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Formulation and *in vitro* evaluation of Metformin HCl mucoadhesive tablets for NIDDM

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Abstract

The objective of the present work was to develop an oral Mucoadhesive Metformin hydrochloride tablet for the sustained-release. Metformin hydrochloride (HCl), a biguanide, has a relatively short plasma half-life and low absolute bioavailability. The tablets were prepared by the Wet Granulation method, using biodegradable mucoadhesive polymer Xanthan gum and pectin at different concentrations. All the batches were evaluated for thickness, weight variation, hardness, drug content uniformity, *in vitro* drug release and mucoadhesion strength. Mean dissolution time is used to characterize the drug release rate from a dosage form, and indicates the drug release-retarding efficiency of the polymer. The *in vitro* studies the formulations containing Pectin showed less retardation than the formulation with Xanthan gum. The Metformin release effectively controlled for 12 h with Xanthan gum, thus, can be successfully employed for formulating mucoadhesive tablets. Fitting the data to the Zero order and Higuchi equation indicated the mechanism of drug release. The study reveals that Xanthan gum highest mucoadhesive strength compared with pectin.

Keywords: Metformin hydrochloride, Xanthan gum, pectin, mucoadhesive tablets.

1. Introduction

Mucoadhesive drug delivery is a topic of interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and thereby to facilitate the intimate contact of dosage form, thus to improve and enhance the bioavailability [1]. The desired characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good mucoadhesive properties, smooth surface, tastelessness, and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval [2]. The mucous area, majorly used for the drug administration and absorption, is gastrointestinal mucus. The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption [3].

In the present research, an attempt was made to develop mucoadhesive tablet of Metformin HCl (MH) using Xanthan gum, and Pectin polymers. Metformin HCl, chemically N,N-Dimethyl imido dicarbonimidic diamide, is a biguanide anti hyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM). The half-life of metformin is 3 hrs. It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract, and the absolute bioavailability of a single 250 mg dose is reported to be 50% to 60%. This indicates the need to develop dosage forms that can retain the drug in the stomach for better absorption. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhoea that especially occur

during the initial weeks of treatment [4]. The compound also has relatively short plasma elimination half-life (1.5-4.5hrs). Sustained release formulations may be administered once or twice daily [5]. The present work was aim to formulate and evaluate Metformin HCl Mucoadhesive tablets by using natural biodegradable polymers such as Xanhane gum and Pectin. The ultimate intend to use those polymers possess anti diabetic activity to synergies effect of drug, controlled release rate with extend period for 12 hours to increase bioavailability, reduce the dosing frequency of Metformin Hcl fluctuation in therapeutic blood level is avoid the patience compliance for in the management of type-II diabetes.

2. Materials and methods

2.1 Materials

Metformin HCl was received as a gift sample from Yarrow Chemicals, Mumbai, Xanthan gum and Pectin was purchased from S.D. Fine chemicals, Mumbai, Magnessium stearate, Talc and Microcrystalline cellulose were obtained NICE laboratory reagent Cochin. All other ingredients were used in analytical grade.

2.2 Compatibility study drug with polymer by Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure drug, individual polymers and optimised formulations were subjected to FTIR study. About 2-3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1}.

2.3 Preparation of Mucoadhesive tablet

Mucoadhesive tablets were prepared by the wet granulation technique using Isopropyl myristate. The powders (F1-F10) were blended and granulated with Isopropyl myristate. The obtained wet mass was pass through sieve number 16 (mesh size: 1000 µm) and the granules were dried at 50ºC for 2h. The dried granules were pass through sieve no.25 (mesh size: 650 µm) and were lubricated with mixture of talk and magnesium stearate in definite proportion. The lubricated granules were compressed using 10 stations Cadmach Mini Rotary Tablet Press [6, 7]. The composition of various formulations was given in (Table 1).

Table 1: Composition of Metformin HCl Mucoadhesive formulation

Ingredients	Formulation Code									
	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
Metformin HCl	250	250	250	250	250	250	250	250	250	250
Pectin	25	50	75	100	125	-	-	-	-	-
Xanthan gum	-	-	-	-	-	25	50	75	100	125
MCC	160	135	110	85	60	160	135	110	85	60
Mg. Stearate	10	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10	10
Total Weight	455	455	455	455	455	455	455	455	455	455

2.4 Evaluation of Tablet:

***2.4.1Tablet weight variation*:** Twenty tablets were randomly selected and accurately weighed and were evaluated for weight variation.

