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FORMULATION AND RELEASE CHARACTERISTICS OF NOVEL MONOLITHIC HYDROXYL PROPYL METHYL CELLULOSE MATRIX TABLETS CONTAINING METRONIDAZOLE

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ABSTRACT

Monolithic matrix tablets of metronidazole were prepared using hydroxyl propyl methylcellulose (HPMC), Starch 1500 (Prejel®), sodium lauryl sulphate (SLS), microcrystalline cellulose (Avicel® PH101) and sodium dihydrogen phosphate (NaH_2PO_4) as excipients. Sustained release matrix tablets containing 500 mg metronidazole were developed using different drug polymer ratios of hydroxyl propyl methylcellulose. The m-HPMC tablets were prepared using a wet granulation method followed by direct compression. Sustained release matrix tablets were found to be highly influenced by amounts of m-HPMC polymer incorporated. Results show that granules can be used to prepare tablets in terms of micromeritic properties and flow behavior. Findings of the results show that BatchF1 have maximum drug release while F6 have minimum drug release. It can be concluded from the obtained results that as the concentration of HPMC increases, %drug release decreases.

KEY WORDS

Metronidazole, sustained release tablets, HPMC, micromeritic properties, drug release.

INTRODUCTION

Metronidazole is a nitroimidazole antibiotic medication used mainly in the treatment of infections caused by susceptible organisms, particularly anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal [1]. It is well absorbed orally with a plasma elimination half-life ranging from 6–7 hours. Because of its short elimination half-life, the controlled release of metronidazole from numerous matrix-type and polymeric-coated formulations has been widely investigated [2]. These controlled release dosage forms can prolong antibiotic, amebicide, and antiprotozoal effects by maintaining average plasma concentrations of metronidazole. The m-HPMC tablets of metronidazole would more effective for patients as these characteristics would allow a rapid onset followed by prolonged antibiotic,

amebicide, and antiprotozoal action. Hydroxyl propyl methylcellulose (HPMC) is used in the formulation for controlled release because of its hydrophilic gel-forming property, non-toxicity, cost effectiveness and its wide pharmaceutical applicability [3, 4]. The swelling rate and erosion of m-HPMC-based matrix tablet in aqueous media show desired release profiles, although the sustained release profile are also affected by numerous other parameters such as the physicochemical properties of the polymer and drug [5], processing conditions, the testing medium used and the formulation composition. The other pharmaceutical excipients such as surfactants, diluents, lubricants, disintegrants and polymers are used in the preparation of m-HPMC matrix tablets to modify drug release profiles.

The objective of this study to prepare sustained release metronidazole tablets using HPMC as polymer. Due to hydrophilic nature of HPMC it can be assumed that drug release may be sustained in terms of drug release profile and swelling behavior of polymer.

MATERIAL AND METHODS

***Materials*:** Metronidazole, microcrystalline cellulose (Avicel®), corn starch 1500 (Prejel®), hydroxy propyl methyl cellulose, (HPMC), magnesium stearate and colloidal silicon dioxide (Aerosil®200), surfactant (sodium lauryl sulphate SLS) and Sodium dihydrogen phosphate (NaH_2PO_4) are purchase from Central Drug House (p) Ltd New Delhi.110002 India.

Preparation of HPMC tablets: Matrix tablets, each containing 500 mg metronidazole and weighing 650 mg were prepared by wet granulation and direct compression techniques using in combination with HPMC as matrices (Table 1). Drug, HPMC polymer and other preparation excipients (except the lubricant) of m-HPMC tablets were mixed thoroughly with a pestle and mortar. Ethanol was added to this mixture drop wise with continuous mixing. Tablet formulations (F1–F6) were blended and granulated with other excipients. The wet mass was passed through a mesh (20 µm) sieve and the granules were dried at 35-45℃ for 6 h. The dried granules were compressed on a single-punch tablet machine, using 12 mm round punches [6]. The detailed formulation compositions used to prepare m-HPMC tablets with metronidazole (500 mg) are given in Table 1.

