DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(17), 1929-1939 (1995)

RESEARCH PAPERS

INFLUENCE OF TABLET FORMULATION AND SIZE ON THE *IN VITRO* SUSTAINED-RELEASE BEHAVIOR OF METOPROLOL TARTRATE FROM HYDROPHILIC MATRICES

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ABSTRACT

Metoprolol tartrate sustained-release tablets were manufactured in 2.8, 7.0 and 10.0 mm diameters. In order to achieve the sustained release of active ingredients, the hydrophilic cellulose polymers methylcellulose, hydroxypropylcellulose and sodium carboxymethylcellulose were used either alone or in combination. It was investigated, in particular, whether the mini-tablets encased in hard gelatine capsules as multiple units allow for the sustained release of the basic active ingredient, which is highly soluble in the acidic pH.

While a sustained release is possible from the 7.0 and 10.0 mm diameter tablets formulated on the basis of HPC and NaCMC mixtures, tablets with 2.8 mm diameter do not allow for an adequate control of metoprolol tartrate release during the gastrointestinal passage. Active ingredient release in the range of up to 80 % release and the tablet surface area above a minimum of approximately 300 mm^2 are correlated in a linear manner.

INTRODUCTION

Sustained-release tablets formulated on the basis of cellulose matrices have been used for over 30 years for controlling the release of active ingredients (1, 2). In water swellable cellulose ethers such as methylcellulose (MC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) (1, 3, 4) are used for this purpose.

As regards the in vitro dissolution behaviour of incorporated active ingredients, either a zero-order release profile (5) or a bimodal release profile (6) is desirable, depending upon the physicochemical characteristics of the active ingredient. Bimodal release is characterised by a rapid initial release, followed

by a period of constant release and then a second phase of rapid drug release. These release mechanisms are difficult to achieve with basic active ingredients (7, 8).

The in vivo efficacy of oral extended release formulations containing a basic drug may be limited by the variability in the solubility and dissolution rate of the drug at different pH values in the gastrointestinal tract, which can be too high in the gastric (acidic) pH with consequent possible problems in controlling drug release in the stomach. When the formulation reaches the neutral/basic pH values of the intestine, the solubility and release rate may decrease dramatically.

The problem can be solved by coating HPMC-containing tablets with enteric coatings (9) or by incorporating organic acids into the matrix and coating the tablets with sustained-release coatings (7). Other authors suggest using mixtures of HPMC and NaCMC (1, 3, 10).

Blending polymers is a potential way of achieving the required release properties. In addition to the possibilities offered by using polymers with different viscosities, blending non-ionic and ionic varieties in the correct proportions can lead to formulations of hydrosoluble active principles with zero-order release profiles. Constant release rates with mixtures of cellulose ethers of differing characteristics have their root in the formation of strong hydrogen bonds between the carboxyl groups of NaCMC, the ionic variety normally used, and the hydroxyl groups of the non-ionic cellulose ether (4).

Some of the studies performed with mixtures of ionic and non-ionic cellulose derivatives have the disadvantage that they describe relatively large single unit dosage forms which do not disintegrate in the gastrointestinal tract and whose gastrointestinal passage is usually subject to higher variabilities than that of smaller tablets (11, 12). Particle diameters of 2 mm were formerly considered to be the upper limit for the relatively rapid emptying of particles into the upper intestine independently from the contractions accompanying the migrating myoelectric complex (MMC) (13).

Recent studies suggest that the much discussed 2 mm cut-off size for the gastric emptying of indigestible solids during the digestive phase is not applicable to human beings. Indeed, it is probable that there will be no exact cut-off size per se, but rather a gradation of size making predictable emptying from the fed stomach uncertain and highly variable (14).

Some authors even suggest that tablets up to 7 mm in diameter can empty from the fed stomach in an apparently linear fashion. There is an increase in the variability of emptying as the tablet size increases in the 5 - 7 mm diameter

range, but no significant difference in gastric emptying due to the tablet size can be found (14).

