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Sustained release solid dispersion of Metoclopramide HCL: formulation, evaluation and pharmacokinetic studies

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ABSTRACT

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 and hence dose related side effect, and increase the safety margin. The objective of present work was prepared sustained release solid dispersion of Metoclopramide HCl by solvent evaporation method. Several polymers like combination of Eudragit RSPO - Eudragit RLPO and Guargum-Egg albumin as synthetic and natural polymers respectively were used. Several parameters like Solubility, Partition coefficient, Drug content, Percent drug release, Bulk density, Tapped density and Carr's index were evaluated and all parameters were found to be in acceptable range. The results of XRD and SEM analysis were showed that the drug was converted into a solid dispersion. The *In vivo* studies were performed on Albino Wistar rats and various pharmacokinetics parameters were determined. The whole study was showed that the solid dispersion of Metoclopramide HCl sustained the release rate of drug for a prolong period of time at least 12 hrs and shows to increase the bioavailability and simultaneously decrease the dosing interval as well as dosing amount. The formulation minimizes the blood level oscillations, dose related adverse effects and cost and ultimately improve the patient compliance and drug efficiency.

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. Sustained release solid dispersion 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 **(**Patel *et al*., 2012).Sustained release drug delivery are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug (Dusane *et al.*, 2011). The USP and FDA, identify specific dissolution requirements for extended release dosage forms which involve sampling three times, expressed as fractions of the normal dosing interval (D). Releasing of 20– 50% of the drug after 0.25 D assures that there is no dose dumping from the dosage form. The intermediate specification assures that drug release (45–75%) over the 0.25–0.5 D period occurs neither too slowly nor too rapidly, while the purpose of the last specification is to assure complete dissolution of the drug. From a practical stand point, sampling through 8 h for a twice daily product and through 12 h for a once daily product may be adequate, provided that not less than 75–80% of drug has been released **(**Welling *et al*., 1988). The selection of is Metoclopramide hydrochloride is used an effective and popular drug for many type of vomiting induced by drug, disease associated(migration), radiation sickness but it less effective in motion sickness. Metoclopramide is used in long term therapy for vomiting induced by highly emetic anticancer drugs (cisplatin, etc). Metoclopramide hydrochloride inhibits gastric smooth muscle relaxation produced by dopamine, therefore increasing cholinergic response of the gastrointestinal smooth muscle. The central anti-dopaminergic (D2) action of Metaclopramide on CTZ is responsible for its antiemetic property.

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It accelerates intestinal transit and gastric emptying by preventing relaxation of gastric body and increasing the phasic activity of antrum. Metoclopramide also decreases reflux into the esophagus by increasing the resting pressure of the lower esophageal sphincter and improves acid clearance from the esophagus by increasing amplitude of esophageal peristaltic contractions. Studies have also shown that high doses of Metoclopramide can antagonize 5-hydroxytryptamine (5-HT) receptors in the peripheral nervous system in animals. Guar gum is a nonionic naturally occurring, hydrophilic polysaccharide obtained from the seeds of *Cyamopsis tetragonolobus*. It is used in solid dosage forms (binder and disintegrant), possess release retarding property and susceptibility to microbial degradation. It swells in cold water and forms viscous colloidal dispersions or sols. It is this gelling property that retards release of the drug from the dosage form. It was observed that guar gum alone acts as the release retarding polymer which follows a first-order release kinetic **(**Anupama *et al.*, 2011).

The increased concentration of guar gum decreases the drug release (Deshmukh *et al.,* 2009). Albumin have been extensively investigated in controlled release polymer as vehicles for the delivery of therapeutic agents to local sites. The exploitable features of Albumin include its reported biodegradation into natural products, its lack of toxicity and its nonantigenicity **(**Aydan *et al*., 2012**).**

Egg Albumin was selected as hydrophilic carriers for this study because of significant differences in their conformation and stability. Several studies on the conformational changes in ovalbumin induced by certain denaturing agents and by chemical modifications of certain amino acid have been reported **(**Ifat *et al*., 2000**)**. In the field of modified drug delivery, interesting potentialities are offered by acrylic polymers, such as Eudragit Retard, extensively used for film coating of solid dosage forms, as well as in the preparation of inert matrices or micromatrices for controlling the drug delivery via oral or other routes. Eudragit RS (RS) and RL(RL) are copolymers of poly(ethyl-acrylate-co methyl-methacrylate-co-trimethylamino-ethyl-methacrylate chloride) [poly(EAMMA- TAMCl)]. The introduction of the hydrophilic ammonium groups (TAMCl) is aimed at modifying the permeability of the acrylic polymer. The main difference in RS and RL consists in the amount of ammonium groups: their composition is in fact EA:MMA:TAMCl=1:2:0.2 (RL) and 1:2:0.1 (RS). These polymers are insoluble in aqueous media, but are able to swell and become permeable to solutes, thanks to the presence of the ionized TAMCl groups, but in a pH-independent manner (Eudragit Technical Sheets, Rohm, Germany) **(**Rosario *et al*., 2004).

MATERIAL AND METHOD

The Metoclopramide HCL was obtained as gift sample from Vaikunth Chemical Pvt Ltd, Gujrat (India). The synthetic polymers Eudragit RSPO and Eudragit RLPO were obtained as a gift sample from Evonic Pvt Ltd, Mumbai (India). The Natural polymers Guargum and Egg albumin was procured from Central Drug House Pvt Ltd, N. Delhi (India). The Potassium dihydrogen phosphate, Hydrocloric acid and di sodium hydrogen phosphate were procured from Central Drug House Pvt Ltd, N. Delhi (India). All chemical and solvent were used of analytical grade.

Formulation Design

The miscellaneous factorial design with independent 2 factors and 3 levels (design expert -8 software, Statease, U.S. A) was apply to design and optimized the delivery system. Total 13 runs with formulation code B1-B13 were obtained. There was two independent factor (Polymer 1and 2) and two dependent factor (% cumulative drug release and drug content uniformity).

Table 1: Formulation design, H-High, M-Medium, L-Lower for formulation prepared by synthetic polymers(Eudragit RSPO –Eudragit RLPO)and natural polymers (Guargum-Egg albumin).

