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Research Article

Formulation and Development of Metformin Sustained Release Tablets by Hydrophilic Polymer

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ABSTRACT

Metformin HCL, the only biguanide still in use today, reduces peripheral insulin resistance and hepatic glucose production in people with Type 2 diabetes. It has a short plasma half-life and a low absolute bioavailability. The primary goal of this study was to create an oral sustained release metformin tablet employing the direct compression technique and rate-controlling ingredients like hydrophilic hydroxypropyl methylcellulose and Xanthan gum polymer. Thickness, weight fluctuation, hardness, consistency of drug content, and in vitro drug release were all assessed for all batches. The term "mean dissolution time," which describes the rate at which a medication is released from a dosage form, demonstrates a polymer's effectiveness in delaying drug release. When coupled with xanthan gum, the hydrophilic matrix of HPMC was able to successfully control metformin release for 12 hours. As a result, it is now possible to create sustained-release matrix tablets. According to data that fits the Korsmeyer equation, both erosion and diffusion could be exploited as drug release mechanisms.

INTRODUCTION

Due to their release behavior of the medication, hydroxypropylmethylcellulose (HPMC) is hydrophilic cellulose ether that is frequently utilized as a pH-independent gelling agent in controlled release preparation. (1) Because the micro-structure and macrostructure of HPMC exposed to water is substantially time-dependent, the transport mechanisms involved in the drug release from hydrophilic matrices are complex. HPMC is frequently utilized as a release retarding substance due to its non-toxicity, ease of handling, and lack of need for a specific technology for the creation of prolonged release tablets. Because the microstructure and macrostructure of HPMC exposed to water is substantially time dependent, the transport mechanisms involved in the drug release from hydrophilic matrices are complex. (2) When in contact with digestive fluid, HPMC expands, gels, and then slowly dissolves (3). Both

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water infiltration and medication efflux from the solution are prevented by the gel's hardening into a viscous covering. Diffusion can control the dissolution depending on the molecular weight and thickness of the diffusion boundary layer. *Xanthomonas campestris*, a gram-negative bacterium, is fermented to produce xanthan gum, a high molecular weight extracellular polysaccharide. (4)Given that xanthan gum is biodegradable, biocompatible, and forms gel in water, the development of matrices with controlled drug release characteristics appears to be becoming more and more popular. Gels that can be produced using XG and HPMC can be used to make dosage forms with sustained release. (5)

In people with Type 2 diabetes mellitus (T2DM), the sole biguanide that is still in use today, metformin HCL, reduces peripheral insulin resistance and hepatic glucose production (D.M. Nathan 2009). Some advantages of metformin include a decreased risk of hypoglycemia, weight neutrality, and a decreased risk of cardiovascular morbidity and mortality. It is an oral anti-hyperglycemic drug, however the gastrointestinal tract does not absorb it well enough. Its plasma half-life is only 1.5 to 4.5 hours, and its absolute bioavailability is between 50 and 60%. (6)

MATERIALS AND METHOD

Materials- Mankind Pharmaceutics provided the Metformin Hydrochloride. Lactose Monohydrate are obtained from Mankind Pharma. Hydropropile Methyl cellulose was obtained from the Bangalore Fine Chem .Xanthan Gum was Obtained from the Loba Chemical Pvt. Ltd .The remaining components were all laboratory reagents that were used without further testing.

Methods-

Determination of Absorption Maxima-A precise weight of 100 milligram's of metformin hydrochloride was used to measure out 100 ml of 6.8 phosphate buffer (stock Solution). 5 ml of the stock solution were obtained, put into a 50 ml volumetric flask, and diluted with pH 6.8 phosphate buffers to a final volume of 50 ml. The outcome was referred to as the typical working solution. In a 10ml volumetric flask, 2ml of the working solution was taken out and diluted to a final volume of 100ml with phosphate buffer at a pH of 6.8. The UV-visible spectrophotometer was used to run the spectrum of this solution in the 200-250 nm regions. The maximum absorbance of metformin hydrochloride was discovered to be 232.8 nm.

