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Quality Evaluation of Sustained-Release Domperidone Formulations

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ABSTRACT

Using hydrophilic Methocel® K4M, the current study sought to design a sustained-releasing and acting formulation of Domperidone, an antiemetic medication used to treat nausea and vomiting, with a typical dosage that is administered twice or three times per day. The sustained-release formulation was made using various ratios of K4M, and its quality and stability were assessed. The optimized formulation was chosen for dissolution studies and similarity profiles after pre-compression and post-compression features were analyzed. Studies on drug dissolution showed that a tablet containing CF2 had the best release profile for once-daily use. The preparation of long-acting domperidone matrices was accompanied by the display of favorable characteristics necessary for the perfect once-daily formulation. The creation of a gel layer followed by gel erosion may be the mechanism, providing a lengthy, slow-releasing pattern and a desired therapeutic effect. The idea of controlled-release formulations benefits patients and carers by decreasing the frequency of doses and the likelihood of missing doses or an overnight interval between doses.

Keywords: Domperidone, Methocel®, Ethocel®, Long-acting, Erosion

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Introduction

Dopamine receptors are blocked by domperidone. It is an antiemetic, enhances the peristaltic movement of the gastrointestinal tract, which causes prolactin to be released, and opens the door for research into several dopaminergic pathways [1].

Domperidone is a peristalsis stimulant and aids in GI emptying. These traits are connected to its ability to inhibit peripheral dopamine receptors. GI motility is improved by the medication. Conversely, it increases the esophageal and gastric peristalsis and slows transit time. Additionally, it lowers the esophageal sphincter's pressure [2-4]. Domperidone's ability to control vomiting stems from its blocking of the dopamine receptor, both at the GI level and at the chemoreceptor trigger zone. It can connect with dopamine receptors (D2 and D3), is located in the chemoreceptor trigger zone, is close to the blood-brain barrier, and regulates nausea [5, 6].

Domperidone is (5-chloro-1-{1-[3-(2, 3-dihydro-2-oxo-1H-benzimidazol-1-yl) propyl] -4- piperidinyl} benzimidazolin-2-one) [7]. The medication has a half-life of seven hours is extremely permeable and has low solubility.

Modifications to the once-daily formulation could improve the delivery of medications that need to be taken multiple times during the day [8, 9]. These formulations offer several advantages over traditional ones, including steady-state plasma concentration, covering of the nightly no-dose interval, and lower dosages [8, 10, 11]. There are numerous techniques to manufacture controlled release dosage forms, and they adhere to a variety of mechanisms, including ion exchange, diffusion, dissolution, erosion, and osmotically regulated systems. To

sustain drug plasma levels over an extended period, these devices precisely and precisely regulate drug release mechanically [11]. The effectiveness and ease of matrix-based systems make them the most often used [12].

The white or off-white powder is the Methocel® [13]. It provides effective control through erosion and gel formation and is inert [14].

The active medicinal ingredient's release can be regulated by these polymers [15-18]. The polymers Methocel® and Ethocel® (EC) work well for creating matrices. In addition, the release profile is controlled by the amount and polymer grade. When HPMC comes into touch with the surrounding medium, it forms a gel and then erodes, delaying release [19]. **Figures 1 and 2** depict the HPMC polymer's chemical and physical structures, respectively. Because of their hydrophobicity, which diverts fluids and wettability, hydrophobic polymers impede the release. The amount of drug dissolved over time is used to calculate the rate of drug dissolution. Both model-independent and model-dependent methods can be used to analyze dissolution profiles [20-23]. The drug's dissolution pattern was replicated in the results displayed by the model parameters [24-29]. The model-independent method may be applied when the dissolution profile at various time intervals is acquired. One differentiation factor (f1) and a similarity factor (f2) are predicted by the approach) [30].

