Available online on 15.07.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Formulation and *In-Vitro* Evaluation of Metformin Hydrochloride Sustained Release Tablets

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ABSTRACT

The objective of the present study was to study the effect of hydrophilic polymers on sustained release of metformin hydrochloride from tablets. Compatibility was studied by Fourier transform infrared spectroscopy. The tablets were prepared by direct compression technique using Xanthan gum alone and in combination with HPMC as release retardant. Di calcium phosphate was used as diluent. The prepared matrix tablets were evaluated for their physicochemical parameters such as weight variation, hardness, friability, content uniformity and in-vitro dissolution. Pre and post compression parameters were evaluated and all the parameters were found within the limit. The drug release data were subjected to different models in order to evaluate release kinetics and mechanism of drug release. Formulation F5 was selected as best formulation. The dissolution of formulation F5 can be described by first order kinetics with fickian diffusion as the release mechanism.

Keywords: Matrix tablets, Metformin hydrochloride, Xanthan gum, HPMCK4M and HPMCK15M.

Article Info: Received 04 May 2019; Review Completed 11 June 2019; Accepted 18 June 2019; Available online 15 July 2019

Cite this article as:

Eswaraiah C, Jaya S, Formulation and *In-Vitro* Evaluation of Metformin Hydrochloride Sustained Release Tablets, Journal of Drug Delivery and Therapeutics. 2019; 9(4):24-29 **http://dx.doi.org/10.22270/jddt.v9i4.3121**

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INTRODUCTION

Diabetes is one of the major causes of death and disability in the world. Diabetes is a condition that impairs the body's ability to process blood glucose [1]. Diabetes mellitus is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action or both [2]. Diabetes mellitus can be classified into two main types. First is type I or juvenile diabetes which is also called as insulin dependent diabetes and second is type II or non insulin dependent diabetes mellitus. Type II diabetes is most common type of diabetes, according to the national institute of diabetes. The type II diabetes mellitus usually develops more in the adult age, affecting mainly the elderly and obese individuals. Metformin hydrochloride is a first line biguanide hypoglycemic agent used in the treatment of non insulin dependent diabetes mellitus, not responding to dietary modification. It does not produce lactic acidosis. Metformin improves glucose tolerance by lowering both basal and post prandial glucose by decreasing intestinal absorption of glucose, decreasing hepatic glucogenesis, lipogenesis and glucose uptake by adipocytes and muscle cells[3]. It is on the world health organization's list of essential medicines the most effective and safe medicines needed in a healthy system. Its oral bioavailability is 50-60% and its average elimination half life is 6.2 hours, require repeated administrations of high doses to maintain effective plasma concentrations, thus reducing patient compliance and enhancing the incidence of side effects.[4-7] Many studies have reported that the oral absorption of metformin is mainly confined to the small intestine. This could be attained by the development of sustained release matrix tablets. Administration of sustained release tablets of metformin hydrochloride could reduce the dosing frequency and improves patient compliance [8, 9].

Sustained release oral drug delivery systems are designed to achieve therapeutically effective concentrations of drug in systemic circulation over an extended period of time. Matrix systems are most popular among oral drug delivery systems because of their simplicity, low cost, ease of manufacturing, reduced dose frequency, improved patient compliance and efficacy [10]. In a matrix system drug was dispersed as solid particles within a porous matrix former of a hydrophilic or hydrophobic polymer, drug release from the tablet was controlled by the nature and properties of polymer. Hydrophilic polymers such as xanthan gum and HPMC which have been utilized individually or in blends to design hydrophilic matrix tablets to achieve controlled drug delivery dosage forms generally have reduced frequency of dosing, increased compliance, increased therapeutic effect, reduced side-effects, improved tolerability and reduced cost of treatment. Blending different hydrophilic polymers improves the physicochemical and release modifying properties of the resultant polymer leading to the design and

formation of an optimized controlled-release product and the proper selection of polymers can help control the release profile of drugs. Hydrophilic matrix systems undergo swelling followed by gel formation, erosion and dissolution in aqueous media. In addition, such systems can sustain high drug loading [11].

The aim of this study was to prepare matrix tablets of metformin hydrochloride using varying proportions of the HPMCK4M, HPMCK15 and xanthan gum.