Run	Formulation code	Polymer1 (mg)	Polymer2 (mg)
1	B1	1500 (M)	1500 (M)
2	B2	1000 (L)	1000 (L)
3	B3	1500 (M)	1500 (M)
4	B4	2000 (H)	2000 (H)
5	B5	2000 (H)	1000 (L)
6	B6	1000 (L)	2000 (H)
7	B7	1500 (M)	1500 (M)
8	B8	1500 (M)	1500 (M)
9	B9	1500 (M)	1500 (M)
10	B10	1500 (M)	2000 (H)
11	B11	2000 (H)	1500 (M)
12	B12	1500 (M)	1000 (L)
13	B13	1000 (L)	1500 (M)

Methods

Specific quantity of Metoclopramide HCl, Guargum, Egg albumin, Eudragit RSPO, and Eudragit RLPO were weighed. The mixture of Drug and Albumin, Guargum in different ratio were weighed and was mixed with distilled water use as a solvent. As the same way the mixture of drug, Eudragit RSPO and Eudragit RLPO were mixed with absolute alcohol with continuous stirring to achieve homogeneous mixture in magnetic stirrer at 40^0C. The solvent was evaporated at 20-40 ^{0}C. After some time the solid residue was remained which was collected and sieved by 80# mesh and was stored in desiccators.

Pre Evaluation

Drug polymer compatibility studies

Drug polymer compatibility studies were performed by taking the combination of Drug + Guargum + Albumin (1:1:1) and Drug + Eudragit RSPO + Eudragit RLPO (1:1:1) was putted in humidity chamber for 30 days at 75 ± 5 % relative humidity and 45 ± 2^0C. After 30 days, these combinations were evaluated by FTIR spectrophotometer (FT/IR-4100 Jasco, Japan). Other Preformulation parameters like solubility, partition coefficient etc were determined to check the authenticity of drug.

Dose determination

The conventional dose of Metoclopramide HCl is 10mg-15mg four times a day but the dose is reduced to 27mg for

formulating sustained release solid dispersion (Hemalatha *et al*., 2011; Kannan *et al*., 2010; Sandip *et al*., 2011).

$$D_t = D_i (1+0.693*t_m/t_{1/2})$$

Where, D_t= total dose; D_i= initial dose; t= time to which the drug is sustained; $t_{1/2}$= half life of the drug. D_t= 10(1+0.693×12/5); D_t= 27mg. After the calculation the 27 mg Metoclopramide is equivalent to 30mg Metoclopramide HCL twice a daily filled in capsule.

Evaluation

Angle of Repose

Angle of repose was determined using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula (Viral *et al*., 2011).

$$\theta = \tan^{-1}h/r$$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Bulk Density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated using the formula (Viral *et al*., 2011).

$$\rho b = M/V_t$$

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (ρt) was calculated using the following formula (Viral *et al*., 2011).

$$\rho t = M/V_t$$

Carr's Compressibility Index (I)

The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules was determined by Carr's compressibility index which is calculated by using the following formula (Viral *et al*., 2011).

$$I = \rho t - \rho b / \rho t \times 100$$

Determination of percent yield

The percent yield of Metoclopramide HCl solid dispersions can be determined by using the following expression (Tyagi *et al*., 2012).

Percent yield = (weight of prepared solid dispersion / weight of drug + carriers) x 100

Drug Content

To determine the actual amount of drug present in each milligram of the formulation. Formulation containing 100 mg drug was taken in 100ml volumetric flask, dissolved in pH 6.8 phosphate buffer and volume was made up to mark with pH 6.8 phosphate buffer then sonicated for 15min. after sonication the solution was filtered. The 1ml sample was pipetted out from the sonicated solution into 10ml volumetric flask then volume was made up the 10 ml with 6.8 phosphate buffer. Absorbance was taken at 272 nm by UV spectrophotometer (Shimadzu 1800, Japan).

***In vitro* dissolution study**

The study was performed by using USP dissolution apparatus I (basket type) at 37^0C & 100 rpm in 500ml 1.2HCL buffer solution for 2 hour. Then in resting time (10 hrs) the test was performed in 400ml 6.8 phosphate buffer to make up the volume 900ml. The 10ml sample was withdrawn in 30, 60, 90, 120, 150….720min at different interval and filtered. The absorbance of the solution was measured at 272 nm. The concentration of metoclopramide HCl was calculated using slope of calibration curve and cumulative percentage release was calculated.

Infrared spectral analysis

Infrared (IR) spectra of solid dispersion prepared by natural polymers(Guargum +Egg albumin) and synthetic polymers (EudragitRSPO+EudragitRLPO) were obtained by using KBr disc method (1800, Shimadzu Asia Pacific Pvt. Ltd, Singapore) in the range of 4000 to 350cm^{-1}.

X-Ray diffraction analysis

The X-ray powder diffractograms of the API, solid dispersion, physical mixture of drug and polymers were recorded using glancing angle X-ray diffraction (GAXRD, Cu Kα radiation of wavelength 1.54 Å, Phillips X'pert PROPW 3040, Indian Institute of Technology,Delhi) at a speed of 4^0/ min from 10- 60 range (2θ) at sample interval 0.02^0 under the voltage and current of 40 Kv and 30 Kv respectively .

Scanning electron microscopy analysis

The sample was mounted in circular metallic sample holder available with SEMCF be arranged in a circular pattern as displayed in the SEMCF keeping under the vacuum and the sample was coated with gold partical by using BIO-RAD POLARAN sputter coater. The sample was placed in a evacuated chamber and scanned in a controlled pattern by electron beam (ZEISS EVO Series Scanning Electron Microscope EVO 50,IIT Delhi). Interaction of the electon beam with specimen produced a verity of physical phenomenon that detected are used to form images and provided the information about specimen.

