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CONTROLLED RELEASE OF AN ANTI- EMETIC AGENT FROM A POLYMERIC MATRIX: FORMULATION AND *IN-VITRO* STUDY

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ABSTRACT

The objective of the present study was to develop once daily controlled-release matrix tablets of Domperidone Maleate, an anti- emetic agent. Several formulations containing an anti- emetic agent (domperidone maleate) and hydrophilic polymers (Hydroxypropyl methylcellulose, Carbopol and Polyethylene oxide) were prepared by wet granulation methods. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability and *in-vitro* release studies. All the tablet formulation showed acceptable pharmacotechnical properties and complied with in house speciation for tested parameters. The results of dissolution studies indicate that formulation FH2 (Drug to HPMC, 1:0.50; purified water as granulating agent) could extend the drug release upto 24 hours. All the formulation exhibited diffusion dominated drug release.

INTRODUCTION: Domperidone maleate is used as anti-emetic in the treatment of some forms of nausea and vomiting by increasing the gastro intestinal motility. It is slightly water-soluble drug and is rapidly and almost completely absorbed from GIT, following oral administration, but undergoes first pass and gut wall metabolism. Through hydroxylation and oxidative N-dealkylation, Domperidone is metabolized to hydroxydomperidone and 2, 3 dihydro- 2 oxo- 1- H-benzimidazole 1- propionic acid respectively [1].

The biological half-life of the drug is 7.5 hr time of peak plasma concentrations occurs about 30 min. after the oral dose [2]. It is typically administered three or four times daily 15 to 30 min before meals, in the form of conventional tablets thus frequent administration leads to a constant change in blood concentration. To overcome the frequent administration and to minimize the peak- to- trough oscillation of blood concentration, sustained release formulation is developed [1, 3].

Multilayered tablet concept has long been utilized to develop prolonged release formulation such a tablet has fast releasing layer and may contain one (bi-layered) or two (triple) layers, to prolong the drug release. The Pharmacokinetic advantages relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state, as the drug is released from the sustaining layer [4-7].

Recently, numerous hydrophilic polymers have been investigated and are currently used in the design of controlled release formulation.

Hydroxypropyl methyl cellulose (HPMC), Carbopol and Polyethylene oxide (PEO) have been widely studied for their application in oral controlled release (CR) system [8, 9]. When in contact with water HPMC, Carbopol and PEO hydrates and form a gelatinous barrier layer around the tablet. The rate of drug release from the matrix is dependent on various factors such as type of polymer, drug, drug polymer ratio, particle size of drug and polymer and the type and amount of fillers used in the formulation [10, 11].

Hence in the present work, an attempt has made to develop once daily controlled release matrix tablets of Domperidone maleate using putative hydrophilic matrix materials such as HPMC, Carbopol and Polyethylene oxide.

MATERIALS AND METHODS: Domperidone maleate was obtained as a gift sample from Morepen Lab. Solan (H.P.), India. HPMC (K-100) was purchased from Colorcon Asia Pvt., Ltd. Mumbai. Carbopol was procured from Noveon Asia Pacific Ltd., Hong Kong. Lactose IP was obtained from Lactose India Ltd. Baroda. Magnesium stearate was procured from Anupam Pvt. Ltd. Polyethylene oxide was obtained from Union Carbide U.S.A. Microcrystalline cellulose was procured from Rank Pharma, Nasik. All the materials were used as received. All the other chemicals used were of high analytical grade.

Preparation of Matrix Tablets: The matrix tablets were prepared by wet granulation. The drug polymers and other excipients used were passed through sieve no. 80 before their use in the formulation. Then layer with sustaining dose was formulated with various amounts of different polymers. The dose in the formulation for fast release was 10 mg. The maintenance dose or sustaining dose of domperidone maleate was calculated as per reported method [12, 13].

Formulation of Fast Release Layer: The fast release layer was formulated by mixing domperidone maleate, uniformly with microcrystalline cellulose by following the formulae as per **Table 1**. Granulation was carried out by wet granulation method by adding sufficient quantity of purified water. The granules were mixed with talc and aerosil.

TABLE 1: FAST RELEASE LAYER OF THE FORMULATION

Ingredients	Quantity for single tablets (in mg)
Domperidone maleate	10.0
Microcrystalline cellulose	37.5
Talc	02.0
Aerosil	00.5

Formulation of Sustaining Layer: Granules for sustaining layer were prepared by mixing maintenance dose Domperidone maleate, with matrix materials (Hydroxypropyl methyl cellulose, Carbopol and polyethylene oxide) following the formula given in **table 2**. The powders were granulated using sufficient quantity of purified water till a wet mass was formed. The cohesive mass obtained was passed through sieve no. 16 and the granules were dried at 40°C.

The dried granules were again sieved by passing through sieve number 24. The granules were mixed with talc, magnesium stearate and aerosil. The required amount of granules for fast release layer compressed lightly using a 10- station- tableting machine using 7mm round s/c punch. These compressed tablets (fast release) were put over the required quantity of granules prepared for the sustaining layer and compressed with maximum force to form a bi-layered tablet (Table 2).

TABLE 2: SUSTAINING LAYER OF THE FORMULATION

Ingredients (mg/tablet)	FC1	FC2	FC3	FH1	FH2	FH3	FP1	FP2	FP3
Domperidone maleate	20	20	20	20	20	20	20	20	20
Lactose Monohydrate	71	66	61	71	66	61	71	66	61
Carbopol 71G	5	10	15	-	-	-	-	-	-
HPMC K-100	-	-	-	5	10	15	-	-	-
PEO (WSR-303)	-	-	-	-	-	-	5	10	15
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Evaluation of the Formulation: Flow properties of the prepared granules were evaluated. Other properties of the granules evaluated were bulk density, true density, apparent density and porosity, using standard reported methods [14]. Hardness and friability of the tablets formulated were evaluated using a Monsanto hardness tester and a Roche friabilator respectively [15].

