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DESIGN AND EVALUATION OF A METRONIDAZOLE CENTRAL CORE MATRIX TABLET

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Abstract

In this paper, a study of different concentration of HPMC K 15 M exerts influence on the drug release process from a new controlled drug delivery system has been realized in order to obtain a constant release rate during a prolonged period of time, for a programmed drug release. The drug release profiles obtained for the different batches have shown an interesting relationship between the particle size of the channeling agent used and the length of different operational periods.

Keywords: Matrix, Metronidazole, Controlled drug delivery system, Tablets

Introduction

The main objective of controlled release drug delivery systems was to ensure safety and to improve efficacy of drugs as well as patient compliance. So, they are designed to provide a therapeutic amount of drug on the specific-site of absorption, and then to maintain the desired drug concentration [1]. This idealized objective constitutes the most important aspect of drug delivery, namely, *spatial placement* and *temporal delivery* of a drug. In recent years, numerous controlled release systems using alternative routes have been designed. However, the oral route still remains as the most desirable one. So, the bulk of research is directed to oral dosage forms: it allows complying with the temporal aspect of drug delivery. On the other hand, modeling of controlled release of a water-soluble drug from matrix systems has been widely

investigated [2, 3, 4]. The use of drug delivery formulations based on porous or 'channeled' polymeric materials has led to re-evaluation of the existing models. In this sense, the mathematical description of the different designs proposed by Higuchi [5], allows us to assume that it is different designs proposed by Higuchi, allows us to assume that it is not possible to obtain a zero-order release kinetic with classical geometries (slab matrix or tablet) and using an inert polymer as matrix excipient. Numerous systems have been designed with the objective of obtaining a constant release rate over a period of time [6, 7, 8, 9, 10]. This phenomenon can be attributed to the saturation of drug into the water filled pores of the matrix. Under these conditions, the dissolution rate becomes slower than the rate of diffusion and determines the release kinetics of the process. In this work, an inert system has been designed. The release kinetic of such device, a matrix tablet containing a centralized drug core, was examined. [11]

The different lag-times found are relevant to design a system which permits to release the drug along the gastrointestinal tract.

Materials

Metronidazole was provided as a gift sample by Medioral Pvt. Ltd. (Satara, India). Hydroxylpropyl methyl cellulose (HPMC K 15 M) and Sodium bicarbonate was purchased from SD-Fine Ltd. (Bangalore, India) and Micro crystalline cellulose (MCC) stearic acid and talc from Cosmo Chem. (Pune, India). Succinic acid and Magnesium stearate were obtained as a gift sample from Signet Chemical Corporation (Mumbai, India). All chemicals used were of analytical grade.

Preparation of the Metronidazole central core matrix tablet

The matrix tablet contained a mixture of drug Metronidazole 200mg, polymer, Succinic acid, microcrystalline cellulose, magnesium stearate. The polymer grade was selected, i.e. HPMC K15 M. Rapidly disintegrating core tablets (average weight 200 mg) of metronidazole were prepared by the direct compression technique. Each core tablet consisted of metronidazole (100 mg), MCC, Succinic acid, Magnesium Stearate. All ingredients were passed through a 150 µm sieve, thoroughly mixed and compressed into tablets, using 6mm round flat faced punches. After passing the quality control tests of drug content uniformity, hardness, friability, disintegration and dissolution rate, core tablets were compression coated using HPMC K 15 M (p.s. < 150 µm). Half the quantity of the coating material was placed in a 12 mm die cavity, the core tablet was carefully positioned in the centre of the die cavity, the other half of the coat was added and compressed using 12 mm round concave punches that have been

surface lubricated with magnesium stearate talc mixture. [13, 11]

The thickness of the core and coated tablets was determined using a micrometer. The coat thickness was taken as half the difference between the core and coated tablet thickness. All the tablet formulations under study were assessed for their drug content uniformity, hardness and *in vitro* drug release. [13]

1- Evaluation of Granules

a- Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated. [14, 15]

b- Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index. [14, 15]

c- True Density

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V bulk) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space. [14, 15]

2- Evaluation of Tablets

a- Thickness

The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated. [16, 17]

b- Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado), and the test was performed according to the official method. [16, 17]

c- Drug Content

Five tablets were weighed individually, and the drug was extracted in water. The drug content was determined as described above. [16, 17]

d- Hardness and Friability

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively. [16, 17]

e- *In-vitro* drug release studies

The dissolution medium consisted of 900 ml 0.1 mol/l HCl for 2 h, then replaced by 900 ml phosphate buffer, pH 6.8 for 3 h, kept at 37 ± 0.5°C and stirred at 100 r/min, using USP dissolution apparatus 1. Samples were withdrawn at specified intervals (2 h and 5 h), filtered and assayed spectrophotometrically for metronidazole, at 320 nm. To assess the susceptibility of the prepared metronidazole delivery systems to the enzymatic action of colonic bacteria, drug release studies were continued in PBS pH 6.8 in the absence (control) and presence of rat caecal contents since these are known to have similar contents to those of human intestinal microflora [17, 21, 22]. After completing the dissolution in 0.1 mol/l HCl (2 h) and phosphate buffer, pH 6.8 (3 h), baskets containing the tablets under study, were immersed in the PBS medium and the release study was continued for up to 24 h. Samples were withdrawn at different time (6, 8, 12 and 24 h), filtered using membrane filters (0.45 μm) and assayed spectrophotometrically for metronidazole at 320 nm. Experiments were carried out in triplicate. [16, 17, 15]

