Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 4, Issue 3, 2012

Research Article

DESIGN AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE USING HYDROPHILIC POLYMERS

PATEL MUBARAK HUSEN, P ASHOK KUMAR*, SURESH V KULKARNI, SOMESHWARA RAO B

Department of Pharmaceutics, Sree Siddaganga College of Pharmacy, Tumkur 572102, Karnataka, India.
Email: ashokkumarscp@yahoo.com

Received: 26 March 2012, Revised and Accepted: 09 May 2012

ABSTRACT

In the present investigation an attempt was made to formulate the oral controlled release metoclopramide hydrochloride matrix tablets by using carbopol 934 and natural gums like guar gum and xanthan gum as rate controlling polymer and to evaluate drug release parameters as per various release kinetic models. The tablets were prepared by direct compression method. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, and in vitro release studies. All the formulations showed compliance with Pharmacopoeial standards. The *in vitro* dissolution study was carried out for 12 hours using paddle (USP type II) method in phosphate buffer (pH 1.2 and 6.8) as dissolution media. Formulation F1, F2, F6, F7, F11, and F12 failed to controlled release beyond 12 hours. 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 mechanism was found to be anomalous (non-Fickian) diffusion.

Keywords: Metoclopramide hydrochloride, Controlled Release, Matrix tablets, Carbopol 934, Guar gum, Xanthan gum, Direct compression.

INTRODUCTION

In recent years oral controlled delivery systems have gained increased importance and interest since it is necessary to improve the systemic absorption of the drugs and patient compliance. In addition, controlled delivery systems maintain uniform drug levels, reduce dose, side effects, and increase the safety margin. Matrix controlled release tablet formulations are the most fashionable and straightforward to formulate on a commercial scale. A wide variety of polymer matrix systems have been used in oral controlled drug delivery to obtain a desirable drug release profile, Cost effectiveness, and broad regulatory acceptance.

Metoclopramide Hydrochloride (MCP) is used as a model drug for the present study, to produce controlled release drug delivery system. MCP is 4-amino-5- chloro-N-[2-(diethyl amino) ethyl]-2 methoxy benzamide monohydrochloride monohydrate. It is one of the potent antiemetic drug. MCP apparently antagonizes dopamine at the receptor sites. This action can explain its sedative, central antiemetic (blocks dopamine in the chemo-receptor trigger zone), extrapyrimidal, and prolactin secretion stimulation effects. 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 but the patient's compatibility can be improved if administered in controlled release dosage form.[1] Metoclopramide Hydrochloride is commonly used for the treatment of nausea and vomiting. This drug is highly water soluble and is rapidly absorbed after oral administration. It has a short biological half life (5 ± 1 hour) and is usually administered in a dose of 10 to 15 mg four times daily in order to maintain effective concentrations throughout the day. In long term therapy, fluctuation in the plasma concentration, with high concentration peaks are common for drugs with rapid absorption and elimination. The secondary effects of metoclopramide hydrochloride on the central nervous system in the form of extrapyramidal symptoms, if plasma levels markedly exceed therapeutic levels. Such characteristics make metoclopramide hydrochloride as best suitable drug candidates for controlled drug delivery.[2, 3]

Carbopol readily absorb water, get hydrated and swell. In addition to its hydrophilic nature, its cross linked structure and its essentially insolubility in water makes carbopol a potential candidate for use in controlled release drug delivery system.[4, 5] Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form[6].Guar gum is galactomannan, obtained from the ground endosperm of the guar plant, Cyamopsis tetragonolobus. It has been investigated as controlled release carrier and regarded as nontoxic and nonirritant material.[7-9] 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.[10]

In the present study, MCP was formulated in matrix tablets using varying proportions of the carbopol934 and natural polymers like guar gum and xanthan gum. Tablets were prepared by direct compression method and subjected to *in vitro* drug release studies to find the utility of polymers in providing controlled release.