2.4.2 Tablet thickness: A vernier calliper was used to determine thickness of 10 randomly selected tablets.

***2.4.3 Drug content uniformity*:** For drug content uniformity, 20 tablets were weight and crushed. An accurately weighed 0.05 g drug equivalent powder was transferred to 100 ml of 0.1 N HCl. This suspension was stirred on a magnetic stirrer for 5 h. The suspension was then filtered and the drug content was determined at 233 nm by making suitable dilutions.

***2.4.4 Tablet friability*:** According to the BP specifications, 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus. The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, de dusted and accurately weighed. The percent weight loss was calculated [8].

2.5 *In vitro* drug release study for mucoadhesive tablet

In vitro release profile for each formulated tablet was performed using USP type II dissolution apparatus (Electrolab, Mumbai, India). Dissolution studies were carried at rotation speed of 100 RPM, in 900 ml of Phosphate buffer of pH 6.8 at 37 ± 0.50ºC. Aliquot of 5 ml was withdrawn from 30 min to 12 hrs. The withdrawn volume was replaced with same volume of dissolution medium in order to keep the total volume constant. The absorbance of sample was measured by an UV spectrophotometer at 233 nm after suitable dilution if necessary. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug [9].

2.6 Kinetic modeling of in vitro drug dissolution profile

In vitro drug release data of all the Mucoadhesive tablet formulations of Metformin HCl was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetics and according to Higuchi's

and Korsmeyer-Peppas models to ascertain mechanism of drug release [10].

2.7 Measurement of ex-vivo mucoadhesive strength

Bioadhesive strength of the tablets was measured on modified physical balance. A piece of goat stomach mucosa was pasted to a petri-dish with cyanoacrylate adhesive and the mucus membrane was wetted with 2-3 drops of 0.01 N HCl media. The tablets were tied with thread and attached with the mucous membrane. Another end of thread tied with one side of the physical balance. The weight required to detach the tablet from the mucosal surface was taken as the measure of mucoadhesive strength [11]. Force of adhesion was calculated from the mucoadhesive strength as per following equation:

Force of adhesion (N) =

(Mucoadhesive strength × 9.81) ÷ 100

2.8 Acceleratory Stability Studies:-

Accelerated stability studies formulated Metformin HCl mucoadhesive tablet were carried out as per ICH guidelines. Stability studies were carried out at 40ºC / 75% RH for the optimized formulation (F9) for 3 months. The matrix tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month. The samples were analyzed for its hardness, drug content and *In vitro* drug release.

3. Result and discussion

3.1 Compatibility study drug with polymer Fourier transforms infra-red spectroscopy (FTIR)

FTIR studies revealed that Metformin hydrochloride showed (**Figure-1**) two typical bands at 3369 and 3296 cm^{-1} due to N-H primary stretching vibration and a band at 3170 cm^{-1} due to N-H secondary stretching, and characteristics bands at 1626 and 1567 cm^{-1} assigned to C=N stretching. No significant shifts of reduction in intensity of the FTIR bands of Metformin hydrochloride were observed. The major peaks are identical to functional group of Metformin HCl [12]. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

