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SUSTAINED RELEASE ITOPRIDE HYDROCHLORIDE MATRIX TABLET

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ABSTRACT

Oral route gets the highest priority for the delivery of the drug as well as better patient compliance in case of self delivery dosage formulation. The aim of present investigation was undertaken with the objective of formulating sustain release formulation of Itopride hydrochloride for oral drug delivery. Itopride hydrochloride is highly water soluble prokinetic drug. Hydroxypropylmethylcellulose K4M (lower viscosity grade) and K100M (higher viscosity grade) were used as a matrix forming agents to control the release of drug. HPMC K4M and HPMC K100M were used individually as well as in combination with different proportion in the preparation of the Sustained release formulation. 3^2 factorial designs were applied to the polymer concentration that affects the drug release profile. Reduced equation for drug release at 2hr,6hr,and10hrwere

$Q_2 = 37.644 - 5.41X_1 - 3.25X_2 - 2.017X_1^2$,

$Q_6 = 72.367 - 8.05X_1 - 4.4X_2 - 3.75X_1^2$,and

$Q_{10} = 90.844 - 5.8X_1 - 2.633X_2 - 2.8X_1X_2$

respectively. Optimized batch F019 shows good tablet properties like hardness(7-9kg/cm^2), thickness(4.48mm), friability(0.024%),assay(99.3%) and nearly similar drug release profile to the targeted reference drug release profile and it was indicated by similarity factor (f2=86.04).

KEY WORDS: Itopride hydrochloride, Hydroxypropylmethylcellulose (HPMC), Sustained release, Prokinetic drug

INTRODUCTION

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules.[1-4] Sustained release drug system is "any drug or dosage form modification that prolongs the therapeutic activity of the drug."[5] Ideally a sustained release oral dosage form is designed to release rapidly some pre determined fraction of the total dose in to GI tract. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate.[5-6] Hypromellose (Hydroxypropylmethylcellulose) is widely used in oral, ophthalmic and topical pharmaceutical formulations.[7] Itopride hydrochloride, a novel prokinetic agent is best candidate for Gastro esophageal reflux disease (GERD). Itopride 50mg is given thrice in a day along with Proton pump inhibitor.[8] By developing the sustain release formulation of Itopride hydrochloride, the frequency of drug administration can be reduce to once only to obtain good therapeutic response. The prepared formulation is usually taken on an empty stomach about an hour before meals and efficient to overcome GERD for 24 hr. Sustain release formulation of Itopride hydrochloride gives better patient compliance by reducing dosage frequency.

MATERIALS AND METHODS:

Material

Itopride hydrochloride was received as a gift sample from Cadila Healthcare ltd, Ankleshvar, India. Hydroxypropylmethylcellulose (HPMC) K4M and K100M were purchased from Dow Chemicals, India. Microcrystalline Cellulose (pH 102) was purchased from FMC Biopolymer, Shangai, China. Lactose (DCL 21) was purchased from DMV International, Veghel, Netherlands. Pregelatinize Starch was purchased from Colorcon Asia Pvt. Ltd, Mumbai, India. Colloidal silicon dioxide was purchased from Cabot sanmar Ltd., Chennai, India. Magnesium Stearate was purchased from Amishi drugs & Chemicals, Ahmedabad, India.

Methods:

Drug excipients compatibility study

API and excipients were been thoroughly mixed in predetermined ratio and passed through the 40# sieve. The blend was to be filled in transparent glass vials and were closed with gray coloured rubber stoppers and further sealed with aluminum seal and charged into stress condition at 25ºCº±2°C / 60%RH± 5 % RH and 40ºC±2°C / 75%RH± 5 % RH. Similarly API was also kept at same condition as for the samples. Samples were withdrawn for analysis within two days of sampling date as per the compatibility study plan. Physical observation should be done at every week up to 1 month and DSC studies were carried out to determine the compatibility of excipients with the drug.[9]

Full Factorial Design:

After studying results from preliminary batches, 3^2 full factorial designs were prepared as shown in table 1. In this design 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible Combinations. The amounts of matrixing agent, HPMC K4M (X1), HPMC K100M (X2) were selected as independent variables. The Q_2, Q_6 and Q_{10} were selected as dependent variables.[10-12]