***In Vivo* study**

In vivo studies were conducting on albino wistar rats. The approval for studies was given by the animal ethical committee, ITS Paramedical (Pharmacy College), Muradnagar, Ghazaibad, UP, India. Wistar Rats were divided into three groups. The animal was fasted overnight. Drug (formulation equivalent to

dose/body weight) was administered orally to each group as a single dose (4mg/kg of Metoclopramide HCL) through oral gauge. Blood sample were withdrawn at predetermined time interval from the orbital plexus of rat and collected in the EDTA coated vacuette tube and then centrifuged at 3000 rpm for 10 min to separate the plasma. Separated plasma was mixed with 4ml of diethyl ether / Acetonitrile to 1 ml plasma sample and mixed .The mixture was again centrifuged for 10 min at 3000 rpm. After centrifugation the upper organic layer is separated and the solvent is evaporated in a oven to dryness. The residue was added in 400µl of mobile phase and evaluated by HPLC (PU-2080Plus Jasco, Japan) (Menaka *et al*., 2013; Rashmika *et al*.,2013; Sushilkumar *et al*., 2011; Zheng *et al*., 2014).

HPLC analysis

The standard curve between area% v_s concentration(ng/ml)of metoclopramide HCL was constructed by using KH_2PO_4(0.05M,Ph 4.6) and acetonitrile in ratio of 60:40v/v as mobile phase. The flow rate and duration of run were 1ml/min 10 min respectively. Various pharmacokinetics parameters like AUC, T_{max} $C_{max.}$ etc were determined for both formulation and API and compared.

Results and discussion

Compatibility study

The IR spectra of pure drug and physical mixture of drug + polymers (Metoclopramide HCL + Guargum+ Egg albumin and Metoclopramide HCL+ Eudragit RSPO+ Eudragit RLPO) was obtained to determined the compatibility of drug and polymer it was found compatible.

Results and inference of Pre Evaluation and evaluation parameters are given in table 2

Table 2: Result and observation of pre eavaluation and Evaluation.

Pre Evaluation	Results		Inference
Solubility	74.88gm in 250ml water		More soluble
Partition coefficient	0.403		More hydrophilic
Evaluation	**B3(Eudragit RSPO+Eudragit RLPO)**	**B7 (Guargum+ Egg albumin)**	
Bulk density	0.53-0.56 g/cm3	0.54-0.57g/cm^3	
Tapped density	0.61-0.67 g/cm3	0.60-0.68 g/cm^3	
Compressibility index	13.1-16.4%	10.00- 16.1%	Good flow
Angle of repose	27.13º-32.68º	26.5 º - 30.9 º	Free flowing

Percentage Yield

The percent yield of solid dispersions prepared by synthetic polymers (Eudragit RSPO + Eudragit RLPO) and natural polymers (Guargum + Egg albumin) was found to be range between 90-95% and 80-98%.

Drug content uniformity

The content uniformity of solid dispersion prepared by synthetic polymers (Eudragit RSPO + Eudragit RLPO) and natural polymers (Guargum +Egg albumin) was found to be range between 81-97 % and 80.90- 94.17% respectively (table 3).

In vitro drug release

The in vitro drug release profile of various formulations was indicated the sustained action of formulation. The formulation is sustained for 12 hrs than the API of drug and physical mixture of drug and polymers. The cumulative drug release of pure drug in 60 min was found to be 98% in pH1.2 HCL buffer and 99% in pH 6.8 phosphate buffer.

The cumulative drug release of physical mixture of Drug + Eudragit RSPO+Eudragit RLPO and Drug + Guargum+Albumin in 60 min was found to be 92% and 95% pH1.2 HCL buffer and 96% and 98% pH 6.8 phosphate buffer respectively. But the drug release was retarded in the formulation of solid dispersion prepared by synthetic polymers B3 (Eudragit RSPO + Eudragit RLPO) and natural polymers B7 (Guargum + Egg albumin) in 60 min was found to be 25.3% and 23.8% respectively. The Dissolution of optimized formulation (B3 and B7) of solid dispersion was prepared by synthetic polymers (Eudragit RSPO + Eudragit RLPO) and natural polymers (Guargum +Egg albumin) in 12 hrs was found to be 95.7% and 99% respectively(Table 3, 4).

As it is shown in tables 5 and 6 Y1, and Y2, were fitted with a quadratic model and significant lack of fit ($P < 0.05$). The positive sign of the factors represent a synergistic effect on the response, while a negative sign means an antagonist relationship. Phrases composed of two factors indicate the interaction terms and phrases with second-order factors stand for the nonlinear relationship between the response and the variable.

Effect of Independent Variables on % Cumulative drug release for formulation prepared by polymer (Eudragit RSPO and Eudragit RLPO)

The second-order polynomial equation relating the response of (Y1) % Cumulative drug release is given below:

$$Y_1=+94.08-6.32A-4.98B-5.00AB-1.14A^2-1.74B^2$$

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. The Model F-value of 137.76 implies the model is significant ($p = <0.0001$). "Lack of Fit F-value" of 4.55 implies the Lack of Fit is not significant ($P= 0.0886$). The ANOVA test indicates that A, B, AB & B^2 are significant model terms. Negative coefficients of A, *B*, AB, A^2& B^2 indicate the antagonistic effect on %cumulative drug release(Table 5). The "Pred R Squared" of 0.9309 is in reasonable agreement with the "Adj R-Squared" of 0.9828, indicating the adequacy of the model to predict the response of %cumulative drug release. The 'Adeq Precision' of 41.778 indicated an adequate signal. Therefore, this model is used to navigate the design space(Table 6). As the concentration of polymers was increased the total %cumulative drug release of the sustained release solid dispersion gets decreased. In the case of Eudragit RSPO and Eudragit RLPO as its concentration was increased it leads to decreased in % cumulative drug release. Therefore, it was suggested to keep its concentration on the upper side to release sustained effect (Fig. 3a)

Table 3: Observation table for cumulative drug release and Drug content uniformity of formulation B1-B13 prepared by Synthetic polymers Eudragit RSPO and Eudragit RLPO.