Preparation of Calibration Curve-

To get concentrations of 0µg, 2 µg, 4 µg, 6 µg, 8 µg, and 10 µg from the standard working solution, 2, 4, 6, 8, and 10 ml were taken out and diluted up to 100 ml by buffer 6.8 in a 100 ml volumetric flask. Using phosphate 6.8 as a blank, the UV-visible spectrophotometer measured the absorbance of each solution at 232.8 nm. Following that, a graph showing the concentration and absorbance along the y-axis produced a straight line. The linearity of the standard curve was assessed using the square of the correlation coefficient (R^2), which was obtained by least-square linear regression analysis. The aforementioned procedure was carried out once more using pH 6.8 phosphate buffer.

Preparation of Metformin Hydrochloride Matrix Tablets-

By utilized varied proportions of polymers, several matrix embedded formulations of metformin hydrochloride were created. Table 1 lists the ingredients of several tablet formulations along with their codes. Utilizing a sieve with a mesh size of 60, the mixture was filtered. It was thoroughly mixed with the prescribed dosage of the drug, the polymer (HPMC, Xantham gum), and the filler (Lactose Monohydrate). As a lubricant, magnesium stearate was used in order to create tablets with a hardness of roughly 5-6 kg/cm^2. The appropriate amount of the mixture was then weighed, and a 14-mm flat-faced punch was

attached to an eight-station rotating press for continuous compression force.

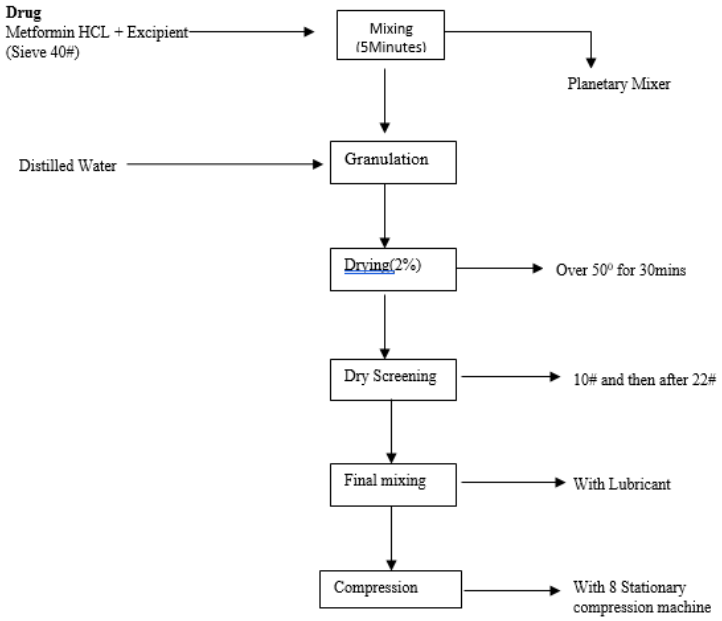


Figure 1- Wet Granulation Technique

Table 1 Composition of the SR tablet's several trial formulations for metformin HCl

Ingredient	F1	F2	F3	F4	F5	F6	F7	F7
Metformin Hcl	500	500	500	500	500	500	500	500
Lactose Monohydrate	159	144	114	99	159	144	114	99
Xanthan Gum	126	141	171	186	-	--	--	--
H.P.M.C K100	--	--	--	--	126	141	171	186
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total	800	800	800	800	800	800	800	800

Release Kinetics Of Sustained Release Dose - Numerous kinetic equations (including zero-order, first-order, and Higuchi's equation) were used to comprehend the drug release rate from matrix systems. (7) (2002) P. Costa Higuchi's equation offered the best fit with the highest correlation for all formulations (r2 = 0.748). However, for two reasons, the applicability of Higuchi's equation to matrix systems is constrained. The effects of matrix swelling (upon hydration) and matrix breakdown over time are not included by this model. Thus, the dissolution data was also fitted using the well-known exponential Korsmeyer-Peppas equation, which is frequently used to describe drug release behavior from polymeric materials.

$$M_t/M_\infty = Kt^n$$

Where,

M_t/M_∞= Partially Solvent Release

t = Release Time of drug

K = Drug/polymer system's kinetic constant property

N = the mechanism of trace release is governed by kinetics constant features.

Based on a number of mathematical models, the size of the release exponent "n" identifies the release mechanism (such as Fickian diffusion, case II transport, or anomalous transport).

