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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE: INFLUENCE OF FILLERS ON HYDROPHILIC NATURAL GUMS

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ABSTRACT

The influence of commonly used excipients lactose monohydrate, microcrystalline cellulose (MCC), and dibasic calcium phosphate (DCP) on drug release from natural gum matrix system has been investigated and to evaluate drug release parameters as per various release kinetic models. The release rate profiles were evaluated through different kinetic equations: zero-order, first-order, Higuchi, and Peppas models. The tablets were prepared by direct compression method. Compressed tablets were evaluated for content of active ingredient, friability, hardness, and *in vitro* release studies. Suitable matrix release profile could be obtained at 1:1.5 drug: gum ratio. Controlled release profiles were obtained for guar gum compared to xanthan gum. Notable influences were obtained for type of fillers. We found that the release rate obtained was highest when microcrystalline cellulose was employed as filler followed by lactose and dibasic calcium phosphate. The *in vitro* release profiles indicated that tablets prepared from guar gum had higher retarding capacity than tablets prepared with xanthan gum. Among all the formulation, F-8 shows 96.84% of drug release at the end of 12 hours. Selected formulation (F-8) was subjected to stability studies for 3 months, which showed stability with respect to release pattern. The drug release follows zero order kinetics and the mechanism was found to be anomalous (non-Fickian) diffusion. The FT-IR study did not show any possibility of metoclopramide hydrochloride / guar gum interaction with the formulation excipients used in the study.

Keywords: Controlled release, Matrix tablets, Guar gum, Xanthan gum, Metoclopramide hydrochloride, Lactose monohydrate, Microcrystalline cellulose, Dibasic calcium phosphate.

INTRODUCTION

In recent years the basic aim has been designing of drug products to reduce the frequency of dosing by modifying rate of the drug release from the formulation. Regular research has been carried in this field for the use of naturally occurring biocompatible polymeric material in designing the dosage form for oral controlled release administration[1]. The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy, for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [2]. Controlled-release technology evolved with matrix technology. The goal behind the development of oral controlled-release formulations at that time was the achievement of a constant release rate of the entrapped drug. Advances in oral controlled-release technology are attributed to the development of novel biocompatible polymers and machineries that allow preparation of novel design dosage forms in a reproducible manner. The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties.[3] Moreover, it has been shown that the suitable combination of more types of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form.[4] Hydrophilic matrices containing swellable polymers are referred to as hydrogel matrices, swellable controlled release systems or hydrophilic matrix tablets. A number of polymers have been investigated to develop in situ gel forming systems, due to the ability of these hydrogels to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross-linking. Gums of natural sources are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media and these have been used for the preparation of single use dosage forms.[5, 6]

Guar gum is naturally occurring galactomannan polysaccharide, consists of a linear chain of β-(1 → 4)-linked D-mannose units with D-galactose attached by α-(1→ 6) linkages to every other mannose unit to form short side chains. Though not self-gelling, guar gum has a high low-shear viscosity. Because it is nonionic, it is not affected by ionic strength or pH. Xanthan gum is a high molecular weight extracellular polysaccharide produced by pure culture aerobic fermentation of carbohydrate with *Xanthomonas campestris* bacteria. Xanthan is a long chained polysaccharide with large number of trisaccharide side chains. The main chain consists of β -(1, 4)-linked D-glucose units. The side chains are composed of two mannose units and one glucuronic acid unit. This gum develops a weak structure in water, which creates high viscosity solutions at low concentration. Although it is highly swellable, it slows drug release in sustained release formulations.[7]

Nausea and vomiting may be manifestations of a wide variety of conditions, including pregnancy, motion sickness, gastrointestinal obstruction, peptic ulcer, drug toxicity, myocardial infraction, renal failure and hepatitis. In cancer chemotherapy, drug induced nausea and vomiting may occur so regularly that anticipatory vomiting occurs when patients return for treatment before the chemotherapeutic agent is given. If not controlled, the discomfort associated with drug induced emesis may cause a patient to refuse further chemotherapy.[8]

Metoclopramide hydrochloride (MCP) is a substituted benzamide used for its prokinetic and anti emetic properties. The drug is very useful in treating nausea and vomiting of varied etiology, e.g. Nausea and vomiting associated with gastrointestinal disorders, radiation sickness, hepatobiliary disorders, pre and postoperative periods and migraine. MCP is commonly used for the management of gastrointestinal disorders, showing anti-emetic action by blocking Dopamine (D2) receptor in brain. It is used to treat the emesis caused due to chemotherapy in cancer patient. Due to Dopamine (D2) receptor blocking action the drug is showing extra-pyramidal (Parkinsonism like) symptoms, if administered in conventional dosage form. It has a relatively short variable biological half life (5±1h) and is usually administered in a peroral dose of 10-15mg four times daily, as immediate release tablets.[9, 10]

