

Original Article

FORMULATION, EVALUATION AND OPTIMIZATION OF SUSTAINED-RELEASE DRUG DELIVERY SYSTEM OF CISAPRIDE TABLET

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ABSTRACT

Objective: Cisapride is a novel prokinetic agent is best candidate for GERD. Cisapride 20 mg can be given thrice in a day given along with Proton pump inhibitor. By developing the sustain release formulation of Cisapride, the frequency of both drug can be reduce to once only to obtain good therapeutic response.

Methods: Cisapride SR Tablets were prepared by direct compression technique with HPMC K4M and HPMC K100M polymers. Followed by various evaluation tests including *in vitro* disintegration and dissolution, the formulation was optimized by 3² full factorial designs with drug release kinetic analysis, compatibility studies (FTIR) and stability studies.

Results: Results of Preformulation studies of the Cisapride indicate that it has poor flow property and compressibility property. To improve the flow and compressibility property, it was beneficial to use the directly compressible grade components in the formulation of tablet. Results of DSC study shown that there is no change in drug's melting peak after the preparation of tablet. Hydrophilic matrix of HPMC K4M and HPMC K100M in combination sustained the Cisapride release effectively for more than 12h. The result indicates that the combination of HPMCK4M and HPMCK100M can be successfully, On the basis of the preliminary trials in the present study a 3² full factorial design was employed to study the effect of independent variables, i.e. concentration of HPMCK4M(X1) and concentration of HPMCK100M(X2) on dependent variables like % drug release Q2, Q6 and Q10. Drug release is also dependent on the size of matrix tablets so, size and surface area was kept constant. Factorial batches F018, F019, F020, and F021 give the f2 value 75-100. Factorial batch F019 gives the highest f2 value 86.04 and also all the hour's drug release was within the specified limits.

Conclusion: The prepared formulation of Cisapride sustains release matrix tablet was stable and effective in treatment.

Keywords: Cisapride, HPMCK100M, Pregelatinize, HPMCK4M

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most prevalent upper gastrointestinal disorders in clinical practice. GERD is a chronic disease with relapsing symptoms, and lifelong treatment is required in 25% to 50% of patients. The cause of GERD is unknown. The Pathophysiology involves contact of the esophagus with noxious substances in refluxed gastric juice. Everyone experiences episodes of GERD, however, and a cornerstone for the development of GERD is that the contact time between noxious substances in gastric juice with the esophagus must be of sufficient duration to result in damage to the epithelium [1]. Sufficient duration to cause GERD can occur in one of two general ways: first, when contact time between epithelium and gastric contents is so prolonged that the noxious agents in gastric juice overwhelm an otherwise healthy esophageal epithelium and second when contact time between epithelium and gastric contents is essentially normal, yet still adequate to produce damage because of the greater potency to the refluxate or presence of defects thins the epithelium [2].

There are two forms of presentation: in children and in adults. In the first case, the symptoms appear during the first months of life and improve up to 12-24 mo in 80% of the cases. Since the 1980s, there have been major advancements in the medical management of gastroesophageal reflux disease (GERD) [3]. The most successful therapies have increased acid secretion and volume with H₂-receptor antagonists and especially proton-pump inhibitors. Sucralfate, a mucosal protector, had minimal effect on the treatment of GERD except in the rare patient with severe ulcerative esophagitis. Despite GERD being considered motility disorder, such promotility drugs as bethanechol, metoclopramide, and cisapride have had marginal efficacy in treating GERD patients except in patients with no erosive disease or dyspepsia with associated delayed gastric emptying [4]. Through various mechanisms, these

drugs were reported to increase lower esophageal sphincter (LES) pressure and improve acid clearance, but in reality, they did little in patients with more severe disease other than improving gastric emptying. None of these promotility agents had an apparent effect on the major motor mechanism underlying reflux episodes, transient lower esophageal sphincter relaxations (TLESRs) [4].

The diagnosis of gastroparesis may be confirmed by demonstrating gastric emptying delay during a 4-hour scintigraphic study [5]. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels [6]. To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems, such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies [7].