Formulation code	Eudragit RSPO (mg)	Eudragit RLPO (mg)	Cumulative Drug release (%)			Drug content uniformity (%)		
			Actual value	Predicd value	Residul value	Actal value	Predicd value	Residl value
B1	1000.00	1000.00	98.00	97.50	0.50	83.87	83.64	0.23
B2	1500.00	1000.00	96.00	97.33	-1.33	83.00	83.16	-0.16
B3	2000.00	1000.00	95.70	94.87	0.83	97.20	97.28	-0.077
B4	1000.00	1500.00	99.00	99.26	-0.26	84.00	84.23	-0.23
B5	1500.00	1500.00	94.80	94.08	0.72	80.20	80.32	-0.12
B6	2000.00	1500.00	85.70	86.63	-0.93	91.40	91.01	0.39
B7	1000.00	2000.00	97.30	97.54	-0.24	89.02	89.02	00.00
B8	1500.00	2000.00	87.50	87.36	0.14	82.00	81.68	0.32
B9	2000.00	2000.00	75.00	74.90	0.097	88.62	88.94	-0.32
B10	1500.00	1500.00	94.00	94.08	-0.083	81.00	80.32	0.68
B11	1500.00	1500.00	93.80	94.08	-0.28	80.00	80.32	-0.32
B12	1500.00	1500.00	94.00	94.08	-0.083	80.20	80.32	-0.12
B13	1500.00	1500.00	95.00	94.08	0.92	80.05	80.32	-0.27

Table 4: Observation table for cumulative drug release and Drug content uniformity of formulation B1-B13 prepared by Natural polymers Guargum + Egg albumin

Formulation Code	Guargum(g)	Albumin(g)	Cumulative Drug release (%)			Drug content uniformity (%)		
			Actal value	Predicd value	Residul value	Actal value	Predicd value	Residl value
B1	1000.00	1000.00	99.00	98.59	0.41	91.20	91.01	0.19
B2	1500.00	1000.00	98.80	99.33	-0.53	93.00	94.10	-1.10
B3	2000.00	1000.00	90	89.88	0.12	93.20	92.29	0.91
B4	1000.00	1500.00	96.90	96.56	0.34	93.60	93.49	0.11
B5	1500.00	1500.00	94.50	95.17	-0.67	93.00	92.76	0.24
B6	2000.00	1500.00	84.50	83.59	0.91	85.80	87.13	-1.33
B7	1000.00	2000.00	98.00	98.74	-0.74	94.17	94.47	-0.30
B8	1500.00	2000.00	97.00	95.23	1.77	89.80	89.92	-0.12
B9	2000.00	2000.00	80.5	81.53	-1.03	80.90	80.48	0.42
B10	1500.00	1500.00	95.20	95.17	0.031	93.50	92.76	0.74
B11	1500.00	1500.00	95.80	95.17	-0.63	92.00	92.76	-0.76
B12	1500.00	1500.00	94.50	95.17	-0.67	93.00	92.76	0.24
B13	1500.00	1500.00	94.60	95.17	-0.57	93.50	92.76	0.74

Table 5: Regression analysis for % Cumulative drug release and Drug content uniformity drug release for formulation B1-B13 prepared by polymers (Eudragit RSPO and Eudragit RLPO).

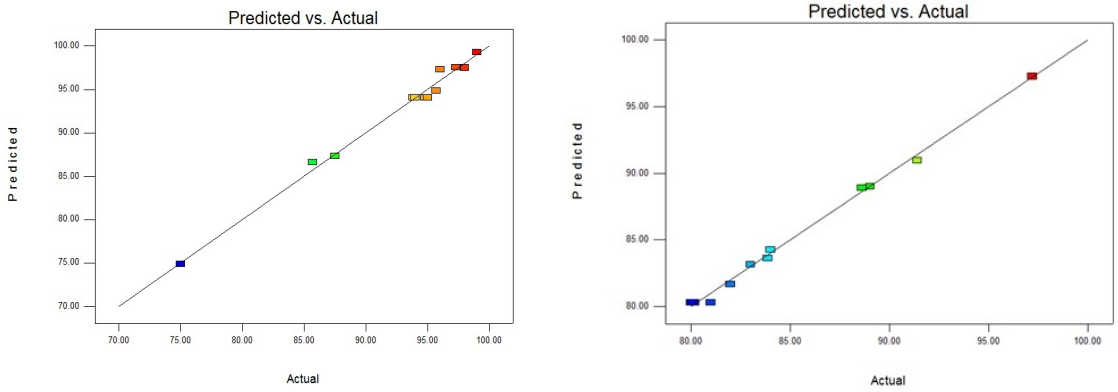
Factor	% Cumulative Drug Release		Drug content uniformity	
	C E	P-Value	CE	P-Value
Intercept	94.08		80.32	
A	-6.32	< 0.0001	3.39	< 0.0001
B	-4.98	< 0.0001	-0.74	0.0030
AB	-5.00	< 0.0001	-3.43	< 0.0001
A^2	-1.14	0.0631	7.30	< 0.0001
B^2	-1.74	0.0119	2.10	< 0.0001

Table 6: Design summary for formulation B1-B13 prepared by polymers (Eudragit RSPO and Eudragit RLPO).

Model summary for response Y1 (% Cumulative drug release)					
Source	**Sequential p Value**	**Lack of fit p Value**	**Adjusted R^2**	**Predicted R^2**	**Model Suggested**
Linear	0.0008	0.0005	0.7096	0.3568	
2 F1	0.0002	0.0099	0.9375	0.8395	
Quadratic	0.0046	0.0886	0.9828	0.9309	Suggested
Model summary for response Y2 (Drug content uniformity)					
Source	**Sequential p Value**	**Lack of fit p Value**	**Adjusted R^2**	**Predicted R^2**	**Model Suggested**
Linear	0.3087	< 0.0001	0.0514	-0.7061	
2 F1	0.2031	< 0.0001	0.1285	-2.0087	
Quadratic	< 0.0001	0.4772	0.9942	0.9828	Suggested

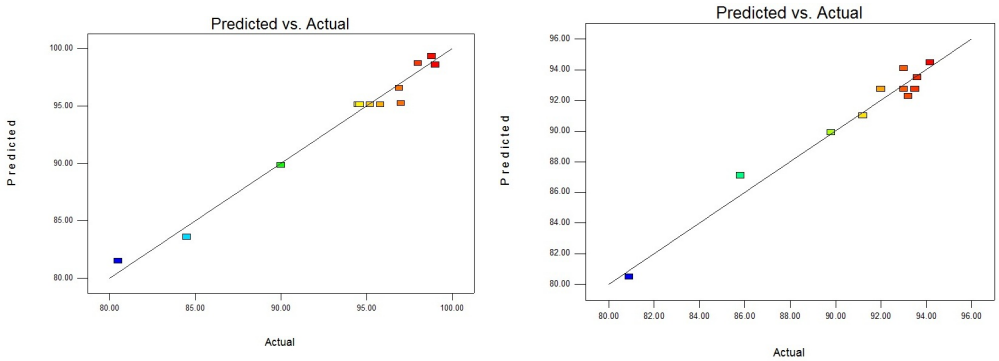
Table 7: Regression analysis for Drug content uniformity and % Cumulative drug release drug release for formulation B1-B13 prepared by natural polymers (Guargum + Egg albumin).