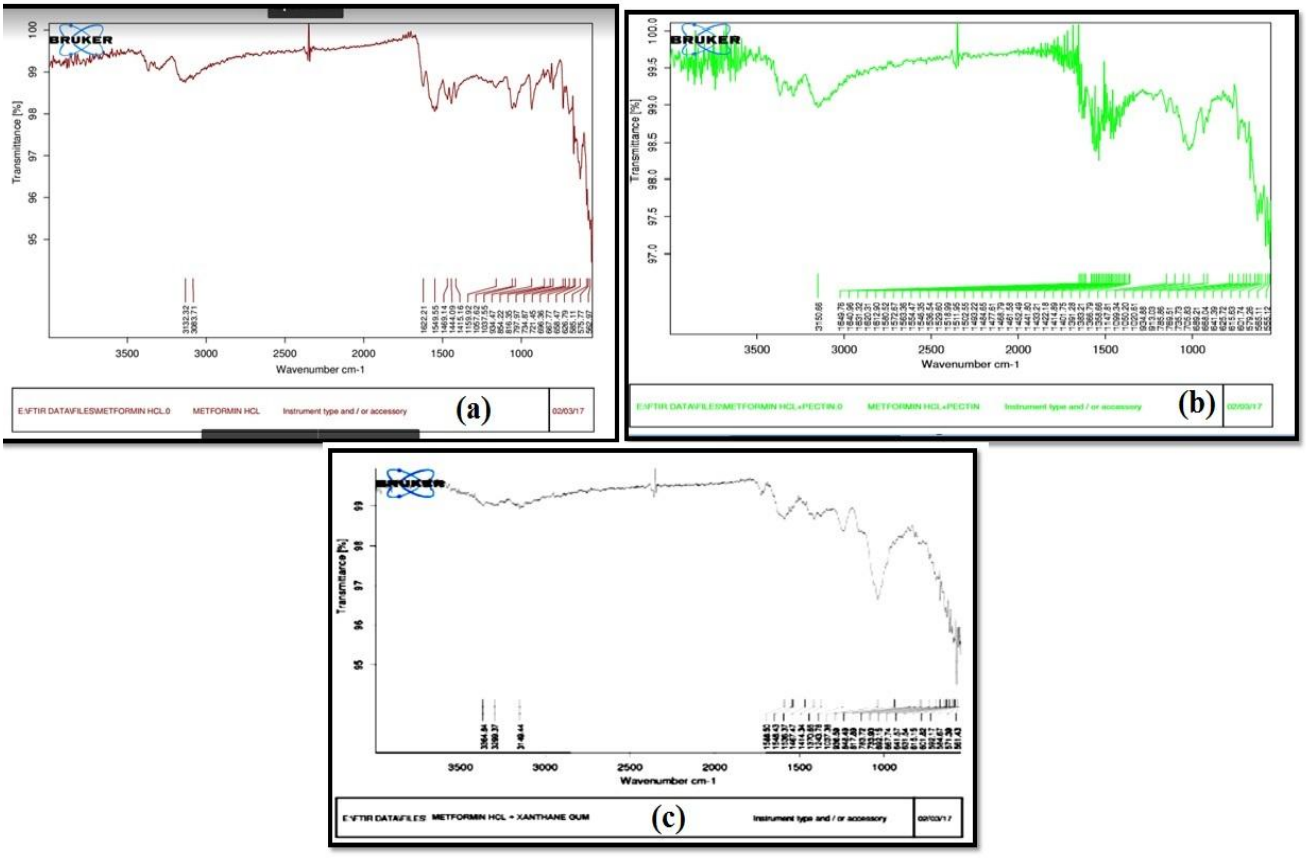

Figure 1: FTIR spectrum (a) Metformin HCl, (b) Metformin HCl + Pectin (c) Metformin HCl + Xanthan gum

3.2 Physical evaluation

The prepared mucoadhesive tablets were evaluated for various physical parameters such as weight variation, hardness, friability and drug content (**Table 2**). All the batches were produced under conditions to avoiding processing variables. Physical evaluation of compressed matrix tablets showed all physical parameters to be within specifications. The weight of the formulations was found to be in the range of 450±0.6 to 455±0.2 mg, the Thickness of the tablets was ranged from 5.1±0.01 to 5.8±0.03 mm, the Hardness of the tablets ranged from 4.00±0.08 to 5.5±0.11 kg/cm^2, and the friability values were less than 0.8% indicating that the tablets were compact and hard. All the formulation with content uniformity of the drug as they contains 98.71 ± 0.36 to 99.5±0.34 of Metformin HCl.