In the present study, objectives are to formulate stable, effective and optimum sustained release dosage form using hydrogel polymers, to study the effect of different excipients in the formulation, to evaluate the prepared sustained release dosage forms and to perform the stability studies.

MATERIALS AND METHODS

Materials

Cisapride Hydrochloride (Cadila Healthcare Ltd, Ahmedabad), Microcrystalline Cellulose (pH 102) (FMC Biopolymer), Hydroxy

propyl methyl cellulose K4M (Dow Chemicals, India), Hydroxy propyl methyl cellulose K100M (Dow Chemicals, India), Pregelatinize Starch (Colorcon Asia Pvt. Ltd., Mumbai, India), Colloidal silicon dioxide (Cabot sanmar Ltd), Magnesium Stearate (Amishi drugs and Chemicals).

Instrument

Electronic weighing balance (Mettler Toledo PG 403-S, Denver Instrument), Cage Blender (Shaan Engineering Pvt. Ltd., Ahmedabad, India), Bulk Density measurement apparatus (Electrolab, ETD-1020), "D" Tooling 8 Station Tablet compression machine (Cadmach machinery Co., Pvt. Ltd., Ahmedabad, India), Tablet Hardness Tester (Monsanto hardness tester, Mumbai), Friability test apparatus (Electrolab, Mumbai), Vernier caliper (Mitutoyo, Mumbai), Dissolution Test Apparatus (Electrolab, TDT-06T, Mumbai, India), UV Spectrophotometer (UV-1700 Double beam Spectrophotometer, Shimadzu Kyoto, Japan).

Characterization of cisapride

Description: A white to off white crystalline powder.

Identification: The Infra-Red absorption spectrum of the finely ground sample in KBr dispersion compressed into a disc should exhibit maxima only at the same wavelengths as that of a similar preparation of working standard [8].

Selection and justification of excipients

Diluents: In view of the low or medium dose of drug it is essential to add bulking agents or diluents to increase the weight of the tablet. Microcrystalline Cellulose (Avicel) was selected as diluents. Microcrystalline cellulose in combination as diluents gives better flowability i.e. both used as diluent in this SR preparation [9, 10].

Matrix-forming polymers: HPMC which is most widely used matrix-forming polymer because of its excellent compatibility, multifunctional property and cost effective, HPMC K4M and HPMC K100M (10 to 80 %) [11].

Lubricants: Magnesium Stearate (0.25-4%) and Colloidal silicon dioxide (0.25-3%) are widely used as lubricating agent. [12].

Preformulation study

Solubility: Freely soluble in water, 0.1N HCl, pH 4.5 Acetate buffer and in methanol, Soluble in pH 6.8 Acetate buffer [13].

Bulk density = Weight of powder/Bulk volume

Tapped bulk density = Weight of powder/Tapped volume

$$\text{Carr's Index (\%)} = \frac{[(TD - BD) \times 100]}{TD}$$

$$\text{Hausner's Ratio} = \frac{TD}{BD}$$

Angle of repose

The diameter of the powder cone was measured and angle of repose was calculated using the equation $\tan \frac{1}{2} = h/r$. Where, h and r are the height and radius of the powder cone, respectively [14].

Drug excipients compatibility study

API and excipients were been thoroughly mixed in predetermined ratio given in below table and passed through the 40 # sieve. The blend was to be filled in transparent glass vials and were closed with gray colored rubber stoppers and further sealed with aluminum seal and charged in to stress condition at above condition. Similarly, API should also be kept at all conditions as for the samples. Samples were withdrawn for analysis within two day of sampling date as per the compatibility study plan. Physical observation should be done at every week up to 1 mo and DSC studies were carried out to determine the compatibility of excipients with the drug [15].

Analytical method development

Calibration curve of Cisapride Hydrochloride: Calibration curve for Cisapride hydrochloride was taken in 0.1 N HCl [16].