Table 1.
Composition of HPMC Tablet of Metronidazole (500mg)

SNo	Ingredients/ Formulations	F1	F2	F3	F4	F5	F6
1	Metronidazole	500	500	500	500	500	500
2	Hydroxy Propyl Methyl Cellulose	50	50	70	70	90	90
3	Aerosil®	6	6	6	6	6	6
4	Lubricant(Magnesium Stearate)	4	4	4	4	4	4
5	Disintegrant (Prejel®)	30	50	30	50	30	50
6	Sodium Lauryl Sulfate	10	10	10	10	10	10
7	Avicel®	25	25	25	25	25	25
8	Sodium Dihydrogen Phosphate	2.5	2.5	2.5	2.5	2.5	2.5

Granules characteristics

***Moisture Content Analysis*:** One gram (1g) of the granules was put into a crucible and dried to

constant weight in a hot air oven at 105ºC. The moisture content (MC) was deduced as difference between the initial (Wo) and final weight (Wf) of the granules, expressed as a percentage and calculated as:

$$MC = \{(Wo-Wf)/Wo\} \times 100 \quad (1)$$

***Angle of Repose*:** Fifty grams (50 g) of the granules was placed in a plugged glass funnel which had a distance of 10cm from the flat surface. The granules were then allowed to flow through the funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (*h*) formed as well as the radius of the heap (*r*) was noted [7]. The angle of repose (*Q*) was calculated as;

$$Q = \tan^{-1} h/r \quad (2)$$

***Bulk and Tapped Densities*:** Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 5 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 50-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 2.0 cm at 2-second intervals. The tapping was continued until no further change in volume was noted [7]. LBD and TBD were calculated using the following formulas.

LBD = weight of the powder/volume of the packing

***Percentage Compressibility (Carr's index) and Hausner's ratio*:** The percentage compressibility (*CI*) was calculated from the difference between the tapped (*Dt*) and the bulk densities (*Bt*) divided by the tapped density and the ratio expressed as a percentage [7]. The Hausner's ratio (*HR*) is the ratio between the tapped and bulk density.

$$CI = [(Dt-Bt)/Dt] \times 100 \quad (3)$$

$$HR = Dt/Bt \quad (4)$$

Tablet Characteristics

***Weight Variation Test*:** Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight [6].

***Tablet Thickness*:** The thickness of ten tablets each selected at random from the formulated batches were determined using a digital vernier calliper (Mitutoyo) and the mean of these readings was taken as the mean tablet thickness [6].

***Hardness*:** The tablet hardness, which is the force required to break a tablet in a diametric compression force. The digital force gauge (Model: EL=500N, Electrolab) hardness tester wasused in the study [6].

***Friability*:** The friability of the tablets was determined using the Roche friabilator. Ten (10) tablets were weighed and put into the Roche friabilator and set to rotate at 25 rounds per minute for about four (4) minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. Friability below 1% was considered acceptable [6].

***Swelling behavior of sustained release matrix tablets*:** The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behaviour of all formulation was studied. One tablet from each formulation was kept in a Petridis containing pH 7.4 phosphate buffer. At the end of 0.083 h, the tablet was withdrawn, dried with tissue paper, and weighed. Then for every 0.25, 0.50, 1, 2, 4, 6 h, weights of the tablet were noted, and the process was continued till the end of 8 h. Percentage weight gain by the tablet was calculated by formula [6];

$$S.I. = \{(M_t-M_o) / M_o\} \times 100,$$

Where, S.I. = swelling index, M_t = weight of tablet at time t (h) and
M_o = weight of tablet at zero time.

***Drug content*:** The tablets were powdered, and 500 mg equivalent weight of Metronidazole in

tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH 6.6) was added and shaken for 10 min. then, the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered, and 1 ml of the filtrate was diluted and analyzed at 276 nm using UV-visible spectrophotometer (Shimadzu UV-2450, Japan). The drug content of the each sample was estimated from their standard curve.

***Disintegration Test*:** Six (6) tablets were placed in each compartment of the Erweka disintegration apparatus, with water thermo stated at 37 ± 0.5^{0}C as the medium.