The constraints taken into consideration in the current investigation were n = 0.45 (which denotes a conventional Fickian diffusion-controlled drug release) and n = 0.85 (which denotes a case II relaxation release transport; a non-Fiction, zero-order release). Drug diffusion in the hydrated matrix and polymer relaxation, both of which are usually referred to as anomalous transport, can both be considered to be indicators of n values between 0.45 and 0.85.

A mean dissolution time (MDT) was determined using the following equation in order to examine the release profiles of several formulas with potential differences in release mechanisms (n values). (8)

$$MDT = (n/n+1).K^{-1/n}$$

And Where n= Release Exponent and K= Release rate constant.

Evaluation of Pre-compression Parameter- (9) (10) (11)

Angle Of repose-Angle of repose was calculated by this formula

$$\text{Angle of Repose} = \Theta^{-1}\frac{h}{r}$$

Where is h= Height and r= Radius

Bulk Density-Bulk density measured by this formula,

$$\text{Bulk Density-} \frac{\text{Mass}}{\text{Bulk Volume}}$$

Tapped Density-Tapped density measured by this formula:

$$\text{Tapped density-} \frac{\text{Mass}}{\text{Tapped Volume}}$$

Compressibility index- Compressibility Index measured by this formula.

$$\%\ CI = \frac{\text{Tapped density- Bulk Density}}{\text{Tapped Density}}$$

Hausner Ratio- It implies that the ratio of tapped density to bulk density is used to measure the flow characteri

$$\text{Hausner Ratio-} \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of Post Compression Parameter (12) (13)-

Shape of Tablets- Under a microscope, compressed tablets were inspected for the tablet's form.

Weight Variation- Weight Variation measured by this formula. Weight variation done by 10 tablets,

$$\text{Percentage Deviation -} \frac{\text{Individual Weight- Average}}{\text{Average Weight}} \times 100$$

Thickness- Six tablets are weight were used to measure the thickness using digital Vernier Calipers Scale and average was taken,

Hardness- Indicating a tablet's ability to withstand mechanical shocks is its hardness. Using the Monsanto Hardness Tester, the hardness of the tablets is determined. Kg/cm2 is how it is expressed.

Friability Test- The percentage of powder lost from the surface of tablets owing to mechanical action is characterized as the "friability" test, which is used to quantify how much weight is lost during transportation. In addition to physical characteristics like as hardness (Tablet Breaking Force), it functions as a test for compressed or uncoated tablets.

$$\text{Weight Loss\%} = \frac{W_1 - W_2}{W_1} \times 100$$

Where, W1= Initial Weight

W2= Final Weight

Determination of drug Content Study-

20 Metformin tablets should be crushed and weighed. The following procedures must be followed: Weight 0.1 g of metformin hydrochloride powder; mix with 50 mL of water for 15 minutes; dilute to 100.0 mL with water; and filter. Add 100.0 mL of water to 10.0 mL of filtrate. The absorbance of the resultant solution will be maximum around 232.8 wavelengths after further dilution with 10.0 ml to 100.0 ml of water. Use the specific absorbance at 232.8 wavelengths

of 807 as a starting point to calculate the quantity of metformin hydrochloride. The drug content determined by this formula-

$$\frac{\text{Absorbance} \times 10 \times 100 \times 100 \times 100 \times \text{Average weight of the tablet}}{\text{Specific absorbance} \times \text{Weight of one equivalent of tablet} \times 10 \times 10}$$

In-vitro Dissolution Study-The dissolution conditions used for studying the drug release from the sustain release matrix tablets of Metformin HCL are

- Apparatus- USP type –II (Paddle Type)
- Agitation Speed- 100rpm
- Medium- Phosphate Buffer 6.8
- Temperature- 37º±0.5ºC
- Time- 0,2,4,6,8,10, 12 Hr. in phosphate Buffer.
- Wavelength- 232.8nm

Procedure-

The USP apparatus II (Paddle Method) was assembled after the vessel had been filled with 900 ml of 6.8 phosphate buffer. It was given enough time to warm up to an equilibrium temperature of 37°C ±0.5°C. The vessel held the tablet, which was then rotated through 100 rotations per minute for up to 12 hours. A 1 ml sample was withdrawn, filtered, and then added back into the medium at predetermined intervals. The media were diluted properly using a UV spectrophotometer, and the results were then measured spectro-photometrically at the proper wavelengths.