MATERIALS &METHODS

Materials

Metformin hydrochloride was purchased from Yarrow chemical Ltd., (Mumbai, India)., HPMCK4M, HPMCK15M, Xanthan gum dicalcium phosphate purchased from research lab (Mumbai, India) talc and magnesium stearate were purchased from Aman scientific traders Vijayawada (India). All other chemicals, solvents and reagents used were of analytical grade.

Methods

Drug excipient compatibility study

Infrared spectra of the pure drug and drug with polymers were recorded on a fourier transform infra red spectrophotometer. The disc method was employed to study possible interactions between drug and selected polymers. Infrared spectrum was taken by scanning the sample in KBr (IR grade) discs and analyzed over a wave number range of 4000-400 cm^{-1}.Transmittance spectra were recorded.

Preparation of matrix tablets

Matrix tablets of metformin hydrochloride were prepared by direct compression technique using varying proportions of hydrophilic polymers alone and in combination. The composition of matrix tablets is given in table -1. All the ingredients were individually passed through a 60 mesh sieve, except glidant and lubricant. For each formulation required quantities of metformin hydrochloride, polymer (HPMC, xanthan gum), diluents (dicalcium phosphate) were accurately weighed according to the composition and mixed in a polybag for about 30 to 45 minutes. The obtained blend was lubricated with talc and magnesium stearate for another 5 minutes. The appropriate amount of the mixture was weighed and then compressed using 12 station rotary tablet press (CEMACH, Ahmedabad, India) equipped with 12 mm flat faced punches at a constant compression force required to produce hardness of tablets about 5-7 kg/ cm^2. All the tablets were stored in airtight containers for further use.

Table 1- Composition of matrix tablets of metformin hydrochloride

Ingridients per tablets (mg)	Composition (mgs) of the prepared formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCL	500	500	500	500	500	500	500	500	500
Xanthan gum	250	300	350	-	-	-	-	-	-
XG+HPMCK4M	-	-	-	250	300	350	-	-	-
XG+HPMCK15M	-	-	-	-	-	-	250	300	350
Di calcium phosphate	230	180	130	230	180	130	230	180	130
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

Micromeritic properties of blended powder [12]

Angle of Repose

The frictional forces in a loose powder can be measured by the angle of repose. Angle of repose is defined as maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose was determined by the fixed funnel method. Angle of repose was calculated using the following equation.

$$tan\,\theta = \frac{h}{r}$$

Where, θ = angle of repose,

h = height of the pile,

r = radius of the pile base

Compressibility Index

The Carr's compressibility index of the powder blend is defines as

$$Carr's\ compressibility\ index = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100$$

Bulk density is the ratio of mass of powder to the bulk volume. Tapped density is the ratios of mass of powder to the tapped volume.

Evaluation of matrix tablets[13]

The prepared matrix tablets were evaluated for their physical properties like weight variation, hardness and friability and drug content.

Weight variation

Twenty tablets of each formulation were weighed individually using an electronic weighing balance. The average weight was calculated and individual tablet weight was compared with average weight.

Hardness Friability

The hardness of six tablets was measured by Monsanto hardness tester. Hardness of tablets was measured in terms of kg/cm^2

Friability

Friability of tablets was measured by using Roche friabilator. Ten tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were dedusted and reweighed. The friability was calculated using following equation.

$$Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Uniformity of drug content

Ten tablets were weighed from each formulation and triturated in mortar to a fine powder. Powder equivalent to 500 mg of metformin hydrochloride was extracted in 100 ml of p^H 6.8 phosphate buffer and liquid was filtered. The drug content was determined by measuring the absorbance at 233 nm (using UV-Visible spectrophotometer, Lab India) after appropriate dilution with p^H 6.8 phosphate buffer. The drug content was determined using calibration curve.

In vitro dissolution study

The in-vitro dissolution study of matrix tablets of metformin hydrochloride was performed using USP type II dissolution apparatus (DBK) at a rotational speed of 50 rpm. In order to simulate gastrointestinal transit conditions, the tablets were subjected to different dissolution media. The dissolution medium used were 900 ml of p^H 1.2 buffer for first two hours and p^H 6.8 phosphate buffer for next ten hours. The dissolution medium was maintained at a temperature of 37 ± 0.5^0 C. At predetermined time intervals, 5 ml of the sample solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium to maintain sink conditions. The collected samples were filtered through a 0.45 µm membrane filter and the drug content in each sample was analyzed by measuring absorbance at 233 nm after suitable dilution using UV-spectrophotometer (LABINDIA). Cumulative percentage of drug release was calculated using equation obtained from a calibration curve.

