

THE INFLUENCE OF FORMULATION FACTORS ON THE RELEASE OF THE METOPROLOL TARTRATE FROM EXTENDED RELEASE TABLETS

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Abstract

The aim of this study was to formulate and evaluate oral sustained drug delivery systems for metoprolol tartrate using hydrophilic polymers. The matrix tablets were prepared with different types and ratios of polymers and diluents. The polymers selected for formulations were hydroxypropyl methylcellulose (HPMC) in concentration of 20%, 30%, alone or combined with sodium carboxymethylcellulose (CMC-Na) in 1:1 ratio. The diluents varied depending on the preparation technique: lactose monohydrate (Pharmatose 200M) for wet granulation method and microcrystalline cellulose (Avicel® 102), pregelatinized starch (Starch® 1500), agglomerated α -lactose monohydrate (Tablettose® 80) and calcium phosphate dihydrate for the direct compression method. The matrix tablets were evaluated for mass variation, friability, hardness, thickness, swelling index, and *in vitro* dissolution. The effect of some formulation variables on the release rate of metoprolol tartrate from polymeric systems has been investigated. The increasing amount of HPMC in the formulation led to a slow release of drug.

Rezumat

Scopul acestui studiu a fost formularea și evaluarea unor sisteme orale de cedare susținută pentru tartratul de metoprolol folosind polimeri hidrofilici. Comprimatele matriceale au fost preparate folosind diferite tipuri și proporții de polimeri și diluanți. În formulări s-a folosit hidroxipropilmetilceluloza (HPMC) în concentrații de 20%, 30%, singură sau asociată cu carboximetilceluloza sodică (CMC-Na), în raport de 1:1. Diluanții folosiți au variat în funcție de tehnica de preparare: lactoza monohidrat (Pharmatose 200M) pentru metoda granulării umede și celuloza microcristalină (Avicel® 102), amidon pregelatinizat (Starch® 1500), α -lactoza monohidrat aglomerată (Tablettose® 80) și fosfat de calciu dihidrat pentru metoda comprimării directe. Comprimatele matriceale au fost evaluate determinându-se uniformitatea masei, friabilitatea, rezistența, grosimea, indicele de umflare și cedarea *in vitro*. A fost analizat efectul variabilelor de formulare asupra

vitezei de cedare a tartratului de metoprolol din sistemele polimerice. Creșterea concentrației de HPMC în formulări a condus la o eliberare scăzută a substanței active.

Keywords: hydrophilic matrix, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, metoprolol tartrate, direct compression, wet granulation, dissolution testing.

Introduction

Polymeric drug carrier systems have been widely studied to sustain, modify, or target drug delivery. Preparation of sustained-release tablets using a matrix of a hydrophilic polymer is a well-established method of achieving prolonged oral drug delivery. Sustained release matrix formulation consists of a drug, one or more water swellable hydrophilic polymers, excipients such as fillers or binders, glidants and lubricants. The most economic manufacturing process is to simply mix dry components and compress them into a tablet. Because many of the resulting powder mixtures exhibit poor flow properties, an intermediate granulation process may be required. Matrix systems containing hydrophilic polymers have been widely studied since drug release from these matrices is controlled by a combination of polymer swelling, erosion and diffusion through the hydrated gel barrier. One mechanism proposed for drug release from hydrophilic matrices involved liquid penetration into the dry matrix, hydration and swelling of polymer, diffusion of dissolved drug, and erosion of the polymer layer. Water-soluble cellulose ethers are the most frequently used hydrophilic matrix polymers for orally administered controlled release systems [2]. The HPMC is one of the most commonly used hydrophilic excipient for developing matrix tablets being a pH-independent, gelling agent [1, 2, 5].

Metoprolol tartrate is a cardioselective beta-adrenergic blocking agent used in hypertension, cardiac arrhythmias, angina pectoris, heart failure, hyperthyroidism and prophylactic, in the treatment of migraine. Metoprolol, with its incomplete bioavailability (due to first-pass metabolism), short half-life (4-6 h), multiple daily dosing, and high aqueous solubility is an ideal candidate for the sustained release system for improving patient compliance.

The aim of this study was to prepare hydrophilic matrix tablets with metoprolol tartrate by direct compression or wet granulation, to characterize the obtained matrix tablets and investigate the influence of the type of polymer, the polymer ratio, and of the nature of the filler on the *in vitro* release of the active substance [3, 6, 8].

Materials and Methods

All materials and solvents used were reagent or analytical grade: metoprolol tartrate (SC Microsin SRL, Romania), HPMC - Metolose 60SH (Shin Etsu, Japan), CMC-Na&H 1500-2500 (Ashland Aqualon, Romania), Pharmatose 200M (DMV Fontera, New Zealand), Tablettose[®] 80 (Meggler, Germany), Avicel[®] 102 (FMC BioPolymer, Ireland), Starch[®] 1500 (Colorcon Inc, SUA), Calcium phosphate dehydrate (S.C. AIS & A Prodimex, Romania), Aerosil[®] (Degussa GmbH, Germany), Magnesium stearate (Undesa Union Derivain SA, Spain), Stearic acid (Merck, Germany), Talcum (Luzenac Val Chisone, SpA, Italy), PVP (BASF, Germany), Alcohol (SC Agronad Proimpex 2000 SRL, Romania).

