Research Article

Formulation and Evaluation of Controlled Release Matrix Tablets Using Eudragit RSPO and Gum Copal

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ABSTRACT

In the present investigation an attempt was made to formulate the oral controlled release metoclopramide hydrochloride matrix tablets by using Eudragit RSPO and natural gums like guar copal as rate controlling polymer and to evaluate drug release parameters as per various release kinetic models. The sustained release matrix tablets of Metoclopramide HCl were prepared by wet granulation process. All tablets were evaluated for their physical parameters for both, pre-compression and post-compression. FTIR and DSC studies proved that no chemical interaction in drug and polymers. The use of synthetic Eudragit RSPO and gum copal were unable to retard the release of drug more than 10 hrs. The combination of both the polymers found to retard the release of drug for 12 hrs. All the batches showed Mixed Matrix and Peppas best fitted model for release kinetics, which showed that, the release of the drug from the prepared tablets is sustained by swelling, followed by drug diffusion and slow erosion of the polymer. Similarity test was performed between marketed and optimized which shows identical release profile.

Keywords: Metoclopramide HCl, Eudragit RSPO. Gum Copal, controlled release, Release kinetics.

Sustained release drug delivery is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug[1]. 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[2].

Eudragit RSPO polymer also referred to as ammonio-methacrylate copolymers, consisting of fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups polymers provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms[3].

The natural gums have been extensively used in the field of drug delivery as they are readily available, sellable, cost-effective, non toxic, eco-friendly, biodegradable and compatible[4]. Gum Copal (GC) obtained from plant *Bursera bipinata* is a natural resinous material. Wide applications of Gum Copal propose their strong hydrophobic nature, substantial binding property and compatibility with the physiologic environment[5, 6].

Metoclopramide HCl is a gastrointestinal prokinetic agent which is used as an antiemetic drug for the treatment of some forms of nausea and vomiting, such as those associated with migraine, cancer therapy, or those following surgery. It has a short biological half life (2.6-5.4 h) recommends a dose (10-15mg) three to four times a day. The activity of metoclopramide is dose dependent, so it is important to control the quantity of drug released from the dosage form. In long term therapy, fluctuation in the plasma concentration, with high concentration peaks are common for drugs with rapid absorption and elimination. Hence, it is essential to formulate a sustained release dosage form of metoclopramide HCl to improve its therapeutic efficacy so that it can be taken once or twice a day. Metoclopramide HCl is freely water soluble drug[7].

The objective of the present investigation is to formulate a sustained release tablet using different combination of synthetic Eudragit RSPO and natural polymers (Gum Copal) that can maintained constant drug concentration for approximately 12 hrs and therefore may improve patient compliance by reducing dosing frequency and reduced side effects related to dose

MATERIALS AND METHOD

Materials

Metoclopramide HCL was obtained as gift sample from IPCA Laboratories Ltd., Mumbai, India. Eudragit RSPO obtained as gift sample from Rohm Pharma, Degussa India. Copal gum was purchased from National Chemicals, Baroda, India. All other ingredients used were of Analytical grades.

Methods

Drug polymer compatibility studies

FT-IR studies

The FTIR spectra of pure Metoclopramide HCL and its physical mixtures (1:1) with Eudragit RSPO and copal gum were carried out using FT-IR (Shimadzu 8400 S, CE). All samples were dried in hot air oven at 50^0C for 2 hours. The samples were prepared as KBr disks compressed under pressure of 10 Ton/nm^2

DSC studies

Thermal analysis of drug and polymer was carried out using Differential Scanning Calorimetry (Mettler Toledo DSC 822).

Formulation Deign

Dose calculation of the sustained release formulation

Pharmacokinetic studies showed that a dose of 10 mg of metoclopramide HCl produces an effective blood level concentration within 0.5 h with the half life of 2.6-5.4 h (mean 4.0 h). Thus, the elimination rate constant k= 0.693/t1/2 = 0.693/4 = 0.1732 mg/h. Hence the availability rate R = k × D = 0.1732 × 10 = 1.732 mg/h, where D is the usual dose of the drug. The maintenance dose Dm= R × h= 1.732 × 12= 20.784 mg, where h is the number of hours for which sustained action is desired. Thus, the total dose of metoclopramide HCl for sustained release formulation was calculated by the following equations using available pharmacokinetic data[8].