The study at hand was performed with the aim of investigating the possibility of formulating mini-tablets for the basic active ingredient metoprolol tartrate using HPC or MC in combination with NaCMC for the zero-order or bimodal release of the active ingredient. Such mini-tablets, encased in hard gelatine capsules, would then allow for a more homogenous emptying from the stomach into the upper intestine due to the reduced effect of MMC.

MATERIALS

The active ingredient used was metoprolol tartrate (Mediolast SPA, Milan, Italy). The cellulose derivatives in Table 1 were used as matrix formers.

METHODS

The batch size was 100 g with 25.0 g metoprolol tartrate (MEP) and various amounts of excipients (Table 2).

Direct tableting

Composition No. 1 and 2:

The raw materials were passed through a 1000 μm sieve into an AR 400 Kubus mixer (Erweka, Heusenstamm, Germany). After blending for 15 min., tableting was performed with an EK 0 eccentric tableting machine (Korsch, Berlin, Germany). The punches used were 2.8 mm in diameter.

Both formulations showed inadequate flow characteristics. The addition of different concentrations of colloidal silicon dioxide (Aerosil 200, Degussa, Frankfurt, Germany) and magnesium stearate (Merck, Darmstadt, Germany) did not markedly improve the flow characteristics.

Wet granulation

Composition No. 3 to 8:

The raw materials were sieved as with direct tableting, mixed and subsequently granulated in a mortar by adding 30 g demineralised water. The wet mass was then dried for 12 hours at room temperature and desagglomerated first via a sieve of 1000 μm and then via one of 630 μm mesh width (Frewitt GLA ORV, Fribourg, Switzerland). Tableting was performed with an EK 0 eccentric press. The punches used were 2.8 mm, 7.0 mm and 10.0 mm in diameter.

TABLE 1

Cellulose derivatives used

Substance	Trade name	Viscosity [cps]
HPC	Klucel HF (Aqualon[1])	1500-3000 (1 %)*
	Klucel MF-NF (Aqualon)	4000-6000 (2 %)
NaCMC	Blanose 7H4XF	40000 (2 %)
	(Aqualon)	40000 (2 %)
MC	Methocel A4M Prem. EP (Colorcon[2])	3500-5600 (2 %)

(1) Aqualon, Düsseldorf, Germany; (2) Colorcon, Königstein, Germany
* 1 % aqueous solution

TABLE 2

Composition of the metoprolol tartrate (MEP) mini-tablets

Composition No.	g per batch				Ratio:
	MEP	NaCMC	HPC	MC	MEP :NaCMC : HPC : MC
			MF-NF		
1	25.0	45.0	30.0	-	1.0 : 1.8 : 1.2 : 0.0
2	25.0	60.0	15.0	-	1.0 : 2.4 : 0.6 : 0.0
3	25.0	60.0	15.0	-	1.0 : 2.4 : 0.6 : 0.0
4	25.0	60.0	-	15.0	1.0 : 2.4 : 0.0 : 0.6
5	25.0	30.0	45.0	-	1.0 : 1.2 : 1.8 : 0.0
			HF		
6	25.0	30.0	45.0		1.0 : 1.2 : 1.8 : 0.0
7	25.0	-	75.0	-	1.0 : 0.0 : 3.0 : 0.0
8	25.0	-	37.5	37.5	1.0 : 0.0 : 1.5 : 1.5

TABLE 3

Analytical trial conditions to determine MEP content and release

Pump system	SP 8810 [1]	Column press.: 200 bar	Flow: 1.0 ml/min	
Column	SAS Hypersil, No. 4 [3]	Column temp.: 30°C		
UV/VIS	SP 8450 [2]	: 230 nm	OD: 0.1	Time const. 0.1 sec
Mobile phase	- 80 parts by weight - 0.02 M Na_2HPO_4 sol. - 0.1% pentane sulphonic acid (adjusted with H_3PO_4 to pH 3.0) - 20 parts per weight Acetonitril			
Detection system	SP 4270 [4]	Atten.: 8		
Detection method	ESTD/area	Inj. volume: 20 μl	RT: 3.57 min	

[1], [2], [4] Spectra Physics Analytical, Darmstadt, Germany,
[3] Shandon, Cheshire, England

Analytics

The analytical trial conditions are shown in Table 3.