Study of Physical Interaction between Drug and Polymer-

A Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan) was used to acquire the infrared spectra of the pure drug and polymer samples over the wave number range of 4000 to 400 cm cm-1. The presence of a polymer caused the drug's spectra to alter, which suggested a physical interaction between the drug's molecule and the polymer.

RESULT

Table 2- Calibration curve

Concentration	Absorbance
0	0
2	0.156
4	0.305
6	0.477
8	0.634
10	0.807

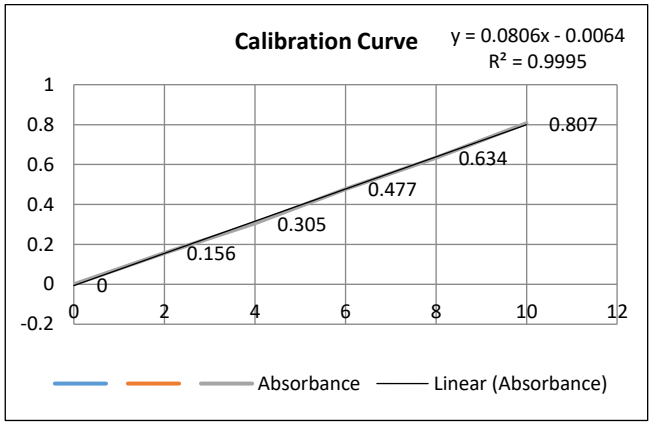


Table 3 -Physical Characteristics of Metformin Hcl Granules

Formulation Code	Angle Of repose	Bulk Density (g/ml	Tapped Density (g/ml)	Hausner Factor	Carr's Index (%)
F1	27°.29	0.51	0.54	1.05	5.55
F2	28°67	0.56	0.62	1.10	9.6
F3	27°58	0.51	0.59	1.15	13.5
F4	26°78	0.54	0.61	1.12	11.4
F5	29°67	0.43	0.49	1.13	12.2
F6	27°84	0.53	0.56	1.05	5.3
F7	29°52	0.43	0.49	1.13	12.2
F8	27°82	0.43	0.47	1.09	8.5

Tablet 4: Physical characteristics of the 500 mg Metformin HCl as SR formulation matrix tablets

Formulation code	Weight Variation (mg)	Hardness (kg/Cm^2)	Thickness (mm)	Friability (%)	Drug content
F1	792-798	4..8	4.33	0.55	96%
F2	789-796	4.3	4.38	0.50	95%
F3	790-797	4.8	4.33	0.52	97%
F4	788-798	4.9	4.39	0.54	97%
F5	791-798	4.9	4.37	0.51	96%
F6	785-799	4.5	4.39	0.52	98%
F7	787-797	4.2	4.38	0.51	95%
F8	785-797	4.7	4.39	0.50	99%

Table 5: In- vitro Drug release study of Sustained release Tab (F1-F4)

Formula	Drug Release						
	0hr	2hr	4hr	6hr	8hr	10hr	12hr
F1	0	47.16	58.220	72.96	75.08	78.09	85.46
F2	0	41.91	65.25	74.18	79.54	88.81	92.83
F3	0	47.05	67.04	75.86	79.32	74.41	74.18
F4	0	43.14	66.26	73.63	80.88	77.87	67.48

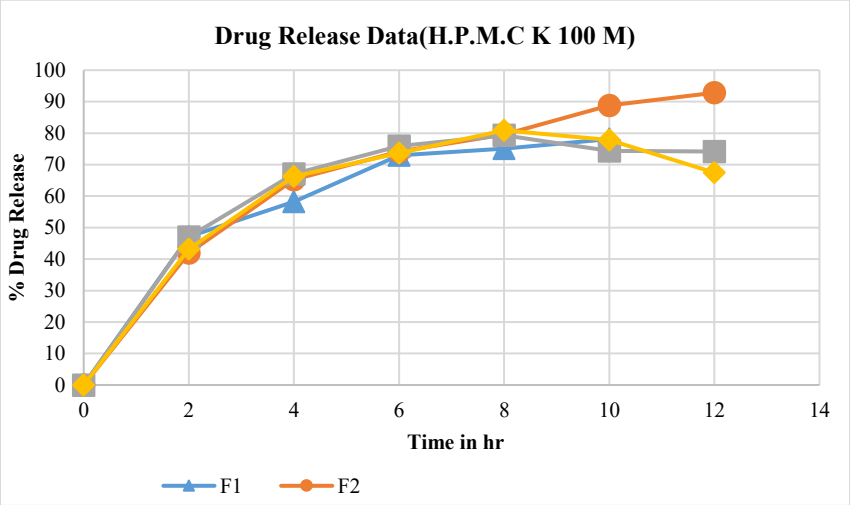


Fig 2: Drug release data of Tablets made by HPMCK100

Table 6: In-vitro drug release study of sustained release tablets(F5-F8)