***Dissolution test*:** *Invitro* drug release was studied using LabIndia dissolution apparatus, with 900 ml of dissolution medium maintained at 37±.5℃ at 50 rpm. 5ml of sample was withdrawn after every hour, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed by UV-visible spectrophotometer (Shimadzu UV-2450, Japan). At a measured wavelength of 276nm, and cumulative percent drug release was calculated. The study was performed in triplicate and result was recorded [6].

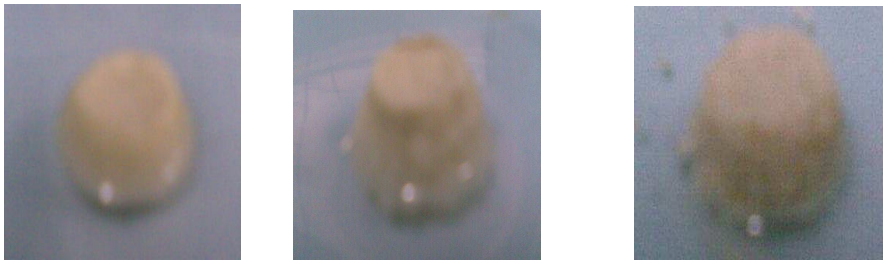
RESULTS AND DISCUSSION

The angle of repose as per the Table 2 was found to be possable (range 30-40) for all formulation. The % compressibility was found to be 12-16. All the tablets confirmed to the requirement of assay, as per USP. Hardness, percentage, friability, and thickness were all within acceptable limits. The disintegration time of metronidazole tablets were found to be more than 90 min. It was found that as the concentration of HPMC increases, disintegration time also increase.

Table 2.
Evaluation of Different Physical Parameters of granules.

S.No.	Parameters	Formulations					
		F1	F2	F3	F4	F5	F6
1	Moisture content	2.0 (0.06)	1.5 (0.08)	1.5 (0.12)	1.0 (0.04)	1.5 (0.03)	1.5 (0.05)
2	Bulk densities	14 (0.13)	13 (0.11)	15 (0.13)	14 (0.10)	14 (0.12)	13 (0.14)
3	Tapped densities	12 (0.11)	12 (0.14)	13 (0.15)	13 (0.12)	12 (0.16)	12 (0.12)
4	Compressibility index	16.66 (0.24)	8.3 (0.16)	15.38 (0.17)	8.69 (0.22)	16.66 (0.27)	8.3 (0.19)
5	Angle of repose	34.5 (0.16)	32.4 (0.10)	35.81 (0.13)	35.13 (0.13)	32.3 (0.17)	31.23 (0.09)

Sustained drug release was shown by all formulations in phosphate buffer (pH 7.4).The swelling index was calculated with respect to time [6, 8]. As time increases, the swelling index also increased, this is because weight gain by tablet was increased proportionally with rate of hydration up to certain limit (Figure1).



t= 0.50 h t= 4 h t= 8 h

Figure1

Swelling Index study of tablet (Batch F6)

Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and polymer concentration (HPMC), and as polymer concentration increases, swelling index was found to increase [6, 8, 9].

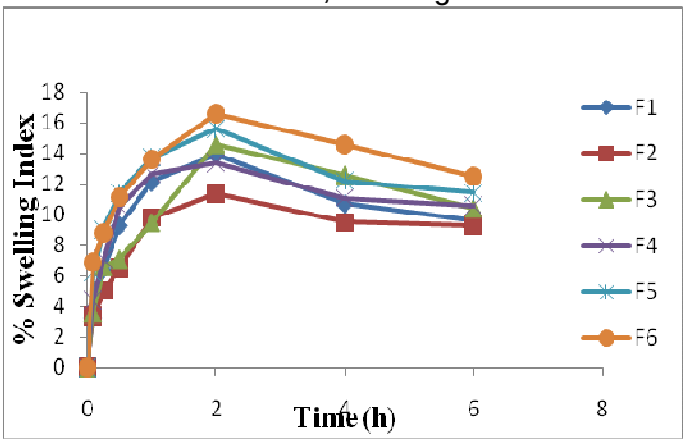


Figure 2

Swelling index profile for different formulation of tablets

It has been observed that the cumulative percent drug release decreases with increasing concentration of polymer and swelling index [10]. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of HPMC polymer. This slow release is because of the formation of a thick gel structure that delays drug release from tablet matrix.

