International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 8, Issue 4, 2016

Original Article

DEVELOPMENT AND EVALUATION OF CHRONOMODULATED DELIVERY SYSTEM OF METOCLOPRAMIDE HYDROCHLORIDE

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Received: 22 Jul 2016, Revised and Accepted: 07 Sep 2016

ABSTRACT

Objective: Metoclopramide hydrochloride (meto) is indicated in the treatment of diabetic gastro paresis. It is also used in the treatment of pregnancy-induced morning sickness. Present work involved the development of a chrono-modulated delivery system of meto, intended to be taken at bedtime which would elicit the therapeutic response early in the morning when needed the most to prevent the symptoms of diabetic gastro paresis and morning sickness.

Methods: Immediate release tablets of meto were prepared and optimized for disintegration time and *in vitro* drug release. Subsequently, these tablets were compression coated using various ratios of glyceryl dibehenate and diluents. The resulting tablets were evaluated for disintegration time and *in vitro* drug release. Optimized formulation was subjected to accelerated stability studies for 3 mo.

Results: The optimized immediate release tablets exhibited disintegration time of 2-3 min and more than 90% drug release within 30 min. These tablets when compression coated with the optimized ratio of glyceryl dibehenate and di-calcium phosphate could delay the disintegration time to 251 min. *In vitro* release study of the tablets showed the lag phase of 4 h after which there was a complete drug release within 1 h. Accelerated stability studies indicated good physical and chemical stability of the formulation.

Conclusion: Chrono-modulated formulation of meto could delay the release of the drug by four h. This lag in the release is expected to modulate the time of therapeutic response of meto early in the morning at 6-7 h interval after the administration of dosage form at bedtime.

Keywords: Metoclopramide hydrochloride, Chrono-modulated, Glyceryl dibehenate, Diabetic gastro paresis, Morning sickness

DOI: http://dx.doi.org/10.22159/ijap.2016v8i4.14252

INTRODUCTION

Meto, a dopamine receptor antagonist, is indicated in the treatment of gastro-esophageal reflux disease, nausea and vomiting, and morning sickness during pregnancy [1, 2]. It is the only approved drug in USA for the management of diabetic gastro paresis also known as diabetic gastric stasis [3]. Diabetic gastro paresis is caused by poorly controlled type 1 and type 2 diabetes. The vagus nerve supplying to the stomach becomes damaged due to high blood glucose and lack of glucose into the cells. It is a chronic gastrointestinal disorder in which the gastric contents are not emptied in the normal way but rather at a slower rate than the usual. This results in severe digestive system symptoms like feeling of fullness very quickly upon eating, nausea, loss of appetite, abdominal pain and discomfort, bloating and heartburn. Lack of adequate gastric motility to propel the contents forward into small intestine can significantly hamper the absorption of glucose and other nutrients into the blood. Administration of anti-diabetic medicines in such a situation where there is inadequate glucose level in the blood can create serious concerns of hypoglycemia [4]. Meto stimulates the contractions of the stomach and intestine and helps to improve the gastric emptying time by acting on the dopamine receptors of the stomach and intestine. It also controls the feeling of nausea and vomiting by its action on chemo-trigger receptor zone in the brain. It helps regulate the sugar levels of diabetic patients suffering from gastro paresis by making the food available in the intestine for absorption in a manner such that the antidiabetic medications can work effectively [2].

Almost 80% of pregnant women suffer from morning sickness in the first trimester of pregnancy. They have to deal with severe nausea and bouts of vomiting in the morning which affects the appetite and eating, resulting in severe weakness and malnutrition. Oral therapy with meto is proven safe in relieving the symptoms of morning sickness [5]. Meto is available in various dosage forms like immediate release tablets, orally disintegrating tablets, solution, as well as controlled release formulations in the market. An extensive work on sustained release formulations, controlled release matrix tablets, flash release films, fast dissolving tablets, bucco-adhesive tablets, gastro-retentive delivery of meto have been reported in the literature [6-13]. However, all these formulations can exercise the therapeutic effect only after 1 to 2 h of oral administration or in a sustained manner depending on the type of dosage form. This would render the medication almost ineffective in curbing the nausea and vomiting that initiates as soon as waking up in the morning in the case of pregnant women or in preventing fluctuation in blood glucose levels of the diabetic patients suffering from gastro paresis.