Formula	Drug Release						
	0hr	2hr	4hr	6hr	8hr	10hr	12hr
F5	0	52.63	62.79	73.96	89.52	92.38	83.90
F6	0	46.71	69.05	88.25	96.04	82.01	87.25
F7	0	40.35	52.30	58.22	77.76	83.34	80.77
F8	0	33.096	48.72	68.49	74.30	80.44	83.12

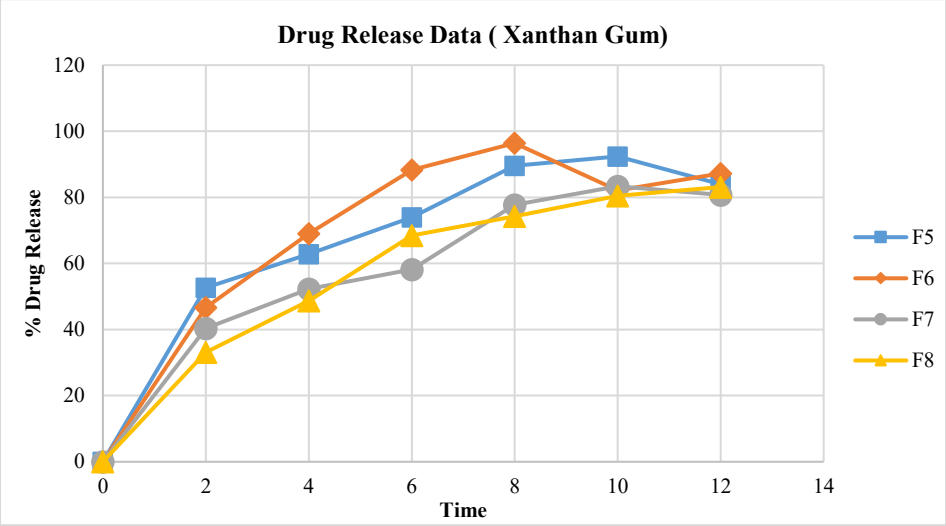
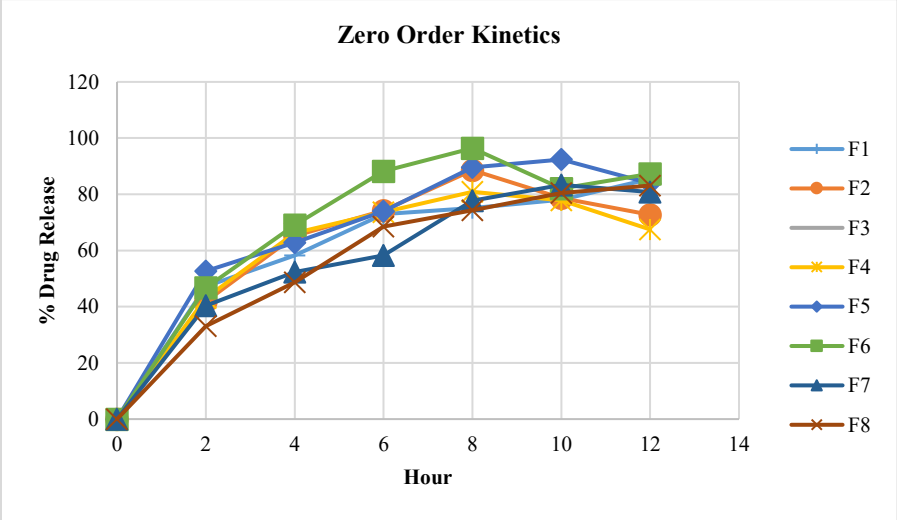