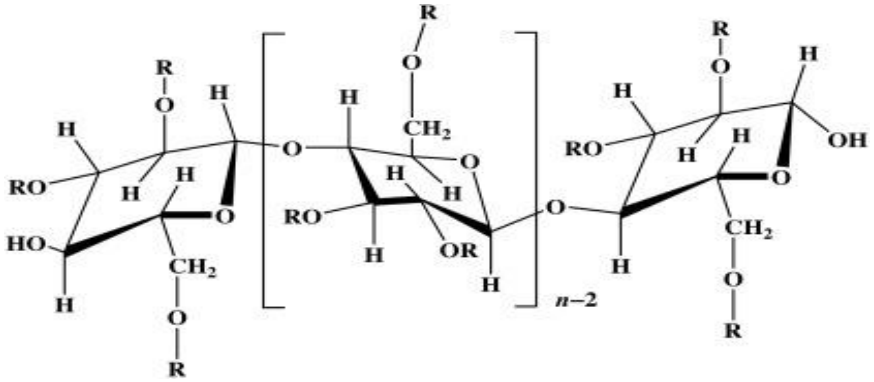
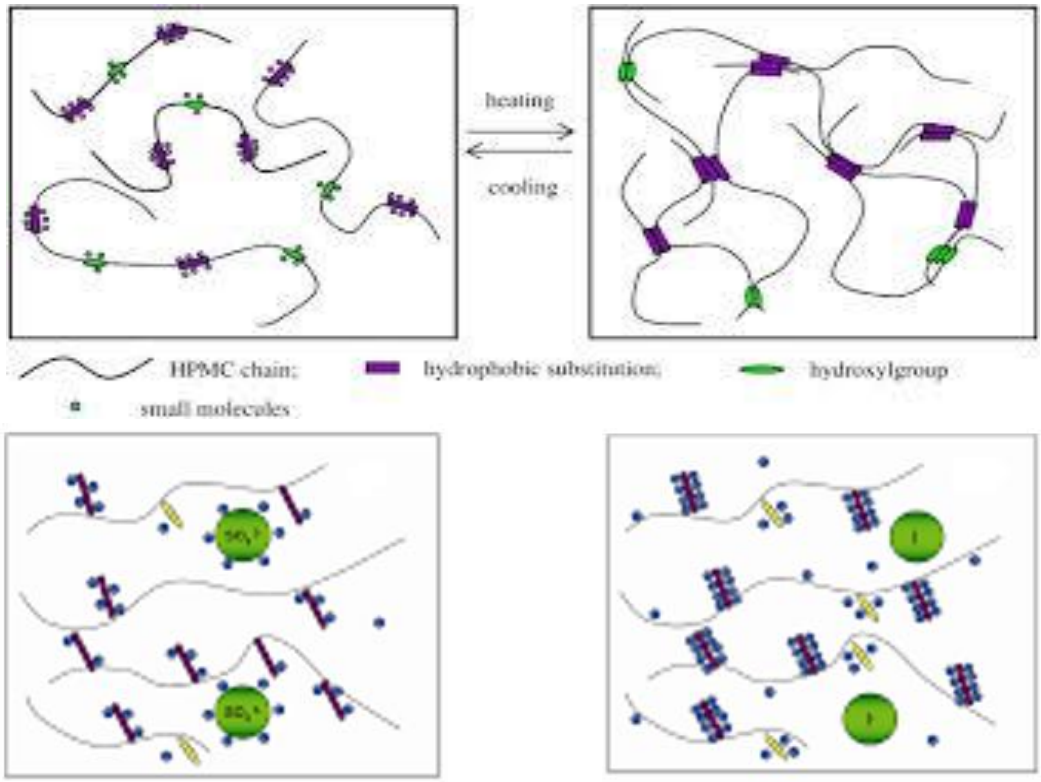
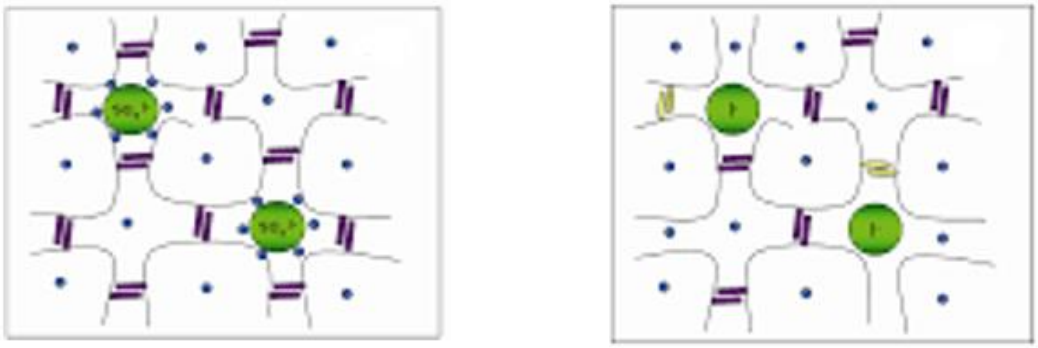


Figure 1. Hydroxypropyl methylcellulose, R = H, $-CH_3$ or - $(OCH_2CHCH_3)_xOH$ [15].



a) b)



c) d)

Figure 2. Physical structures of HPMC hydrogels (a), (b) at lower temperatures and (c), (d) at higher temperatures) [16].