Total Dose = D + Dm

But, D corrected = D – Rtp = 10 – (1.732 × 0.5) = 9.134 mg, where tp is the time period required to achieve a peak plasma level.

Therefore, Total Dose corrected = D corrected + Dm = 9.134 + 20.784 = 29.918 mg

30.0 mg

Formulation of sustained release tablets of Metoclopramide HCl

Sustained release Tablets were prepared with wet granulation techniques according to the formula given in Table 1. Before granulation, all the ingredients were passed through sieve no. 100. Weighed quantities of the drug and other excipients were mixed by trituration in a glass mortar-pestle. This mixture was then granulated using ethanolic solution of PVP K-30 (10% w/v) as a granulating agent. Granules were prepared by passing the wet mass through sieve no. 16. Then, all the granules were dried at 45 °C for 1 h and again passed through sieve no. 22. Magnesium stearate (2 %w/w) was added to it and was properly mixed. Tablet compression was carried out in rotary compression machine. Compression force was kept constant throughout the study. Compression was carried out using 8 mm flat faced punches and weight was adjusted to 150 mg.

Pre compression properties of granules

The granules were evaluated for their flow properties. Angle of repose of granules was determined by the funnel method. Loose bulk density (LBD) and tapped bulk densities (TBD) were determined, according to the method reported by Raghuram et al[9]. The Carr index (compressibility index) and Hausner ratio determined from the LBD and TBD[10].

Table 1: Formulation of sustained release tablets of Metoclopramide HCl

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	HS1	HS2	HS3
Metoclopramide HCl	30	30	30	30	30	30	30	30	30
Eudragit RSPO	30	45	60	-	-		22.5	15	7.5
Gum Copal	-	-	-	30	45	60	7.5	15	22.5
MCC	87	72	57	87	72	57	87	87	87
Mg Stearate	3	3	3	3	3	3	3	3	3

Evaluation of tablet

Prepared tablet were evaluated for quality control tests like weight variation test, hardness test, friability test and content uniformity study[11, 12].

***In vitro* drug release study**

The in-vitro release of metoclopramide HCl from formulated sustained release tablets was carried out in hydrochloric acid buffer pH 1.2 for 2 h and continued in phosphate buffer pH 6.8 from 3 to 12 h (900 mL). The studies were performed in USP dissolution apparatus II, (Electrolab Tablet Dissolution tester – USP, Model No. TDT – 06P) at 37 ± 0.5°C and 50 rpm speed . Samples were withdrawn (10 mL) at hourly interval for first four hour and at two hour interval after that. After each withdrawal, the sample was replaced by an equal amount of fresh dissolution medium. All collected samples were filtered and analyzed for metoclopramide HCl content at 273.2 nm by using UV–visible spectrophotometer (Mode No. UV 2300, Techcomp). The cumulative % drug release at different time intervals were calculated The release studies were conducted in triplicate and the mean values were plotted versus time with SDs.

Determination of release kinetics and release mechanism

Model dependent methods are based on different mathematical functions, which describe the dissolution profile. The release data obtained were treated according to zero-order, first-order, Higuchi and Korsmeyer-Peppas equation models[13, 14] as shown in table 2.

Table 2: Mathematical release kinetics models

Model	Equation
Zero Order	Qt = Q0 + K0 t
First Order	ln Qt = ln Q0 + K1 t
Higuchi	Qt =Kh $t^{1/2}$
Hixson - Crowell	$Q0^{1/3}$ - $Qt^{1/3}$ = Ks t

Where, Qt is amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution, K0 is zero order release constant, K1 is first order release rate constant, Kh is Higuchi dissolution constant and Ks is constant incorporating surface volume relation.

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to Kosmeyer et al's equation[15] as:

$$M_t/M_\infty = K.t^n$$

Where,

M_t/M_∞ = fraction solute release

t = release time

K = kinetic constant characteristic of the drug/ polymer system

n = exponent that characterizes the mechanism of release of traces

Comparative Evaluation of Formulation with Marketed product

To evaluate and compare dissolution data, the dissolution profile was statistically analyzed using dissolution similarity factor f_2. The equation for calculating f_2 is given below.

