms, have been widely employed. Polysaccharides such as starch, pectin, guar gum, and others are utilised in the manufacture of various medicinal dosage forms.

Pre formulation studies:

Pre-formulation may be defined as the determination of fundamental physical and chemical characteristics of drug molecules as well as identification, authentication and compatibility of the drug powder with excipients. Before beginning the formulation of any new pharmaceutical product, the physico-chemical characteristics of the drug molecule as well as the excipients utilised in formulation must be evaluated. [9],[10]

Identification, Authentication and compatibility studies:

UV – Visible Spectroscopy:

UV and Vis Spectroscopy is a fast yet effective and simple process to identify the organic compounds containing conjugated dienes in their structure. When organic molecules are exposed to UV light such organic molecules absorb the light of specific wavelength which is specific for compound and termed as. λmax can be used to identify the organic molecule by analysing sample in UV spectroscopy.

Procedure

Stock solution preparation: 100 mg of drug was accurately weighed and dissolved in 100 ml of ethanol in volumetric flask to prepare stock solution. The resultant stock solution is of concentration of 1mg/ml or 1000 µg/ml.

Spectrum in distilled water: Above mentioned stock solution containing drug concentration of 1mg/ml is further diluted to form the final concentration of 10µg/ml. The sample is analyzed in UV spectrophotometer (Shimadzu 1800) in the range of 200-400nm. (Figure no.1)

Calibration curve [11]

Calibration curve is also known as standard curve is a general method for determining the concentration of a substance in an unknown sample by comparing the unknown to a set of standard sample of known concentration

Procedure

To perform calibration of the drug the first step is to prepare the stock solution by weighing 100 mg of the drug accurately than dissolved in the 100 ml of 6.8 phosphate buffer. Then the process was followed by making the dilutions of this solution of different concentrations from 4-20 microgram/ml. (Table no.4) These serial dilutions were one by one taken and absorption of the solution was determined by spectrophotometer at the wavelength of 232.5 nm.

FT-IR spectrophotometric studies

Infrared Spectroscopy (FTIR)

It is one of the effective and widely used technique for functional group identification of structure of drug. It is used to form fingerprint spectrum for identification of any chemical substance.[12]

Analytical technique was carried out using Potassium Bromide Pellets as sample. In this technique the powder which was converted in to pellet using carrier and the material was than placed in sample holder for analysis. Metformin HCL sample

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was analysed using FTIR. Spectrum of Metformin HCL pure drug within range of wave-number (400-4000 cm^{-1}) and characteristic functional group peaks were shown in Figure no.3.

Metformin HCL, gaur gum and polymer were analysed by using FTIR within (400-4000 cm^{-1}) range and characteristic functional group peaks were shown in Figure no.4.

Similarly Metformin HCL, gaur gum and polymer were analysed by using FTIR within (400-4000 cm^{-1}) range and characteristic functional group peaks were shown in Figure no.5.

DSC analysis

DSC is a thermo-analytical technique used to determine the energy phenomena produced during the heating or cooling of a substance, as well as the change in enthalpy. It quantifies the temperature dependency of phase transitions and conformational changes by determining their enthalpy and understand the nature of drug in formulation.[11] Analysis of pure Metformin HCL drug and the optimized formulation was recorded using sample of 3-4 mg at temperature range of 30° to 300°C with heating rate of 20°C/min. (Figure no. 6.7)

Solubility Analysis

The quantity of material that goes into a solution and forms equilibrium at a constant temperature and pressure is referred to as a substance's solubility.[13]

Pre-compression Parameters Sustained Release Matrix Tablets :

Various parameters sustained release matrix tablets like bulk density, tap density, angle of repose, Hausner's ratio, and Carr's index were determined. [11]-[13] Table No.

II. MATERIAL & METHODS

Material Sustained Release Matrix Tablets :

By utilizing a variable mix of polymers, several matrix embedded formulations of metformin hydrochloride were created using the direct compression technique. The Table No. shows the composition of several tablet formulations along with their codes.

Different material used in formulation of Metformin HCL tablets:

Table no.1: Different material used in formulation

S.No.	Ingredients	Uses
1	Metformin (HCL)	API
2	Guar gum	Natural polymer (Binder)
3	HPMC	Semi synthetic polymer (Binder)
4	Mg. Stearate	Lubricant
5	Talk	Glidant
6	Lactose	Filler

Method of preparation of sustained release Matrix Tablets:

The components were sifted using a sieve with a mesh size of 60. The calculated amount of medication, polymer, and filler was well combined. As a lubricant, magnesium stearate was added; the appropriate amount of the mixture was weighed, and the tablets weighing around 800 mg per tablet were compressed using an eight station rotary press (Rimek Minipress I Ahmadabad, India) at a constant compression force equipped with 14-mm flat-faced punches. All of the pills were kept in sealed containers for future research.