Preparation of Itopride HCl SR Tablets:

Itopride HCl SR Tablets were prepared by direct compression technique as follow. Drug was passed through 40# sieve. HPMC K4M & HPMC K100M was passed through 30# sieve. All the other ingredients were passed through 40 # sieve accept Mg Stearate which was passed through 60# sieve. Itopride HCl, Lactose DCL 21 & MCC Avicel pH102 were mixed in double cone blender for 10minute at 18 RPM. Add polymer and colloidal silicon dioxide into above mixture and again mixed for 10minute at 18 RPM. Add Mg Stearate into above mixture and mixed it for 3minute at 18 RPM. The prepared blend was compressed (14/32 diameter, flat punches) using 16 station tablet compression machine (Cadmach, Ahmedabad, India).

Evaluation of SR Tablets

The tablet geometry was determined by a means of Digital vernier calipers. Five tablets were used, and average values were calculated. While the breaking strength (hardness) of five tablets was determined using the Benchsavertm Series type hardness tester and the average values were calculated. Twenty tablets of each formulation were checked visually for any discoloration or surface roughness in the tablet formulation. To study weight variation test, twenty tablets of the formulation were weighed using a Mettler Toledo electronic balance and the test was performed according to the official method. The friability of twenty tablets was measured by Roche friabilator for 4 minute at 25rpm for 100 revolutions. Accurately weigh twenty tablets placed into Roche friabilator for 100 revolutions than dedust the tablets and weigh.[13]

$$\%Friability = \frac{W_0 - W}{W_0} \times 100 \quad (1)$$

In-vitro dissolution profile of prepared Itopride HCl SR Tablets

The release rate of Itopride HCl from SR tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl (PH=1.2), at 37°C ± 0.5°C at 50rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at different time interval. The samples were replaced with fresh dissolution medium of same quantity. Drug released were analyzed at 258 nm wavelength using 0.1N HCl as a reference standard by Shimadzu UV1700 Double beam Spectrophotometer, Shimadzu (Kyoto, Japan.).[14]

Comparison of dissolution profiles by statistical analysis with marketed product

The similarity factor (f_2) was defined by CDER, FDA and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products". Moore and Flanner give the model independent mathematical approach for calculating a similarity factor f_2 for comparison between dissolution profiles of different samples. The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles of products were compared using f_2. The similarity factor is calculated by following formula.[15]

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

Where, **n** is the number of dissolution time points

$\mathbf{R_t}$ – The reference profile at the time point t

T_t - The test profile at the same point.

A value of 100% for the similarity factor suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar whilst smaller values imply an increase in dissimilarity between release profiles.[16]

Accelerated Stability study

Reproduce large scale batch F019 in blister pack (PVDC – Alu blister packing), was placed for stability study at 40˚C/75% RH for 3 months. Sample was collected at every 1 month interval and evaluated for dissolution in 0.1N HCl, USP- II paddle apparatus, 50rpm. F2 value was applied to stability study to show the effect of storage on in-vitro drug release of formulation.[17]

RESULT AND DISCUSSION:

Drug excipients compatibility study:

From the DSC Study and physical observation it was concluded that there was no significant Drug-Excipient interaction found. There was no change in drug's melting peak after the preparation of tablet. So we can conclude that drug and other excipients were compatible with each other in tablet dosage form.

Evaluation of SR Tablets

The prepared tablet formulations as shown in table.1 were evaluated for different parameters like hardness, friability, assay, weight variation. Results of these parameters were shown in table 2. Hardness of the prepared tablets was found in range of 6-8 KP. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability. The size and surface area were kept constant by adding required quantity of lactose as a diluent, as it is well known fact that the drug release is also dependent on the size and surface area of matrix tablets.

