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COMMUNICATION

Formulation Optimization of Controlled-Release Pellets of Metoclopramide Hydrochloride Using Dissolution Fit Factor Approach

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ABSTRACT

The purpose of this study was to optimize the formulation variables for the preparation of ethyl cellulose–coated nonpareils loaded with metoclopramide hydrochloride (MCL). The approach to evaluate the effectiveness of formulation parameters was monitored by release rate testing using dissolution fit factors as a tool. The content of ethyl cellulose used in the formulation was based on the drug-loaded weight. The interrelationship of each developed formulation and the reference formulation Gastro-Timelets® and their respective dissolution curves were evaluated using Moore's equation: $f_2 = 50 \times log\{[1 + 1/n \sum_{t=1}^{n} Wt(Rt - Tt)^2]^{-0.5} \times 100\}$. *The relationship between the ethyl cellulose content in the formulation and the dissolution fit factor* f_2 *can be described as the following regression equation:* $Y = -0.054X^2 + 3.347X - 1.915$ ($r^2 = 0.99$). *The optimum ethyl cellulose content obtained from the equation was 30.8%. The type and content of plasticizer used in the formulation to achieve the greatest* f_2 *were determined to be Myvacet 9-40 at the concentration of 25%. Results indicated that using the release rate testing approach with the dissolution fit factor as a tool could provide valuable information for formulation optimization.*

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INTRODUCTION

Metoclopramide hydrochloride (MCL) is a dopamine receptor antagonist, an antiemetic drug, and a stimulant of upper gastrointestinal motility (1,2). MCL was selected as a model drug in the formulation development of multiparticulate controlled-release pellets because of its short human plasma half-life (3,4). In the process of product development and formulation optimization, the degree of significance in differentiating dissolution curves obtained from different formulations is always a challenge. It is rather interesting if the fit factors, two indices proposed by Moore and Flanner to measure the closeness of two dissolution profiles, could serve as a tool for formulation optimization of MCL multiparticulate controlled-release dosage form. The objectives of this study were to develop a correlation between the fit factor and formulation variables and to determine whether the fit factors can provide good predictions for formulation optimization.

EXPERIMENTAL

Materials

Metoclopramide hydrochloride, nonpareils, and ethyl cellulose were purchased from Anphar Laboratories Pvt., Limited (India), Werner (Germany), and Dow Chem., respectively. Propylene glycol (PEG) and diethylphalat (DEP), used as plasticizers, were purchased from Nakarai Chemicals (Japan) and E. Merck Company, Limited, respectively. Gastro-Timelets® (30 mg/capsule) were purchased from Temmler Pharma (Germany). All other chemicals were analytical reagent grade. A fluidized bed rotor (Glatt GPCG–1, Glatt GmbH Process Technology) was employed in the coating process.

Methods

Preparation of Metoclopramide Hydrochloride–Loaded Pellets

For the preparation of MCL-loaded pellets (5–7), the drug-layering process was employed by applying 80 g of MCL onto 800 g of nonpareil in a fluid bed rotor processing unit. The coating conditions are listed in Table 1. Various concentrations of the binder, Tween 80, were investigated to evaluate its effects on the efficiency of the process. Among the factors being evaluated, content uniformity and particle size were of primary interest.

Table 1

Operating Conditions for Preparing Pellets Containing Metoclopromide Hydrochloride

Operating Condition	Setting
Inlet temperature	38°C
Outlet temperature	36°C
Flow rate of coating solution	8 ml/min
Atomizing air pressure	20 psi
Rotor speed	180 rpm

Preparation of Metoclopramide Hydrochloride Controlled-Release Pellets

For each batch of MCL controlled-release pellets (8,9), 800 g MCL-loaded pellets were coated with coating solution containing ethyl cellulose, plasticizer, and other excipients in a fluidized bed rotor using the operating conditions listed in Table 2. The coating solution was prepared by dissolving ethyl cellulose in the acetone/ethanol (80/20) solvent system. The coating levels were 10.0%, 20.0%, 26.0%, 30.0%, 35.0%, 37.5%, 40.0%, and 43.7% of the MCL weight in the coating process. At the coating level equal to 30.8%, four types of plasticizers (triethyl citrate [TEC], PEG, DEP, and acetylated monoglyceride [Myvacet 9-40]) were investigated. To study the effect of plasticizer concentration on the drug release from the controlled-release pellets, Myvacet 9-40 at the concentration levels of 20%, 25%, 30%, and 35% w/w in the coating solution were employed.