***In- vitro* drug release kinetic study**

To study the release mechanism of metformin hydrochloride from the sustained release matrix tablets, the invitro drug release data were fitted to the following the mathematical models:

Zero order	$Q_t = Q_0 + k_0 t$	(1)
First order	$\log C = \log C_0 - k_1 t/20303$	(2)
Higuchi	$Q_t = k_h t^{½}$	(3)
Korsmeyer – Peppas	$Q_t/Q_\alpha = k_p t^n$	(4)
Hixon- Crowell cube root	$(W_0^{1/3} - W_t^{1/3}) = k_h t$	(5)

Where Q_0, Q_t and Q_α are the amounts of drug dissolved initially, at time t and at time infinite. C_0 and C are the concentrations of drug initially and at time t, W_0 and W_t are the amounts of drug in the pharmaceutical dosage form initially and at time t and k_0, k_1, k_h and k_p refer to the rate constants obtained from the linear curves of the respective models. n is the diffusional exponent that characterizes the mechanism of drug release. The values of the coefficient were calculated using regression analysis between log Q_t/Q_α and log time. The diffusional exponent n value was obtained from the slope of the regression equation and k_p was calculated from antilog of the intercept value.

If the value of n for a cylinder is < 0.45 it suggests the Fickian release (diffusion controlled), if n > 0.45 and < 0.89 it is non – Fickian release (diffusion and polymer relaxation), 0.89 is case II release (only relaxation and swelling) and > 0.89 it suggests super case II release (relaxation and erosion) for swellable systems

For cylindrical systems like tablets, the n values of 0.45 and 0.89 represent pure diffusion or erosion release respectively[14].

RESULTS AND DISCUSSION

Powder characterization

The powder mixture of all the formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and their values were shown in table 2. The bulk densities and tapped densities were 0.78±0.01 to 0.81±0.03 g/cm^3 and 0.88±0.02 to 0.92±0.01 g/cm^3 respectively. Powder blend indicated good flow properties with an angle of repose values ranging from 29 to 33^0. The Carr's compressibility index for all the formulations were found to be less than 13 %, which indicates that the powder mixture has good flow properties. Hausner's ratio was also calculated, the ration was ranged between 1.11 and 1.15.

Table 2: Micromeritic properties of formulation blends

Formulation	Bulk density (gm/cm^3)*	Tapped density (gm/cm^3)*	Compressibility index (%)	Hausner's ratio	Angle of repose(^{0})
F1	0.79±0.01	0.88±0.02	11.02	1.12	30.32
F2	0.78±0.02	0.89±0.01	12.30	1.14	29.96
F3	0.79±0.01	0.90±0.02	12.20	1.13	32.68
F4	0.80±0.03	0.90±0.01	11.27	1.12	31.54
F5	0.78±0.01	0.88±0.03	11.36	1.14	29.85
F6	0.81±0.03	0.92±0.01	12.57	1.14	32.42
F7	0.78±0.03	0.90±0.03	12.83	1.15	30.64
F8	0.79±0.02	0.88±0.02	10.22	1.11	31.36
F9	0.80±0.02	0.91±0.02	12.08	1.13	32.52

*All values are expressed as mean ± SD, n=3

Evaluation of physical parameters

Sustained release matrix tablets of metformin hydrochloride were prepared by direct compression technique. Total nine formulations were prepared. The tablet weight variation, hardness, friability and content uniformity for each formulation are shown in table 3. The weight variation test indicated that the percentage deviation of all tablet formulations was found to be within pharmacopoeial acceptable limit. The hardness of all the tablets was within the range of 5.24±0.09 to 6.46±0.12 kg/cm^2. The percentage weight loss in the friability test was found to be below 0.8 % in all the cases indicated that all the tablets had good mechanical strength. The drug content in all the batches was determined by measuring absorbance of sample at 233 nm using double beam UV spectrophotometer (LABINDIA). The content uniformity among different formulations was found to be higher and the drug content was more than 98% which indicates uniform drug distribution in all the formulations.