Chronotherapeutic drug delivery systems are gaining importance in the field of pharmaceutical technology as these systems reduce dosing frequency, toxicity and deliver a drug that matches the circadian rhythm of that particular disease when the symptoms are maximum to worse. Chrono-modulated delivery also known as the pulsatile delivery system is typically designed for treating cardiovascular conditions, asthma, arthritis wherein the symptoms are most intense early in the morning. Hence the Chrono modulated delivery is to be administered at the bed time and expected to elicit optimum therapeutic benefits early in the morning by virtue of lag time of 4 to 5 h in the drug release. Such a delivery offers the advantage of optimum pharmacological effect when needed the most, without causing the inconvenience of waking up in the middle of the night to administer the medicine in order to have a therapeutic effect early in the morning, thus improving the patient compliance [14-16].

With this in view, the aim of the present study was to develop a chrono-modulated delivery system for meto that can be administered at bedtime and would elicit the therapeutic effect after 6-7 h, i.e. early in the morning, preventing morning sickness in the case of pregnant women. In the case of diabetic patients suffering from gastro paresis, such a formulation would facilitate gastric emptying of food into intestine for absorption so that the glucose absorbed could be effectively acted upon by the antidiabetic therapy preventing hypoglycemia.

MATERIALS AND METHODS

Chemicals and reagents

Meto was procured from IPCA laboratories pvt. ltd., Mumbai, India; microcrystalline cellulose, magnesium stearate and dicalcium

phosphate was procured from Signet chemicals ltd, glyceryl dibehenate as a gift sample from Gattefosse (India) pvt. ltd., lactose spray dried was obtained from DFE pharma ltd. and crospovidone from Ashland specialties ltd. All these suppliers were based in Mumbai, India.

Methods

Preparation of immediate release core tablets of me to

Trials to formulate the core immediate release tablets of meto were initiated (table 1).

Table 1: Composition of immediate release tablets of meto

Ingredients	Qty in mg/tablet		
	F1	F2	F3
Meto	11.82	11.82	11.82
Microcrystalline cellulose	24.18	23.93	22.43
Lactose spray dried	12	12	12
Crospovidone XL	1.5	-	-
Crospovidone XL 10	-	1.5	2.5
Colloidal silicon dioxide	-	-	0.5
Magnesium stearate	0.5	0.75	0.75

Manufacturing process

1. Meto and lactose were sifted through 30 mesh sieve. The resultant material was mixed in a blender for 10 min.

2. Microcrystalline cellulose and crospovidone XL in the case of formula F1, microcrystalline cellulose and crospovidone XL 10 in formula F2 and for formulation F3-microcrystalline cellulose, crosspovidone XL 10 and colloidal silicon dioxide were sifted through 30 mesh sieve and transferred to the blender and mixed with the blend of step 1 for 10 min.

3. Magnesium stearate was sifted through 40 mesh sieve and transferred to the blend of step 2.

4. The blend was mixed for 3 min.

5. The lubricated blend was transferred to the hopper of the compression machine and tablets were compressed at the hardness of 2-4 kilopascals (kp) using 4.7 mm circular, biconcave, plain punches using Cadmach CMD4 single rotary compression machine.

Evaluation of tablets

Tablets of all the three batches were evaluated using following parameters.

Average weight and weight variation-20 tablets were selected randomly and weighed. The average weight of the tablets was determined. These tablets were weighed individually and the weight variation was determined.

Hardness was measured using Dr. Schleuniger hardness tester (Model 8M).

Thickness was determined using vernier caliper (Mitutoyo, 500-197-30).

Disintegration time was performed as per Indian Pharmacopoeia specifications using disintegration test apparatus (EIectrolab tablet disintegration test apparatus ED2L).

Assay-Tablets, 10 numbers, were powdered. Powder equivalent to 11.82 mg meto was dissolved in the diluents mentioned below, diluted suitably and subjected to assay using reverse phase HPLC (Agilent technologies 1260 Infinity).

Column–C18, 5-micron packing

Wavelength–276 nm

Flow rate–1 ml/min

Injection volume–5 microlitre

Diluent–water: acetonitrile (75:25)

Buffer solution–5.4g/litre (l) of sodium acetate in water

Mobile phase–buffer solution: acetonitrile: tetra methyl ammonium hydroxide (70:30:0.2)

In vitro release study-Tablets of the batch, F3 were subjected to *in vitro* drug release studies using USP Type 2 dissolution test apparatus employing 900 ml distilled water as a medium at 50 rpm for 30 min [17]. The aliquots were analyzed by High-performance liquid chromatography (HPLC) using the same method used for the assay.