Dissolution Studies

The in vitro dissolution of each batch of the formulated MCL controlled-release pellets was conducted using the USP basket method at 37°C ± 0.5°C and 50 rpm.

Table 2

Operating Conditions for Preparing Metoclopromide Hydrochloride Controlled-Release Pellets

Operating Condition	Setting
Inlet temperature	38°C
Outlet temperature	36°C
Flow rate of coating solution	12 ml/min
Atomizing air pressure	20 psi
Rotor speed	180 rpm

For the first 2 hr, 750 ml of 0.1 N hydrochloric acid was used; then, 250 ml of 0.2 M tribasic sodium phosphate was added. At the predetermined time intervals, an automated dissolution tester (Hsiangtai dissolution apparatus, Istitatec sa peristaltic pump, and Shimadzu model UV-1201 spectrophotometer) was programmed to record absorbance at 390 nm (replication = 6 for each formulation). The absorbance was then converted to concentration using a standard plot. The dissolution profile was then generated using the cumulative percentage dissolved versus time.

Generating the Fit Factor f_2 from the Dissolution Curves

To compare the dissolution profiles of studied formulations versus the reference formulation Gastro-Timelets, an approach using the dissolution fit factors f_2, as proposed by Moore and Flanner (10) in the following equation was used:

$$f_2 = 50 \times \log\{[1 + 1/nWt(Rt - Tt)^2]^{-0.5} \times 100\},$$

where Rt is cumulative percentage release of Gastro-Timelets at time point t, Tt is the cumulative percentage release of studied formulation at time point t, n is the number of time points, and Wt is an optional weight factor.

RESULTS AND DISCUSSION

Optimization Surfactant Level in Preparation of Pellets Containing Metoclopramide Hydrochloride

The use of a surfactant in the drug-layering process is rather important. It reduces the interfacial tension between the drug moiety and the nonpareil beads. In this study, the Tween 80 at the concentration range of 6% to 15% was used. The recovery (percentage of drug layered onto the beads) and the particle diameter after drug layering are listed in Table 3.

The results showed that an increase in the recovery rate was obtained as the concentration of Tween 80 was increased from 6.3% to 15%. The optimal effect of Tween 80 appeared to take effect at 10% and leveled off at the 15% concentration. The average particle size of the beads increased from 712 ± 3.1 μm to 757.7 ± 2.9 μm as the Tween 80 concentration increased from 6.3% to 15%. Three more batches of beads containing MCL were prepared. The data confirmed the prior observations. The Tween 80 concentration at 15% was chosen for further studies.

Table 3

Characteristics of Pellets Containing Metoclopromide Hydrochloride

Batch Number	Content of Tween 80 (%)	Recovery Rate (%)	Mean Diameter of Pellets (μm)
C1	6.3	90.90 ± 0.33	712.3 ± 3.1
C2	10.0	99.20 ± 0.05	732.9 ± 1.7
C3	15.0	99.30 ± 0.29	757.7 ± 2.9
C4	15.0	99.30 ± 0.13	749.3 ± 1.1
C5	15.0	98.90 ± 0.15	752.6 ± 3.9
C6	15.0	98.50 ± 0.15	755.3 ± 2.5

Correlation of Ethyl Cellulose Content with Dissolution Fit Factor During the Controlled-Release Pellet Preparation

The influence of ethyl cellulose content on ultimate drug release rate is shown in Fig. 1. The data indicate that the MCL release rate decreased as the ethyl cellulose