Table-3: Physical properties of metformin hydrochloride matrix tablets

Formulation	Weight variation (mg)*	Hardness (kg/cm²)#	Friability (%)	Content uniformity (%)
F1	988.89±1.62	5.24±0.09	0.76	98.92
F2	989.64±1.43	5.56±0.13	0.72	99.68
F3	989.57±1.54	5.72±0.12	0.70	98.23
F4	988.75±1.46	6.24±0.08	0.64	101.36
F5	989.23±1.82	6.45±0.13	0.68	99.86
F6	988.29±1.56	6.46±0.12	0.67	100.16
F7	989.38±1.67	6.24±0.14	0.69	99.74
F8	989.65±1.72	6.32±0.07	0.65	98.86
F9	989.62±1.88	6.36±0.08	0.59	99.75

*All values are expressed as mean ± SD, *n=20; #n=6.

In vitro dissolution study

Metformin hydrochloride release from the matrix tablets was studied for first two hours in p^H 1.2 buffer and the next ten hours in p^H 6.8 phosphate buffer. Total nine formulations were made with Xanthan gum alone and combination of xanthan gum with HPMCK4 and HPMCK15 in different ratios. The results of dissolution studies indicated that the first three formulations with Natural hydrophilic polymer, Xanthan gum alone released 46.82, 40.36 and 35.85% of drug at the end of 2 h and 98.42, 85.64 and 76.84% of drug at the end of 6 h. Formulations containing HPMCK4M in combination with xanthan gum released 37.36, 28.36 and 26.36 % at the end of 2 h and 99.82, 98.63 and 95.66 % at the end of 12 h. Formulations containing HPMCK15M in combination with xanthan gum released 30.69, 24.83 and 19.38 % at the end of 2 h and 98.58, 90.43 and 82.26 % at the end of 12 h. Marketed formulation Glycomet from USV showed 23.24% at 2h and 98.48% at 12h. The comparative dissolution profile of all the formulations is given in fig.-1. The results shown in fig.- 1 indicate that the release rate of metformin hydrochloride from all the sustained release matrix tablets was dependent on concentration of release retardant contained in the tablet. The drug release rate was decreased from the tablets as the concentration of release retardant was increase. Xanthan gum alone could not control the release of metformin hydrochloride from the tablets because burst release was observed due to high dose of drug. Two grade of hydroxyl propyl methyl cellulose could control the drug release when combined with high molecular weight xanthan gum up to 12 h. This may be due to the formation of thick gel layer around the tablets by quick hydration of xanthan gum. These results indicated that the Xanthan gum could control the release of metformin hydrochloride up to 12 hrs when it combined with hydroxy propyl methyl cellulose (semi synthetic).

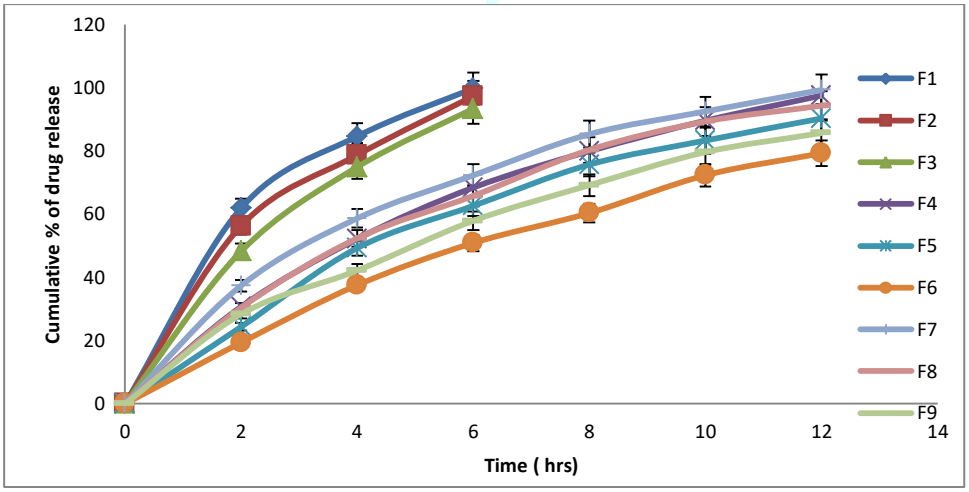

Fig.- 1: Comparative *in-vitro* dissolution profile of all the formulations mean ± SD, n=3.