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{t} Wt \left(R_t - T_t \right)^2 \right]^{-0.5} \times 100 \right\}$$

Where, n = numbers of dissolution time point

W_t = Optional weight factor

R_t = Reference dissolution point at time t

T_t = Test dissolution point at time t

The f_2 value between 50 and 100 suggest that the dissolution is similar. The f_2 values of 100 suggest that the test and reference profile are identical and as the value becomes smaller, the dissimilarity between releases profile increases.

Surface morphology

Electron micrographs of matrix tablets before and after dissolution were obtained using a scanning electron microscope (model JSM T200, Joel Ltd., Japan). The specimens were coated under vacuum with gold in an argon atmosphere prior to observation. The scanning electron microscope was operated at an acceleration voltage of 30kV.

RESULTS AND DISCUSSION

Drug polymer compatibility studies

The FT-IR specra of pure drug and its physical mixture with polymers eudragit RSPO and copal gum revealed no considerable changes in IR peaks of Metoclopramide HCl indicating absence of interaction between drug and polymer used. The results of DSC studies also confirmed that there was no appreciable change in the melting endotherm which further supports the IR spectroscopy results. . These results clearly indicate the usefulness of the utilized materials for preparation of controlled release tablets.

Pre compression Evaluation

Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. All the batches of granules showed good flow properties since all batches had angle of repose of between 25°-30° which indicate excellent flow of granules. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. All batches had compressibility index between of between 11-15% and hausner's ratio between 1.12-1.18 which indicates good flow character of granules. The results are as depicted in table 3.

Post compression Evaluation of tablet

The tablet hardness, thickness, weight variations, and friability for each formulation are presented in Table 4. The hardness of all the compression coated tablets was found to be within 6-7 kg/cm^2. The percent weight loss in the friability test was less than 1% in all the batches. In determinations of tablet weights, all formulations weights were found to be within pharmacopoeia limits. . The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets, and drug content was more than 95%.

Table 3: Pre compression properties of granules

B. No.	Bulk density (g/mL)	Tapped density (g/mL)	Angle of Repose (°)	% Compressibility	Hausner ratio
F1	0.317	0.364	26.20±0.86	12.94	1.14
F2	0.405	0.468	26.95±0.34	13.46	1.15
F3	0.422	0.482	26.77±0.89	12.50	1.14
F4	0.330	0.380	25.30±0.79	13.16	1.15
F5	0.476	0.557	26.18±0.32	14.54	1.17
F6	0.474	0.550	26.00±0.55	13.72	1.15
HS1	0.260	0.317	25.74 ± 0.50	18.18	1.22
HS2	0.299	0.345	26.40 ± 0.81	13.43	1.15
HS3	0.308	0.351	25.70 ± 0.44	12.31	1.14

Table 4: Post-compression Study

B. No.	Friability	Hardness	Thickness	% Weight variation#	% Content*
F1	0.145 ± 0.061	8.42 ± 0.74	2.44±0.04	151.70 ± 1.99	97.34±0.4
F2	0.214 ± 0.120	8.04 ± 0.44	2.48±0.02	151.22 ± 2.03	97.24±0.5
F3	0.130 ± 0.047	7.92 ± 0.34	2.47±0.03	150.77 ± 1.99	96.32±0.9
F4	0.195 ± 0.037	8.17 ± 0.52	2.33±0.07	150.94 ± 1.45	98.45±0.7
F5	0.289 ± 0.117	7.92 ± 0.74	2.45±0.03	150.95 ± 2.37	97.22±0.4
F6	0.220 ± 0.089	7.67 ± 0.68	2.42±0.02	150.83 ± 2.09	98.22±0.4
HS1	0.145 ± 0.061	8.42 ± 0.74	2.45±0.03	151.70 ± 1.99	96.54±0.7
HS2	0.214 ± 0.120	8.08 ± 0.66	2.48±0.04	151.22 ± 2.03	97.88±1.2
HS3	0.130 ± 0.047	7.92 ± 0.38	2.47±0.03	150.77 ± 1.99	98.55±0.5

***In vitro* drug release study**

The percentage of the drug released from the formulations F1, F2 and F3 containing Eudragit RSPO was found to be 95.69± 0.63 %, 90.15 ± 0.35 % and 90.63 ± 0.42 %, in 8 hrs respectively. The percentage of the drug released from the formulations F4, F5, and F6 containing gum copal was found to be 93.63± 0.54 %, 91.65 ± 1.48, and 92.12 ± 0.87 % at 10 hrs respectively. The percentage of the drug released from the formulations HS1, HS2 and HS3 comprise of combination of both the polymers was found to be 94.38 ± 1.29 %, 92.37 ± 01.23 and 94.14 ± 1.36 % at 12 hrs respectively as depicted in figure 1 and 2.