Preparation of reagents: (i) 0.1 N Hydrochloric acid (pH = 1.2): 112, 8.5 ml of concentrated Hydrochloric acid was taken and added to 1000 ml of water and measured the pH of the solution. (ii) Standard (Stock) solution: Cisapride hydrochloride 100 mg was dissolved in 0.1N HCl and volume was made up to 1000 ml in 100 ml volumetric flask. This stock solution was 100 mcg/ml. This Stock solution was diluted with 0.1N HCl to make the concentration of 5, 10, 15, 20, 25 mcg/ml. Absorbance of each solution was measured at 258 nm using Shimadzu UV/Visible double beam spectrophotometer by using 0.1N hcl [17, 18].

Formulation of preliminary trials

Trial batches with HPMC K4M and HPMC K100M

Formula method of Preparation of Cisapride SR Tablet

Method

Cisapride SR Tablets were prepared by direct compression technique. Sifting: Drug was passed through 40# sieve. HPMC K4M and HPMC K100M were passed through 30# sieve. All the other ingredients were passed through 40 # sieve accept Mg Stearate. Mg Stearate was passed through 60# sieve [19, 20].

Mixing and lubrication

Cisapride, MCC Avicel pH102 was mixed in a blender for 10 min. at 18 RPM. Add polymer and colloidal silicon dioxide into the above mixture and again mix for 10 min. at 18 RPM. Add Mg Stearate into above mixture and mixed it for 3 min. at 18 RPM.

Evaluation

Uniformity of weight

The USP-XXIX weight variation test was carry out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight. The tablet meets USP-XXIX test if no tablet differs by more than two times of percentage deviation USP-XXIX Standards for Weight Variation Test [21, 22].

Thickness

Thickness of tablets was determining using a venire caliper. Three tablets were evaluated and an average value was calculated. The thickness was measure in mm.

Hardness test

Hardness was measure using Pfizer hardness tester. For each batch ten tablets was test. The force required to break the tablet is recorded. The hardness of tablets of each batch was measured in kg/cm².

Friability test

Twenty tablets was weighed and placed in the Roche friabilator and apparatus was rotate at 25 rpm for 6 min. After revolutions the tablets was deducted and weighed again. The percentage friability was measured using the formula.

Uniformity of content

Amount of the powder equivalent to 10 mg of Cisapride and was dissolved in 100 ml of 0.1N HCl pH 1.2, filtered, diluted suitably and analyzed for drug content at 227 nm using UV-spectrophotometer.

In vitro disintegration time

In vitro disintegration time of three tablets was determined by using digital tablet disintegration apparatus. *In vitro* disintegration test was carried out at 37±2 0C in 900 ml 0.1 N HCL pH 6.8 [23].

In vitro dissolution study

In vitro dissolution study of Cisapride was performed using USP Type II dissolution apparatus (Paddle type) at 37±0.5 °C and a paddle speed of 75 rpm, 900 ml of 0.1 N HCL pH 6.8 was utilized as dissolution medium [24, 25]. The temperature of the medium was maintained at 37±0.5 °C. Aliquot of dissolution medium (5 ml) was withdrawn at specific time intervals (10, 20, 30, 45 min.) and filtered

each with (0.45 μm) whatman filter paper. Equal amount of fresh dissolution medium was replaced immediately after each withdrawal. The amounts of drugs present in each sample were determined by a UV-Visible spectrophotometer after Cisapride. Dissolution studies were performed in triplicate ($n = 3$), and calculated mean values of cumulative drug release were used to plot the release curves [26, 27].

Formulation and optimization of sustained-release matrix tablets by using 3^2 full factorial designs

It is desirable to develop an acceptable pharmaceutical formulation in the shortest possible time using the minimum number of man-hours and raw materials. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses [28]. A 3^2 randomized full factorial design was utilized in the present study. In this design, two factors were evaluated, each at three levels and experimental trials were carried out at all nine possible combinations. The factors were selected based on a preliminary study [29]. The concentration of HPMC K4M (X1) and concentration of HPMC K100M (X2) were selected as independent variables. The % drug release at 2, 6 and 8th hours were Q2, Q6 and Q8 respectively selected as dependent variables [30, 31].

Comparison of dissolution profiles by statistical analysis

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 [32].