Analysis of release data

The release data of matrix tablets were fitted into various mathematical models (zero order, first order, higuchi, Peppas and hixon crowel) to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient value in various models. The model that gives high R^2 value considered as the best fit of the release data. The kinetic parameters for metformin hydrochloride release from the matrix tablets are shown in table 4. The results indicated that the drug release from the matrix tablets were followed first order kinetics. To evaluate drug release mechanism from the matrix tablets plots of percent drug released verses square root of time as per Higuchi's equation were constructed. The invitro release profiles of drug from all the formulations could be best expressed by higuchi equation as the plots showed high linearity with correlation coefficient values were in the range of 0.988 to 0.998. Release of the drug from the matrix tablets containing hydrophilic polymers generally follows diffusion. Diffusion is related to drug transport from the matrix tablet into the dissolution fluid. To confirm the diffusion mechanism, the *invitro* data was fitted into Koresmeyer's Peppas equation. For matrix tablets release exponent an 'n' value of near 0.5 indicates diffusion control and an 'n' value of near 1 indicates erosion or relaxation control. Intermediate values indicates that diffusion and erosion as the release mechanism. The release exponent 'n' values were found to be in the range of 0.39 -0.50 indicating that the fickian diffusion is the mechanism of drug release from the matrix tablets.

Table 4: Correlation coefficients and release exponent n according to the different kinetic equations used for describing metformin hydrochloride release behavior from sustained release matrix tablets.

Formulation	Zero order	First order	Higuchi	Peppas		Hixon-Crowell
				R^2	n	
F1	0.865	0.923	0.998	0.999	0.42	0.975
F2	0.839	0.922	0.987	0.991	0.39	0.974
F3	0.894	0.935	0.993	0.993	0.45	0.983
F4	0.890	0.942	0.998	0.999	0.46	0.984
F5	0.833	0.933	0.993	0.997	0.50	0.947
F6	0.894	0.935	0.993	0.993	0.45	0.983
F7	0.897	0.818	0.990	0.993	0.43	0.934
F8	0.917	0.979	0.995	0.996	0.51	0.984
F9	0.963	0.987	0.988	0.992	0.50	0.990

Drug excipient compatibility study

Fourier transform infra red spectroscopy studies revealed that pure metformin hydrochloride and best formulation showed two typical bands at 3368.99 and 3289.11 cm^{-1} due to N-H primary stretching vibration and a band at 3151.40 cm^{-1} due to N-H secondary stretching, a weak intensity band at 1058 cm^{-1} assigned to C-N stretching vibration and characteristics strong absorption bands at 1622.33 and 1539.21 cm^{-1} assigned to C=N stretching vibrations. No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride were observed as shown in figure 2. From the FTIR spectra shown in fig 2, it is very clear that there are no interactions between drug and excipients. All the peaks responsible for the active functional groups were present in the best formulation (F5).