MATERIALS AND METHODS

Materials

Metoclopramide hydrochloride was received as gift sample from Vaikunth Chemicals, Ankleshwar, Carbopol934 was purchased from (Loba Chemie Pvt. Ltd. Mumbai), Guar gum and Xanthan gum was obtained from (HiMedia Laboratories Pvt. Ltd. Mumbai), Lactose Monohydrate was purchased from (S D Fine- Chem Limited. 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. Three different polymers like carbopol 934, guar gum and xanthan gum were used as retardants and lactose monohydrate used as diluent in different ratio. Talc and magnesium stearate is used as a lubricant to reduce die wall friction (Table 1).

Table 1: Composition of Metoclopramide HCl Controlled Release Matrix Tablets

Formulation Code	Drug (mg)	Polymers (mg)			Lactose (mg)	Magnesium Stearate (mg)	Talc (mg)
		Carbopol 934	Guar gum	Xanthan gum			
F1	30	15	-	-	145	05	05
F2	30	30	-	-	145	05	05
F3	30	45	-	-	145	05	05
F4	30	60	-	-	145	05	05
F5	30	75	-	-	145	05	05
F6	30	-	15	-	145	05	05
F7	30	-	30	-	145	05	05
F8	30	-	45	-	145	05	05
F9	30	-	60	-	145	05	05
F10	30	-	75	-	145	05	05
F11	30	-	-	15	145	05	05
F12	30	-	-	30	145	05	05
F13	30	-	-	45	145	05	05
F14	30	-	-	60	145	05	05
F15	30	-	-	75	145	05	05

Tablet weight was increased when polymer concentration increased.

Evaluation of tablets

All prepared matrix tablets were evaluated for its hardness, friability, drug content, and thickness according to official methods[11] shown in Table 2.

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.

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.

Table 2: Postcompression Parameters Metoclopramide HCl Controlled Release Matrix Tablets.

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)
F1	3.12	5.7 ± 0.27	0.38	99.89±0.73
F2	3.16	5.8 ± 0.52	0.40	98.67±0.26
F3	3.19	5.9 ± 0.31	0.37	99.58±0.36
F4	3.21	5.9 ± 0.25	0.32	99.53±0.56
F5	3.23	6.0 ± 0.27	0.24	98.20±0.44
F6	3.10	5.4 ± 0.15	0.25	99.91 ±0.31
F7	3.12	5.6 ± 0.20	0.30	99.19 ±0.19
F8	3.16	5.5 ± 0.30	0.28	99.08±0.34
F9	3.20	5.6 ± 0.18	0.34	99.62 ± 0.45
F10	3.23	5.7 ± 0.05	0.40	99.78 ±0.13
F11	3.10	5.4 ±0.26	0.25	98.76±0.16
F12	3.14	5.5 ± 0.17	0.24	97.91±0.57
F13	3.17	5.6± 0.19	0.22	99.93±0.33
F14	3.20	5.4±0.16	0.25	98.32±0.27
F15	3.23	5.6± 0.17	0.28	99.18±0.15

Stability Studies

The optimized formulation was subjected to stability study at 40 ± 2ºC and 75 ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes, hardness, friability, drug content and percentage drug release.

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]

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

Where C_0 is the initial concentration of drug,

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

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

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.

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

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]

Table 3: 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 4: 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	0.987	0.879	0.977	0.992	0.695
F2	0.997	0.875	0.979	0.997	0.838
F3	0.990	0.914	0.991	0.997	0.879
F4	0.988	0.990	0.993	0.997	0.852
F5	0.993	0.988	0.987	0.999	0.845
F6	0.980	0.877	0.981	0.992	0.655
F7	0.990	0.883	0.984	0.995	0.750
F8	0.992	0.867	0.986	0.997	0.771
F9	0.982	0.989	0.991	0.997	0.813
F10	0.996	0.957	0.969	0.994	0.812
F11	0.986	0.873	0.976	0.992	0.687
F12	0.994	0.816	0.976	0.994	0.760
F13	0.987	0.911	0.993	0.996	0.873
F14	0.989	0.988	0.993	0.997	0.872
F15	0.998	0.955	0.966	0.994	0.882

[1]Zero order equation, $C=K_0 t$, [2]First order equation, $\text{Log } C = \log C_0 - Kt/2.303$, [3]Higuchi equation, $Q = Kt^{1/2}$, [4]Korsmeyer et al's equation, $Mt/M \infty = Ktn$.