In-Vitro Drug release study

The drug release profiles were characterized by an initial burst effect Q_2 i.e. initial 30-35% drug release required in 2 hrs. The biphasic release is often observed from hydrophilic matrix systems. As the release rate limiting polymer like HPMC changes from a glassy state to rubbery state, a gel structure is formed around the tablet matrix, which considerably decreases the release rate of drug since the drug has to diffuse through this gel barrier into bulk phase. The strength of the gel depends on the chemical structure and molecular size of the polymer. It is known that higher viscosity grade polymer i.e. HPMC K100M hydrates at faster rate and therefore, it is capable of forming gel structure quickly than a low viscosity grade HPMC K4M polymer.

Table 1. Formula of Factorial batches

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Trials	**Ingredients (%w/w)**							
	Itopride HCl	**Lactose Anhydrous (DCL 21)**	**MCC (Avicel PH 102)**	**HPMC K4M DC Grade**	**HPMC K100M DC Grade**	**Colloidal Silicon Dioxide**	**Magnesium Stearate**	**Total**
F01	47.29	20.71	10.00	5.00	15.00	1.00	1.00	**100.00**
F02	47.29	15.71	10.00	5.00	20.00	1.00	1.00	**100.00**
F03	47.29	10.71	10.00	5.00	25.00	1.00	1.00	**100.00**
F04	47.29	18.21	10.00	7.50	15.00	1.00	1.00	**100.00**
F05	47.29	13.21	10.00	7.50	20.00	1.00	1.00	**100.00**
F06	47.29	8.21	10.00	7.50	25.00	1.00	1.00	**100.00**
F07	47.29	15.71	10.00	10.00	15.00	1.00	1.00	**100.00**
F08	47.29	10.71	10.00	10.00	20.00	1.00	1.00	**100.00**
F09	47.29	5.71	10.00	10.00	25.00	1.00	1.00	**100.00**

Table 2. Evaluation of tablets of Factorial batches

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Factorial Batches	**Hardness (kP)**	**Thickness (mm)**	**Friability (%)**	**Avg. Wt. (mg)**	**Assay (%)**
F01	7-8	4.66	0.045	351.3	99.8
F02	7-9	4.47	0.104	352.1	100.2
F03	6.5-8	4.43	0.128	350.1	100.1
F04	7-8	4.57	0.059	349.9	98.8
F05	7-8	4.58	0.002	350.4	98.7
F06	7-9	4.48	0.029	350.3	99.3
F07	7-9	4.41	0.019	351.2	99.4
F08	7-8	4.64	0.019	350.2	98.4
F09	7-8	4.62	0.052	350.4	99.3

Table 3 Effect of independent variables on dependent variables by 3^2 full factorial of Itopride HCl Sustained release matrix tablet

Table 3. Effect of Independent variable on dependent variable by 3^2 full factorial design of Itopride HCl Sustained release matrix tablet

Batch No.	Independent variable		Dependent variable		
	X_1	X_2	Q_2 (%)	Q_6 (%)	Q_{10} (%)
F01	-1	-1	43.2	79.4	94.3
F02	-1	0	40.1	76.9	96.4
F03	-1	+1	38.2	73.5	93.5
F04	0	-1	40.1	75.2	90.4
F05	0	0	37.8	72.0	89.8
F06	0	+1	33.4	69.7	87.4
F07	+1	-1	32.9	67.9	87.8
F08	+1	0	31.0	60.7	85.8
F09	+1	+1	25.1	52.9	75.8

Independent Variables	Real Value		
	Low (-1)	**Medium (0)**	**High (+1)**
HPMC K4 M (X_1)	5.0%	7.5 %	10.0 %
HPMC K100 M(X_2)	15.0%	20.0 %	25.0 %

Fig. 1 Comparative dissolution profile of Factorial batches of F01 to F09 and innovator