Using hydrophilic Methocel® K4M, the current study sought to design a sustained-releasing and acting formulation of Domperidone, an antiemetic medication used to treat nausea and vomiting, with a typical dosage that is administered twice or three times per day.

Materials and Methods

Chemicals

K4M (Methocel®), magnesium stearate, Avicel PH-10, methanol, potassium dihydrogen phosphate, and disodium hydrophosphate were acquired from Life Science, Germany, while domperidone was a gift from Medisure Pharmaceuticals, Pakistan.

Instruments

Electronic balance (Shimadzu, Japan), single punch compression machine (Shanghai, China), vernier caliper (China), hardness tester (Fujiwara, Japan), friabilator (Curio, Pakistan), FT-IR spectrometer (Germany), disintegration tester (Germany), dissolution tester (Erweka, Germany), UV spectrophotometer (UV-1800, Shimadzu, Japan), HPLC system pump (SPD-10AVP CBM 102, Shimadzu), column (Bondapak C-18 4.6 × 250 mm 10 µm Germany), ultrasonic bath (Germany), filter assembly (Millipore, England) and microliter syringe (Switzerland). pH meter, membrane filter (USA), and vacuum pump (China) were utilized.

Softwares

Software for Excel plugins MS Excel® was used to estimate before-and-after compression data, while DDSolver was used to analyze dissolution models [31].

Methodology

Micromeritic evaluation of blends

Micromeritic characteristics of powder blends were estimated through official methods. The following equations (1)–(5) were applied to estimate bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index, respectively [32]:

$$\text{Bulk density} = M/V_{bulk} \quad (1)$$

$$\text{Tapped density} = M/\text{-}V_{tapped} \quad (2)$$

$$\tan(\theta) = \text{height}/0.5\text{base} \quad (3)$$

$$\text{Hausner ratio} = (V_o/V_f) = (\rho_{tapped}/\rho_{bulk}) \quad (4)$$

$$\text{Carr's index} = 100 \times [(\rho_{tapped} - \rho_{bulk})/\rho_{tapped}] \quad (5)$$

Where M stands for weight in grams (g), Vbulk and Vtapped in milliliters (mL) for powder volumes before and after tapping, and Pbulk and Ptapped for bulk and tapped densities, respectively [32].

Preparation of tablets

In a polybag, HPMC K4M was combined in different ratios with Domperidone and Avicel PH 101 to create tablet formulation blends. The final ingredient was magnesium stearate, which was combined and compressed straight into a single-punch compression machine. The tablet weighed 150 milligrams in the end. Tablet composition is presented in **Table 1**.

Table 1. Domperidone matrices

Formulation code	Ingredients percentage (%)			
	Active ingredient	**Matrix former**	**Diluent**	**Lubricant**
	Domperidone	**Methocel K4M**	**Avicel PH 101**	**Magnesium stearate**
CF-1	23.33	20	55.33	1.3
CF-2	23.33	30	45.33	1.3
CF-3	23,33	40	35.33	1.3
CF-4	23.33	50	25.33	1.3

FT-IR analysis

FT-IR analysis of the domperidone drug and controlled release formulation was performed on an FT-IR Spectrometer by ATR technique.

Scanning electron microscopy (SEM)

A scanning electron microscope, or SEM (Japan), was used to assess the morphological characteristics of the optimized formulation (CF2).

Assay of domperidone

The domperidone content in matrices was determined by the following method [32].

Chromatographic conditions

A 0.2 µ membrane filter was used to filter and degas the mobile phase, which was made up of phosphate buffer and methanol (30:70 v/v). A UV detector with a sensitivity of 0.0001 was used to regulate the wavelength at 280 nm and set the flow rate at 1.0 mL/min.

Preparation of standard solution

10 mg of domperidone was dissolved in 50 ml of mobile phase to create the standard solution, which was then transferred to a 100 ml volumetric flask and diluted with mobile phase to reach a concentration of 20 mcg/mL.

Preparation of sample solution

Twenty tablets were precisely weighed, chosen at random to determine their average weight, and then ground into powder. A 50 ml volumetric flask containing mobile phase was filled with precisely weighed tablet powder equal to 10 mg of domperidone. The tablets were then shaken for approximately 15 minutes and filtered using Whatman filter paper. To get a final concentration of 20 mcg/ml, the filtered solution was further diluted with a mobile phase.