The release profile indicates that Eudragit RSPO can retard the drug release upto 8 h. Here, profile of sustained release formulation was good but our main objective was to formulate a formulation which provides upto 12 hours sustained action. Due to rapid diffusion of the dissolved drug through the hydrophilic gel network, use of Eudragit RSPO alone is restricted for extending drug release.

It was also observed that as the amount of polymer increases in the formulation there was decrease in drug release rate, which may be due to the drug entrapped in hydro gel by forming hydrophilic polymers. Gum copal provides extended drug delivery for 10 hrs only. Combination of Eudragit RSPO with gum copal shows good sustained release properties than with individual polymers.

ANOVA was carried out using Bonfferroni post test between the drug release data of formulation, F1-F3 of plain polymer batches and combination of polymers batches F4 to F9, with their respective combinations are analyzed, ***p*** values were less than 0.001 indicating statistical significant difference existing between release profile of tablets containing different polymer-polymer combinations and different combination ratio.

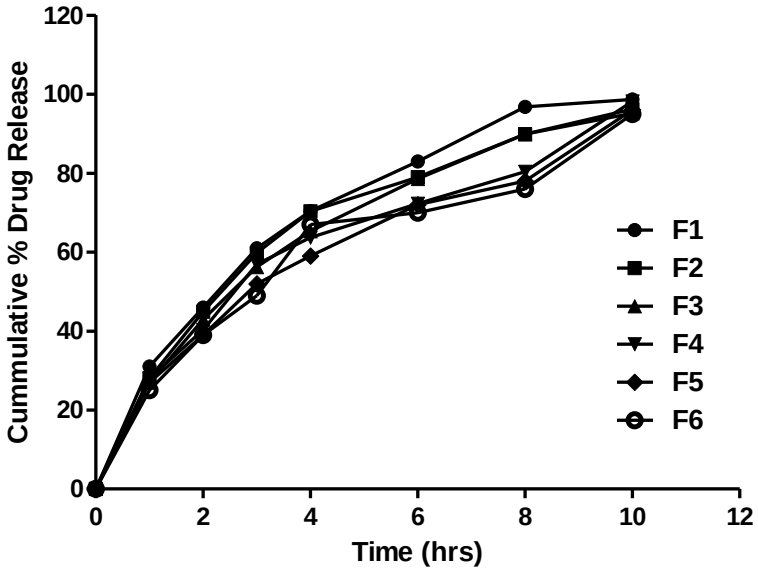


Fig. 1: Cumulative percentage release of Batch F1-F6

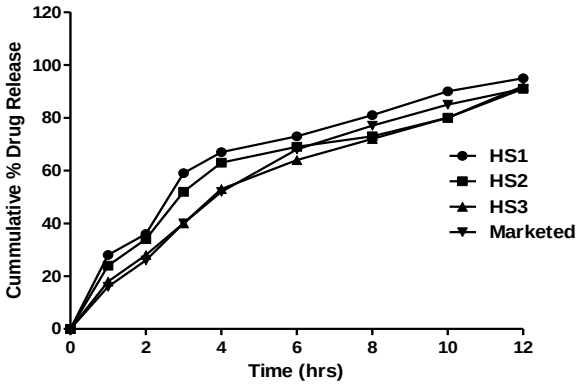


Fig. 2: Cumulative percentage release of Batch HS1-HS3 and Marketed tablet

Determination of release kinetics and release mechanism

The best fitting model for all formulation was calculated. Batch F2, F3 and F6, the best fitted models were found to be Higuchi kinetics. The batch F1, F4, F5, F7, F8, F9 and Marketed formulation followed Korsmeyer peppas model as shown in Table 5.

The values of *n* as estimated by linear regression of log (M_∞ / M_t) vs. log (*t*) of formulations indicated a non-Fickian release behavior, which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms. Thus, the release of the drug from the prepared tablets is sustained by swelling of the polymer; followed by drug diffusion through the swelled polymer, slow erosion of the polymer.