Sample preparation: -1 mini-tablet dissolved in demineralised water and stored overnight in a 200 ml volumetric flask, subsequently suspended with 1.5 ml 32 % HCL, filled up to volume and immediately transferred into a vial
-1 tablet 200 mg as above, but with 1 : 10 dilution
-1 tablet 400 mg dissolved in a 500 ml volumetric flask, suspended with 3 ml HCL 32 % and diluted 1:4.

The release of MEP was investigated using a DT 6-2 (Erweka), paddle, according to German Pharmacopoeia - DAB 10 - at a speed of 100 U/min in 900 ml test liquid 0.08 M HCl (pH 1.2) at a temperature of 37°C or at pH 6.8 (phosphate buffer USP XXII).

In the case of the 20 mg MEP-containing tablets, 10 mini-tablets were tested.

RESULTS AND DISCUSSION

Table 4 shows the target/actual MEP contents of tablets of different shapes and dosages for composition No. 5 and 6.

All tablets show swelling during the dissolution test. In the case of the mini-tablets (= 2.8 mm diameter), the uptake of water resulted, after approx. 15 - 30 minutes, with the formation of a transparent cylinder. In the 7.0 mm and 10.0 mm diameter tablets, a white core remained stable during the dissolution test over a prolonged period of time. While these tablets have not disintegrated even after 24 hours, the mini-tablets disintegrate after a 2 to 3 - hour contact with the dissolution medium. The tablets of composition 7 and 8 did not show the previously observed slow swelling, but disintegrated into small pieces after only 1 hour (comp. 7) or within 15 minutes (comp. 8) and rapidly dissolved thereafter.

Figure 1 shows a comparison of the MEP dissolution rates from 10 mini-tablets containing 5 mg metoprolol tartrate each at pH 1.2 and 6.8 (composition 3). The dissolution was much too rapid in both trials.

Figures 2 and 3 show the results obtained from compositions 5 and 6 at pH 6.8. From composition 4, the active ingredient release from all tablets was more rapid than that from the tablets of compositions 5 and 6.

From the formulations containing Klucel MF-NF, the sustained release of the active ingredient at pH 6.8 is observed only in the case of the 7 mm and 10 mm diameter tablets. An increase in the molecular weight (Klucel HF) does not further reduce the active ingredient release from the 2.8 mm and 7.0 mm diameter tablets, whereas the 10.0 mm diameter tablets show an almost linear active ingredient release at pH 6.8.

For the 10.0 mm diameter tablet, this confirms the results obtained by Ranga et al (3), who attribute the zero-order release rate to the formation of strong hydrogen bonds between the carboxyl groups of sodium carboxymethylcellulose and the hydroxyl groups of the non-ionic cellulose ether.

TABLE 4

Target/actual MEP content of the manufactured tablets

Composition No.	Tablet diameter	Tablet weight	Target content metoprolol tartrate	Mean content	SDR
	[mm]	[mg]	[mg]	[mg]	[%]
5	2.8	20	5.0	4.80	6.6
5	7.0	200	50.0	49.34	2.0
5	10.0	400	100.0	110.13	3.4
6	2.8	20	5.0	5.01	5.1
6	7.0	200	50.0	52.00	4.8
6	10.0	400	100.0	100.10	5.0

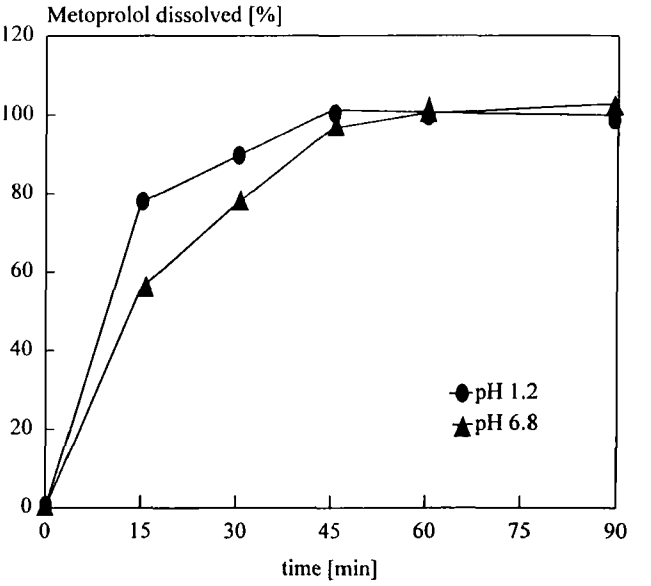

FIGURE 1

10 mini-tablets (according to composition 3) containing a total of 50 mg MEP.