Drug release kinetic analysis by using different release model of Cisapride HCl sustained release matrix tablet

To know the mechanism of drug release from these formulations, the data were treated according to first-order (log cumulative percentage of drug remaining vs. time), Higuchi's118 (cumulative percentage of drug released vs. square root of time), and Korsmeyer *et al.*'s119 (log cumulative percentage of drug released vs. log time) equations along with zero-order (cumulative amount of drug released vs. time) pattern the results shown below. The *in vitro* release profiles of the drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity ($R^2 = 0.9898$, table 5.33). To confirm the diffusion mechanism, the data were fit into Korsmeyer-Peppas's equation. The formulations F019 showed good linearity ($R^2: 0.9942$), with slope (n) values ranging from 0.665, indicating that diffusion is the dominant mechanism of drug release with these formulations [33]. This n value, however, appears to indicate a coupling of diffusion and erosion mechanisms so-called anomalous diffusion. The relative complexity of this formulation and its components may indicate that

the drug release is controlled by more than one process. From the above data analysis by using the different model the Korsmeyer model was a good fit with a linearity value 0.9942 [34].

Stability study

Formulation was placed for stability study at 40°C and 75% RH for 1 mo. Sample was collected at every week interval and evaluated for dissolution in 0.1N HCl, USP-II paddle apparatus, 50 rpm. f_2 value was applied to stability study to show the effect of storage on *in vitro* drug release of the formulation [35].

RESULTS AND DISCUSSION

Identification of drug

Melting point

The observed melting point of Cisapride was 110-113 °C. Melting point of Cisapride was found to be in the range of 113 °C as reported in the literature, thus indicating the purity of the drug sample.

Infrared spectroscopy of drug

Observed characteristics were N-H stretching at 3400 cm^{-1} , CH alkane stretching at 2926 cm^{-1} , CO-NH stretching (C=O) at 1640 cm^{-1} , NH bending at 1425 cm^{-1} and CN aromatic amine at 1243 cm^{-1} as shown in fig. 1.

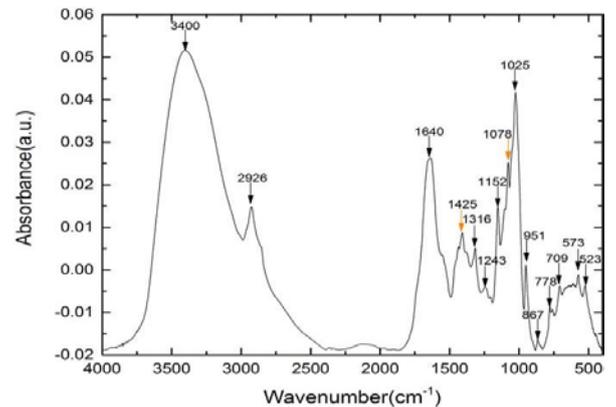


Fig. 1: FTIR of cisapride

Infrared spectroscopy drug and excipient

IR spectrum of, physical mixture of Cisapride+MCC+HPMC K100M+Pregelatinize Starch and Drug+Colloidal Silicon Dioxide+Mg-Stearate are shown in fig. 2 and 3. From IR spectra of drug and physical mixture, no significant change in peak pattern was observed. Hence, it was concluded that absence of drug excipients interaction and drug was compatible with excipients used in the present work.