Preparation of hydrophilic matrix tablets

Matrix tablets of metoprolol tartrate were prepared using the direct compression method, for formulations P1-P6, or the wet granulation method, for formulations P7, P8. The composition of various formulations is detailed in Table I.

Direct Compression. Metoprolol tartrate and HPMC were manually passed through the 0.8 mm sieve and mixed at 125 rpm, for 15 min, in Erweka Double Cone Mixer Type DKM. All excipients except the lubricants and glidant were added, manually sieved through 0.8 mm sieve, and mixed for 15 min. Lubricants and glidants were added and mixed for 5 min. Tablets were obtained by direct compression on rotary tablet machine Vanguard VSP-Model 8, with 8 outlets, punches with Ø 12 mm, working with $v=15$ rpm, with a constant compression force (10 kN).

Wet Granulation. Metoprolol tartrate and polymer (HPMC alone or mixed with CMC Na&H) were triturated well and passed through the sieve 0.80mm and mixed thoroughly; the powder was granulated using the sufficient quantity of selected granulating solvent (alcohol or water) till a wet mass was formed. The cohesive mass obtained was passed through sieve 1.5mm and the granules were dried at 50°C (when water was the granulating solvent) and at 40-45°C (when alcohol was the granulating solvent) for 2 hr. The dried granules were mixed for 5 minutes with talcum, stearic acid and magnesium stearate. The tablets were obtained on the same machine as described above.

Evaluation of the tablets

The tablets prepared by both methods were round, biconvex, white and had a 12mm diameter, 600mg average weight and 100mg metoprolol tartrate per tablet.

The mass uniformity, friability, the hardness and the thickness of tablets were determined according to the stipulations of the 2001 Supplement of the Romanian Pharmacopoeia Xth edition [10].

Table I

Qualitative and quantitative composition of matrix tablets containing metoprolol tartrate

Formulation/ Ingredients (mg)	P1 (mg)	P2 (mg)	P3 (mg)	P4 (mg)	P5 (mg)	P6 (mg)	P7 (mg)	P8 (mg)
Metoprolol tartrate	100							
Metolose 60SH	120			180	120		180	
CMC-Na	-				120	-		
Tablettose® 80	350	-	290	290	230	-		
Avicel® 102	-	350	-			60		
Amidon 1500	-		60	-		60		
Calcium phosphate	-					230	-	
Pharmatose 200M	-						260	
Polyvinylpyrrolidone K30	-						30	
Alcohol	-						25	-
Water	-							10
Aerosil®	6						-	
Magnesium stearate	6							
Stearic acid	6							
Talcum	12						18	
Total	600							

The thickness of the tablets was determined using Hardness Tester VK200 (Thick unit-mm). Ten tablets for each formulation were used. The mass uniformity was determined on 20 tablets for each formulation, using an electronic balance (Mettler Toledo, Basel, Switzerland). The hardness of tablets was determined using a hardness tester (VK 200, Vankel, Varian Inc.). Hardness values were reported in kiloponds (Kp).

The friability test was performed on 20 tablets. The tablets were placed in the friabilator (Roche Friabilator), rotated precisely for 4 min at 25 rpm, then were dedusted and weighed. The friability was expressed as the percentage weight loss. The acceptable limit of weight loss was not more than 1.00% (Table II).

The swelling of matrix tablets was measured in percentage weight gain by the tablets. One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 6.8. At the end of 2, 4, 6, and 8 hours, tablets were withdrawn, soaked and weighed. The percentage weight gain by the tablet was calculated using the formula:

$$\text{Swelling index} = \frac{M_t - M_0}{M_0} \times 100$$

M_t = Weight of tablet at time 't' and M_0 = Weight of tablet at time '0'.

The *in vitro* dissolution tests were performed on USP 2 apparatus, at $37 \pm 0.5^\circ\text{C}$. The dissolution medium was 900mL of degassed phosphate buffer, pH=6.8 and the rotation speed was 50rpm. Samples of 5mL were collected at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 hours and filtrated through immersed cannula filters. The sampled volume was replaced with fresh dissolution medium. All the test were performed in triplicate. Two types of vessels, with different hydrodynamics were used for the *in vitro* dissolution tests, the classic one and the peak vessel.

The quantitative analysis of metoprolol was performed using a validated spectrophotometric method, $\lambda = 273\text{nm}$, using a double fascicle, Jasco V-530 spectrophotometer.