The objective of the present work was to evaluate the suitability of natural gum as polymeric materials for directly compressed matrix tablets able to adequately extend drug release using a suitable rate controlling polymer. The influence of the drug polymeric matrix

ratio on drug release behavior has been investigated and influence of different content levels of microcrystalline cellulose (MCC), dibasic calcium phosphate (DCP), and lactose has been investigated. Microcrystalline cellulose (MCC) and dibasic calcium phosphate (DCP) were chosen as release modifiers, and lactose as water-soluble diluent. Another objective of this study was to achieve a zero-order release of the model drug from these guar gum and xanthan gum matrices. The technological properties of the tablets obtained with the different formulations were also examined.

MATERIALS AND METHODS

Materials

Metoclopramide hydrochloride was received as gift sample from Vaikunth Chemicals, Ankleshwar. Guar gum, Xanthan gum and Dibasic calcium phosphate was obtained from (HiMedia Laboratories Pvt. Ltd. Mumbai), Lactose monohydrate was purchased from (S D Fine- Chem Limited. Mumbai). Microcrystalline cellulose was obtained from (Research- Lab Fine Chem Industries. Mumbai) Magnesium stearate and talc were obtained from (Loba Chemie Pvt. Ltd. Mumbai.). All other ingredients used were of analytical grade.

Preparation of matrix tablets

In the present work the metoclopramide hydrochloride tablets were prepared by direct compression method. The drug and the excipients were passed through 72# size mesh prior to the preparation of dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes in double cone blender to ensure uniform mixing in geometric ratio. The tablets were prepared by direct compression technique using 8.5mm punch. Two different polymers like guar gum and xanthan gum were used as retardants and lactose monohydrate, dibasic calcium phosphate and microcrystalline cellulose used as fillers in different ratio. Talc and magnesium stearate is used as a lubricant to reduce die wall friction (Table 1-2).

Table 1: Tablet composition of metoclopramide hydrochloride controlled release matrix tablets

S. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Drug	30	30	30	30	30	30	30	30	30	30
2	Xanthan gum	15	30	45	60	75	-	-	-	-	-
3	Guar gum	-	-	-	-	-	15	30	45	60	75
4	Lactose	145	145	145	145	145	145	145	145	145	145
5	Magnesium Stearate	05	05	05	05	05	05	05	05	05	05
6	Talc	05	05	05	05	05	05	05	05	05	05

Tablet weight was increased when polymer concentration increased.

Table 2: Tablet composition of metoclopramide hydrochloride controlled release matrix tablets containing guar gum with different fillers

S. No.	Ingredients (mg)	F11	F12	F13	F14	F15	F16
1	Drug	30	30	30	30	30	30
2	MCC	115	145	-	-	-	-
3	DCP	-	-	115	145	-	-
4	Lactose	-	-	-	-	115	145
5	Guar Gum	45	45	45	45	45	45
6	Magnesium Stearate	05	05	05	05	05	05
7	Talc	05	05	05	05	05	05

Tablet weight was increased when filler concentration increased.

Table 3: Precompression parameters of metoclopramide HCl controlled release matrix tablets

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	3.10	5.4 ± 0.15	0.25	99.91 ±0.31
F2	3.12	5.6 ± 0.20	0.30	99.19 ±0.19
F3	3.16	5.5 ± 0.30	0.28	99.08±0.34
F4	3.20	5.6 ± 0.18	0.34	99.62 ± 0.45
F5	3.23	5.7 ± 0.05	0.40	99.78 ±0.13
F6	3.10	5.4 ±0.26	0.25	98.76±0.16
F7	3.14	5.5 ± 0.17	0.24	97.91±0.57
F8	3.17	5.6± 0.19	0.22	99.93±0.33
F9	3.20	5.4±0.16	0.25	98.32±0.27
F10	3.23	5.6± 0.17	0.28	99.18±0.15
F11	3.15	5.2 ± 0.27	0.35	99.70±0.58
F12	3.20	5.6 ± 0.31	0.33	101.58±0.40
F13	3.10	5.3 ± 0.27	0.36	99.20±0.95
F14	3.15	5.8 ± 0.20	0.35	99.39 ±0.64
F15	3.11	5.4 ± 0.16	0.31	99.60 ± 0.85
F16	3.16	5.5 ± 0.35	0.36	99.66±0.06

Evaluation of tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods[11] shown in Table 3.