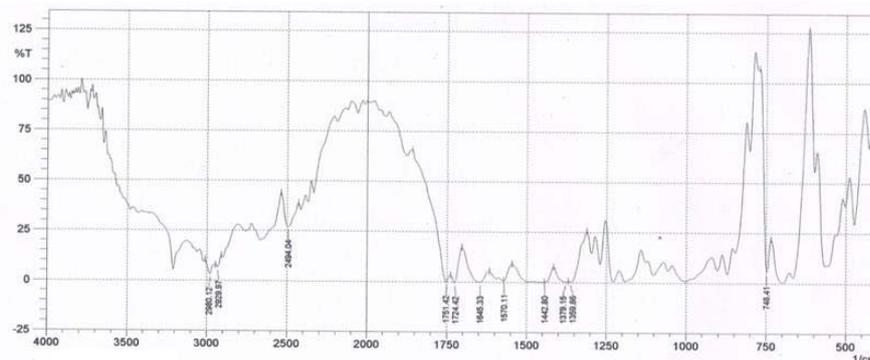


Fig. 2: Drug+MCC+HPMC K100M+pregelatinize starch

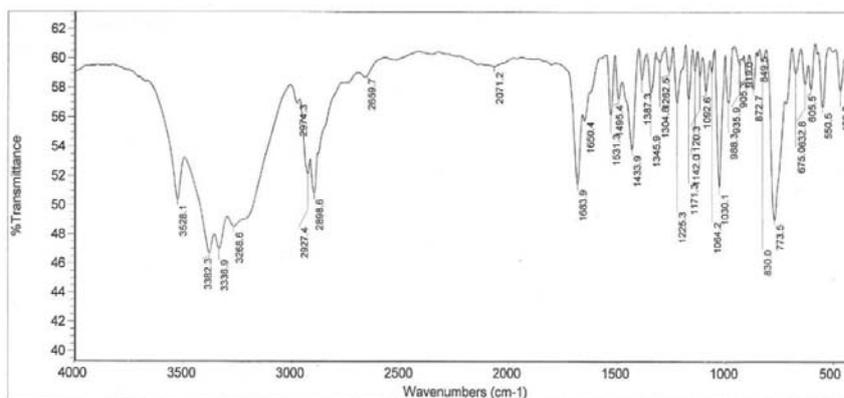


Fig. 3: Drug+colloidal silicon dioxide+Mg-stearate

Drug excipients compatibility study

Drug excipients compatibility study was done with Drug: MCC, Drug: Pregelatinize Starch, Drug: Methocel K100M at (1:1) ratio and Drug: Colloidal Silicon Dioxide, Drug: Mg Stearate at (1:0.25) followed by Drug+MCC+Pregelatinize Starch+HPMC K100M+Colloidal silicon Dioxide+Mg-Stearate propositional mixture at 25 °C ±2 °C/60%RH±5% RH and 40 °C±2 °C/75%RH±5% RH for 4 w duration.

DSC study

From the DSC Study results shown with physical observation, it was concluded that there was no significant Drug-Excipient interaction was observed. The results of DSC study shown that there is no change in drug's melting peak after the preparation of tablet. So we can conclude that drug and other Excipients are compatible which each other [36].

Preformulation study results

From the Results of Preformulation studies of the API, It was concluded that Cisapride has poor flow property and compressibility property. So, to improve the flow and compressibility property, it was beneficial to use the directly compressible grade components in the formulation of the tablet [37].

Analytical method development

UV spectroscopy

As shown in table 1, Stock solution (1 mg/ml) of drug was prepared in water. This solution was appropriately diluted with water to obtain a concentration of 200 µg/ml. The solution was kept in a silica cuvette 10 mm. The UV spectrum was recorded in the range 200-400 nm on Shimadzu 2501 PC double beam spectrophotometer at 1 nm, slit width [38].

Table 1: Preformulation study of cisapride

| Drug | Angle of repose (°) | Loose bulk density (g/ml) | Tapped bulk density (g/ml) | Carr's index (%) | Hausner's ratio |
|-----------|---------------------|---------------------------|----------------------------|------------------|-----------------|
| Cisapride | 27.34±0.52 | 0.375±0.05 | 0.516±0.03 | 27.32±0.4 | 1.37±0.04 |