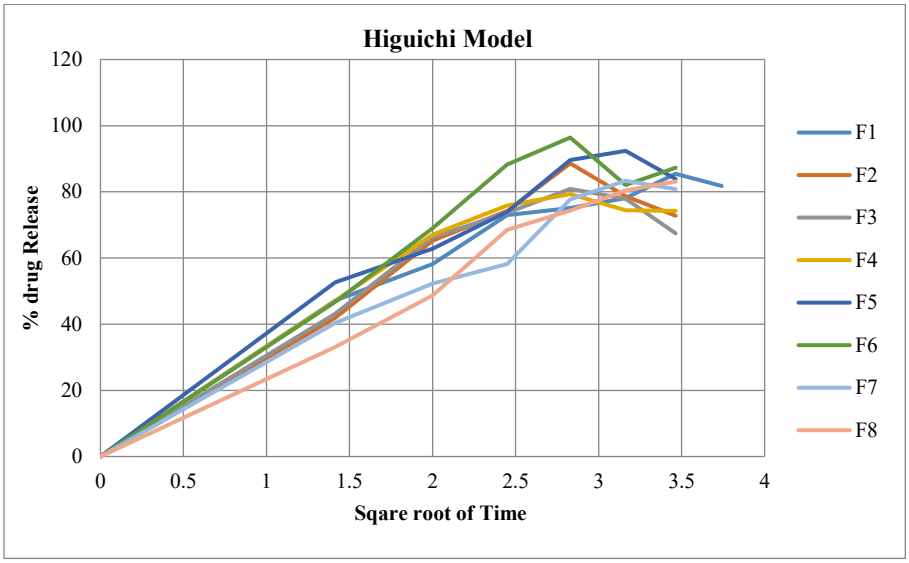
Table 7: Release kinetics data for optimized formula

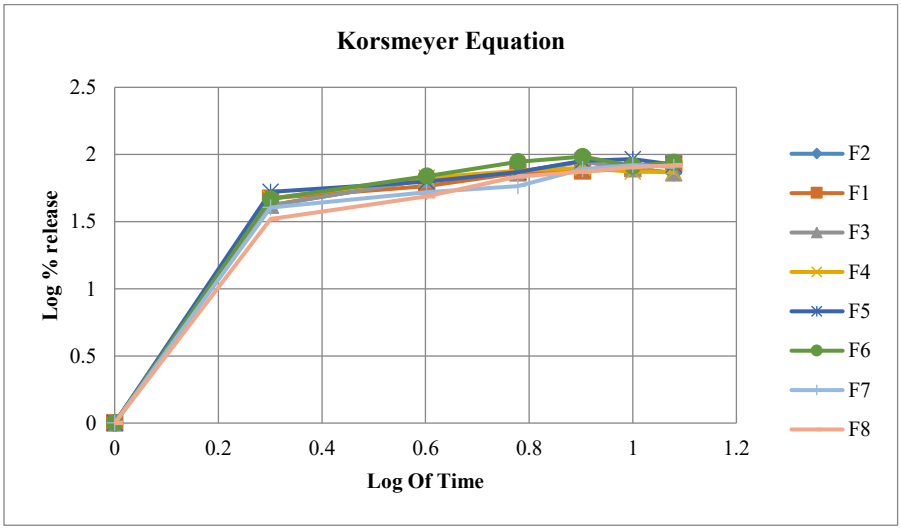
Formula	Zero order Study	First order Study			Higuichi Study			Korsmayer Study		
	N	C	R^2	N	C	R^2	N	C	R^2	N
F1	5.984	23.66	0.780	0.113	0.892	0.490	24.14	6.7246	0.962	1.324
F2	6.625	26.44	0.640	0.111	0.902	0.474	23.67	8.376	0.866	1.463
F3	5.116	27.76	0.597	0.108	0.912	0.455	22.06	10.18	0.841	1.431
F4	5.170	28.67	0.617	0.108	0.922	0.451	22.25	11.00	0.865	1.426
F5	6.393	26.68	0.741	0.114	0.917	0.482	26.08	7.967	0.933	1.479
F6	6427	28.55	0.674	0.115	0.921	0.479	26.76	8.553	0.885	1.502
F7	6.317	18.20	0.853	0.116	0.845	0.531	24.54	2.389	0.975	1.478
F8	6.600	15.85	0.881	0.119	0.814	0.561	25.36	-0.051	0.985	1.517

N is a slope and C is Concentration and R^2 Is intercept




First Order Reaction
Log% Amount Release
Time
F5 First order
F1 First Order
F2 First Order
F3 first order
F4 First Order
F6 First order
F7 First Order
F8 First Order