Table 2: Physical parameters data of Metformin HCl Mucoadhesive tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	452±0.6	4.5±0.23	5.5±0.04	0.71	99.03±1.34
F2	451±0.7	4.6±0.08	5.6±0.01	0.78	98.85±0.97
F3	454±0.5	4.8±0.09	5.4±0.01	0.68	99.19±0.91
F4	451±0.5	4.9±0.12	5.0±0.04	0.64	99.11±0.69
F5	453±0.4	5.0±0.07	5.1±0.02	0.14	98.91±0.56
F6	454±0.3	4.7±0.13	5.7±0.01	0.13	98.95±0.83
F7	454±0.7	4.9±0.07	5.4±0.02	0.21	99.15±0.86
F8	451±0.4	5.1±0.11	5.8±0.03	0.11	99.45±0.36
F9	455±0.2	5.4±0.11	5.1±0.01	0.14	99.95±0.34
F10	450±0.6	5.4±0.09	5.2±0.04	0.09	98.71±0.36

3.3 *In-Vitro* dissolution studies

In vitro dissolution studies of all the formulations of sustained release tablets of Metformin HCl were carried out in 0.1N HCl for first 2 hours and pH 6.8 phosphate buffers for next 10 hours respectively. The study was performed for 12 hours, and percentage drug release was calculated at 30 min to 12 hours with precise time intervals. The results of *in vitro* dissolution studies of all formulations were shown in (**Figure 2** and **3**).

The drug release rate from Pectin was found to be less as compared to xanthan gum. This might be due to slow hydration of its property to form a thick gel layer, which retards the drug release from the tablet. The formulations code F1- F5 containing pectin as a mucoadhesive material which is used as a thickening and gelling agents in pharmaceutical preparation.

In F1 and F2 the drug release was sustained only for 8 - 10 h. Because the concentration of Pectin is less than drug so it releases faster thus % drug release was out of acceptance criteria. In F3 concentration of pectin was 50% so moderate sustained release was obtained compare to F1 and F2. But in F4 and F5 the sustained release was slow compare to F3 because the concentration of Pectin was 75%. From F1-F5 the best formulation was F3 because it release moderately.

In Formulation F6 - F10 containing Xanthan gum which is used as a thickening agents in pharmaceutical preparation. In F6, F7 and F8 the drug release was sustained only for 6 - 10 h.

Because the concentration of Xanthan gum was less compare to drug so it releases faster. In F9 concentration of Xanthan gum was 75 % but moderate sustained release was obtained compare to F6, F7 and F8 because at this Stage the polymer gives best thickening property compare to another concentrations. But in F10 the sustained release was slow compare to F9 because polymer concentration is more. Over all from F1-F10 optimised formulation is F9 because it release moderately compare to remaining.

The optimized formulation F9 giving comparative *in vitro* release behavior with the marketed formulation of Metformin HCl (Glycomet 250mg).

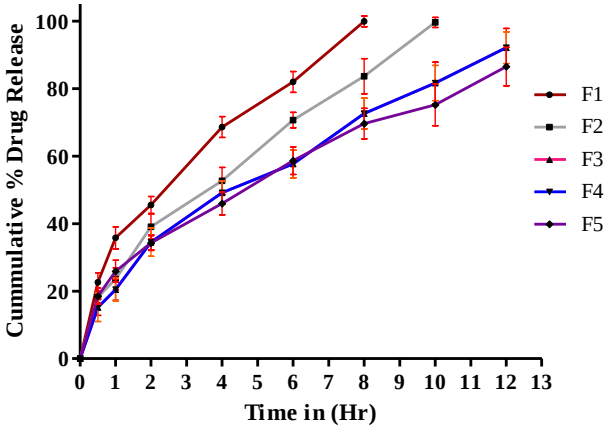

Figure 2: *In vitro* dissolution of formulation F1-F5

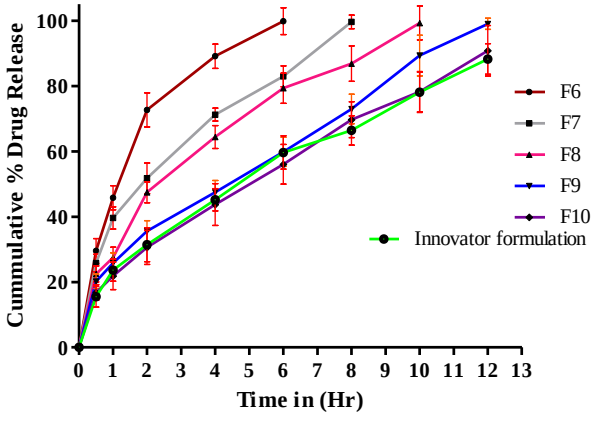

Figure 3: *In vitro* dissolution of formulation F6-F10 with Innovator formulation (Glycomet 250mg)