RESULT & DISCUSSION

The supplied drug passed the various tests of identification and analysis. The pure drug and the solid admixture of drug and various excipients used in the preparation of controlled release tablet formulations were characterized by FT-IR spectroscopy to know the compatibility. The FT-IR study did not show the interaction between metoclopramide hydrochloride and guar gum/other excipients used in the matrix tablets, figure 1-2.

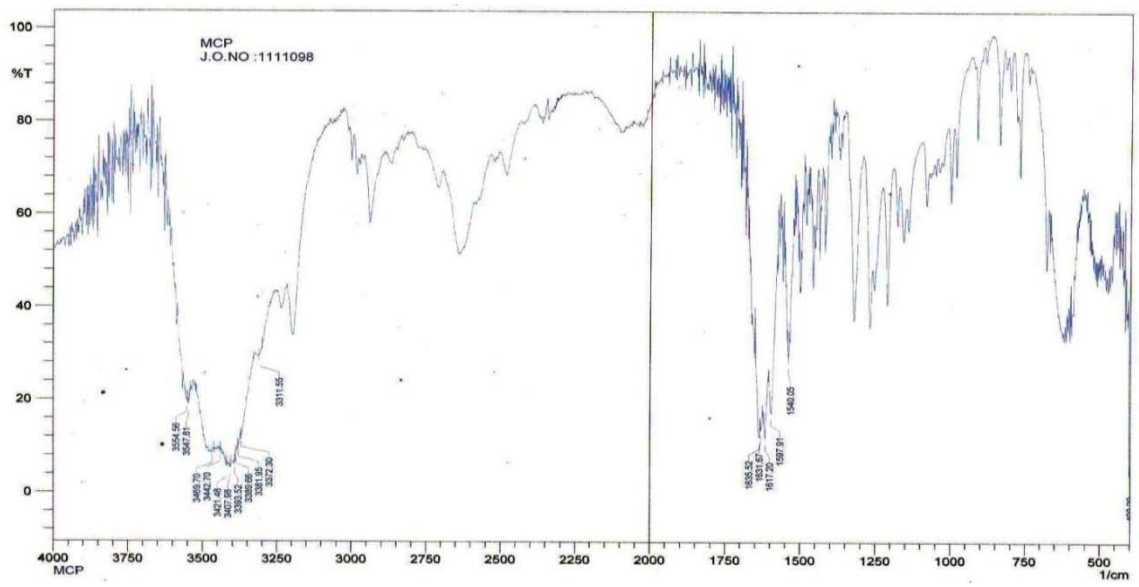

Fig. 1: FTIR spectra of pure metoclopramide hydrochloride

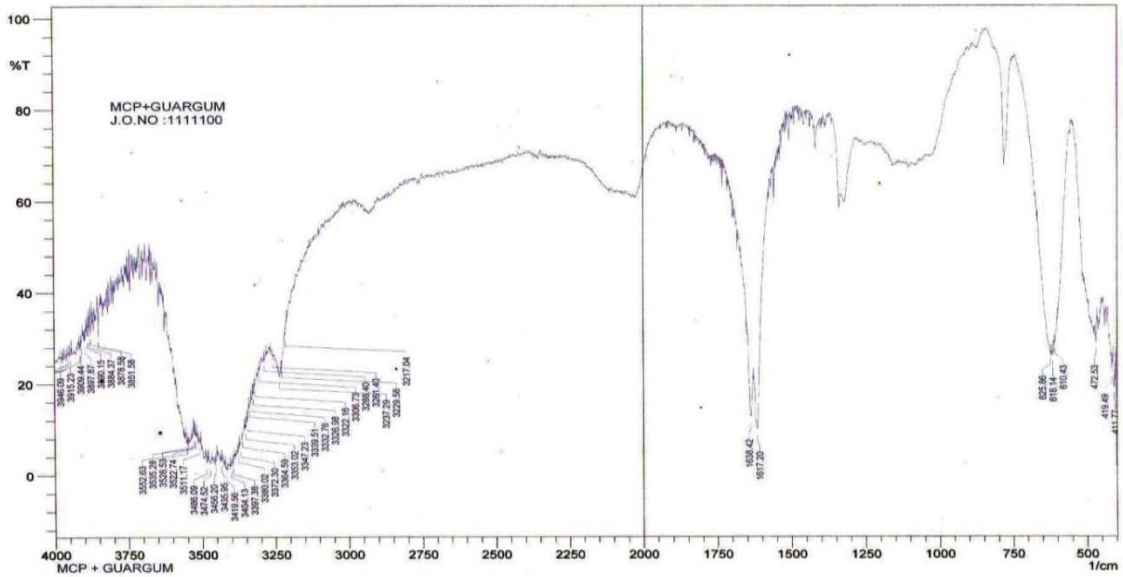

Fig. 2: FTIR spectra of metoclopramide hydrochloride with guar gum (F-8)

The physical properties of different batches of developed matrix tablets are given in (Table 2). The thickness of the tablets ranged from (3.10 to 3.23) mm. All the batches showed uniform thickness. The average percentage deviation of 20 tablets of each formulation was less than (5%), and hence all formulations passed the test for uniformity of weight as per official requirements (Pharmacopoeia of India 1996). The hardness of the tablets of all the formulations ranged from (5.4 ± 0.15 to 6.0 ± 0.27) kg/cm^2. Tablets hardness is, however, not an absolute indicator of strength. The percentage friability of the tablets of all the formulations ranged from (0.24% to 0.40%). In the present study, the percentage friability for all for formulations was below 1% w/w, indicating that the friability is within the prescribed limits (Banker and Anderson 1987). Drug content was found to be uniform among different formulations of the tablets and ranged from (97.91±0.57 to 99.93±0.33).