Table 3.

Different physical and chemical parameter of formulated tablets

S.No.	Parameters	Formulations					
		F1	F2	F3	F4	F5	F6
1	Weight variation(mg)	627.5 (0.30)	647.5 (0.25)	647.5 (0.25)	667.5 (0.38)	667.5 (0.42)	687.5 (0.25)
2	Tablet thickness	4.14 (0.14)	4.11 (0.14)	4.19 (0.13)	4.44 (0.16)	4.34 (0.25)	459 (0.15)

3	Tablets diameter	12.08 (0.15)	12.07 (0.13)	12.04 (0.14)	12.04 (0.12)	12.05 (0.13)	12.09 (0.14)
3	Hardness(Kg/cm^2)	20.80) (0.12)	21.35 (0.21)	22.15 (0.12)	21.58 (0.16)	23.22 (0.18)	21.72 (0.14)
4	Friability (%)	0.091 (0.13)	0.833 (0.18)	0.82 (0.12)	0.82 (0.16)	0.81 (0.19)	0.82 (0.21)
5	% Drug Release	94.38 (0.20)	86.87 (0.26)	77.11 (0.19)	73.72 (0.17)	71.00 (0.27)	65.48 (0.31)

The *invitro* releases of metronidazole from different formulation were shown in Figure 2.
The concentration of polymer HPMC was increases the rate of release of drug from tablets were decreases. When concentration of HPMC was lower (50 mg) it releases maximum drug but as concentration of HPMC increases the rate of release drug consistently decreases [6, 8].
The release rate of metronidazole significantly depend on small amounts of SLS (10 w/w %).By decreasing the surface tension of the dissolution medium, SLS allowed more rapid and possibly more water penetration into the HPMC matrix. The SLS (surfactants) affect the different physical characteristics of tablets such as hydrophilic–lipophilic balance, melting points [9, 10], and solubility in the dissolution medium also influenced drug release rate.

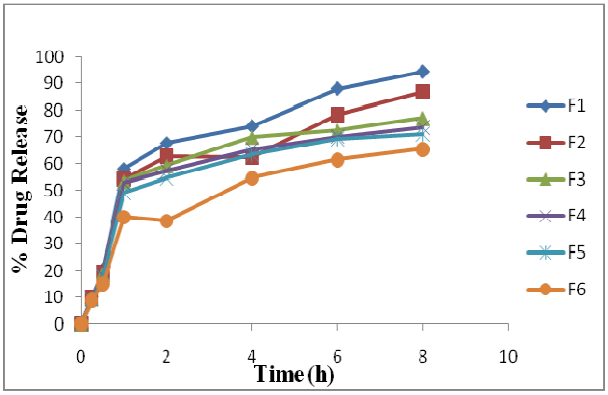


Figure 3. ***% drug release profile for different formulation of tablets***

The amount HPMC in formulation was also found to be a key factor in terms of controlled drug release rate [11]. It is widely known that high HPMC contents usually retard drug release [6, 12]. Therefore, we compared the effect of HPMC content on the drug release characteristics of m-HPMC tablets is shown in Figure 2. The release rate was found to gradually decrease as the amount of HPMC (50–70 mg) increased. As a viscous gel layer is formed, it will not only increase the diffusion path length but also the resistance to diffusion [6, 11, 13]. However, HPMC contents affected drug release rates. Thus, HPMC was found to play a key role in modifying the metronidazole release from m-HPMC tablets.

CONCLUSIONS

Sustained release matrix tablets of metronidazole were prepared successfully using HPMC as polymer which retard the release and achieve required dissolution profile. The types

and amounts of pharmaceutical excipients such as surfactant, disintegrants and solubilizers in m-HPMC tablets were found to crucially control metronidazole release characteristics. Release profiles were governed by water uptake, tablet erosion and diffusion in aqueous media. . It was also demonstrated that the release of drug metronidazole from HPMC matrix tablets could be modified by changing the type and amount of polymer in the matrix tablets.

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