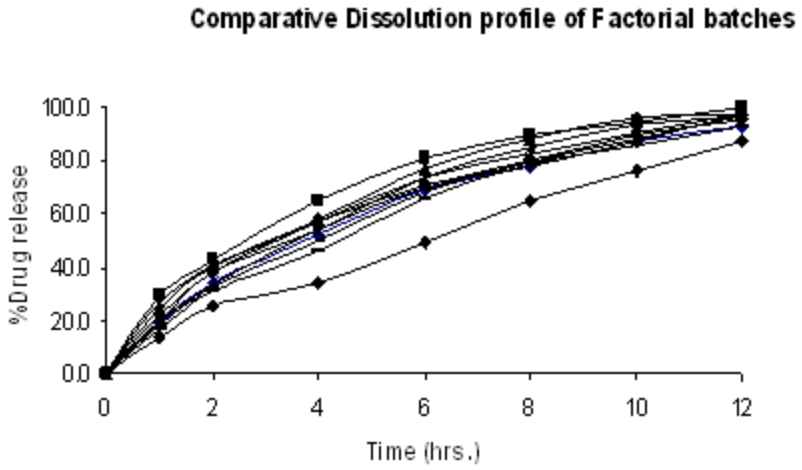
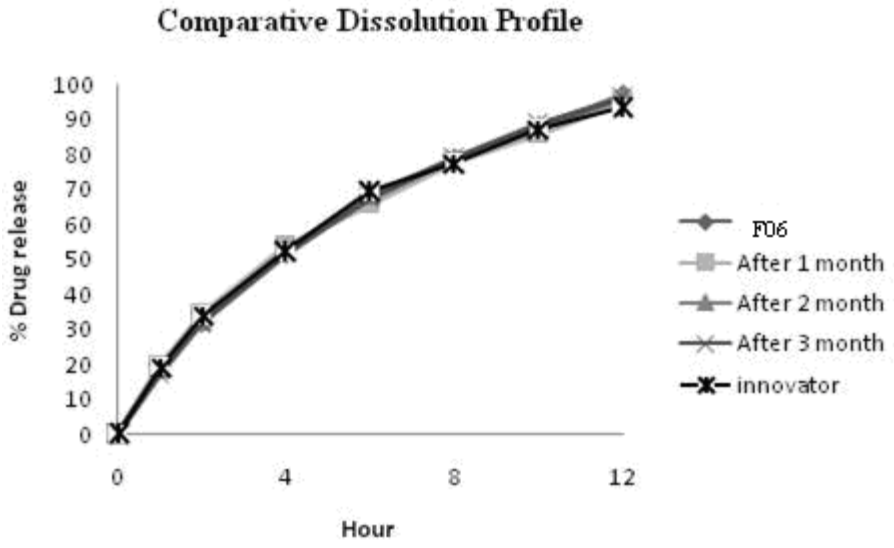


Fig. 2 Comparative dissolution profile of Accelerated stability study



The drug release is significantly dependent on the proportion and type of the polymer used. HPMC K4M was responsible for initial burst effect and HPMC K100M was used to sustained drug release. Factorial batches formulated using combination of HPMC K4M and HPMC K100M of Itopride HCl SR tablet were evaluated for dissolution study. Data of drug release are graphically represented in figure 1. f2 value of F01 to F09 batches are 50.89, 57.53, 67.45, 64.87, 75.85, 86.04, 82.81, 74.71, 46.18. F06 batch showing very good similarity to the innovator batch release profile. (86.04)

Effect of Independent variable on dependent variable

The factorial batches were prepared by using independent variable, concentration of HPMC K4M(X_1)and HPMC K100M(X_2) and its effect were check on dependent variable like Q_2, Q_6, and Q_{10}.Factorial batches of Itopride HCl sustained release matrix tablets were evaluated for the in-vitro drug release (table 3), the effect of the individual polymer and combination of the polymers were studied.

Accelerated Stability study

Reproduce large scale batch F06 in blister pack (PVDC – Alu blister packing), was placed for stability study at 40˚C/75% RH for 3 months. Sample was collected at every 1 month interval and evaluated for dissolution in 0.1N HCl, USP- II paddle apparatus, 50rpm. f_2 value was applied to stability study to show the effect of storage on in-vitro drug release of formulation. The results of accelerated stability studies were shown figure 2.

CONCLUSION

Results of present study suggested that Itopride HCl Sustained release matrix tablet can be successfully formulated using combination of HPMC K4M (7.5%) and HPMC K100M (25%). F06 Batch of Itopride HCL SR tablets were good in terms of tablet physical properties, minimum drug excipients incompatibility and nearly similar drug release profile to that targeted release profile.

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