The results of the dissolution studies for formulations F- 1 to F-5, F-6 to F-10, and F-11 to F-15 are shown in the Figure 3, 4 , and 5 respectively. The cumulative percentage drug release for F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, F-9, F-10, F-11, F-12, F-13, F-14 and F-15 was (96.10%, 96.18%, 95.07%, 76.51%, 70.07%, 96.61%, 96.44%, 96.84%, 82.76%, 77.66%, 97.18%, 97.75%, 95.92%, 79.43, and 74.69%) at the end of 12 hours respectively. Formulation F1, F2, F6, F7, F11, and F12 failed to controlled release beyond 12 hours. Among all the formulation, F8 shows 96.84% release at the end of 12 hours. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration.

Effect of carbopol 934

To investigate the effect of carbopol 934, the formulations F-1 to F-5 were prepared in the ratio of 1:0.5, 1:1, 1:1.5, 1:2 and 1:2.5, respectively. The formulations were subjected to dissolution test study. The results are shown in Figure 3.

From the Figure 3, it was observed that the formulations F-1 and F-2 (1:0.5 and 1:1 respectively) were not able to controlled the drug release over a period of 12 hours. The formulation F-3 (1:1.5) showed controlled drug release rate and showed 95.07% drug release in 12 hour. The formulation F-4 and F-5 (1:2 and 1:2.5 respectively) showed more retardation of drug release rate and was found to release 76.51%, and 70.07%, in 12 hour. Among all the formulation, F-5 shows 95.07% of drug release at the end of 12 hours.

From the results, it was also observed that, when the concentration of carbopol 934 is increased the release rate of drug is decreased. Carbopol showed slower release than natural gums over a period of 12 hours.