Comparative Evaluation of Formulation with Marketed product

Similarity in release profile between marketed and optimized formulations was also calculated from the similarity factor ($f2$). Similarity test was performed between Perinorm CD and HS3 and f_2 values found to be 79.24 which clearly suggest that the test and reference profile are identical.

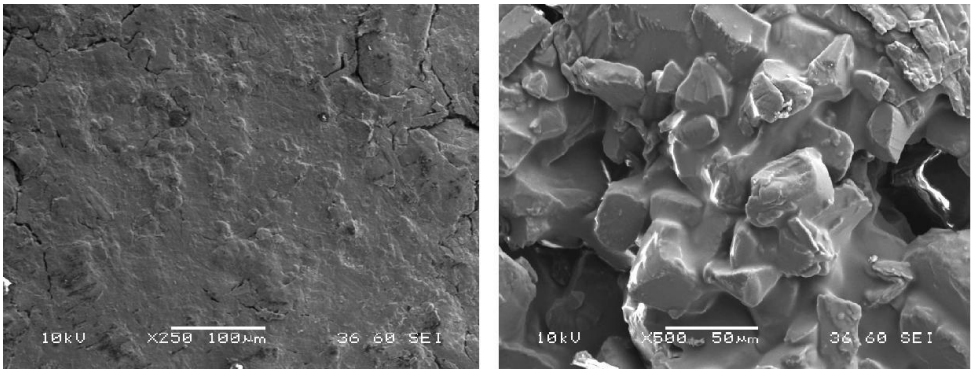
Marketed and optimized formulations were also compared statistically using one way ANOVA (95.00% CI) followed by Dunnett test. No significant difference was observed. It may be concluded that marketed and optimized formulation are identical to each other in release rate of drug.

Surface morphology

The SEM images of the tablet were taken before and after dissolution. Figure 3 showed intact surface without any perforations, channels, or troughs. After dissolution, revealed many pores with increasing diameter. The solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium, which clearly indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of drug from formulated matrix tablets.

Table 5: Determination of release kinetics and release mechanism

B No	Zero order		1st order		Matrix		Hix.Crow		Korsmeyer -Peppas		
	R	k	R	k	R	K	R	K	R	n	K
F1	0.897	2.347	0.9348	-0.026	0.9859	7.3986	0.924	-0.0086	0.9861	0.5606	16.445
F2	0.795	10.100	0.9883	-0.269	0.9965	29.9332	0.9823	-0.0606	0.9943	0.6554	14.793
F3	0.856	9.325	0.9568	-0.213	0.9922	27.4423	0.9868	-0.0515	0.9663	0.8766	10.2673
F4	0.671	9.1001	0.9221	-0.179	0.9758	25.2721	0.8446	-0.0465	0.9865	0.5651	16.615
F5	0.856	11.357	0.8625	-0.404	0.8636	24.5758	0.7101	-0.0796	0.9863	0.645	52.4913
F6	0.926	10.812	0.843	-0.295	0.9861	32.9457	0.9533	-0.0664	0.9245	0.7628	53.242
HS1	0.986	6.884	0.9688	-0.113	0.9333	19.602	0.9799	-0.0315	0.9968	0.4802	15.544
HS2	0.855	9.534	0.9882	-0.215	0.9908	28.1065	0.9749	-0.0526	0.9897	0.6233	10.383
HS3	0.869	10.626	0.8962	-0.279	0.8914	32.2489	0.7632	-0.0639	0.9976	0.7271	50.8577
Marketed	0.887	11.455	0.8745	-0.259	0.9675	29.665	0.7565	-0.0655	0.9921	0.792	12.623



(a) **(b)**

Fig. 3: SEM photomicrographs of Batch HS3(a) before and (b) after dissolution study

CONCLUSION

The tablets were prepared by wet granulation process. FTIR and DSC studies proved that no chemical interaction. The initial work was carried out using individual polymer at different Drug: Polymer ratio to select optimum ratio for drug and polymer concentration. All tablets were evaluated for their physical parameters for both, pre-compression and post-compression The use of synthetic Eudragit RSPO and gum copal were unable to retard the release of drug more than 10 hrs. th combination of both the polymers retard the release of drug for 12 hrs. The release kinetics and SEM study clearly indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of drug from formulated matrix tablets. Similarity test was performed between Perinorm CD and HS3 and f_2 values found to be 79.24 which clearly suggest that the test and reference profile are identical.

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