Factor	% Cumulative Drug Release		Drug content uniformity	
	C E	P-Value	C E	P-Value
Intercept	95.17		92.76	
A	-6.48	< 0.0001	-3.18	< 0.0001
B	-2.05	0.0020	-2.09	0.0009
AB	-2.12	0.0050	-3.82	< 0.0001
A^2	-5.09	< 0.0001	-2.45	0.0031
B^2	2.11	0.0126	-0.75	0.2196



A B

Fig. 1: Graph of actual value vs. predicted value of formulation B1-B13 prepared by synthetic polymers (Eudragit RSPO and Eudragit RLPO) for (a) % Cumulative drug release of formulation (b) Drug content uniformity of formulation.



A B

Fig. 2: Graph of actual value vs. predicted value of formulation B1-B13 prepared by natural polymers (Guargum + Egg albumin) for (a) % Cumulative drug release of formulation (b) Drug content uniformity of formulation.

Effect of independent variables on Drug content uniformity for formulation prepared by polymer (Eudragit RSPO and Eudragit RLPO)

The second-order polynomial equation relating the response of % drug release (Y2) is given below:

$$Y_2=+83.32+3.39A-0.74B-3.43AB+7.30A^2+2.10B^2$$

The Model F-value of 413.87 implies the model is significant (p= < 0.0001). The "Lack of Fit F-value" of 1.01 implies the Lack of Fit is not significant (P=0.4772).The ANOVA test indicate that A, B, AB, A^2, B^2 are significant model terms. Positive coefficients of A, A^2& B^2 indicate the synergistic effect on drug content uniformity. Negative coefficients of B, & AB indicate the antagonistic effect on drug content uniformity (Table 5).

The "Pred R-Squared" of 0.9828 is in reasonable agreement with the "Adj R-Squared" of 0.9942. indicating the adequacy of the model to predict the response of drug content uniformity. The 'Adeq Precision' 61.277 of indicated an adequate signal. Therefore, this model is used to navigate the design space (Table 6).

As it is shown in tables 7and 8, Y1, and Y2, were fitted with a quadratic model and insignificant lack of fit (P > 0.05). The positive sign of the factors represent a synergistic effect on the response, while a negative sign means an antagonist relationship. Phrases composed of two factors indicate the interaction terms and phrases with second-order factors stand for the nonlinear relationship between the response and the variable.

Effect of Independent Variables on % Cumulative drug release for formulation prepared by natural polymers (Guargum + Egg albumin)

The second-order polynomial equation relating the response of (*Y1*) % Cumulative drug release is given below:

$$Y_1=+95.17-6.48A-2.05B-2.12AB-5.09A^2+2.11B^2$$

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

The Model F-value of 66.21 implies the model is significant (p= < 0.0001). "Lack of Fit F-value" of 6.58 implies the Lack of Fit is not significant (P= 0.0501). The ANOVA test indicates that A, B, AB,A^2,B^2 are significant model terms. Positive coefficients of B^2 in equation (1) indicate the synergistic effect on % cumulative drug release while negative coefficients of A, *B*, AB & A^2 indicate the antagonistic effect on %cumulative drug release (Table. 7).

The "Pred R Squared" of 0.8398 is in reasonable agreement with the "Adj R-Squared" of 0.9645, indicating the adequacy of the model to predict the response of %cumulative drug release. The 'Adeq Precision' of 24.879 indicated an

adequate signal. Therefore, this model is used to navigate the design space (Table. 8). As the concentration of polymers was increased the total %cumulative drug release of the sustained release solid dispersion gets decreased. In the case of Guargum and Albumin as its concentration was increased it leads to decreased in %cumulative drug release. Therefore, it was suggested to keep its concentration on the upper side to release sustained effect (Fig 4.a).

Effect of independent variables on Drug content uniformity for formulation prepared by natural polymers (Guargum + Egg albumin)

The second-order polynomial equation relating the response of % drug release (Y2) is given below:

$$Y_2=+92.76-3.18A-2.09B-3.82AB-2.45A^2-0.75B^2$$

The Model F-value of 40.29 implies the model is significant (p= < 0.0001). The "Lack of Fit F-value" of 3.94 implies the Lack of Fit is not significant (P=0.1092). The ANOVA test indicates that A, B, AB & A^2 are significant model terms. Negative coefficients of A, B, A^2, B^2& AB indicate the antagonistic effect on drug content uniformity(Table 7).

The "Pred R Squared" of 0.7732 is in reasonable agreement with the "Adj R-Squared"0.9424, indicating the adequacy signal of the model to predict the response of drug content uniformity. The 'Adeq Precision' 22.372 of indicated an adequate signal. Therefore, this model is used to navigate the design space(Table 8).

Infrared spectral analysis

IR spectroscopy was performed on pure drug Metoclopramide HCL and its solid dispersion. Pure MCP spectra showed sharp characteristic peaks at 2977.55(C-H stretching in CH_3 group), 3216.68(N-H stretching in NH2 group), 1731.76(C=Ostretching in C=O group), 624.8(C-Cl alkyl halides group) and1508.06(C-C stretching in aromatic ring) cm^{-1}. All the above characteristic peaks appear in the spectra of Metoclopramide HCl solid dispersion prepared by natural polymer Guargum+Eggalbumin and synthetic polymers (Eudragit RSPO+ Eudragit RLPO) at same wave number indicating no modification or interaction between the drug and polymers (Fig 5).

X ray diffraction analysis

The retardation of peaks height or no peak observation in XRD of optimized formulation prepared by synthetic polymers B3 (Eudragit RSPO-Eudragit RLPO) natural polymers B7 (Guargum-Albumin) was found that the crystalline pure drug was completely changed into amorphous solid dispersion (Fig 6).