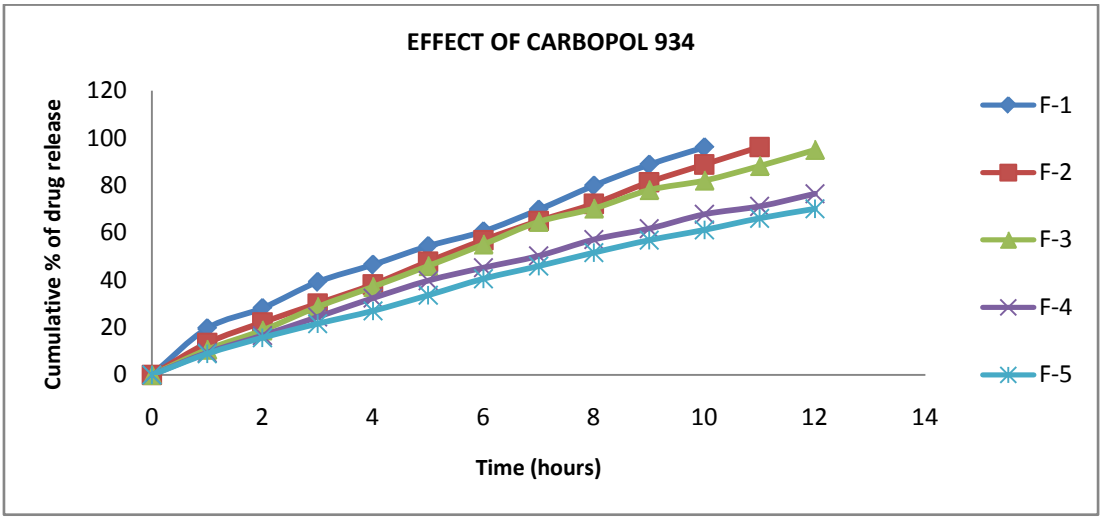

Fig. 3: Results of *in-vitro* Drug Release Profile of F1 to F5.

Effect of Guar Gum

To investigate the effect of Guar Gum, The formulations F-6 to F-10 were prepared in the ratio of 1:0.5, 1:1, 1:1.5, 1:2 and 1:2.5, respectively. The formulations F6 to F10 were subjected to dissolution study. The results are as shown in Figure 4.

From the Figure 4, The F-6 showed 96.61% and F-7 showed 96.44% were not able to control the drug release over a period of 12 hours, F-6 shows burst release. The formulation F-8 showed 96.84% controlled drug release rate. F-9 and F-10 showed 82.76% and 77.66% drug release rate respectively.

Effect of Xanthan Gum

To investigate the effect of xanthan gum, the formulations F-11 to F-15 were prepared in the ratio of 1:0.5, 1:1, 1:1.5, 1:2 and 1:2.5, respectively. The formulations F11 to F15 were subjected to dissolution study. The results are as shown in Figure 5.

From the Figure 5, it was observed that the formulations F-11 and F-12 were not able to control the drug release over a period of 12 hours and F-11 shows burst release. The formulations F13 showed 95.92% release in 12 hour while F-14 and F-15 showed slower drug release rate of 79.43%, and 74.69% in 12 hour, respectively.

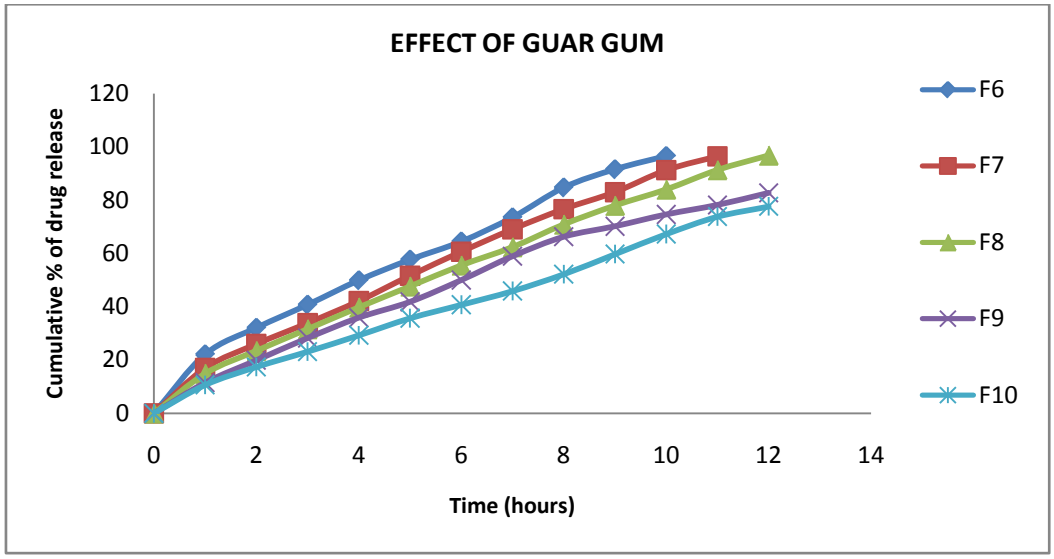

Fig. 4: Results of *in vitro* Drug Release Profile of F-6 to F-10.