Table no.2: Formulation Composition Sustained Release Matrix Tablets:

Ingredients (mg)	F1	F2	F3	F4	F5	F6
METFORMIN	500	500	500	500	500	500
GUAR GUM	100 (12.5%)	150 (18.7%)	200 (25%)	-	-	-
HPMC (K15M)	-	-	-	100 (12.5%)	150 (18.7%)	200 (25%)
MG.STEARATE	5	5	5	5	5	5
TALC	5	5	5	5	5	5
LACTOSE	190	140	90	190	140	90
Total	800	800	800	800	800	800

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Organoleptic Properties of tablets:
Properties like color, odor, taste, shape, touch, and texture were determined.

Post-Compression Parameters of Sustained Release Matrix Tablets:
Post compression evaluation for weight variation, hardness, friability, and thickness were determined for compressed tablets.34 14

In-vitro dissolution study:
Drug release studies were carried out using USP type - II dissolution test apparatus, rotating paddle method (Electro lab). The study was conducted at 37 °C ± 5 °C and 50 rpm. The dissolution medium used was 900 ml of phosphate buffer pH 6.8 and study was carried up to 12 h 10 ml of sample was withdrawn at different time intervals and replaced with fresh medium to maintain sink condition. The withdrawn samples were diluted suitably, and drug release percentage was estimated by spectrophotometer at 232.60 nm, using phosphate buffer as blank.[14],[15]

III. RESULT AND DISCUSSION:

Pre formulation studies:
The polysaccharide was characterized by various organoleptic properties such as color, odor, taste, touch, and texture are shown in Table No.

Table no. 3: Preformulation study of drug sample (Metformin HCL)

S.No.	Parameter	Observations
1	Colour	White
2	State	Crystalline
3	loss on drying	0.69%
4	Partition Coefficient	0.0622±0.0021
5	Melting point	221.6ºC -225º C.

Identification, Authentication and compatibility studies:
Uv- Spectroscopy:
UV spectra of drug were obtained by scanning drug solutions (10µg/ml) showed maximum absorption at 232.60 nm. Reported absorbance maxima Metformin HCL is λmax at 233 nm.

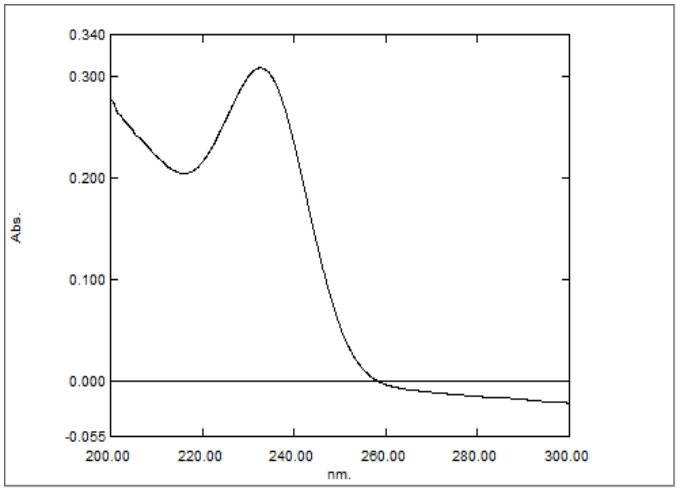

Fig. 1 UV spectrum of metformin sample in distilled water

Calibration curve
The graph was plotted with taking concentration on x axis and absorbance on y axis. (Figure No.) From the plotted graph linear regression analysis was performed to calculate straight line equation.