Compression coating of the core tablets

Immediate release tablets of batch F3 were taken up for compression coating trials (table 2).

Table 2: Formulae for the compression coating of meto immediate release tablets

Ingredients	mg/tablet					
	F4	F5	F6	F7	F8	F9
Core tablets of F3	50	50	50	50	50	50
Glyceryl dibehenate	127	127	127	136	156	146
Dicalcium phosphate	110	90	167	156	136	146
Microcrystalline cellulose	57	77	-	-	-	-
Colloidal silicon dioxide	3	3	3	3	3	3
Magnesium stearate	3	3	3	5	5	5

Manufacturing process

1. Glyceryl dibehenate, dicalcium phosphate, microcrystalline cellulose (only in case of formula F4 and F5) and colloidal silicon dioxide were sifted through 30 mesh sieve and mixed in a blender for 15 min.

2. Magnesium stearate was sifted through 40 mesh sieve and mixed with the blend of step 1 for 3 min.

3. The coating material was compressed around the core tablets using 9 mm circular biconcave punches set on Cadmach press coater CPC 900 machine.

Tablets were evaluated for average weight, hardness, thickness, disintegration time in a similar manner as conducted for core tablets. *In vitro* dissolution studies were conducted for 5 h duration, using similar conditions and apparatus as that for the immediate release tablets. The aliquots were drawn at 4, 4.5 and 5 h intervals.

Hardness challenge study

The blend of batch F9 was subjected to hardness challenge during compression. This involved compressing half the lot at lower compression pressure and rest of the lot at higher pressure.

Reproducibility trial and accelerated stability studies

Batch F10 was prepared similarly to the composition of batch F9 in order to evaluate the reproducibility and the stability profile of the formulation. The tablets were packed in aluminum foil sachets and subjected to accelerated storage conditions of 40 °C/75 % RH. Samples were evaluated at the time intervals of 1, 2 and 3 mo.

Statistical analysis

One way analysis of variance (ANOVA) was employed to assess the difference between the assay values of initial and that of stability samples using Sigma Stat software (Sigma stat 2.03, SPSS). The observed p values of>0.05 were considered statistically significant for the test. The similar statistical test was applied to find a difference in the *in vitro* drug release at each time point among stability samples.

RESULTS AND DISCUSSION

Preparation of immediate release core tablets of meto

The aim of the present study was to develop the chrono-modulated delivery system for meto using compression coating technique. For this, core tablets containing the drug needed to be developed initially which would release the drug immediately upon dissolving the external barrier coat. Immediate release tablets of meto were hence prepared by direct compression technique.

The powder blend of formula F1 lacked appropriate flow properties which resulted in poor flow from the hopper onto the feed frame. Also, the tablet surface appeared slightly rough. It was required to improve the flow of the powder blend and improve the appearance. Magnesium stearate concentration was increased to 1.5 % and finer grade of crospovidone XL10 was used in batch F2. Tablets disintegrated within 2 min. However, a small portion of core remained which took 2-3 min for complete disintegration. It was essential to improve the disintegration time since the formulation needs to release the entire contents after the lag period. Formulation F2 was modified by increasing the crospovidone content and incorporation of colloidal silicon dioxide. This was done in order to enable the formulation to draw water for complete disintegration. Thus tablets of batch F3 showed quick disintegration time of 2-3 min without leaving behind the core and *in vitro* release of more than 90 % within 30 min (table 3). Formula F3 was thus considered as optimized for further development of a chrono-modulated formulation of meto.

Compression coating of core tablets

Glyceryl di-behenate is a chemically inert and highly compatible lipid of high melting point. In combination with suitable diluents, it forms a good water repellant barrier layer which provides adequate mechanical and chemical barrier preventing the core from releasing the contents [18, 19]. The chrono-formulation of meto is intended to be administered at bedtime and elicit the therapeutic response early in the morning after a lag time of 6-7 h. Various combinations of glyceryl dibehenate, dicalcium phosphate and microcrystalline cellulose were tried to prepare the compression coated tablets of meto which would delay the release at least by 4 h. The resulting tablets were evaluated for hardness, thickness, disintegration time and the *in vitro* release studies.