Drug content

5 tablets were finely powdered and an amount equivalent to 30 mg of metoclopramide hydrochloride was accurately weighed and transferred to a 100ml volumetric flask, 70 ml of phosphate buffer

pH 1.2 was then added. The flask was shaken for 10 min. Finally, the volume was made up to the mark with phosphate buffer pH 1.2. The mixture was then filtered and 1 ml of the filtrate was suitably diluted with phosphate buffer pH 1.2 to obtain a solution containing about 30 mg of metoclopramide hydrochloride and analyzed for its content at 272 nm using a double beam UV/Visible spectrophotometer and phosphate buffer pH 1.2 as blank.

Effect of Filler

The effects of different type of fillers were investigated on the matrix structure. The fillers selected were lactose, MCC and DCP.

***In-vitro* drug release studies**

In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of pH 1.2 and pH 6.8 phosphate buffer, maintained at 37+ 0.5°C. Samples were removed at the interval of 1 hour. Each time 5 ml of sample was removed and replaced with 5 ml of solvent. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 272 nm. The study was performed in triplicate.

Drug release kinetics

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug release vs time, first order (Equation 2) as log cumulative percentage of drug remaining vs time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs square root of time.

$$C = K_0 t \quad \ldots (1)$$

Where, K_0 is the zero order rate constant expressed in units of concentration / time and *t* is the time in hours.

A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.[12]

$$\text{Log } C = \text{Log } C_0 - K_t/2.303 \quad \ldots (2)$$

Where, C_0 is the initial concentration of drug.

K is the first order constant, and t is the time.

$$Q = Kt^{1/2} \ldots \quad (3)$$

Where *K* is the constant reflecting the design variables of the system and *t* is the time in hours.

Hence, drug release rate is proportional to the reciprocal of the square root of time.[13,14]

Mechanism of drug release

To evaluate the mechanism of drug release from metoclopramide hydrochloride controlled release tablets, data of drug release were plotted in Korsmeyer et al's equation (Equation 4) as log cumulative percentage of drug release vs log time and the exponent *n* was calculated through the slope of the straight line.

$$Mt/M\infty = Kt^n \quad \ldots (4)$$

Where $Mt/M\infty$ is the fractional solute release, *t* is the release time, *K* is a kinetic constant characteristics of the drug/polymer system, and *n* is an exponent that characterizes the mechanism of release of tracers.[15] For cylindrical matrix tablets, if the exponent n=0.45, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of case-II Transport or typical zero-order release.[16]

RESULTS AND DISCUSSION

FTIR spectroscopy

Infrared spectra of drug and excipients were used to study the compatibility between them. No change in peak shows that there was no interaction between drug and excipients. The IR spectrum of the pure drug (metoclopramide hydrochloride) and optimized formulation F8 is given in figure 1-3.

Table 4: Release Mechanism with Variations of n Values

n Value	Mechanism	dm_t/d_t Dependence
n < 0.5	Quasi-Fickian diffusion	$t^{0.5}$
0.5	Fickian diffusion	$t^{0.5}$
0.5 < n< 1.0	Anomalous (non-Fickian) diffusion	t^{n-1}
1	Non-Fickian case II	Zero order
N > 1.0	Non-Fickian super case II	t^{n-1}

The diffusional exponent is based on Korsmeyer-peppas equation. $Mt/Mt = kt^n$

Table 5: Kinetic values obtained from different plots of formulations F1 to F15.

Formulation Code	Zero Order[1] R^2	First Order[2] R^2	Higuchi[3] R^2	Korsmeyer[4] R^2	Slope n
F1	0.980	0.877	0.981	0.992	0.655
F2	0.990	0.883	0.984	0.995	0.750
F3	0.992	0.867	0.986	0.997	0.771
F4	0.982	0.989	0.991	0.997	0.813
F5	0.996	0.957	0.969	0.994	0.812
F6	0.986	0.873	0.976	0.992	0.687
F7	0.994	0.816	0.976	0.994	0.760
F8	0.987	0.911	0.993	0.996	0.873
F9	0.989	0.988	0.993	0.997	0.872
F10	0.998	0.955	0.966	0.994	0.878
F11	0.983	0.908	0.990	0.996	0.697
F12	0.984	0.912	0.985	0.993	0.675
F13	0.990	0.913	0.982	0.987	0.769
F14	0.992	0.895	0.977	0.990	0.728
F15	0.988	0.894	0.988	0.998	0.737
F16	0.989	0.757	0.985	0.995	0.728

[1]Zero order equation, $C=K_0 t$, [2]First order equation, $\text{Log } C = \text{log } C0 - Kt/2.303$, [3]Higuchi equation, $Q = Kt^{1/2}$, [4]Korsmeyer et al's equation, $Mt/M\infty=Kt^n$.