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Table no.4: Calibration curve of Metformin HCL

Sample No.	Concentration (µg/ml)	Absorption
1	4	0.429
2	8	0.654
3	12	0.949
4	16	1.274
5	20	1.586

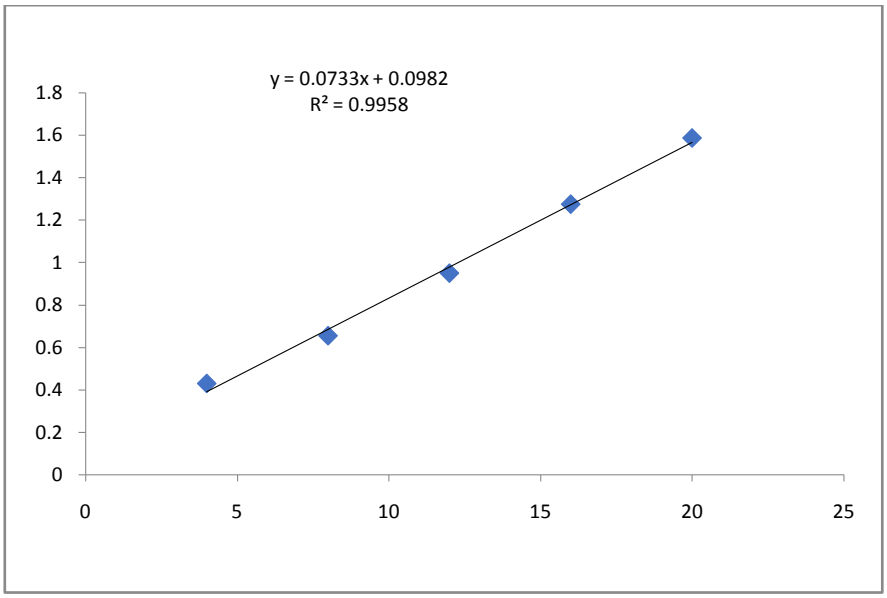

Fig. 2 calibration curve of metformin in 6.8 phosphate buffer

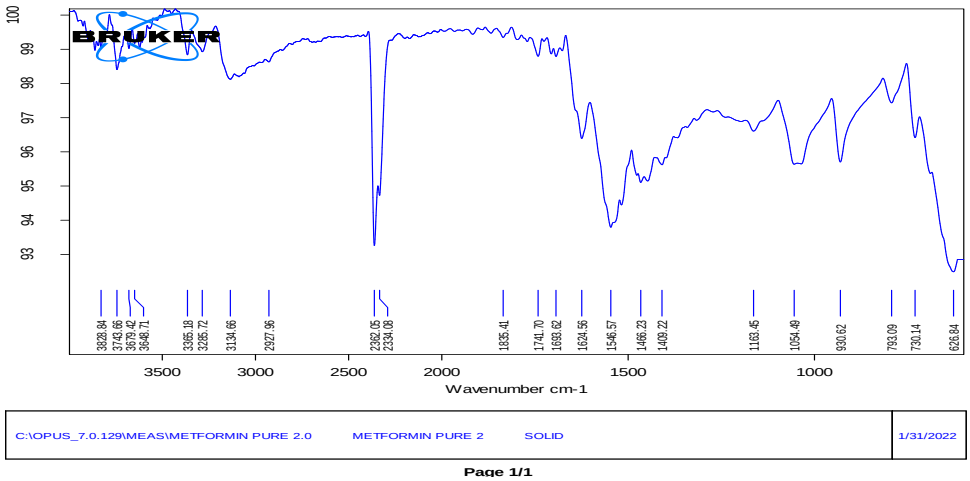

Fig. 3 FTIR spectra of pure metformin drug

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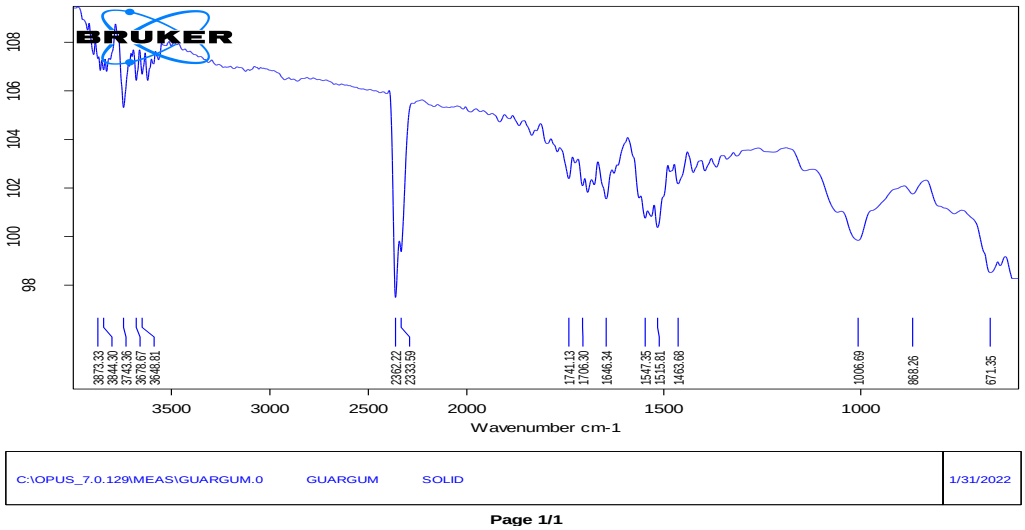