Scanning electron microscopy analysis

The SEM analysis was also used to determine the surface structure of solid dispersion. The structure of optimized formulation prepared by synthetic polymers B3 (Eudragit RSPO-Eudragit RLPO) natural polymers B7 (Guargum-Albumin) was found to be amotphous after comparison with drug structure (Fig 7).

***In vivo* study**

The pharmacokinetic graph between between concentration (µg/ml)v_s time(hrs) was shown that increased sustained effect of Formulation prepared by synthetic polymers B3 (Eudragit RSPO+ Eudragit RLPO) and optimized formulation prepared by natural polymers B7 (Guargum+ Egg albumin) over the effect of pure drug over the effect of pure drug (Fig 8). The in vivo study of solid dispersion of Metoclopramide HCl was done for determination of pharmacokinetic parameters of solid dispersion of Metoclopramide HCl and was compared with pharmacokinetic parameter of pure drug Metoclopramide HCl (Table 10).

Table 8: Design summary for formulation B1-B13 prepared by natural polymers (Guargum + Egg albumin).

Model summary for response Y1 (% Cumulative drug release)					
Source	**Sequential p Value**	**Lack of fit p Value**	**Adjusted R^2**	**Predicted R^2**	**Model Suggested**
Linear	0.0012	0.0011	0.6879	0.4544	
2 F1	0.1864	0.0012	0.7175	0.3443	
Quadratic	0.0003	0.0501	0.9645	0.8398	Suggested
Model summary for response Y2 (Drug content uniformity)					
Source	**Sequential p Value**	**Lack of fit p Value**	**Adjusted R^2**	**Predicted R^2**	**Model Suggested**
Linear	0.0341	0.0016	0.3895	-0.2644	
2 F1	0.0028	0.0094	0.7617	0.3972	
Quadratic	0.0029	0.1092	0.9424	0.7732	Suggested

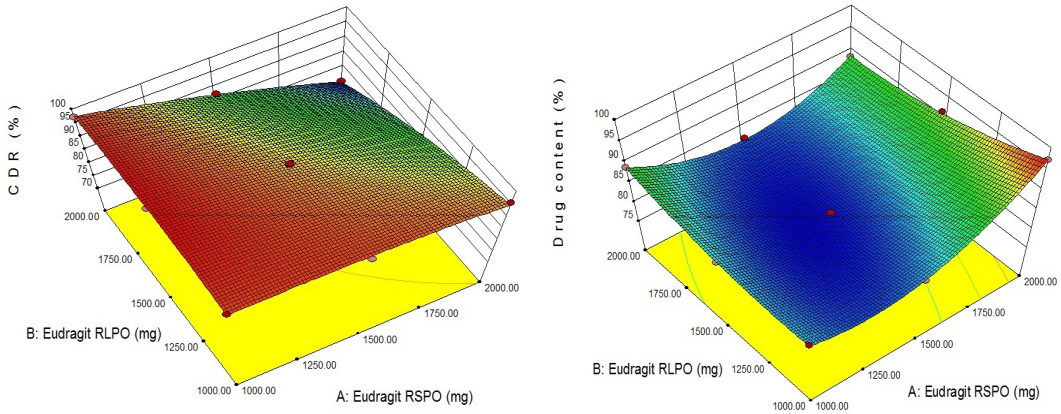
Table 9: Table of concentration (µg/ml) of drug and optimized formulation prepared by synthetic polymers B3(Eudragit RSPO+ Eudragit RLPO) and natural polymers B7 (Guargum+ Egg albumin) calculated by standard curve using HPLC.

Time (hrs)	**Concentration in µg/ml**		
	Drug	**Formulation prepared by Eudragit RSPO+ Eudragit RLPO**	**Formulation prepared by Guargum+ Egg albumin**
1	5.813437	2.55866	2.44342
2	10.95343	4.85943	5.4563
3	8.7366	8.99682	8.46824
4	7.2944	12.00791	14.75855
5	6.05861	16.3991	12.85675
6	5.34405	13.31046	11.15903
8	4.404676	11.10713	10.23006
10	3.20369	9.26147	9.57003
12	2.00619	8.44577	9.07581

Table 10: Value of pharmacokinetic parameter of drug and Solid dispersion of optimized formulation prepared by synthetic polymers B3(Eudragit RSPO+ Eudragit RLPO) and natural polymers B7 (Guargum+ Egg albumin).

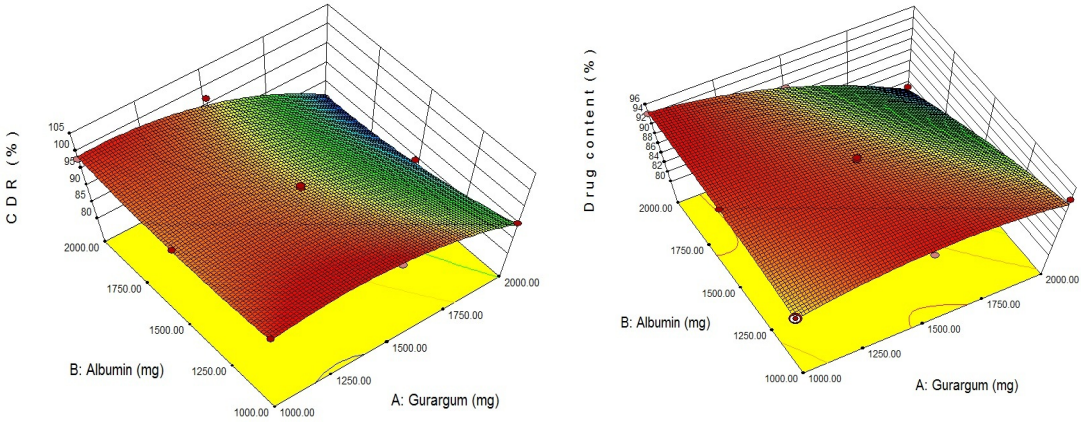
Sample	Cmax	Tmax	Eli(K_E)	AUC0_t	AUC0_inf	Half life
API	10.95343	2	0.125552	317.2134	333.1923	5.520799
F-SP A3	16.3991	5	0.069022	752.1027	235.0541	10.04236
F- NP A7	14.75855	4	0.070088	725.2795	237.6681	9.889695

API: Drug, F-SP A3: Formulation prepared by synthetic polymers, F-NP A7: formulation prepared by natural polymers.