Higuichi Model
% drug Release
Sqare root of Time
F1
F2
F3
F4
F5
F6
F7
F8


Korsmeyer Equation
Log % release
Log Of Time
F2
F1
F3
F4
F5
F6
F7
F8

Drug- Excipient Comparative study

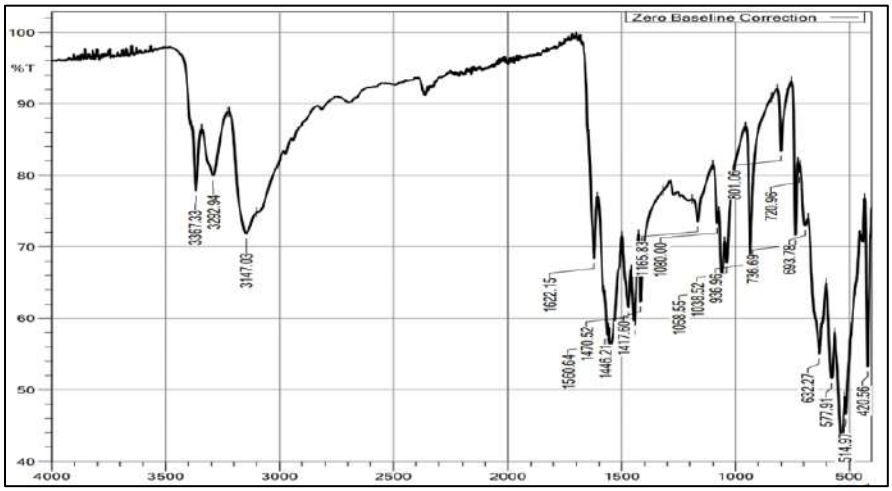


Fig 3: FTIR data OF Metformin Hydrochloride

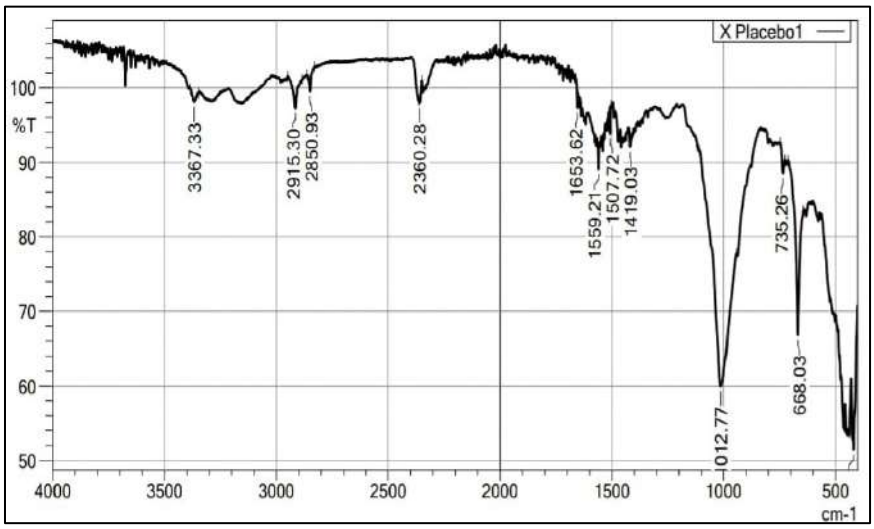


Fig 4: FTIR data for the Optimized H.P.M.C. K 100 Formula

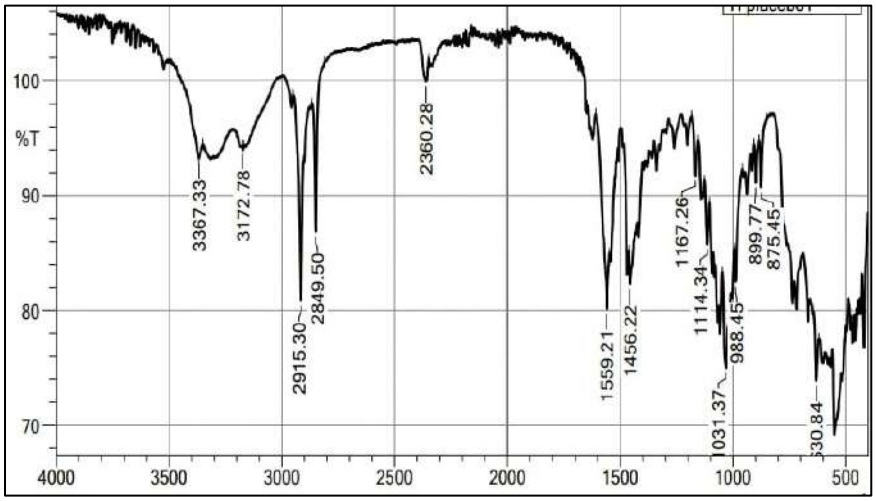


Fig 5: Optimized Formula of Xanthan Gum FT-IR Data

DISCUSSION

Drug and Polymer Physical Interaction Research Discussion-

FTIR analyses demonstrated that metformin hydrochloride displayed two types of bands at 3367.33 cm-1 and 3292.94 cm-1 due to N-H primary stretching vibration and a band at 3147 cm-1 due to C-H secondary stretching, as well as characterized bands at 1622 cm-1 assigned to C=N stretching. No significant modifications in the FTIR bands of metformin HCL's intensity were noticed.

Tablets Characteristics-

All of the tablets from different formulations showed positive findings for weight variation, medication content homogeneity, and friability. When tablet weights were determined, it was confirmed that all formulation weights were within pharmacopoeia's bounds. The changes in tablet radius were not statistically significant ($P > 0.05$) since all formulations were punched with the same simple punch, which had the same radius. The friability of the tablet was well within the acceptable range of 1%, indicating that the tablet surfaces are robust enough to withstand mechanical shock or attrition throughout storage, transportation, and until they are consumed. Since the average percentage deviation of all tablet formulations was found to be within the above limit, all formulations were found to have met the uniformity of weight requirement according to official standards. (14)The manufactured tablets had a high degree of homogeneity in the drug content across multiple batches of the tablets, a drug content of more than 99%, insignificant weight variations, and a drug content of more than 99%.

