MATRIX SUSTAINED RELEASE TABLET OF WATER SOLUBLE PROKINETIC AGENT: ITOPRIDE HYDROCHLORIDE

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ABSTRACT

Itopride hydrochloride is highly water soluble prokinetic drug that is used in the Gastro esophageal reflux disease (GERD). Aim of present investigation was formulating sustained release formulation of Itopride hydrochloride for oral drug delivery. Oral route gets the highest priority for the delivery of the drug as well as better patient compliance in case of self medication. Pregelatinized Starch, Hydroxy methyl propyl cellulose (HPMC) K4M, HPMC K100M and Ethyl Cellulose were used to control the release of the drug from the sustained release tablet. Optimization of polymers concentration that can control the release of the drug as like the hypothetical release profile was based on trial and error. Optimized batch F11 was showing good tablet properties like hardness (7-8kg/cm^2), thickness (4.61mm), friability (0.061%), assay (99.3%) and nearly similar drug release profile to the hypothetical drug release profile and it was indicated by similarity factor (F2=80.25). Mathematical model application was applied to the release profile of optimized batch. The obtained value of regression coefficient was 0.9962 which indicate that formulation was following the higuchi model.

KEY WORDS: Itopride hydrochloride, Hydroxypropylmethylcellulose (HPMC), Sustained release, Prokinetic drug, Gastro esophageal reflux disease (GERD).

INTRODUCTION

Itopride hydrochloride, a novel prokinetic agent is best candidate for GERD. Itopride 50mg is given thrice in a day given along with Proton pump inhibitor. By developing the sustained release formulation of Itopride hydrochloride, the frequency drug administration can be reduce to once a day and one can 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.[1-6]

Oral route is one of the best convenient route for the drug administration in patient. This route has several advantages like painless administration of the drug, self medication of drug. Formulation that is modify in such a way that it prolongs the release and hence the therapeutic activity of drug is called the sustained release

formulation.[2] Itopride hydrochloride is a water soluble compound hence various release rate retardant polymers were used to control the release of drug like Pregelatinize Starch, Hydroxy methyl propyl cellulose(HPMC) K4M, HPMC K100M, Ethyl Cellulose. Sustained release oral dosage form is designed in two ways, sustained dosage form with burst release and without burst release. 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.[7-8]

Materials and Methods

MATERIALS

Itopride hydrochloride was received as a gift sample from Cadila Healthcare ltd, Ankleshvar, Gujarat, India. Hydroxypropylmethylcellulose (HPMC) K4M, HPMC K100M and Ethyl cellulose 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 Excipient Compatibility Study

Drug excipients compatibility study was being done using Differential scanning colorimetry instrument. For this study Itopride hydrochloride and other excipients were been thoroughly mixed in predetermined ratio and passed through the appropriate sieve no 40#. 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]

Preparation SR Tablets

Initial 5 batches of SR Tablets were prepared using single polymer, HPMC K4M, HPMC K100M. Next 5 batches were prepared using ethyl cellulose, pregelatinized starch and HPMC K100M were used in combination and final 3 batches using combination of HPMC K4M and HPMC K100M. All the batches were evaluated for different evaluation parameter.

Drug was passed through 40# sieve. Polymers were 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 3 minute 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.[10]

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

$W_\circ$= initial weight of 20 tablets
W= weight of 20 tablets after 100 revolutions

In-vitro Dissolution Profile

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.).[11]

Comparison of Dissolution Profiles By Similarity Factor

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.[12]

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

Where, **n** is the number of dissolution time points
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.[13]

Mathematical Model Application

Mathematical model application is one of the best methods to check that the prepared formulation following the which type of release kinetics. Release profile of the optimized batches were put in the software to check that the formulation was following the which type of model, whether it was following the Higuchi, korsemayer, zero order or first order kinetics[14].

Accelerated Stability Study

Reproduce large scale batch F12 in blister pack (PVDC – Aluminum 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.[15]

RESULT AND DISCUSSION

Drug Excipient 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

Comparative dissolution profile of innovator to F1-F7 batches and F8-F13 batches is given in Figure 1 and Figure2. The results of in-vitro dissolution study of trial batches F1 and F2 which was taken with HPMC K4M showed the faster drug release as compared to the targeted drug release. Formulation F1 was failed to generate sustained release of drug up to 12 hr and drug was completely release at 10 hrs. Same problem was persists in F3 to F5 batches, those were prepared with HPMC K100 M 20%, 25%, 30% respectively. In further formulation development process, trial batches F6 and F7 was modified by incorporation of retarding polymer Ethyl Cellulose 5% and 2% respectively, in combination with 25% HPMC K100M showed the slower drug release than targeted drug release at all the time points and the drug was not completely release from the matrix within 12h. F8, F9, and F10 batches those were prepared with pregelatinized starch and HPMC K100 M showing the slower release as compared to the innovator batches. F11 to F13 batches were prepared with combination of HPMC K4M and HPMC K100M. It is known that higher viscosity grade polymer HPMC K100M hydrates at faster rate and therefore, it is capable of forming gel structure quick than a low viscosity grade HPMC K4M polymer. The best comparable release profile was obtained in batch F11 having the F2 value 80.25.