n = 3, mean±SD

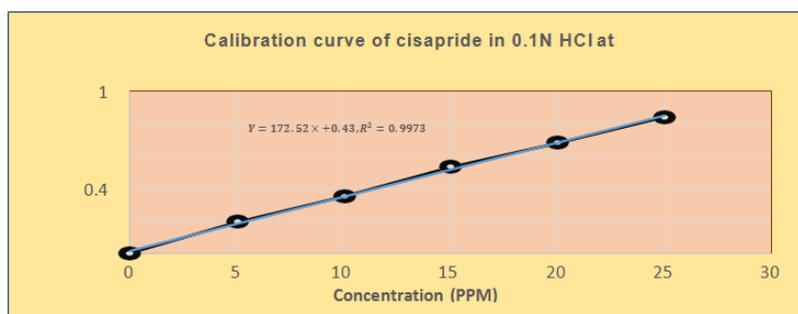


Fig. 4: Calibration curve of cisapride in 0.1N HCl

Table 2: Absorbance at different concentrations of cisapride

| S. No. | Concentration (mcg/ml) | Absorbance | | | Avg. Absorbance ±SD ^a |
|--------|------------------------|----------------|----------------|----------------|----------------------------------|
| | | A ₁ | A ₂ | A ₃ | |
| 1 | 0 | | | | 0 |
| 2 | 5 | 0.198 | 0.186 | 0.189 | 0.191±0.003 |
| 3 | 10 | 0.351 | 0.359 | 0.352 | 0.354±0.002 |
| 4 | 15 | 0.534 | 0.530 | 0.526 | 0.530±0.005 |
| 5 | 20 | 0.688 | 0.687 | 0.686 | 0.687±0.003 |
| 6 | 25 | 0.843 | 0.851 | 0.850 | 0.848±0.005 |

^amean±SD, n = 3.

Formulation of preliminary trials

Trial batches with HPMC K4M and HPMC K100M

Table 2: Formula of trial batches F001 to F005

| Trial | F001 | F002 | F003 | F004 | F005 |
|--------------------------|--------|--------|--------|--------|--------|
| Cisapride | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 |
| MCC(Avicel PH 102) | 35.00 | 25.00 | 35.00 | 25.00 | 30.00 |
| HPMC K4M | 30.00 | 40.00 | ... | ... | ... |
| HPMC K100M | ... | ... | 30.00 | 40.00 | 35.00 |
| Colloidal SiliconDioxide | 6.00 | 6.00 | 6.00 | 6.00 | 6.00 |
| MagnesiumStearate | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 |
| Talc | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| Total | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |

MCC: Microcrystalline cellulose, HPMC: hydroxypropyl methylcellulose

The results of angle of repose and compressibility index ranged from 23.31±0.42 to 25.14±0.32 and 11.83±0.22 to 15.28±0.40, respectively. The results of Hausner's ratio and blend uniformity ranged from 1.13±0.05 to 1.18±0.04 and 98.23±0.15 to 99.21±0.39, respectively [1]. The results of the angle of repose (<30) indicate good flow properties of the powder. This was further supported by lower compressibility index values. Generally, compressibility index values up to 15% results in good to excellent flow properties.

Evaluation of tablets

Hardness of the prepared tablets was found in the range of 6-8 kP. All the tablet formulations showed acceptable pharmaco technical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

In vitro release study

The results of *in vitro* dissolution study of trial batches F001 to F005 which was taken single polymer like HPMC K4M and HPMC K100M. From the results as shown in fig. 5, concluded that by using single polymer like HPMC K4M and HPMC K100M, release profile was not desirable. However, among these formulations, F004 and F005 were selected for further development because they shown comparatively

less deviation from the targeted release profile. So, further study was planned by using some release retardant polymer like Ethyl cellulose and Pregelatinize starch in different concentrations [40].

Trials with ethyl cellulose and pregelatinize starch in combination with HPMC K100M

The results with release retardant polymer in combination with HPMC K100M indicate that the formulations still need modification to get desired release profile. Based on this study, it was proposed to use the combination of both water-soluble matrix-forming polymer HPMC K4M and HPMC K100M in proper concentration.

Trials with the combination of HPMC K4M and HPMC K100M

Hydrophilic matrix of HPMC K4M and HPMC K100M in combination sustained the Cisapride release effectively for more than 12 h. From the result, it concluded that the combination of HPMC K4M and HPMC K100M can be successfully utilized to create desire release profile similar to the targeted release profile in further study. On the basis of the preliminary trials in the present investigation, a 3² full factorial design was applied to study the effect of independent variables, i.e. concentration of HPMC K4M (X1) and concentration of HPMC K100M (X2) on dependent variables like %drug release Q2, Q6 and Q10.