Drug Release Studies- The results of the dissolution trials, which are shown above, reveal that Formulations F1, F2, F3, and F4 release different amounts of drug at different times. For example, Formulation F3 releases 74.18% of the medication after 8 hours, whereas Formulation F4 releases 67.18%. After two hours, formulations F5, F6, F7, and F8 release 52.63%, 46.71%, 40.35%, and 33.09% of the medication, respectively. Furthermore, F5, F7 release 92.38%, 83.34% in 10 hours, and 92.38%, 83.12% in 12 hours.

Release Kinetics- To explain the kinetics of drug release, data on the release of drugs from matrix tablets was examined in accordance with different kinetic equations. The top table shows the regression coefficient value (R2) for each batch after applying the regression coefficient method to analyze the data. Higuchi's equation was able to effectively depict the drug release profiles from each of these formulations in vitro since the plots showed the highest levels of linearity (R2 = 0.841-0.985). The Korsmeyer-Peppas equation was used to fit the data in order to validate the diffusion mechanism. The formulations showed high linearity (r2 = 0.656–0.748) and a slope (n) that ranged from 1.324–1.517.

CONCLUSION

The objective of the current study was to develop, assess, and improve the oral hypoglycemic medication metformin Hcl. There are a total of 8 formulations created using various concentrations of xanthan gum and HPMC 100. There are 20 tablets in each of the 8 formulations. Separately, the Granules are produced in a Mixer.

Bulk Density, Tapped Density, and Angle of repose are pre-compression parameters that show flow qualities throughout the data. The tablets are compressed using a single rotating compression machine, and post-compression parameters such weight variation, hardness, friability, disintegration, and dissolution parameter are assessed for the tablets. H.P.M.C. K 100 is used as a drug release controller in F1–F4, but xanthan gum is not used in F5–F8, and H.P.M.C. K 100 is not used as a drug release controller in F5–F8. Only 83% of the drug is released in the course of

12 hours in the F8 formulation, which results in a perfectly sustained release of the drug. The F8 composition included 23% xanthan gum, 500 mg of metformin, 5 mg of talc, and 10 mg of magnesium stearate as a lubricant. In light of the investigation, it can be said that Formulation F8 (which contained 23% xanthan gum) can be manufactured as a sustained release formulation.

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