Mathematical Model Application
Data of the release profile of the optimized batch were treated with the software to find out that which type of model was being followed by the formulation. Data of all the model was given in table 3.

Accelerated Stability Study
Reproduce large scale batch F11 in blister pack (PVDC – Aluminum 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. F2 value after the stability study was found 81.07. The results of accelerated stability studies were shown figure 3. From the stability result, concluded that there was no change in the formulation after 3 month accelerated stability study. It indicate that prepared formulation of Itopride HCl was stable.

Conclusion
From the results of the present study experiment, it was concluded that by using the combination of HPMC K4M and HPMC K100M, one can obtain the good control on the release profile of water soluble drug and sustained release formulation can be successfully prepared. HPMC K 100M hydrates and form gel at a higher rate as compared to HPMC K 4M and helpful for initial controlling the release rate of water soluble Itopride hydrochloride drug.

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Table 1. Formula of Sustained Release Tablet of Itopride HCL

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
	All weights are in %w/w												
Itopride HCl	47.3	47.3	47.3	47.3	47.3	47.3	47.3	47.3	47.3	47.3	47.3	47.3	47.3
Lactose Anhydrous (DCL 21)	15.7	5.7	20.7	15.7	13.7	10.7	13.7	0.7	5.7	3.2	16.42	13.56	15.7
MCC (Avicel PH 102)	10	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K4M	25	35	…	…	…	…	…	…	…	…	7.14	10	10
HPMC K100M	…	…	20	25	30	25	25	30	25	30	17.14	17.14	15
Ethyl cellulose	…	…	…	…	…	5.00	2.00	…	…	…	…	…	…
Pregelatinised starch	…	…	…	…	…	…	…	10.0	10.0	7.5	…	…	…
Colloidal Silicon Dioxide	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total	**100**	**100**	100	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Tablet Weight (mg)	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Table 2. Evaluation of Sustained Release Tablet of Itopride HCL

Batches	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Avg. Wt. (mg)	Assay (%)	F2 value
F1	7-8	4.52	0.062	352.3	102.3	37.58
F2	7-8	4.51	0.052	351.1	99.7	61.46
F3	6.5-8	4.56	0.048	350.5	100.3	62.26
F4	7-8	4.47	0.049	349.9	101.1	54.09
F5	7-8	4.57	0.053	350.7	99.5	64.25
F6	7-8	4.53	0.082	350.3	99.3	44.15
F7	7-8	4.56	0.072	350.4	99.6	46.11
F8	6.5-8	4.54	0.084	350.1	98.4	63.42
F9	7-8	4.53	0.072	350.9	99.1	77.09
F10	7-8	4.54	0.047	351.1	99.6	76.77
F11	7-8	4.61	0.061	350.7	99.3	80.25
F12	7-8	4.53	0.057	350.3	99.6	75.53
F13	6.5-8	4.68	0.011	351.1	98.9	75.00

Table 3. Mathematical Data of Various Release Kinetic Model.

Model	**Regression coefficient value**
Higuchi	0.9962
Korsemayer	0.9895
Zero order	0.9627
First order	0.8439
Hixson Crowell	0.9627