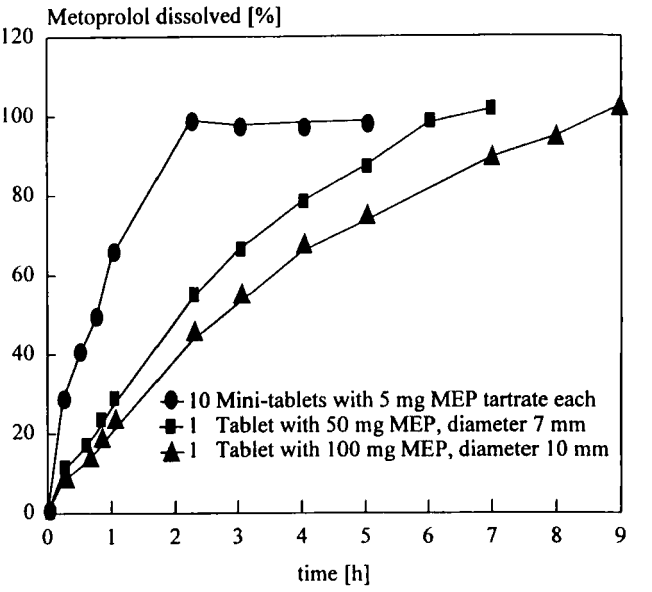

FIGURE 2

MEP release from tablets of different sizes and dosages formulated on the basis of NaCMC and HPC (composition 5).

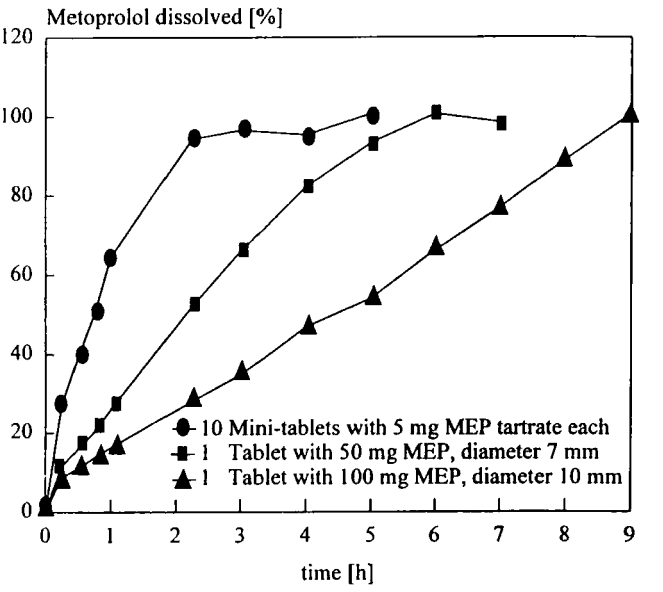

FIGURE 3

MEP release from tablets of different sizes and dosages formulated on the basis of NaCMC and HPC (composition 6).