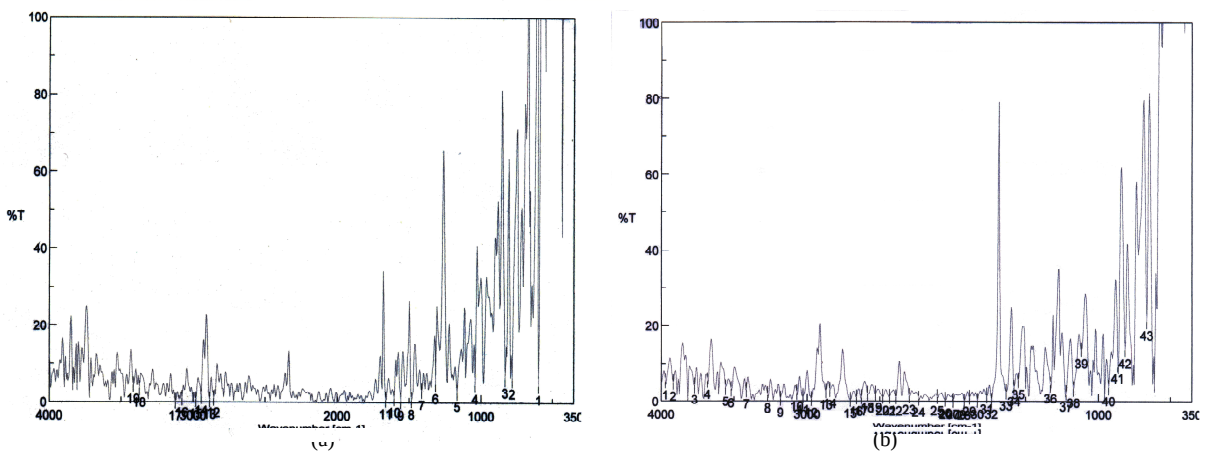
(a) (b)

Fig. 3: 3-D surface response plots showing relative effects of Eudragit RSPO and Eudragit RLPO on (a) % cumulative drug release (b) drug content uniformity for formulation B1-B13 prepared by Eudragit RSPO and Eudragit RLPO.



(a) (b)

Fig. 4: 3-D surface response plots showing relative effects of Guargum and Egg albumin on (a) percent Cumulative drug release (b) drug content uniformity for formulation B1-B13 prepared by Guargum and Egg albumin.



(a) (b)

Fig. 5: IR spectrum of (a) Optimized formulation prepared by synthetic polymers B3 (Eudragit RSPO-Eudragit RLPO) (b) optimized formulation prepared by natural polymers B7 (Guargum-Albumin).

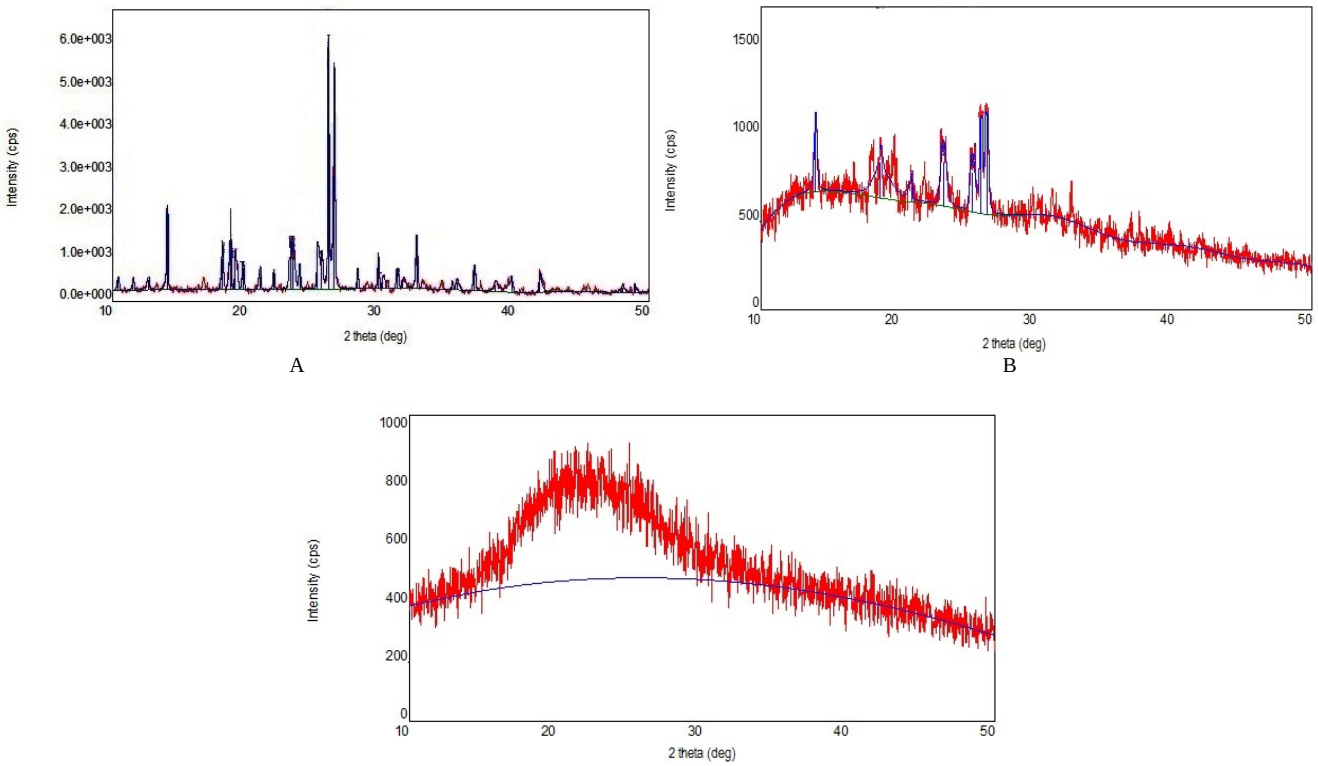


Fig. 6: XRD of (a) Metoclopramide HCL (b) Optimized formulation prepared by synthetic polymers B3 (Eudragit RSPO-Eudragit RLPO) (b) optimized formulation prepared by natural polymers B7 (Guargum-Albumin).