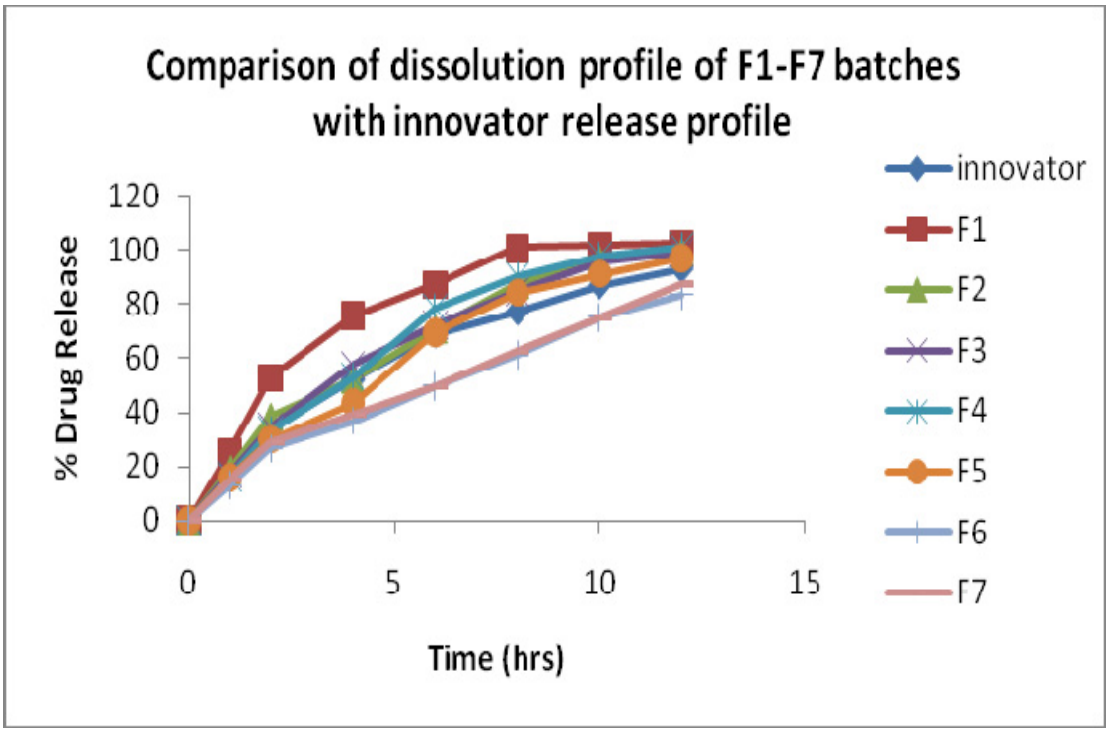

Figure 1 *Comparative dissolution profile of F1-F7 batches of Itopride HCL sustained release tablets and innovator*

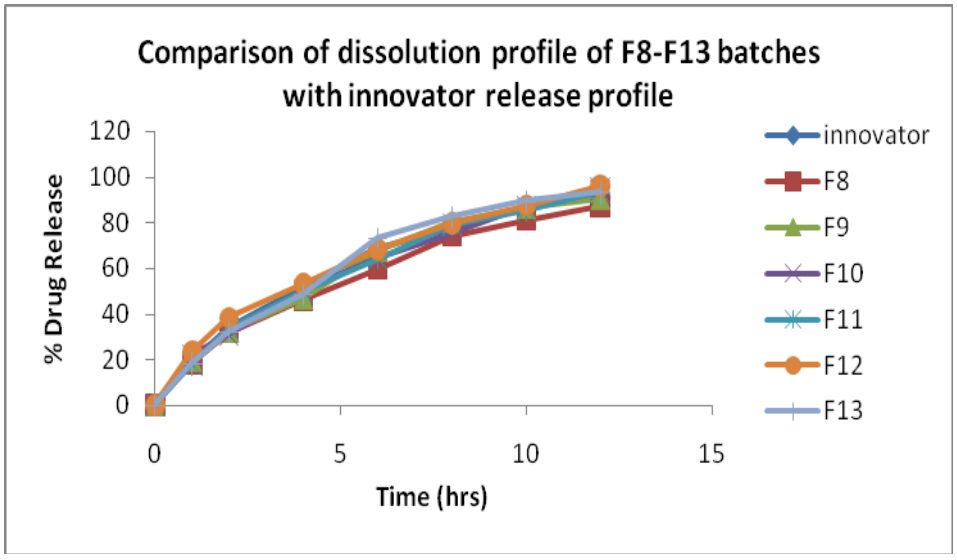

Figure 2 *Comparative dissolution profile of F8-F13 batches of of Itopride HCL sustained release and innovator*

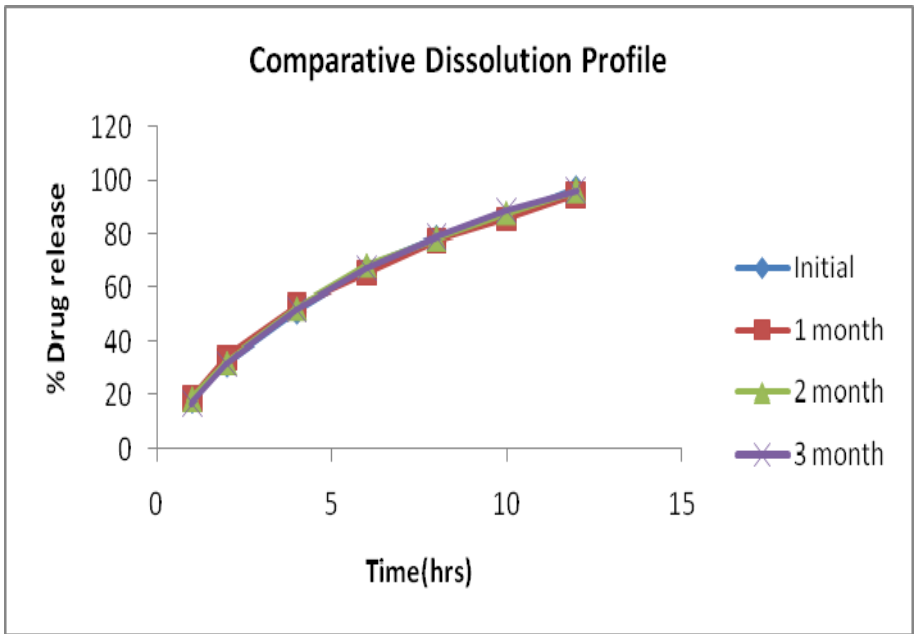

Figure 3 *Comparative dissolution profile of Accelerated stability study of optimized batch of*
Itopride HCL sustained release tablet