Fig. 4 FTIR spectra of metformin + guar gum + polymers

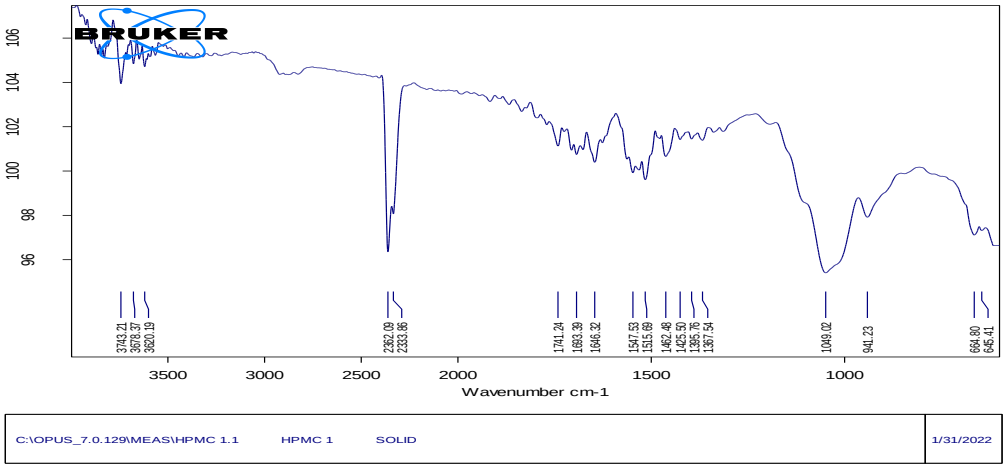

Fig. 5 FTIR spectra of metformin + HPMC + polymers

DSC:

The DSC analysis of pure drug metformin revealed a clear peak at 232°C, equal approximately to its melting point, this indicating the drug's crystalline nature.

The DSC analysis of metformin based mixture which contain Metformin HCL, HPMC and guar gum were revealed clear distinct peaks to each other at 232°C, 250°C. and 270°C equals approximately to their melting points, this indicating the drug's and polymers crystalline nature. Metformin based physical mixture which indicates of no interaction between the drug and polymers, which was confirmed by the thermogram of DSC.

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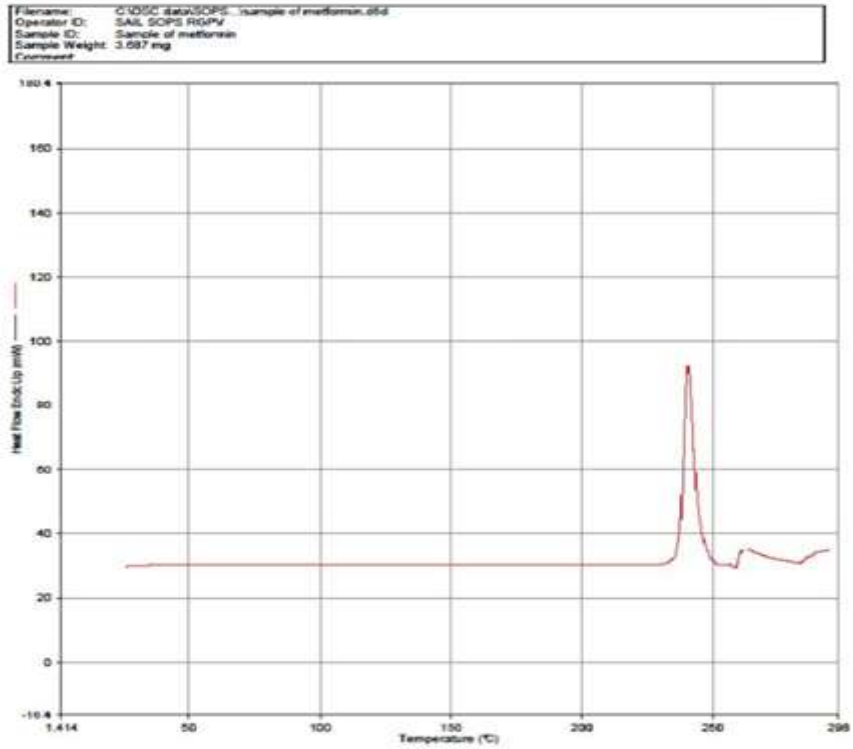