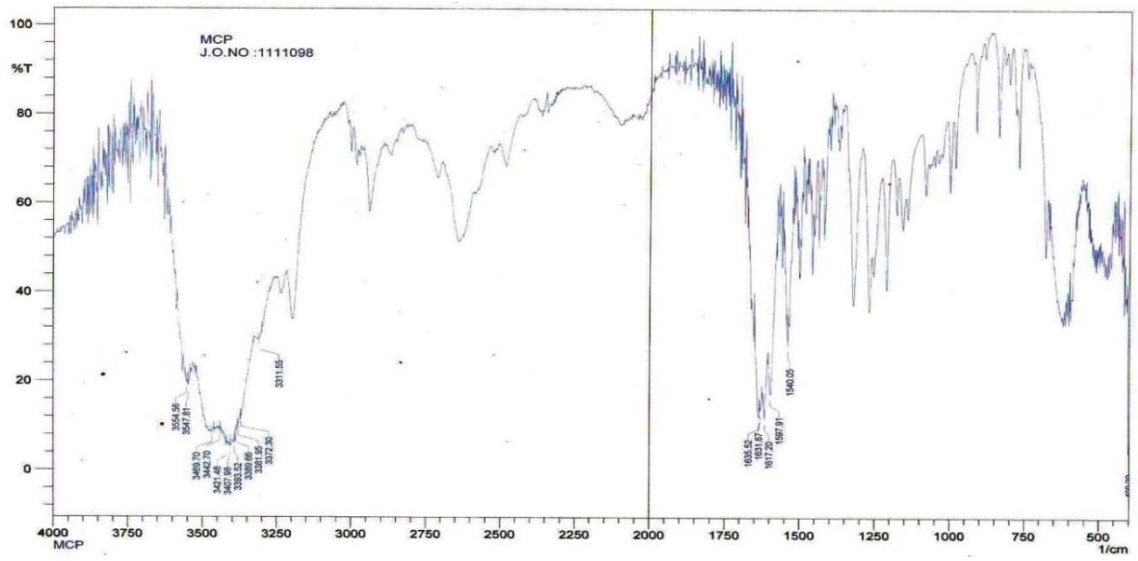

Fig. 1: FT-IR spectra of pure metoclopramide hydrochloride.

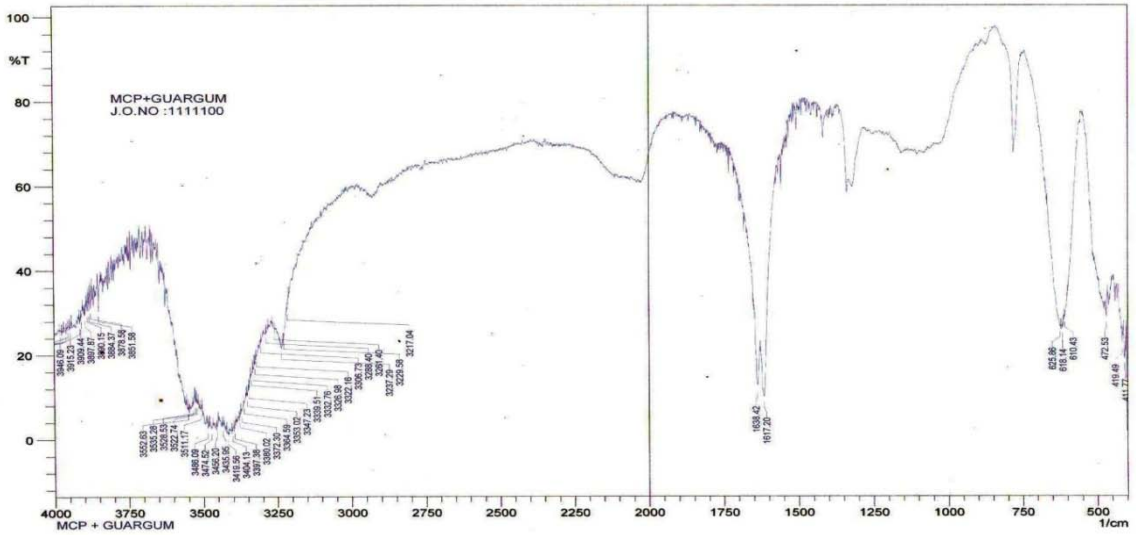

Fig. 2: FT-IR spectra of metoclopramide hydrochloride with guar gum (F8)