Tablets of batch F4 and F5 containing varying quantities of microcrystalline cellulose disintegrated in less than 2 h thus making them unsuitable for achieving the desired drug release lag time of 4 hr. Elimination of microcrystalline cellulose in formula F6 could delay the disintegration time of the tablets to 3 h but failed to achieve the target of 4 h. Formulation F7 prepared with a higher quantity of glyceryl dibehenate and magnesium stearate could prolong the disintegration time to 210 min, however, releasing around 50 % of the drug at 4 h interval which was undesirable. The considerably higher concentration of lipid in formulation F8 prolonged the disintegration time to more than 4 h thus curbing the release completely at 4 h. The tablets of this formula showed incomplete release at 5 h. Hence the quantity of glyceryl dibehenate was reduced in formula F9 which resulted in achieving desired release profile and the formulation was considered optimum (table 4).

Table 3: Evaluation of immediate release tablets of meto

Evaluation parameter	F1	F2	F3
Average weight (mg)	51.5±2.3	50.1±3.2	50.8±1.7
Thickness (mm)	2.1-2.2	2.1-2.2	2.1-2.2
Hardness (kp)	2-4	2-4	2-4
Disintegration time (min)	5	5	2-3
Assay (%)	-	-	100.4±1.3
Drug release at 30 min (%)	-	-	94.3±2.3

Values of assay and drug release are represented as mean±standard deviation, n=3, n=6 respectively

Table 4: Evaluation of chrono-modulated formulations of meto

Evaluation parameter	F4	F5	F6	F7	F8	F9
Average weight (mg)	351.5±2.2	350.1±4.6	355.5±2.4	353.0±1.4	354.3±3.2	352.1±3.7
Thickness (mm)	3.3-3.5	3.3-3.5	3.3-3.5	3.3-3.5	3.3-3.5	3.3-3.5
Hardness (kp)	3-5	3-5	3-5	3-5	3-5	3-5
Disintegration time (min)	112	87	190	210	263	251
Assay (%)	99.5±2.2	99.8±2.2	100.3±2.7	99.5±1.8	100.8±0.9	101.2±2.2
Drug release at 4 h (%)	-	-	-	50.8±1.8	0	0
Drug release at 4.5 h (%)	-	-	-	97.0±0.9	57.2±2.4	70.4±4.5
Drug release at 5 h (%)	-	-	-	100.2±1.9	85.3±2.1	99.1±1.4

Values of the assay and drug release are represented as mean±standard deviation, n=3, n=6 respectively.

Hardness challenge studies

To study the impact of hardness on dissolution characteristics of the formulation, powder blend of batch F9 was compressed at low and high hardness. Tablets compressed at the low hardness of 1.5–2.5 kp demonstrated a failure to comply with the dissolution specifications. Drug release of more than 10% was observed at the time interval of 4 h (table 5). At lower hardness, the press coated layer was not adequately formed and lacked the mechanical strength to withstand the agitation and subsequent ingress of dissolution fluid. The tablets compressed at hardness range of 6-7 kp complied with the dissolution specifications (table 5).