Quality characteristics of formulated tablets

Domperidone-formulated tablets were assessed for prerequisite quality parameters to establish and assess weight uniformity, crushing strength, friability, disintegration time, assay, and dissolution [33].

Weight uniformity

Each tablet of the randomly selected sample was weighed individually using an analytical balance. The mean and the standard deviation were calculated on MS Excel®.

Crushing strength: From each prepared experimental batch, a randomly chosen sample's crushing strength was thoroughly inspected and recorded. MS Excel® was used to calculate the mean and standard deviation.

Friability: Tablets chosen at random were weighed, put through a friability test, and then reweighed. Friability was then determined using the following formula:

$$Friability\ (\%)\ = \frac{W1 - W2}{W1} \times 100 \quad (6)$$

Where W1 and W2 are the initial and final weight of tablets, respectively.

Disintegration test: The test was conducted according to USP specifications at 37 ± 2 °C in 900 mL distilled water until the tablets disintegrated [33].

Swelling studies

A beaker containing 250 mL distilled water was taken and a single tablet from each lot was taken and immersed in it for 10 hours at ambient conditions. The swollen tablet was reweighed after every hour. The swelling ratio was calculated by using the equation:

$$\text{Swelling Index}\ = \frac{\text{W2} - \text{W1}}{\text{W1}} \times 100 \quad (7)$$

Weight of tablet before and after swelling denoted by W1 and W2 [34].

In-vitro dissolution studies

Using a USP dissolution apparatus type-II (Paddle device) rotating at 50 rpm and maintaining the dissolution medium temperature at 37 ± 0.5 °C, in vitro drug release was carried out. The samples were analyzed for 24 hours using 900 milliliters of phosphate buffer pH 6.8 as the dissolving medium. A 5 ml sample (replaced with a new dissolving medium) was taken at pre-arranged intervals of 30 minutes, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours to assess the drug release. A UV spectrophotometer was used to measure absorbance at 384 nm after the sample solution was filtered using a 0.45 µm Whatman filter. The mean of six pills was included in the cumulative drug release percentage calculation [35].

Dissolution profiles comparison

The similarity factor (f2) was calculated using the model-independent technique. The technique was used to compare the release kinetics of the formulations that were created (Eq. (8)). The logarithmic reciprocal square root transformation of the sum of squared errors yields the similarity factor or f2. It determines how comparable the two curves' percentage ages of dissolution are. The release is deemed equivalent if the reading falls between 50 and 100. Dissimilar dissolution kinetics are indicated by a declining value of f2 [35].

$$f_2 = 50 \times log\left\{\left(1 + {}^{1}/_{N}\sum_{t=1}^{n}(R_t - T_t)^2\right)^{-0.5} \times 100\right\} \quad (8)$$

Where Ti denotes the % of the drug under test, reference drug % is denoted by Ri, number of total samples is represented by N.

Results and Discussion

Table 2 presents the findings of the formulation blends' pre-compression properties.

Table 2. Pre-compression characteristics of domperidone blends

Formulation code	Mass	Bulk volume	Tapped volume	Bulk density	Tapped density	Hausner ratio	Carr's index	Angle of repose	Flow properties
	(g)	(mL)	(mL)	(g/mL)	(g/mL)		(%)	(θ)	(USP35-NF30)
CF-1	10	19	16	0.53	0.63	1.19	15.7	36.3	Fair
CF-2	10	19	17	0.52	0.58	1,11	10.3	33.2	Good
CF-3	10	17	14	0.58	0.71	1.22	18.30	44.1	Passable
CF-4	10	20	18	0.50	0.55	1.1	9.09	33.12	Good

Domperidone's FT-IR spectra were examined, and all of its distinctive peaks were seen. **Table 3** lists the formulations' assay findings and post-compression physical properties. According to USP's permitted range of variation of ± 5 mg, the weight uniformity results fell between 149.78 ± 1.82 and 153.21 ± 1.99 mg. Friability was within limits (less than 1%) for all formulations. The pills' crushing strength ranged from 8.91 ± 1.33 to 12.82 ± 1.68 kg, and their disintegration time was between 4.67 and 6.89 hours. According to assay results, formulations' drug concentrations ranged from 98.21-101.74%.