3.4. Release mechanism of kinetics

The results of in vitro release studies were also fitted into below models to investigate the release as follows:

The release kinetics data of optimized formulation F9 is mentioned in (**Table 3**). Based on the highest regression value 0.984 suggesting that the drug release was diffusion follows non-Fickian behaviour.

Table 3: Release data Kinetics

Model Name	Batch no	R^2
Zero order	F9	0.965
First order	F9	0.797
Higuchi	F9	0.984
Kors-peppas	F9	0.611

3.5 *Ex-vivo* Mucoadhesion strength determination

The mucoadhesive strength determination was performed using Modified Physical balance. The mucoadhesive strength all formulation were varied from 07.00 to 24.20g. The Formulation F1 has lowest Mucoadhesive strength and the formulation F9 has highest Mucoadhesive Strength .From this we conclude that the mucoadhesive strength increases with the increase in Polymer concentration, and decreases with decrease in Polymer concentration. The mucoadhesive performance of pectin less because it contain low amount of H-bond forming groups was mainly influenced by its high molecular weight which facilitates coil entanglement. The mucoadhesion of pectin, however, could be explained by a large amount of H-bond forming groups, which promote secondary chemical bond formation in mucoadhesion process [13]. The Xanthane gum higher degree of esterification demonstrated a stronger mucoadhesion, some carboxylic groups in the structure produce strong H-bond forming groups to strengthen the mucoadhesive bonding [14]. The rank order of mucoadhesive performance of examined pectins and Xanthane gum on to the GI mucosa appeared to be similar to the rank order of their degree of esterification and concentration of polymer (i.e. **F9 > F10 >F8 > F5 > F4 >F3> F7 >F2 >F6> F1**). This may be due to increase in availability of adhesive sites of natural polymer with mucin that tends to increase in bond strength. The results are shown in (**Table 4**) and (**Figure 4**).

Table 4: *In Vitro* Mucoadhesive Strength Study of Prepared Mucoadhesive Tablets

Formulation code	Mucoadhesive strength (gm) (mean ± SD)	Mucoadhesion force (n)
F1	07.00 ± 1.20	0.69
F2	16.50 ± 1.60	1.62
F3	19.40 ± 0.12	1.90
F4	20.10 ± 2.20	1.97
F5	21.40 ± 0.30	2.10
F6	14.00 ± 1.12	1.37
F7	17.40 ± 1.15	1.71
F8	22.15 ± 1.21	2.27
F9	24.20± 0.33	2.37
F10	23.15 ± 0.73	2.27

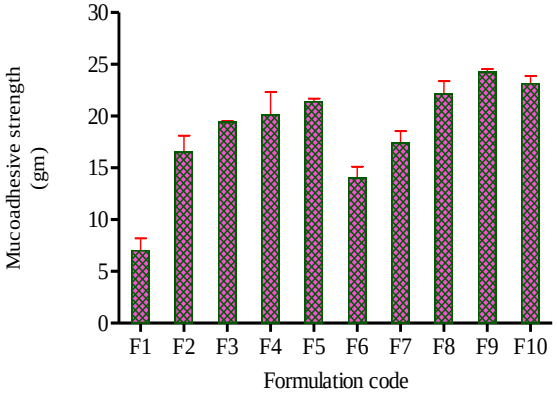

Figure 4: Mucoadhesive strength of formulations (F1-F10)

3.6 Accelerated stability studies

The optimized formulation, F9 was found to be stable for three months at accelerated stability conditions at a temperature (40 ± 2° C) and relative humidity 75 ± 5% as per ICH norms. Prominent changes in physical evaluation parameters like Weight variation, Thickness, Hardness, Friability, Assay and *in-vitro* drug release were not noticed and the formulation F9 was found to be stable even after exposing to accelerated temperature and humidity condition and (**Table 5**) gives the results of accelerated stability study data of optimized formulation (F9).