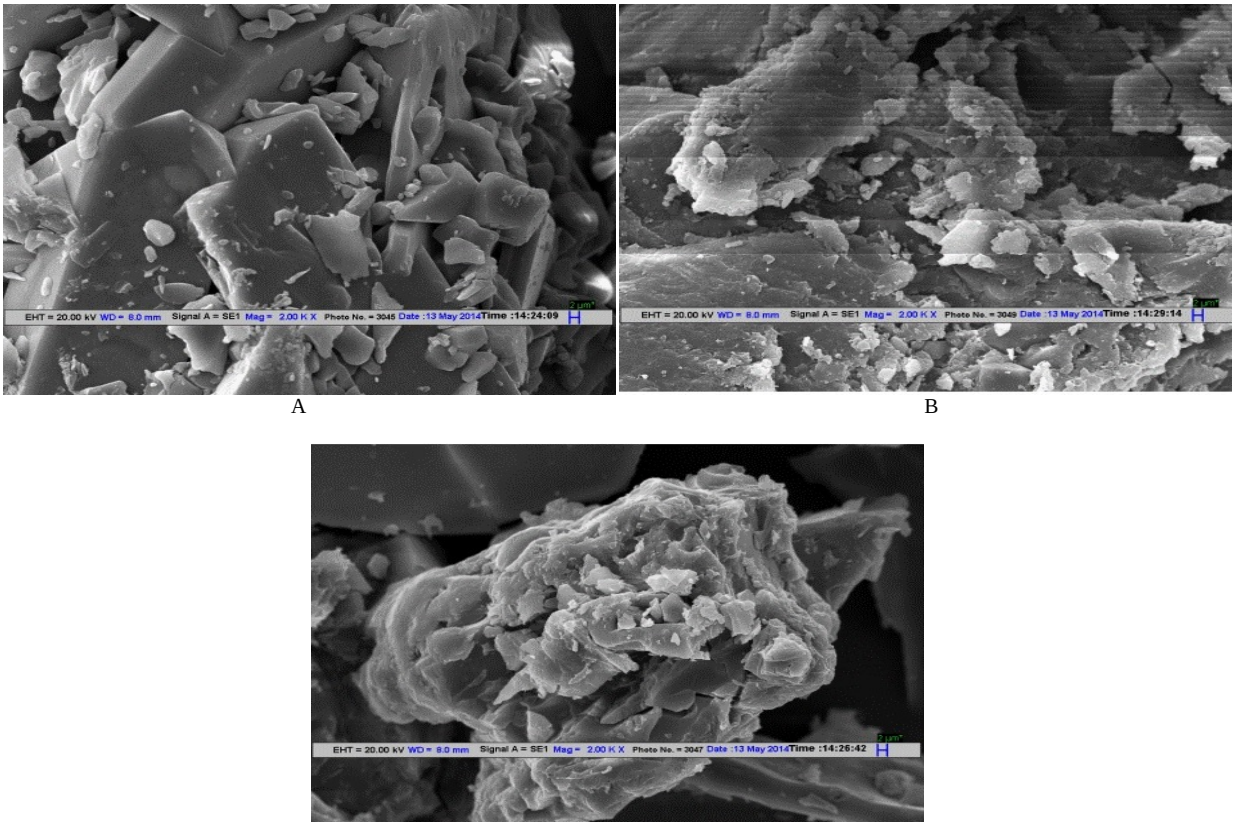


Fig. 7: SEM analysis of (a) Metoclopramide HCl (b)) Optimized formulation prepared by synthetic polymers B3 (Eudragit RSPO-Eudragit RLPO) (b) optimized formulation prepared by natural polymers B7 (Guargum-Albumin).

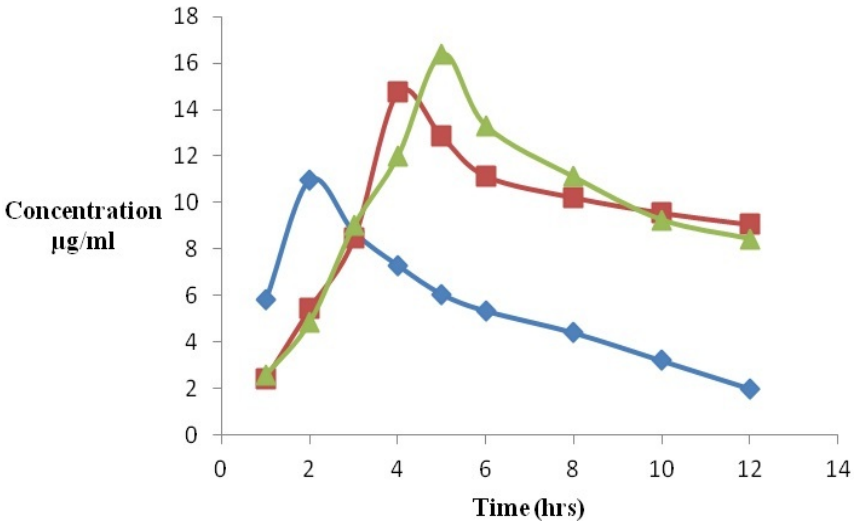


Fig. 8: Pharmacokinetic graph ploted between concentration(µg/ml)v_s time(hrs) of Drug (◆),Optimized Formulation prepared by synthetic polymers H-L(Eudragit RSPO+ Eudragit RLPO)(▲) and Formulation prepared by natural polymersL-H (Guargum+ Egg albumin)(■).

CONCLUSION

In this study, the statistical analysis of cumulative drug release and drug content uniformity shows that the solid dispersion of Metoclopramide HCl sustained the release rate of drug for a prolong period of time 12 hrs and shows shows to increase the bioavailability and simultaneously decrease the dosing interval as well as dosing amount. The formulation minimizes the blood level oscillations, dose related adverse effects and cost and ultimately improve the patient compliance and drug efficiency.The in vivo study show that the the half life of soild dispersion was increased than the API of metoclopramide HCl.As well as the study show that both formulation prepared by separately synthetic and natural polymers are produced sustained release drug profile but formulation prepared by eudragit RSPO and eudragit RLPO is more sustained than formulation prepared by Guargum and Egg Albumin.

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