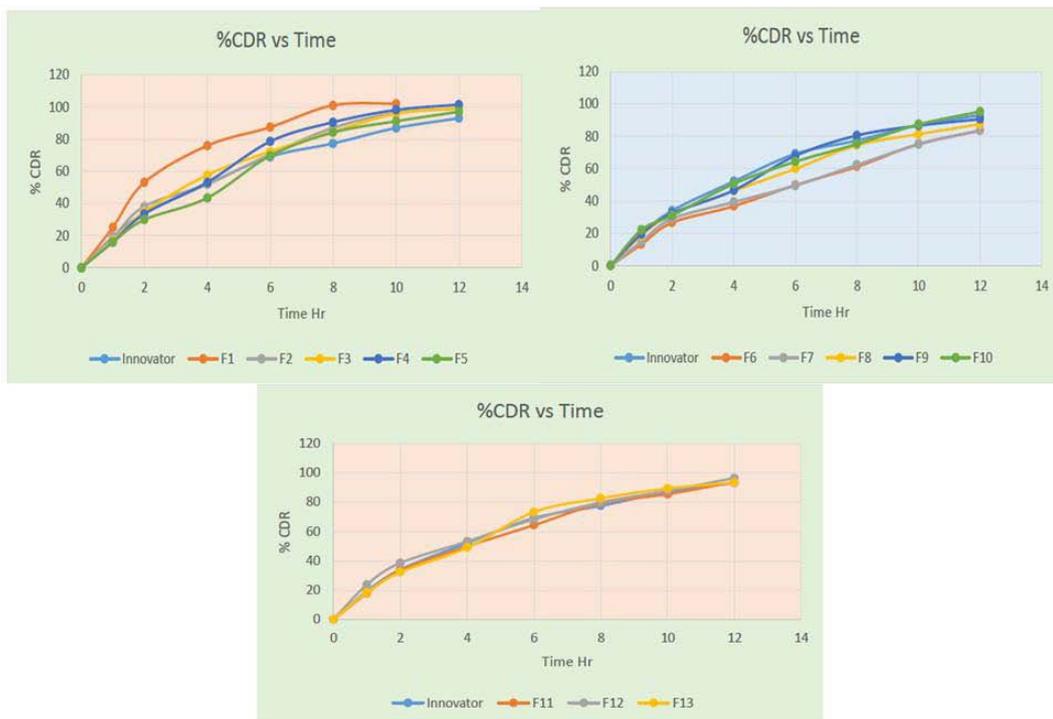


Fig. 5: Comparative dissolution profile of Trial F01 to F013 and Innovator

Formulation and optimization of sustained-release matrix tablets by using 3² full factorial designs: 3² full factorial design

layout of Cisapride sustained release matrix tablet of selected formulations.

Table 3: Formula of factorial batches

| Trial | F014 | F015 | F016 | F017 | F018 | F019 | F020 | F021 | F022 |
|---------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Cisapride | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 |
| MCC (Avicel PH 102) | 30.00 | 25.00 | 20.00 | 25.00 | 20.00 | 15.00 | 20.00 | 15.00 | 10.00 |
| HPMC K4M DC Grade | 15.00 | 15.00 | 15.00 | 20.00 | 20.00 | 20.00 | 25.00 | 25.00 | 25.00 |
| HPMC K100M DC Grade | 20.00 | 25.00 | 30.00 | 20.00 | 25.00 | 30.00 | 20.00 | 25.00 | 30.00 |
| Colloidal silicon dioxide | 6.00 | 6.00 | 6.00 | 6.00 | 6.00 | 6.00 | 6.00 | 6.00 | 6.00 |
| Magnesium stearate | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 |
| Talc | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| Total | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

MCC: Microcrystalline cellulose, HPMC: hydroxypropyl methylcellulose

In vitro drug release

The result of regression analysis showed that all the co-efficient bear a negative sign, which indicates that by increasing the concentration of both the polymers the drug release was sustained. Drug release at 2nd hr (Q2) gives a correlation co-efficient 0.9907.