Table 3. Physical parameters and assay of domperidone matrices

Formulation code	Weight	Hardness	Friability	Disintegration time	Assay
	(mg)	(kg)	(%)	(h)	(%)
CF1	151.67 ± 1.36	8.91 ± 1.33	0.89	4.67	99.34
CF2	150.64 ± 1.53	12.82 ± 1.68	0.57	6.21	101.76
CF3	149.78 ± 1.82	11.45 ± 1.45	0.78	6.89	98.66
CF4	153.21 ± 1.99	11.23 ± 1.76	0.23	5.66	98.21

The results of the assay complied with USP specifications i.e. 95-105% [USP].

Swelling studies

Swelling studies were conducted to estimate the tendency of swelling in HPMC matrix formulations. The Swelling behavior of formulated tablets is indicative of the release behavior of tablets. The hydration of domperidone formulations showed that the swelling percentage increased with ascending concentrations of Methocel® in formulations. The polymer concentration decides the fate of release because the higher the concentration of polymer the lesser the drug release.

Scanning electron microscopy (SEM)

The SEM of the optimized formulation showed uneven surfaces and grooves as shown in **Figure 3**.

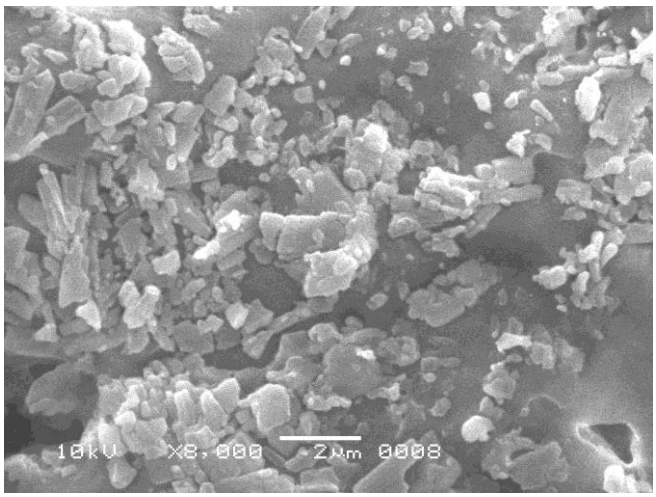


Figure 3. SEM of optimized formulation CF2

Dissolution studies

At various time points, the drug release pattern from CR formulations was examined. As seen in **Figure 4**, release profiles were examined at pH values of 1.2, 4.5, and 6.8. The CF2 (30% polymer) release profile was 19% at 4 hours, 73% at 16 hours, 80% at 18 hours, and 91% at 24 hours. A higher polymer concentration produced sufficient release control. Gel layer development and subsequent erosion are caused by higher polymer concentrations. Other teams also observed the same polymer behavior with CR pills. **Figure 4** displays the release profiles. The zero-order kinetics were followed by the release pattern. According to **Figure 4** of the current investigation, the release profiles of two formulations—CF2 and CF3—were similar, whereas the others were not.

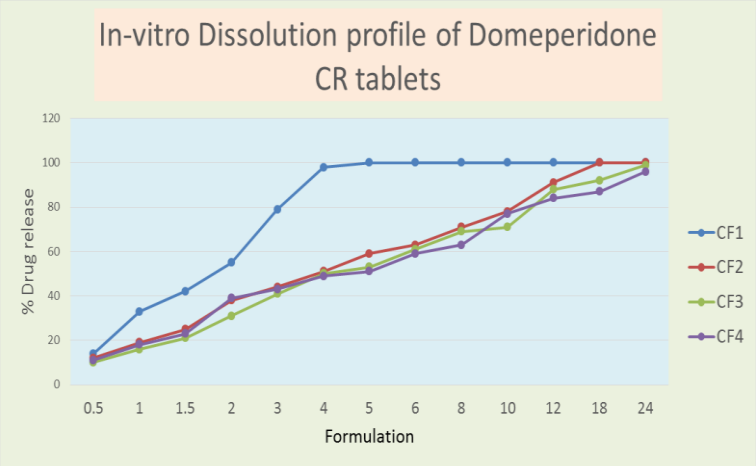


Figure 4. Release profile of domperidone controlled release matrix tablets

Conclusion

Domperidone was created and estimated for several quality control tests, assays, and dissolutions using a sustained releasing and acting formulation. The results showed that because of the higher viscosity grade caused by excess entanglement of a polymer, the formulation containing 30% Methocel® K4M provides the necessary drug release pattern and pace. The optimized formulation can be used once daily to treat nausea and vomiting. Additionally, it is economical and would have resulted in patient compliance.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: In-vitro testing of the formulated tablets was performed and no animal or human testing was conducted. An ethics statement is not required for such analysis.

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