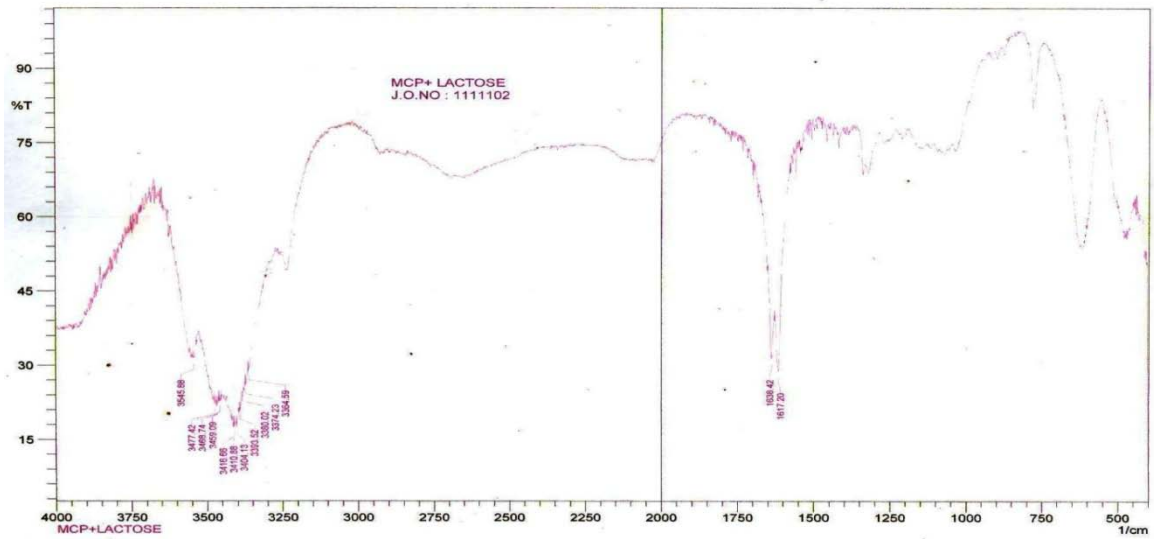

Fig. 3: FT-IR spectra of metoclopramide hydrochloride with lactose

Physicochemical evaluation of matrix tablets

Tablets with a weight of 200 mg, 215 mg, 230mg, 245mg, and 260mg were obtained and subjected to quality control tests such as hardness, friability and drug content (Table 3). The contents of the formulations were found to be uniform, since the amount of the active ingredient in each of the10 units tested was within the range of 97.91±0.57 to 101.58 ± 0.40 and the relative standard deviations were less than 2.0%, indicating uniform mixing of drug and excipients. All formulations exhibited a friability of not more than 0.4% during the friability determination. The punches used to compress the tablets were 8.5mm, flat shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 5.2 ± 0.27 to 5.7 ± 0.05 kg/ cm^2. It was within the range of monograph specification. Thickness of the tablets was found to be in the range of 3.10 to 3.23 mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

Effect of polymers on drug release

For the purpose of developing formulation with different release rates, matrix tablets containing natural gums in the ratio of 1:0.5, 1:1, 1:1.5, 1:2, and 1:2.5 were prepared. The dissolution was performed in phosphate buffer pH 1.2 for first 2 hrs and pH 6.8 up to 12 hrs at 50 rpm. The release profiles are depicted in Fig. 4-5, which indicates that the release rate is greatly influenced by the matrix concentration.

Xanthan gum in the drug: gum ratio of 1:0.5, 1:1, 1:1.5, 1:2, and 1:2.5, retarded the release of metoclopramide HCl for 10, 11, and 12 h, respectively (Fig. 4). Xanthan gum containing tablets take up water on contact with the release medium, thus allowing dissolution of a certain percent of the drug found at and near the tablet surface prior to gel or viscous medium formation. This is followed by hydration and swelling of the polymer, creating porous pathways that could lead to an initial burst release. Xanthan gum release the drug faster than guar gum at the same drug: gum ratio.