Fig. 6 DSC analysis of Metformin HCL

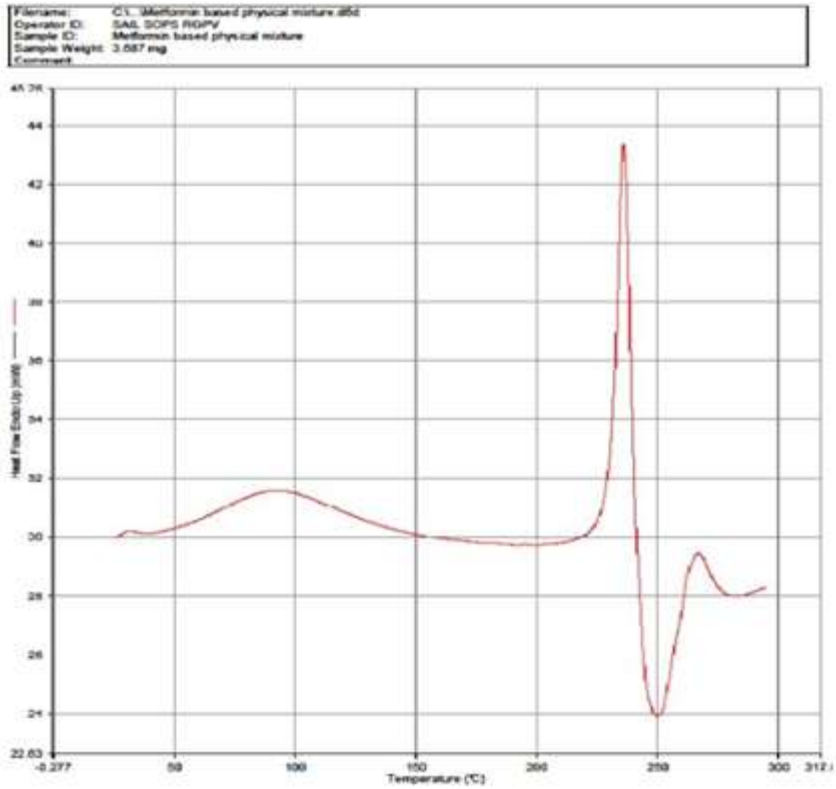

Fig. 7 DSC analysis of Metformin HCL based physical mixture

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Solubility:

The solubility behavior of the Metformin HCL was carried out which shows that the Metformin HCL was soluble in methanol, freely soluble in distilled water, sparingly soluble in ethanol, whereas partially insoluble in chloroform, poly ethylene glycol.

Table no.5: Solubility profile of drug sample

S.No	Solvent	Solubility	Specified in I.P. 2007
1	Distilled water	Freely soluble	Freely soluble
2	Methanol	Soluble	-
3	Ethanol	Slightly soluble	Slightly soluble
4	Chloroform	Partially insoluble	Partially insoluble
5	Poly ethylene glycol	Partially insoluble	-
6	Acetone	Partially insoluble	Partially insoluble

Pre-compression Parameters:

Before preparing the batches of tablets, several pre-compression parameters were evaluated for the granules used in the formulation of tablets. Some of the precompression parameters evaluated were the angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index and mentioned in Table 4.

Table No.6: Pre-compression Parameters of Powder

S. No.	Parameters	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Bulk density	0.53±0.005	0.51±0.005	0.5±0.007	0.53±0.000	0.51±0.005	0.5±0.005
2	Tapped density	0.75±0.009	0.71±0.007	0.68±0.009	0.75±0.008	0.71±0.007	0.68±0.006
3	Carr's Index	29.33±0.355	28.16±1.125	26.47±1.325	29.33±1.222	28.16±1.313	26.47±1.126
4	Hausner's Ratio	1.41±0.009	1.39±0.022	1.36±0.034	1.41±0.021	1.39±0.029	1.36±0.005
5	Angel of repose	33.7±0.626	34.5±0.921	35.6±0.772	34.1±0.606	34.2±0.695	35.4±0.646

Organoleptic properties of tablets :

The tables were characterized by various organoleptic properties such as color, odor, taste, touch, and texture are shown in Table No.