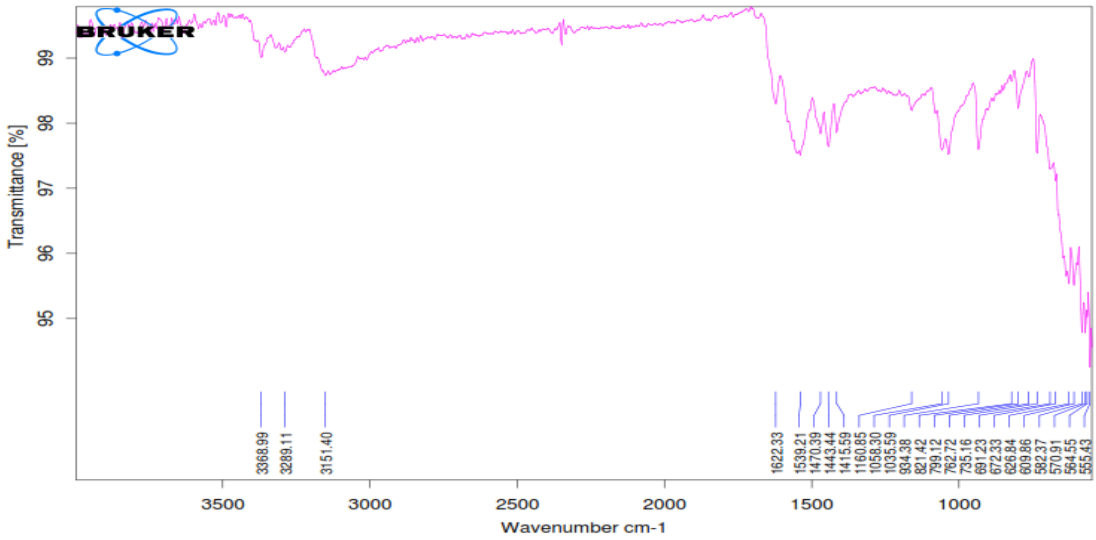

Fig.- 2 a) : FTIR spectra of pure metformin hydrochloride

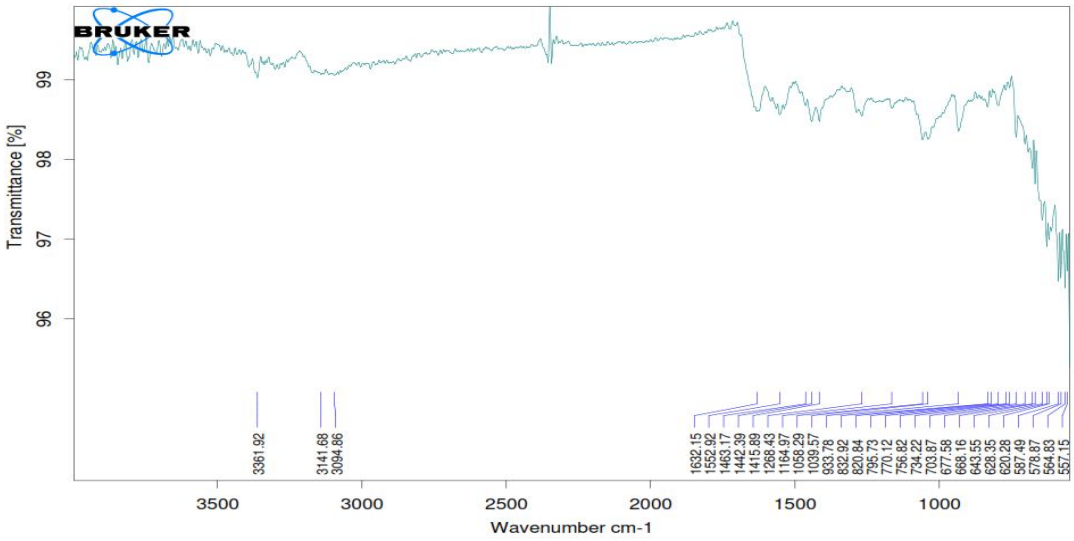

Fig.- 2 b) : FTIR spectra of metformin hydrochloride matrix tablet containing xanthan gum and HPMCK4 (F5)

CONCLUSION

Sustained release matrix tablets of metformin hydrochloride were prepared using different ratios of xanthan gum and HPMCK4 and HPMCK15 cellulose by direct compression method. The results of the present study demonstrates that the xanthan gum alone could not control the metformin hydrochloride release effectively for 12 hrs, where as when combined with HPMCK4 and HPMCK15M, it could control the release of metformin hydrochloride from their matrices. It is concluded that sustained release of metformin hydrochloride over a period of 12 hours was obtained with formulation (F-5) containing xanthan gum and HPMCK4. The mechanism of drug release from the matrix tablets was found to be diffusion controlled i.e fickian diffusion with first order kinetics. Sustained release matrix tablets of metformin hydrochloride can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional metformin hydrochloride tablets.

ACKNOWLEDGEMENT

The authors are thankful to the principal and management of Anurag Pharmacy College, for providing necessary facilities to carry out this work.

CONFLICT OF INTERESTS

Declared none.

AUTHORS CONTRIBUTION

All the authors have contributed equally

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