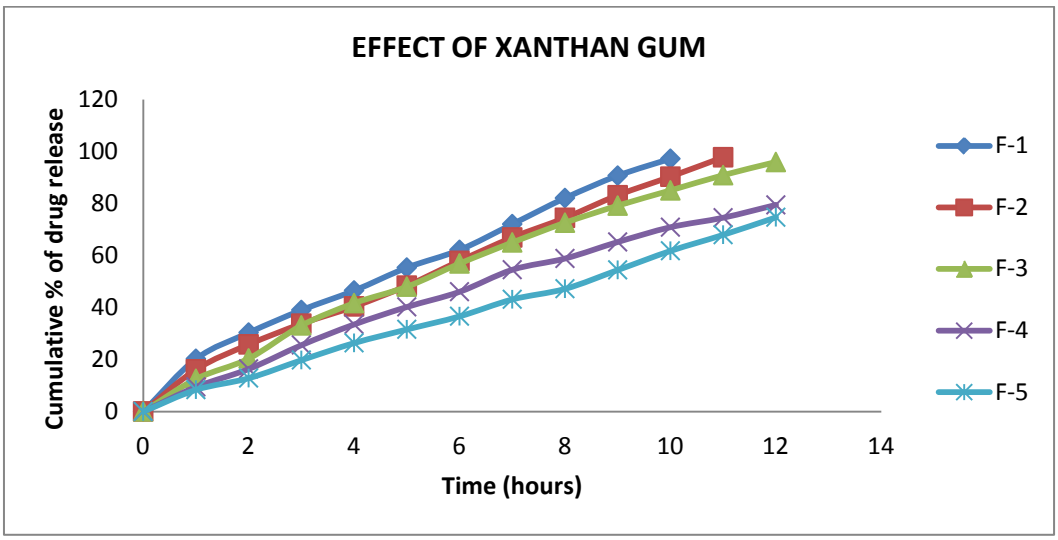

Fig. 4: Results of *in vitro* Drug Release Profile of F1- F5.

Guar gum in the drug: gum ratio of 1:0.5, 1:1, 1:1.5, 1:2, and 1:2.5, retarded the release of metoclopramide HCl for 10, 11, and 12 h, respectively (Fig. 5). At each of the five ratios, 1:1.5 (F8) was best able to controlled drug release up to 12 hrs. Increasing the level of polymer in the formulation can further control the release of the drug, apparently due to a thicker gel or a more viscous region. The gel or viscous aqueous region inhibits further entry of release medium due to its high water content. With time, the diffusion path length increases, resulting in slower drug release. With sufficient viscosity, the gel or viscous region can resist erosion.

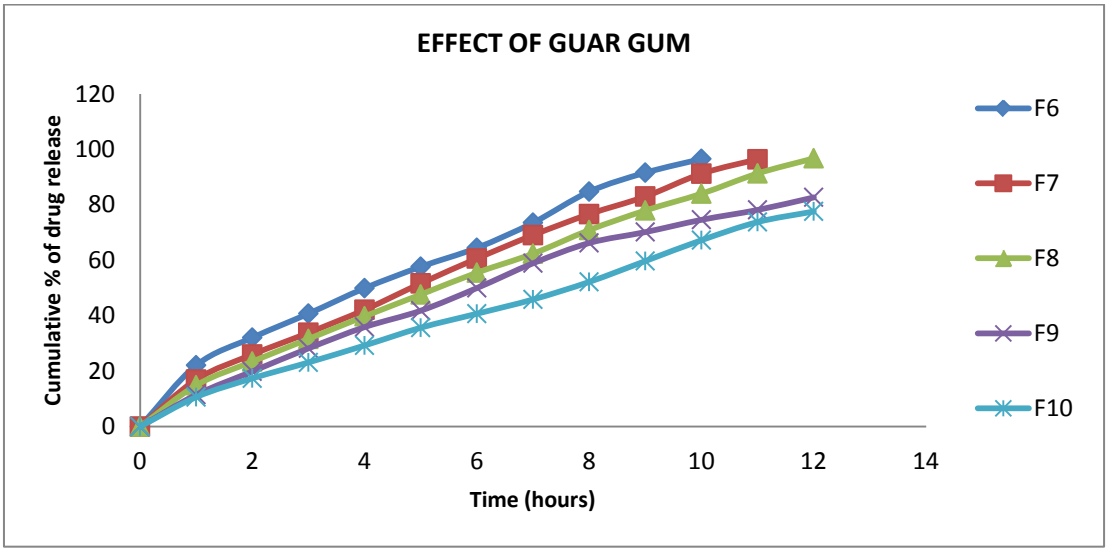

Fig. 5: Results of *in vitro* Drug Release Profile of F6- F10.

It has been observed that the cumulative percent drug release decreases with increasing concentration of gum[17]. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of guar gum. This slow release is because of the formation of a thick gel structure that delays drug release from tablet matrix, where hydration of individual xanthan gum particles results in extensive swelling. As a result of rheology of hydrated product, the swollen particles coalesce. This results in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet, and retarding further penetration of the dissolution medium. From the findings, obtained so far it can be concluded that guar gum in the concentration ratio of 1:1.5 (F-8) was promising concentration for oral controlled release tablet of metoclopramide hydrochloride.