Table No.7: Organization properties of tablets

.No.	Parameter	Observations
1	Colour	White
2	Diameter	7.2 ± 0.04 mm
3	Shape	Round

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Post-compression permanents:
The sustained release matrix tablet formulations were evaluated for thickness, hardness, friability, weight variation, % of drug content, and shown in Table No.

S.No.	Parameters	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Weight variations (mg)	0.53±0.005	0.51±0.005	0.5±0.007	0.53±0.000	0.51±0.005	0.5±0.005
2	Thickness(mm)	0.715±0.004	0.733 ±0.002	0.725 ±0.008	0.712 ±0.005	0.729±0.007	0.732 ±0.004
3	Hardness (kg/cm2)	5.6±0.187	6.6±0.205	9.4±0.287	6.1±0.249	7.5±0.241	9.1±0.225
4	Friability (%)	0.06	0.08	0.06	0.07	0.08	0.05
5	Drug content (%)	92.6±8.856	94.7±15.824	93.4±8.866	91±15.722	91.8±8.462	91.6±15.722

Table No.8: Post-compression permanents of sustained release matrix tablet

Table No.9: In-vitro dissolution study

S.No.	Time (Minutes)	Cumulative% drug release in different trials					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	30	5.29	3.23	1.7	12.86	9.78	7.16
3	60	8.45	5.06	4.3	23.17	17.81	12.29
4	120	13.52	10.22	8.45	51.78	31.63	25.86
5	240	24.34	19.87	16.23	82.62	57.65	48.62
6	360	37.8	32.67	25.76	88.91	84.56	70.81
7	720	80.78	70.32	55.27	89.1	86.43	85.21

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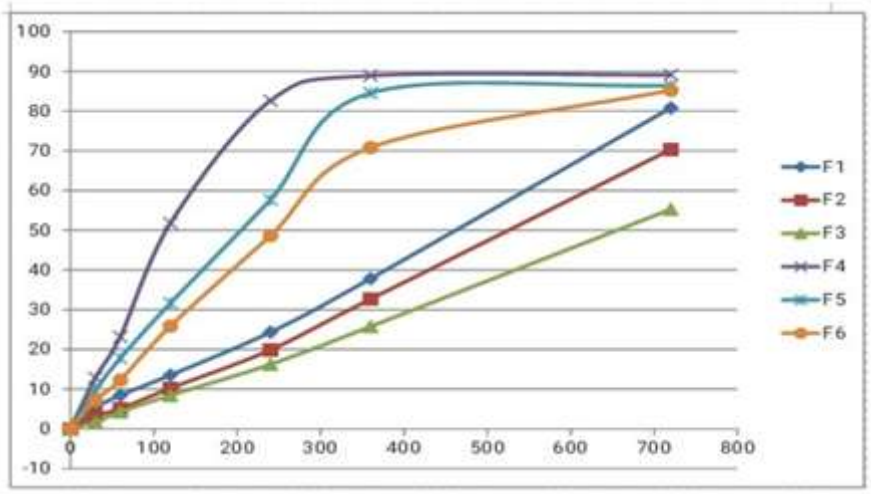

Fig. 8 Comparative in-vitro Drug Release Profiles of F1, F2, F3, F4, F5 and F6

IV. CONCLUSIONS:

In the present study, an attempt is being made to develop a comparatively simple, more effective, and cost-effective formulation of a Sustained release matrix tablet of metformin HCL. From the present study, various conclusions can be drawn.

Totally 6 formulations were prepared by using different ratios of two different types of polymer. One natural polymer (guar gum) and one semi synthetic polymer (HPMC) is chosen for the formulations for the comparative study. F1, F2, F3 Contains natural polymer guar gum and the other group: F4, F5, F6 contains semi synthetic polymer HPMC (K15M)

Preformulations evaluation parameters were performed and their results shows in tablet no.6. Post-Compression evaluation parameters were performed and their results shows in table no.8.

According to dissolution studies all the formulations (F1-F6) performed differently according to both quality and quantity of the polymers. In qualitative analysis 3 formulations F1, F2 and F3 which contain guar gum sustained the drug release more time as compare to the formulations F4, F5, F6 which contain HPMC. In qualitative analysis, results shows that more quantity of both polymers is more effective in slowing down the drug release. F3 was considered as best formulation, because it shows ideal drug release for sustained release model and release approximately 50% of the drug in 12 hours, which is slowest in all 6 formulations.

This study also proves that using guar gum could give more impressive results in drug dissolution, in less quantity as compare to HPMC.

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