Table 5: Accelerated stability studies Temperature maintained 40° ± 2°C

Parameters	Time in month			
	0 (initial)	1 month	2nd month	3rd month
Hardness (kg/cm^2)	5.81±0.11	5.81±0.11	5.81±0.11	5.81±0.09
Thickness (mm)	5.5±0.073	5.5±0.070	5.5±0.070	5.5±0.070
Drug content (%)	99.67±0.34	99.52±0.32	99.50±0.25	99.50±0.13
In vitro drug release (%)	99.11	99.10	99.09	99.07

4. Conclusion

Pharmaceutical research is leading towards innovations in the area of drug delivery at much faster pace as compared to the last two decades. Vital aspects of a new drug delivery system are: improved patient compliance and effectiveness. Oral route offers an attractive and convenient route of drug administration. Mucosal delivery is one of the modes that allow rapid uptake of drug into the systemic circulation avoiding first pass metabolism. This attributes to the relative permeability of mucous membrane. This type of delivery system allows drug to circumvent some of the body's natural defence mechanisms. Mucoadhesion refers binding of materials to mucin layer of a biological membrane [15].

Metformin hydrochloride selected as active ingredients for this mucoadhesive formulations. The compatibility of the Xanthan gum and Pectin and blends of the above set with the active pharmaceutical ingredients was studied by FTIR. The study suggested that there was no

incompatibility between the drug and the polymer taken for the research.

Ten different tablet formulations containing Metformin hydrochloride with different proportions of Xanthan gum and Pectin were prepared. All the ten formulations that were subjected to analyze the Physical parameters, *in vitro* drug release, ex-vivo mucoadhesion strength and accelerated stability study. The formulation containing pectin F3 showed the drug release of 92.98 ±0.17 % at 12 h. The formulation containing pectin F3 showed the drug release of 92.98 ±0.17 % at 12 h. The Xanthane gum containing formulation (F9) showed following paramount results among all the formulation (Weight variation (mg) 455±0.2, Hardness (kg/cm^2) 5.4±0.09, Thickness (mm) 5.1±0.01, Friability(%) 0.14, Drug Content % 99.95±0.34, drug release of 99.00 ± 0.17% at 12 h).

From the *in vitro* studies the formulations containing pectin showed less retardation than the formulation with Xanthan gum. The probable mechanism of drug release from the best formulations containing Xanthan gum was concluded based on the *in vitro* drug release data that were analyzed according to Zero order, First order, Higuchi and Korsmeyer & Peppa's equation. The optimized formulation F9 showed zero order drug release for Metformin hydrochloride. The release exponent value determined from Higuchi plot indicated non-fickian drug release that means drug release occurred by diffusion. The mucoadhesive strength increases with the increase in polymer concentration the F9 formulation showed 24.20 ± 0.33 mucoadhesive strength and mucohesive force 2.37. The Xanthane gum higher degree of esterification demonstrated a stronger mucoadhesion, some carboxylic groups in the structure produce strong H-bond forming groups to strengthen the mucoadhesive bonding. The optimized formulation, F9 was found to be stable for three months at accelerated stability conditions at a temperature (40 ± 2° C) and relative humidity 75 ± 5% as per ICH norms.

To conclude this research the Xanthan gum shows good retardation of drug release than the pectin. Xanthan gum exerted potential effects on management of Type 2 diabetes mellitus by lowered fasting and post load serum glucose and reduced fasting levels of total plasma cholesterol in diabetic subjects [16]. Xanthan gum also tended to lower fasting and post load levels of gastrin and gastric inhibitory polypeptide (GIP) and fasting levels of total and VLDL triglyceride and cholesterol in VLDL and LDL fractions. Subjects reported a sense of fullness after consuming xanthan gum (12gm/day) no severe digestive symptom [17-19]. The xanthan gum plays the dual role in the formulation such as anti-diabetic action and suitable material to retard the drug release of pharmaceutical formulations. The success of this research makes xanthan gum promising synergistic to Metformin hydrochloride effects in the treatment of Type 2 diabetes mellitus and favors reduction in number of dosage units to be consumed by the patients thereby improves patient compliance.

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