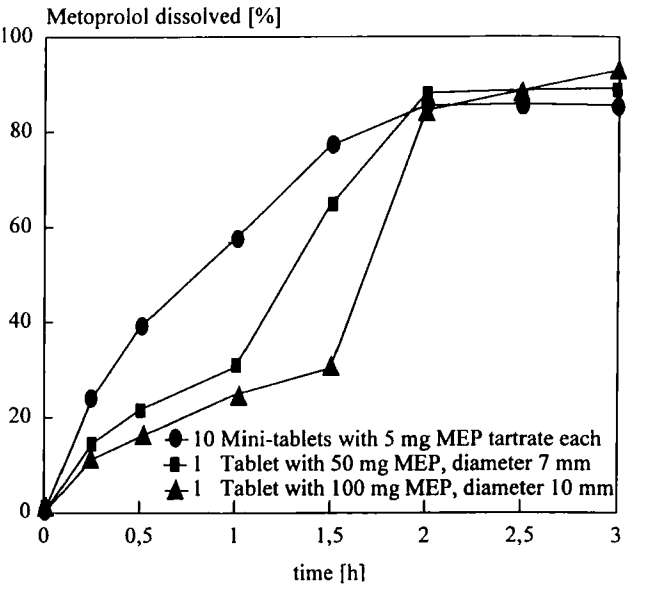

FIGURE 4

MEP release from tablets of different sizes and dosages formulated on the basis of HPC (composition 7).

Figure 4 shows the active ingredient release at pH 6.8 from tablets formulated solely on the basis of HPC. As described previously, the tablets disintegrate after approximately 60 minutes, resulting in a sigmoidal and generally too rapid release profile of the 7.0 and 10.0 mm tablets. While the release from mini-tablets is reduced compared to tablets of the same diameter containing NaCMC and HPC, this reduction is insufficient to allow for the sustained release of the active ingredient during the gastrointestinal passage.

From tablets of all 3 sizes containing identical amounts of HPC and MC (composition 8), the active ingredient is completely released within 60 minutes which is in accordance with the rapid disintegration of the tablets.

Figure 5 shows the ratio of the dissolution rate and tablet surface area (calculated as cylinder) (compositions 5 and 6). The dissolution rate of MEP with up to 80 % release from matrix tablets formulated on the basis of HPC and NaCMC shows a zero-order release profile. The dissolution rate and the tablet surface area are correlated in a linear manner above a minimum surface area of approximately 300 mm^2 .

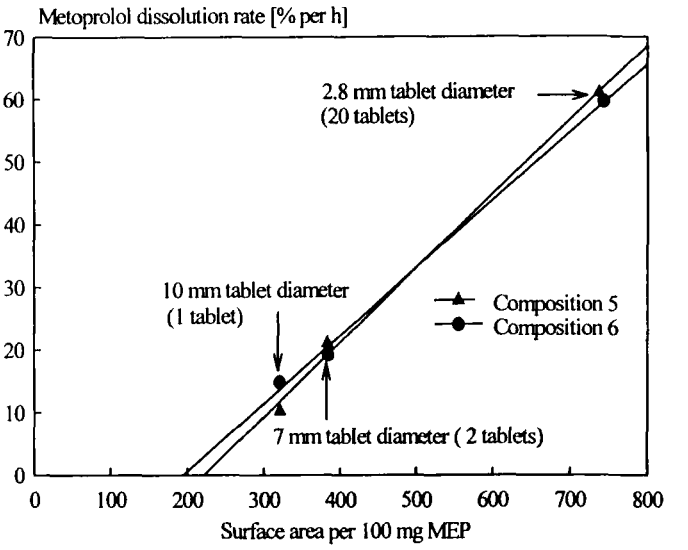

FIGURE 5

Ratio of dissolution rate and tablet surface area from tablets of different sizes and dosages formulated on the basis of HPC and NaCMC (compositions 5 and 6).

CONCLUSIONS

Matrix tablets formulated on the basis of HPC and NaCMC allow for the sustained release of metoprolol tartrate within a period of approximately 6 hours using the 7 mm diameter tablets and 9 hours for the 10 mm diameter tablets. NaCMC in combination with HPC of higher viscosity results in the zero-order release of the active ingredient from tablets with a 10 mm diameter. For the 2.8 mm diameter mini-tablets, none of the formulations used are sufficient to allow for the sustained release of the active ingredient during the gastrointestinal passage.

At up to 80 % active ingredient release, dissolution rate and tablet surface area are correlated in a linear manner for matrix tablets formulated on the basis of HPC and NaCMC above a minimum surface area of approximately 200 mm^2 .

Tablets formulated only with HPC allow for the bimodal release of the active ingredient within 2 to 3 hours, while tablets formulated on the basis of mixtures with MC permit a more or less spontaneous release of the active ingredient.

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