***In- Vitro* drug release study:** The *in- vitro* dissolution studies were carried at using USP-II apparatus at 50 rpm. The dissolution media consisted of 0.1 N hydrochloric acid for the first 2 hours and phosphate buffer pH 7.4 from 3-24 hours (900 ml), maintained at 37°C ± 0.5°C. Samples of 5 ml each were withdrawn at appropriate time intervals throughout the dissolution study of 24 hours, for analysis. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium, the drug release at different time intervals was measured by UV- spectrophotometer at λmax 280 nm [3, 16, 17].

RESULT AND DISCUSSION: Over the last few years a large number of hydrophilic polymers were evaluated as release retardants since they are non-toxic, biocompatible and cheaper. The composition of immediate release layer of matrix tablet as shown in table 1 is constant for all the formulations. However the composition of sustaining layer (table 2) differs only in drug to matrix material (HPMC, CP and PEO) ratio. The matrix tablets were round shape, s/c with diameter 7 mm. The hardness of tablets ranged from 3.17-3.93 Kg/cm². The percentage friability of all the formulations was between 0.06- 0.10 %. The values of hardness test and percentage friability indicates good handling property of the prepared bi-layered tablets. The drug content of the formulations was uniform (> 98.83) in all the cases.

The release of Domperidone maleate from the prepared formulations was analyzed by plotting the cumulative percent drug release vs. time (h) shown in fig. 1-3. Simple visual observation of the plot shown an initial burst effect from all formulations our 30% of Domperidone maleate was released within the first hour of dissolution study. The initial high amount of Domperidone maleate release can be attributed to release of drug from immediate release layer of the formulations. However, further release of Domperidone maleate from the formulation was sustained for 24h. It is known that HPMC retards the dissolution rate and it was observed that as the amount of HPMC increased, the dissolution rate decreases [18]. Hence, formulation FH_2 shows the desired release rate and consider as best formulation. The analysis of regression value indicated that mechanism of drug release was primarily by diffusion [19].

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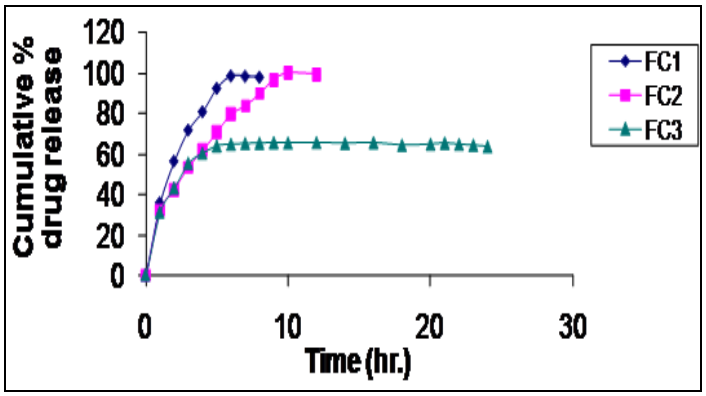

FIG. 1: RELEASE PROFILE OF FORMULATIONS FC1, FC2 & FC3

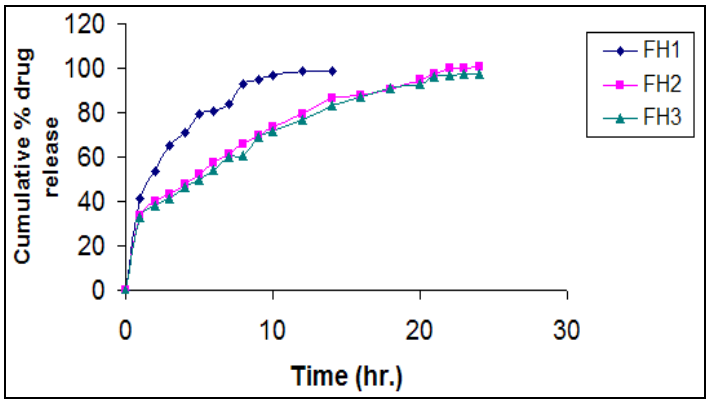

FIG. 2: RELEASE PROFILE OF FORMULATIONS FH1, FH2 & FH3

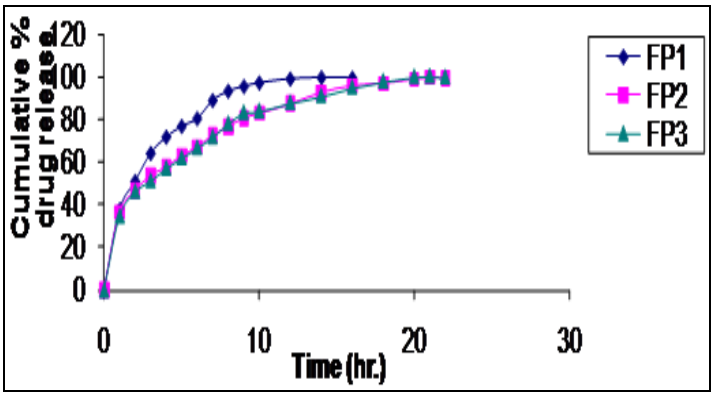

FIG. 3: RELEASE PROFILE OF FORMULATIONS FP1, FP2 & FP3

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