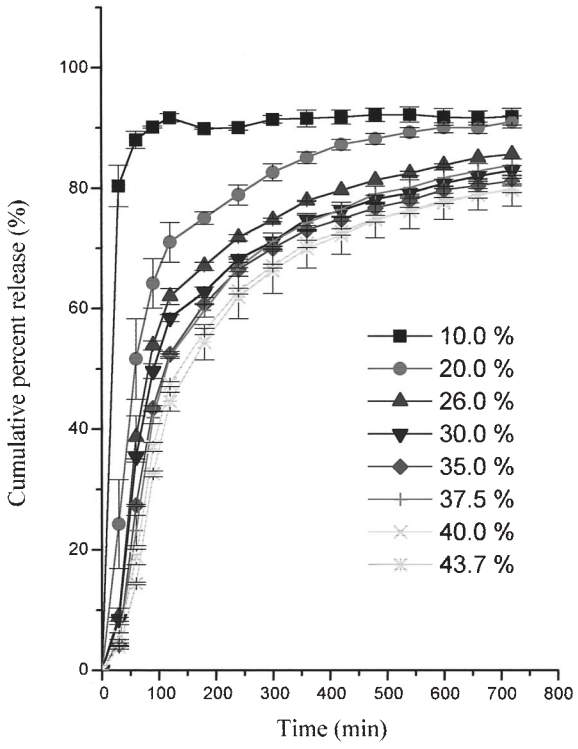

Figure 1. The influence of ethyl cellulose amount on the MCL release rate.

content increased, probably because of the increase of the membrane thickness of the controlled-release pellets.

Figure 2 shows that the relationship between the ethyl cellulose content and the corresponding dissolution fit factor f_2 can be described by the following regression equation: $Y = -0.054X^2 + 3.347X - 1.915$, where X is the ethyl cellulose content, and Y is the corresponding f_2. Good correlation, with a correlation coefficient of 0.99 (Table 4), indicates that the equation correlated the ethyl cellulose content with f_2 quite well.

The optimum ethyl cellulose content that provided a maximum f_2 from the above equation was determined to be 30.8%. Its corresponding fit factor was calculated to be 49.97. Another batch of MCL controlled-release pellets was prepared using the optimal ethyl cellulose content of 30.8% to ensure the same regression equation held. Results indicated that a fit factor of 50.3 was obtained from the equation, which confirmed the prior obtained value of 49.97.

Table 4

The r² and Accuracy for the Correlation of Ethyl Cellulose Content with f_2

Ethyl Cellulose Content (%)	f_2	r^2	f_2 Converted from Equation	Bias (%)
10.0	25.60	0.986	20.15	2.16
20.0	44.45		43.35	2.48
26.0	49.62		45.65	1.96
30.0	48.68		49.80	2.32
35.0	48.06		49.01	1.99
37.5	47.90		47.61	0.60
40.0	45.00		45.53	1.19
43.7	42.00		41.17	1.98

Effect of the Plasticizer Type and Its Amount on the Release Rate of Controlled-Release Pellets

Plasticizers were used to increase the flexibility of the barrier properties of the polymer coatings (11). Based on the 30.8% ethyl cellulose content, the influence of type

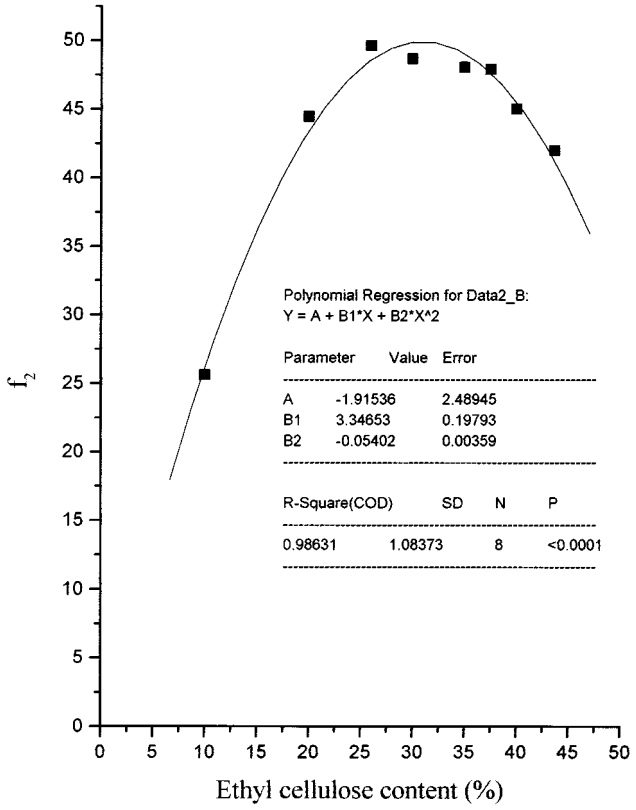

Figure 2. The relationship between the ethyl cellulose content and f_2.