Stability studies

To assess the long-term stability, selected metronidazole delivery systems were stored at ambient temperature (25°C) and 40% RH for 2 months, and assessed for any change in physical properties and drug release, at a sampling frequency of 15 days. Drug release studies were conducted under conditions mimicking mouth-to-colon transit, in the absence of rat caecal contents, as described above. [18]

Results and discussion

Metronidazole matrix tablets (F1-F5) (Table 1-2) are prepared in the present study complied with the official requirements for the drug content uniformity test and showed an acceptable mechanical strength (friability < 1%, hardness values in the range of 4–8 kg, (Table 3). The ability of the various delivery systems, under study, to protect the drug in the physiological environment of the stomach and small intestine and allow its release into the stomach was assessed by carrying out drug release studies in 0.1 mol/l HCl for 2 h, pH 7.4 buffer for 3 h and PBS pH 6.8 in the absence (control) for 12 h.

The results can be interpreted on the basis of the HPMC ratio. In this sense, it concluded that for matrix tablets formulated with different ratio of HPMC with respect to other formulations, the release profile constitutes an interesting model which permits to explain phenomena associated to the dosage form. In recent years, various theories have been applied to study the release mechanism and the biopharmaceutical properties of inert matrix tablets. The present investigation was undertaken to design, formulate and evaluate

metronidazole matrix tablets for sustained release dosage form. IR studies indicated good compatibility between drug, polymer and excipients.

The granules of different formulation were evaluated for loose bulk density, tapped bulk density and compressibility index. The results of loose bulk density, tapped bulk density and compressibility index are shown (Table 3). The result of compressibility index was between 11.42±0.03 to 13.35±0.03, which is below 15%, indicating well to excellent flow properties.

All tablet formulations were subjected to various evaluation parameters and the results obtained were within the range (Table 3, 4). The weight variation test indicates that all the tablets were uniform with low standard deviation values.

Table 1: Formulation of Matrix Tablets

Components	Composition (mg)				
	M1	**M2**	**M3**	**M4**	**M5**
Metronidazole	120	120	120	120	120
MCC	280	280	280	280	280
HPMCK15 M	33	43	53	63	73
Succinic acid	100	100	100	100	100
Magnesium Stearate	2	2	2	2	2

Table 2: Formulation of Core of Tablets

Components	Core Composition (mg)
	C1
Metronidazole	120
MCC	260
Succinic acid	50
Magnesium stearate	2

Table 3: Physical evaluations of granules

Formulation Code	Loose bulk density (LBD) (g/ml)	Tapped bulk density (TBD) (g/ml)	Compressibility Index (%)
F1	0.461±0.04	0.530±0.02	13.35±0.03
F2	0.472±0.05	0.543±0.03	12.45±0.032
F3	0.479±0.04	0.547±0.04	14.21±0.06
F4	0.486±0.04	0.550±0.05	11.42±0.03
F5	0.512±0.03	0.555±0.04	12.84±0.05

The thickness values ranged from 3.52±0.47 to 3.72±0.38 mm. The hardness of all the tablets was between 5.4±0.9 to 5.9±0.6 kg/cm2. The loss in total weight in friability test was in the range of 0.20 to 0.25%. The percentage drug content for different tablets formulations were varied from 99.8±0.4 to 101.2±0.5 indicating the uniformity in drug content as shown (Table 4).

Table 4: Physical evaluations of compressed

matrix tablets

Formulation Code	Drug content (%)	Friability (%)	Hardness (kg/cm2)	Thickness (mm)
F1	99.8±0.4	0.20	5.4±0.9	3.59±0.41
F2	99.5±0.9	0.25	5.5±0.5	3.65±0.47
F3	99.7±0.6	0.21	5.9±0.6	3.62±0.33
F4	101.2±0.5	0.23	5.5±0.7	3.52±0.47
F5	99.8±0.5	0.24	5.5±0.5	3.72±0.38

An inverse relationship was observed between concentration of polymer and release rate of Metronidazole from the matrix tablets. The selected formulation M4 was subjected to curve- fitting analysis using the software, 'Prism', version 3.0. The results are given (table 5). It can be interpreted from the analysis that the probable mechanism for drug release from these tablets followed higuchi model which is characterized by diffusion of the drug accompanied by chain relaxation of the polymer.