Effect of fillers on drug release

Influence of Fillers Concentration

Although diluents are normally considered inert ingredients, they may affect the biopharmaceutical, chemical, and physical properties of the final tablet. The tablets in the experiment were prepared with lactose as the filler. The effect of other fillers on release of metoclopramide hydrochloride was also investigated. Microcrystalline cellulose (MCC) and dibasic calcium phosphate (DCP) were used for this purpose. Lactose was selected due to its water solubility; MCC and DCP were selected for its insolubility. MCC is swellable filler while DCP is non-swellable. MCC and DCP replaced lactose with lower and higher amount of filler in those formulations. The effect of fillers on guar gum matrix tablets is represented in Fig. 6. Since, the diffusional release of a soluble drug such as MCP may primarily be controlled by the gel thickness (diffusion layer), the effect of filler on drug release was studied by holding guar gum level at 45%. The release of MCP was significantly different for all the fillers added in the tablets.

Effect of MCC

As shown in Fig. 6 the metoclopramide hydrochloride tablets containing microcrystalline cellulose, as co-excipient, exhibited faster release rates at extended dissolution time periods, as compared to the same type of formulations with respective drug-to-polymer ratios those containing lactose and DCP. In this case, the swelling behavior of MCC allowed further penetration of the aqueous medium, resulting in rapid erosion of the polymer matrices. The faster release rates and shorter dissolution time observed with microcrystalline cellulose is due to its inherent disintegrant properties, so quick release of the drug from the matrix tablets[18, 19].

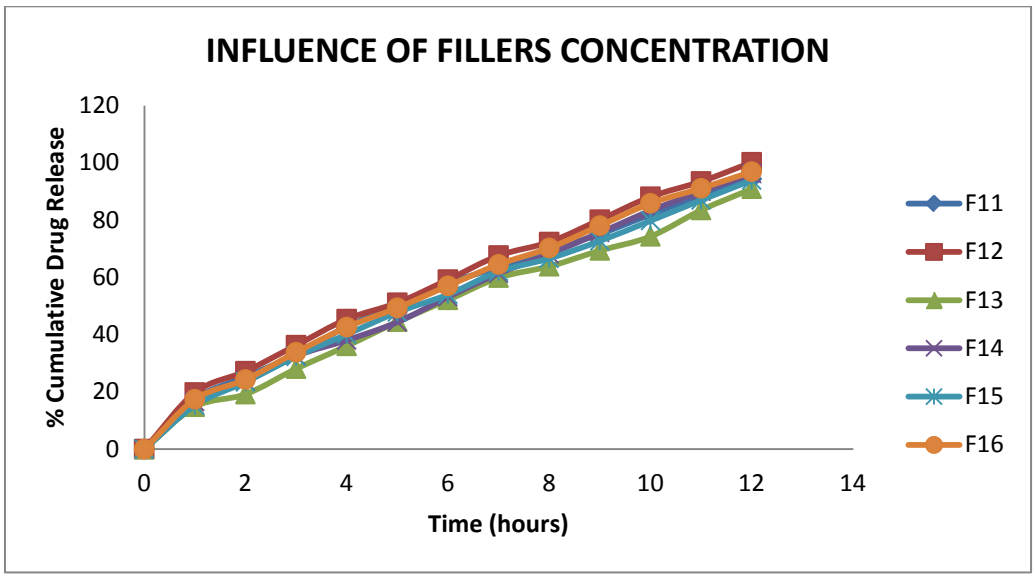

Fig. 6: Results of *in vitro* Drug Release Profile of F11- F16.

Effect of DCP

DCP is insoluble, non-swelling filler was used (F-13, F-14), and metoclopramide hydrochloride did not diffuse out and rather became entrapped in matrix. It showed slower release compared to MCC and lactose[18].

Effect of lactose

Lactose is the most useful filler used for tablet formulations. It is water-soluble and would modify the drug release for undergoing dissolution. Drug release from the tablets compressed with metoclopramide hydrochloride, guar gum, and lactose, are shown in Fig 6. While the batch F-15 (115 mg of lactose/ tablet weight), the 93.95% drug was released up to 12 h, when the amount of lactose increase in the formulations F-16 (145 mg of lactose/ tablet weight) the release rate was markedly increased up to 96.91%, compared to a F-15. Lactose demonstrating slower release behavior as compared to microcrystalline cellulose[20]

From Figure 6, it is evident that increase in the amount of fillers results in gradually increase release of metoclopramide hydrochloride from guar gum matrix tablets. This may be due to the structural reorganization of the hydrophilic polysaccharide matrix.