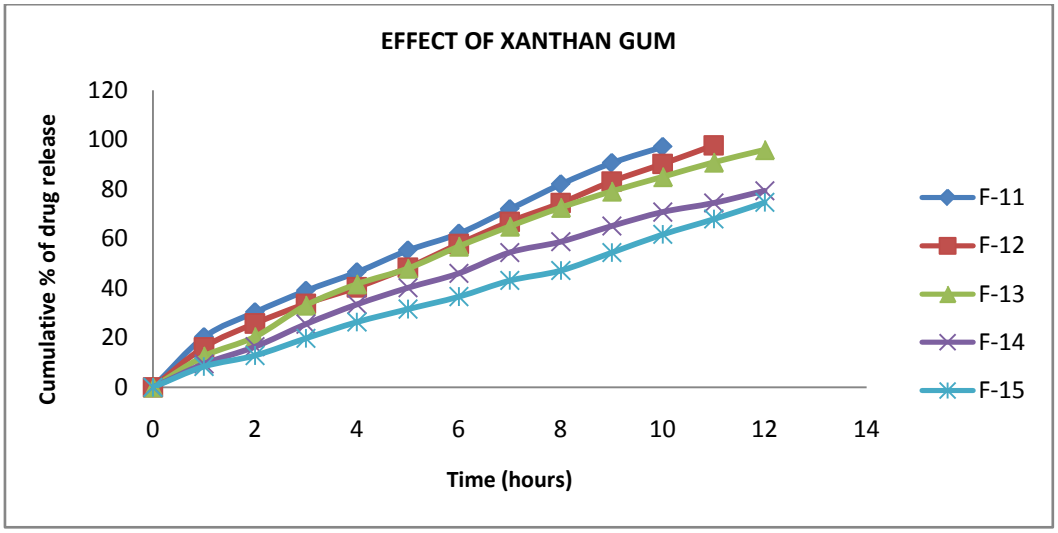

Fig. 5: Results of *in vitro* Drug Release Profile of F-11 to F-15.

The inverse relationship was noted between amount of gum and release rate of metoclopramide hydrochloride. Increasing the amount of polymer in the formulation from 15 % w/w to 75 % w/w, resulted in slower rate, and decreased amount of drug release from the tablet (Figure 3, 4, and 5). This slow release is because of the formation of a thick gel structure that delays drug release from tablet matrix, where hydration of individual polymer particles results in extensive swelling. Thus, maintain the integrity of the tablets, and retarding further penetration of the dissolution medium, prolonged the drug release.[17]

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of the drug release (Table 4). The regression coefficient obtained from zero order kinetics were found to be higher(R^2 : 0.982 to 0.998) when compared with those of first order kinetics (R^2: 0.816 to 0.990) indicating that the drug release from all the formulations followed zero order kinetics except formulation F4 and F9 follows first order kinetics(R^2=0.990 and 0.989 respectively). 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 0.999). When the data were plotted according to Korsmeyer-Peppas equation, all the formulations showed high linearity (R^2 : 0.992 to 0.999) 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. Hence, anomalous (non-Fickian) diffusion might be the mechanism for the drug release from matrix tablets.

CONCLUSION

Matrix tablet containing metoclopramide hydrochloride can be prepared successfully by using direct compression method. From the above observations it is concluded that slow and controlled release of metoclopramide hydrochloride over a period of 12 hours was obtained from matrix tablets (F-8). Use of natural hydrophilic polymer like guar gum was successful in the formation of matrix and at the same time it is effective in retarding the drug release compared to carbopol934 and xanthan gum. Among all the formulation, F-8 shows that 96.84% of drug release at the end of 12 hours. The cumulative percentage drug was decreased by increase in polymer concentration. The mechanism of drug was anomalous (non-Fickian) diffusion. Based on the FT-IR studies, there appears to be no possibility of interaction between metoclopramide hydrochloride and polymers/ other excipients used in the tablets. The stability studies show that there was no significant change in hardness, friability, and drug content of selected formulation F-8. Thus, the proposed formulation F-8 can be successfully used in the treatment of chemotherapy induced emesis in cancer patient. It is devoid of the drawbacks of that of the conventional tablets, like extra-pyramidal symptoms. It can be concluded that the release of freely water soluble drug like metoclopramide hydrochloride can be effectively controlled by using polymer like Guar gum.