In vitro release studies

Fig. 1 illustrates the effect of HPMC K 15 M concentration on the release of metronidazole from matrix tablets. As the concentration of HPMC increased from (F1) to (F5) w/w, the rate of drug release fell relatively. Also a relative reduction in the extent of drug release was observed. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. HPMC used in hydrophilic matrix drug delivery systems has been employed to formulate sustained release tablets of Metronidazole. The hydration rate of HPMC depends in the nature of these substitutions.

Table 5: Curve fitting analysis of best formulation

Zero order Model	
K	9.62
R2	0.7453
Koresmeyer-peppas Model	
K	23.05
N	0.54780
R2	0.994
T 0.5	3.554
Higuchi Model	
K	29.32
R2	0.997
T0.5	3.152

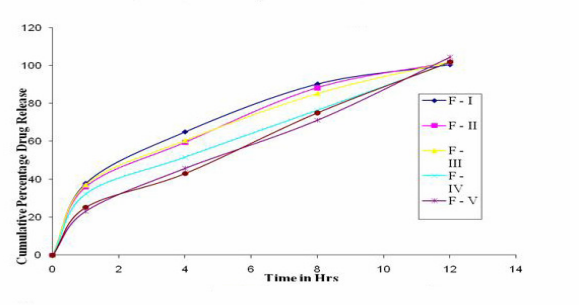

Fig.1- *In- vitro* release profile of Metronidazole compressed core tablets

The hydration rate of HPMC increase with an increase in the Hydroxy Propyl content. The solubility of HPMC is pH independent [11,

12]. HPMC forms a strong viscous gel on contact with aqueous media which may be useful in controlled delivery of highly water soluble drug. respect rates and ascertain whether it release the drug in a predetermined manner [12] according to the theoretical sustained release profile an sustained release formulation of Metronidazole should provide a release of 23.2% in 1 h, 45.8% in 4 h, 71.2% in 8 h and 104.4% in 12 h. formulation V tablets gave release profile near to theoretical sustained release needed for Metronidazole. The lag-time required for the hydration of HPMC form the gel layer around the tablets was also an important factor in this respect. Drug diffusion through the gel layer and erosion of the gel may be regarded as the rate-limiting steps for further drug release occurring in HCL, and buffer pH 6.8. The use of mixtures of polymers represents a potential way of achieving the required release properties. Mixtures of polymers have been used previously to give different viscosity efficiencies and provide delivery systems with modified drug release. In the present study, MCC, HPMC mixtures were used to prepare metronidazole matrix tablets (F1, F2, F3, F4 and F5, respectively) with total polymer content (Table 1). The prepared tablets showed a significant ($P < 0.005$) delayed drug release. The integrity of the tablets was maintained during the dissolution study and a thick hydrated gel layer was formed. Metronidazole release profiles can be considered as being composed of two parts. The first part involves the drug release during establishment of a fully hydrated gel layer and the second involves the release through this hydrated layer. At the beginning, the matrix tablets allowed the free dissolution of metronidazole directly in contact with the dissolution medium (0.1 mol/l HCl). In pH 6.8 medium, tablets showed lower release profiles, compared with release in HCL, indicating hydration of the mixed polymers and formation of a stable gel layer. A combination of the MCC with HPMC seems to produce a synergistic increase in viscosity. This may be attributed to the stronger hydrogen bonding between the carboxyl groups of pectin and the hydroxyl groups of HPMC, leading to stronger physical cross-linking between the polymers. Mechanical erosion of the swollen layer then occurs, allowing further hydration and swelling of the polymer and further drug release [16]. However, multilayer tablets are unable to protect the tablet cores from premature drug release in the physiological environment of the stomach and small intestine.

Stability studies

The selected formulations F 4, F5 were stored in closed glass containers on the shelf, at 25°C/ 40% RH for 2 months. The protocol of

the study was in accordance with the recommendation in the WHO document for stability testing [8]. At each sampling time (every 15 days), the formulations were tested for their mechanical strength, drug content and *in-vitro* drug release. There was no significant ($P > 0.05$) difference occurred in the cumulative percent of metronidazole released, after 14 h, from the formulations during the storage period of 2 months, when compared with that released from the same formulations before storage. In addition, no changes in drug content and mechanical strength of all the tablet formulations were observed during the storage period.

Conclusion

In conclusion, the results which derived from the release pattern of compressed tablets in the dissolution test indicate that the system designed permits to target drugs to different parts of the gastrointestinal tract as a function of the lag-time achieved. However, further investigations have to be realized in order to improve the system, and to study other variables such as, hardness, friability, compressibility index, drug content, wt variations etc.

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