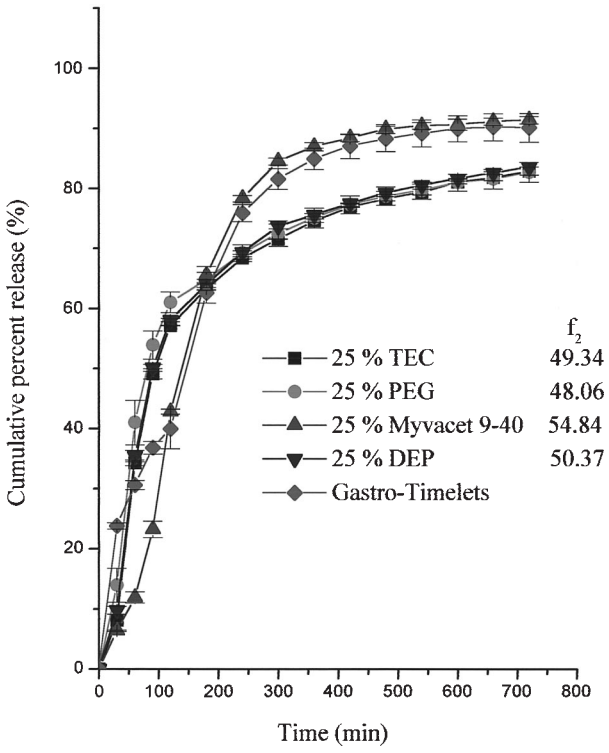

Figure 3. Dissolution profiles of MCL controlled-release formulations containing four different plasticizer types.

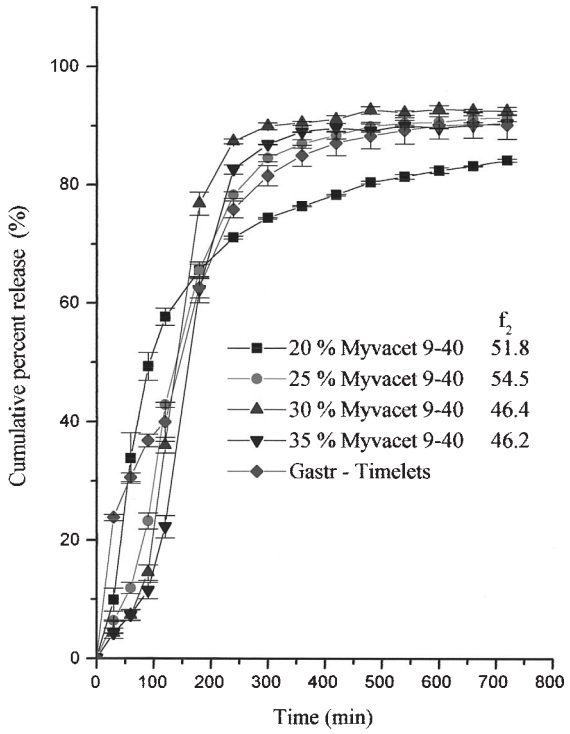

Figure 4. Dissolution profiles of MCL controlled-release formulations containing four plasticizer concentrations.

and amount of plasticizer on the ultimate drug release rate from the MCL controlled-release pellets is shown in Fig. 3 and Fig. 4. The data indicate that changing the type of plasticizer resulted in an increase or a decrease of drug release rate, depending on the nature of the plasticizer. However, with the same plasticizer, Myvacet 9-40, an increase in its content decreased the release rate of MCL. The optimal plasticizer concentration to yield a maximum f_2 was determined to be 25% Myvacet 9-40.

CONCLUSION

Development of formulation parameters can be obtained through the use of dissolution fit factor theory. Results indicated that an MCL controlled-release pellet formulation can be developed by optimizing its plasticizer and polymer content selection through the use of dissolution fit factor theory. In this study, Myvacet 9-40 at the 25% level and ethyl cellulose at a 30.8% concentration, obtained from the dissolution fit factor calculation, were deemed to produce an optimal controlled-release profile of MCL.

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