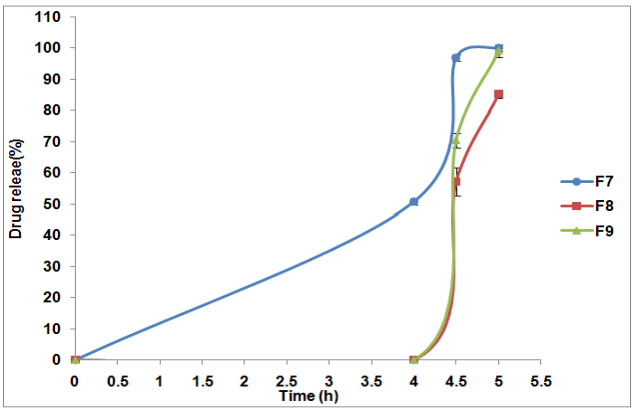

Fig. 1: *In vitro* release of meto from tablets of formulations F7, F8 and F9

Values of *in vitro* drug release are represented as mean+ SD, n=6

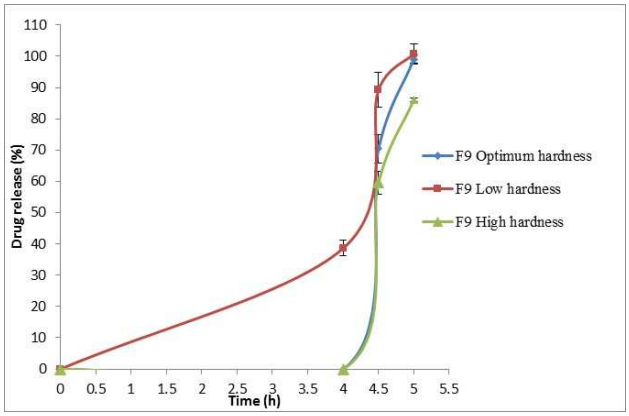

Fig. 2: Impact of hardness on *in vitro* drug release of formulation F9

Values of *in vitro* drug release are represented as mean+ SD, n=6

Table 5: Hardness challenge studies

Parameter	Tablets of F9 with low hardness	Tablets of F9 with high Hardness
Average weight (mg)	348.5±1.9	351.5±1.8
Hardness (kp)	1.5–2.5	6-7
Disintegration time (min)	173	267
Drug release at 4 h (%)	38.6±2.5	0
Drug release at 4.5 h (%)	89.2±5.6	59.6±3.6
Drug release at 5 h (%)	100.8±3.2	86.1±0.5

Values of drug release are represented as mean±standard deviation, n=6

Accelerated stability studies

Stability samples of batch F10, when evaluated at various time intervals, showed no significant difference in appearance, hardness or other physical traits as compared to initial samples (table 6). Statistical analysis of assay values of stability samples indicated no significant difference. *In vitro* release profiles of samples when compared with that of initial using ANOVA exhibited no significant difference thus indicating good overall stability of the formulation at accelerated conditions.

Table 6: Evaluation of stability samples of batch F10

Test	Specification	Initial	1 mo	2 mo	3 mo
Description	White to off-white coloured circular, biconvex tablets	White to off-white coloured circular, biconvex tablets	White to off-white coloured circular, biconvex tablets	White to off-white coloured circular, biconvex tablets	White to off-white coloured circular, biconvex tablets
Average weight	350 mg+3%	complies	complies	complies	complies
Hardness	3–7kp	3–5kp	3–6kp	3–5kp	3–6kp
Disintegration time	230–300 min	256 min	266 min	263 min	270 min
Assay	90-110%	99.8%±0.7	100.3%±1.7	99.3%±1.1	99.1%±2.0
Drug release	4 h: NMT 10%	0%	0%	0%	0%
	4.5 h: NLT 50%	65.8%±4.1	63.9%±2.7	66.4%±3.5	62.6%±3.2
	5 h: NLT 85%	97.2%±3.8	93.2%±1.4	95.2%±2.5	91.5%±1.9

Values of assay and drug release are represented as mean±standard deviation, n=3, n=6 respectively

The reported literature on meto involves development of fast release oral films, mouth dissolving tablets [10, 11] which would release the drug quickly after oral administration, however, the time to peak plasma level (t_{max}) would still be around 2 h and hence the drug would not be able to elicit therapeutic response immediately upon administration which is needed in treating morning sickness or gastroparesis. Review of literature also indicates the development of modified release formulations of meto which would release the drug slowly over a period of 12 h [6-9, 12, 13]. Such formulations could reduce the symptoms to some extent; however the optimum response may not be achieved since the plasma levels of the drug would be lower as compared to the ones attained in the case of chrono-modulated formulation, which would release the drug at once and exert highest therapeutic response at the time when needed the most.

CONCLUSION

Compression coated tablets of meto prepared using glyceryl dibehenate as a release modifier could delay the *in vitro* release of the drug up to 4 h and subsequently exhibited complete release within 1 h. This chrono-modulated formulation of meto when administered at bedtime, can thus be expected to achieve maximum therapeutic effect early in the morning to relieve the pregnant women from symptoms of morning sickness and prevent the serum glucose level fluctuations in diabetic patients suffering from gastroparesis.

ACKNOWLEDGMENT

Authors would like to acknowledge Gattefosse India Pvt. Ltd for generously providing the gift sample of glyceryl dibehenate.

CONFLICT OF INTERESTS

Declare none

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How to cite this article

- Sandhya Rajendra Shenoy, Pritam Jain, Madhur Kulkarni. Development and evaluation of the chronomodulated delivery system of metoclopramide hydrochloride. Int J Appl Pharm 2016;8(4):38-42.