The P-value for variable X1 and X2 were 0.0006 and 0.002 respectively (P<0.05), it indicate that both variable shown significant effect on drug release and combination co-efficient was negative but the P value was not less than 0.05, which indicates that combination of an independent variable did not show significant effect at 2nd h release

$$Q2 = 37.644 - 5.417X1 - 3.25X2 - 0.7X1X2 - 2.017X2 - 0.817X2$$

Drug release at 8h (Q8) has less linearity compared to Q2 with a correlation coefficient 0.9849. The P-value for variable X1 and X2 were 0.013 and 0.007 (P<0.05), it indicate that both variable has a significant effect on the drug release at 6h. and the combination co-efficient was negative but the P-value was not less than 0.05 so, we say that the combination of independent variable was not giving the significant effect at 6h release. The co-efficient of X1 and X2 were negative indicate that when the concentration of both the variable increase than drug release was decreased.

$$Q8 = 72.367 - 8.05X1 - 4.4X2 - 2.275X1X2 - 3.75X12 - 0.11X2$$

Drug release at 10h (Q10) has the P-value for variable X1, X2 and X1X2 were 0.002, 0.024, 0.035 respectively (P<0.05), it indicate that both variable has a significant effect and also the combination of variable has a significant effect on drug release at 10h. The co-efficient of X1 and X2 were negative indicate that when the concentration of both the variable increase than drug release was decreased.

$$Q12 = 90.844 - 5.8X1 - 2.633X2 - 2.8X1X2 - 0.26X12 - 2.467X2$$

The Q2, Q8, and Q10 for all the batches F014 to F022 varied from 43.2% to 25.1%, 79.4% to 52.9%, and 94.3% to 75.8% with correlation coefficient as 0.9907, 0.9849 and 0.9760 respectively. The dissolution profile of all the formulation batches prepared by using 32 factorial designs was compared by similarity factor f2 value. Factorial batches F018, F019, F020 and F021 give the f2 value 75.85, 86.04, 82.81, 74.71 respectively. In factorial batch F018 the drug release obtained was 57.1%, 70.8% and 80.1% at 4h, 6h, and 8h, respectively, was faster than the targeted release profile. In trial batch F020, f2

Value was above 75 but 4th hr release was outside the specified range. Trial batch F021 also has the f2 value nearer 75, but 4h release was slower than we required. Trial batch F019 the highest f2 value 86.04 was obtained and also, all the hour's drug release was within the specified range. Based on the f2 value and targeted release profile, the suggested optimized batch was F019.

CONCLUSION

Factorial batches F018, F019, F020, and F021 give the f2 value 75-100. Factorial batch F019 gives the highest f2 value 86.04 and also

all the hour's drug release was within the specified range. Based on the f2 value and targeted release profile, the optimized batch was F019. The co-efficient of X1 and X2 were negative indicate that when the concentration of both the variables increase than drug release was decrease. From the result of 3² full factorial design and regression analysis for Cisapride Sustained release matrix tablet, it was concluded that factorial batch F019 taken with the combination of 7.5% HPMC K4M and 25% HPMC K100M give drug release comparable to the targeted release profile with f2 value 86.04.

In the present study, to check the reproducibility, batch was taken with larger batch size and carried out accelerated stability study. From the result, it concluded that the reproducible batch taken with 7.5% HPMC K4M and 25% HPMC K100M has good reproducibility. The result of regression analysis showed that all the co-efficient bear a negative sign, which indicates that by increasing the concentration of both the polymers the drug release was sustained. The drug release was followed the Korsmeyer model and which indicate a coupling of diffusion and erosion mechanisms, so-called anomalous diffusion. From the stability result we said that there was no change in the formulation after 1 mo accelerated stability study. The prepared formulation of the Cisapride sustain release matrix tablet was stable.

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DECLARATIONS

Availability of data and materials: The datasets were used and analyzed during the current study available from the corresponding author on reasonable request.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

AUTHORS' CONTRIBUTIONS

All authors are contributed equally.

FUNDING

Nil

CONFLICT OF INTERESTS

The author declares that they have no conflict of interest.

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