Influence of Types OF Filler

The fastest release from direct compressible metoclopramide hydrochloride tablets with guar gum (45%) was observed in the case of microcrystalline cellulose, followed by lactose and dibasic calcium phosphate – Figure 7 (145 mg of filler/ tablet weight). Microcrystalline cellulose has disintegrating properties when incorporated at high use level and this caused tablet erosion and fast drug release. The swelling behavior of MCC allowed further penetration of the aqueous medium, resulting in rapid erosion of the polymer matrices. The difference in the filler solubility explains the slower release observed for the tablets with dibasic calcium phosphate (insoluble) as compared to lactose (soluble).

These results are in agreement with those observed by some other investigators where rapid release rates of water soluble drugs, from the formulations containing microcrystalline cellulose as filler excipient, were observed.

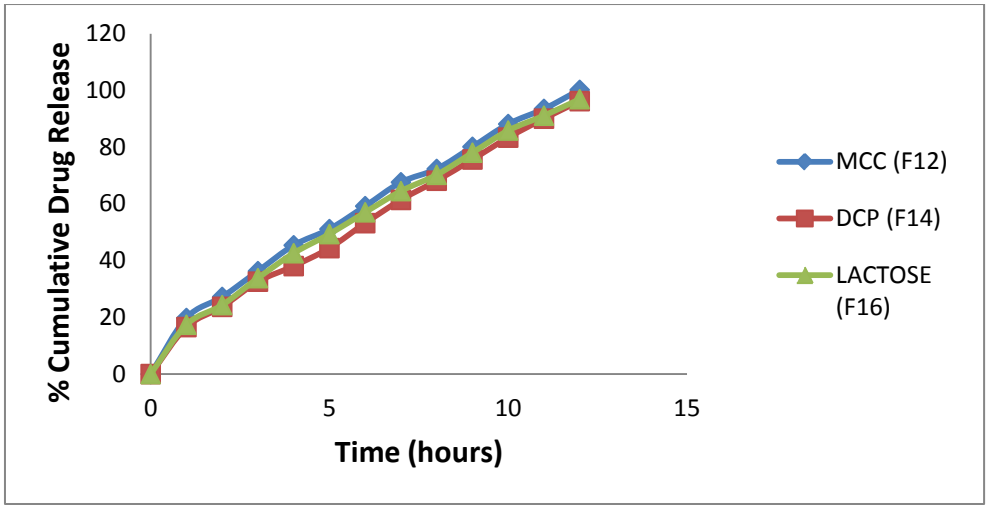

Fig. 7: Effect of fillers on *in vitro* release of MCP from guar gum (45%) matrix tablets

Release kinetics

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of the drug release (Table 6). The regression coefficient obtained from zero order kinetics were found to be higher (R^2 : 0.980 to 0.998) when compared with those of first order kinetics (R^2: 0.757 to 0.988) indicating that the drug release from all the formulations followed zero order kinetics except formulation F4 follows first order kinetics (R^2= 0.989). In this experiment, the *in vitro* release profiles of drug from all these formulation could be best expressed by korsmeyer equation as the plots showed highest linearity (R^2 : 0.992 to 0.998). When the data were plotted according to Korsmeyer-Peppas equation, all the formulations showed high linearity (R^2 : 0.992 to 0.998) with a comparatively high slope (n) values of > 0.5 which appears to indicate a coupling of diffusion and erosion mechanisms so called anomalous (non-Fickian) diffusion.

CONCLUSION

In the present study, the effects of various excipients on MCP matrix tablets were studies with guar gum and xanthan gum were used as release retarding agents. Metoclopramide hydrochloride containing granules that demonstrated good flow could be produced, and controlled release matrix tablets with good physical properties could be obtained. MCP tablets passes for hardness, friability, drug content, and *in vitro* dissolution profile. Guar gum in the ratio of 1:1.5 (F-8) was best able to retard MCP release and exerted its influence on the release mechanism When the data were plotted according to Korsmeyer-Peppas equation, all the formulations showed high linearity (R^2 : 0.992 to 0.998) with a comparatively high slope (n) values of > 0.5 which appears to indicate a coupling of diffusion and erosion mechanisms–so called anomalous diffusion. The study of the effect of the filler on a MCP formulation tablets at 45% guar gum level concluded that filler solubility had a limited effect on release rate. Replacement of portions of lactose within the tablet by the MCC and DCP, Lactose release MCP slower than MCC and faster than DCP. But the presence of swelling insoluble filler like microcrystalline cellulose changed the release profile to a small extent due to a change in swelling at the tablet surface.

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