ACKNOWLEDGEMENT

The authors are thankful to the Management, Sree Siddaganga College of Pharmacy, for providing necessary facilities to carryout this work.

REFERENCE

1. Modi SA, Bankar VH, Gaikwad PD, Pawar SP. Design and evaluation of sustained release drug delivery system of metoclopramide hydrochloride for emesis. Int J Pharm Sci & Tech 2011; 3(2): 2590-8.
2. Yadav D R, Ayyappan T, Shanmugam S, Sundaramoorthy K, Vetrichelvan T. Development and in-vitro evaluation of buccoadhesive metoclopramide hydrochloride tablet formulations. Int J PharmTech Research 2011; 3(1): 516-25.
3. Sayed AR, Gamal MM, Badry M. Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J 2009; 17:283-8.
4. Carnali J O, Naser M S. The use of dilute solution viscosity to characterize the network properties of carbopol microgels. Colloid & Polymer Sci 1992; 270(2): 183-93.
5. Garcia Gonzalez N, Kellaway I W, Fuente H, Anguiano, I S, Charro B Otero, Espinar F J et al. Influence of glycerol concentration and carbopol molecular weight on swelling and drug release characteristics of metoclopramide hydrogels. Int J Pharm 1994; 104:107-13.
6. Nakano M, Ogata A. In vitro release characteristics of matrix tablets: Study of karaya gum and guar gum as release modulators. Ind J Pharm Sci 2006; 68(6):824- 6.
7. Gohel MC, Patel KV, Doctor BB, Shah PD. Application of simplex lattice design to preparation of sustained release diltiazem hydrochloride tablets using modified guar gum. Int J Pharm 1999; 61(3):162-7.
8. Krishnaiah YS, Karthikeyan RS, Satynarayna V. Three layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartarate, Int J Pharm 2002; 241(2): 353-66.
9. Patra CN, Bhanoji ME, Yadav KS, Prakash K. Influence of some cellulose ethers on the release of propanol hydrochloride from guar gum matrix tablets; Ind J Pharm Sci 2004; 66(5): 635-41.
10. Pahwa1 R, Bhagwan S, Kumar V, Kohli K. Role of natural polymers in the development of floating drug delivery systems. J Pharm Research 2010; 3(6): 1312- 8.
11. R. Chang, J. R. Robinson. Sustained release from tablets and particles through coating In: H. A. Libreman, L. Lachman and J. B. Schwartz (Eds), Phamaceuticls dosage form: Tablets, 2nd Edn, vol.3, Marceel Dekker, 1990, pp. 199-302.
12. T. P. Hadjiioannou, G. D. Christian, M. A. koupparis. Quantitative calculations in pharmaceutical practices and research New Dehli, NY- VCH publishers Inc, 1993, pp. 345- 348.
13. D. W. Bourne. Pharmacokinetics. In: G. S. Banker, C. T. Rhodes, eds. Modern Pharmaceutical, 4th ed. New York, NY, Marcel Dekker Inc, 2002, pp.67-92.
14. T. Higuchi. Mechanism of sustained action medication, Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52:1145-1149(1963).
15. Korsmeyer R W, Gurny R, Doelker E, P. Buri, and N. A. Peppas. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983; 15: 25-35.
16. J. Siepmann, N. A. Peppas. Modeling of drug release from delivery system based on hydroxypropyl methylcellulose (HPMC), Adv Drug Deli Rev.2001; 48:139-57.
17. M. C. Re, I. Bon, P. Monari, R. Gorini, P. Schiavone, D. Gibellini, M. La Placa, New Microbiol. 2003; 26: 405- 413.