Results and Discussion

The physical characteristics of the matrix tablets are summarized in table II. All the tablets formulations presented acceptable pharmacotechnical properties, percentage friability and weight variation passing the test as per standard pharmacopoeial limits [10,11,12].

Table II
Physical characteristics of the hydrophilic matrix tablets

Formulation	Thickness (mm) Mean $\pm$ SD	Hardness (Kp) Mean $\pm$ SD	Mass variation(mg) Mean $\pm$ SD	Friability (%)
P1	5.75 $\pm$ 0.06	5.45 $\pm$ 0,26	605.65 $\pm$ 5.14	0.93
P2	6.01 $\pm$ 0.04	6.45 $\pm$ 0.33	606.2 $\pm$ 5.13	0.30
P3	5.86 $\pm$ 0.09	3.53 $\pm$ 0.65	604.85 $\pm$ 3.88	0.57
P4	5.81 $\pm$ 0.09	4.14 $\pm$ 0.57	600.4 $\pm$ 4.39	0.94
P5	5.90 $\pm$ 0.06	3.29 $\pm$ 0.40	596.4 $\pm$ 3.97	0.99
P6	5.47 $\pm$ 0.08	2.96 $\pm$ 0.16	604.8 $\pm$ 5.94	0.82
P7	5.74 $\pm$ 0.03	13.04 $\pm$ 1.03	603 $\pm$ 4.86	0.17
P8	5.76 $\pm$ 0.04	11.68 $\pm$ 1.82	602.35 $\pm$ 5.08	0.19

For all prepared tablets, the standard deviation of mass variation was below 6% (3.88-5.94). It was observed that the variation of thickness was minimal. The friability of tablets varied between 0.17-0.99%. The European and US Pharmacopoeias state that a loss up to 1% is acceptable [11,12]. The friability increased by increasing the polymer level (P5). The hardness of the tablets varied from 2.96 to 13.04 kP. The lowest hardness was reported

for tablets (P6) obtained by mixture of three diluents, soluble and insoluble. The tablets granulated by water (P8) showed a lower hardness than those granulated by ethanol (P7). Increasing the polymer concentration resulted in a decrease in the hardness of tablets.

The swelling index values of the different formulations are presented in figure 1.

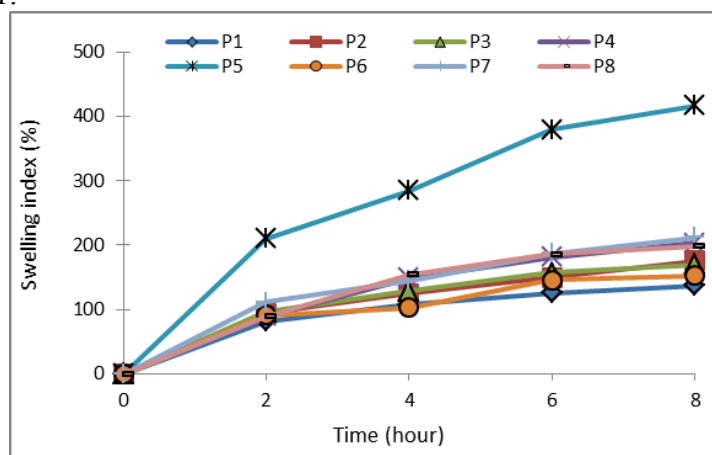


Figure 1

The variation of the swelling index

It has to be noted a significant increase of the swelling index after two hours, being practically double after 8 hours. In the case of P5 formulation, the association of two types of polymers induced an important increase of the swelling index.

The influence of the type of hydrophilic polymer, different excipients, and the method of preparation was analyzed by means of *in vitro* release profile of metoprolol tartrate.

According to the USP requirements for metoprolol succinate extended release tablets, [12], the dissolution medium was phosphate buffer, pH = 6.8, apparatus 2, 50 rpm, but taking into consideration the different salt of metoprolol used in formulation, tartrate instead of succinate, the dissolution volume was 900mL, compared with 500mL recommended by USP monograph.

The sampling schedule was also adapted, the main issue being establishing a rapid and discriminatory test for research purpose rather than a quality control one.

The comparative analysis of dissolution profiles of metoprolol tartrate from modified release formulations was performed based on the general pharmacopoeial specifications for extended release dosage forms: time point

1 – to prevent „dose dumping” ~ 20-30% drug release, time point 2 – to characterize the release profile ~ 50% drug released, time point 3 – to check for complete drug release ~ 80% drug released. The tolerances specified in the case of metoprolol succinate extended release tablets are: 1 hour – not more than 25% amount dissolved, 4 hours – between 20 and 40% amount dissolved, 8 hours – between 40 and 60% amount dissolved, 20 hours – not less than 80% amount dissolved [12].

The influence of the type and ratio of hydrophilic polymer on the *in vitro* dissolution profiles of metoprolol tartrate was presented in figure 2. Three modified release formulations of metoprolol tartrate were investigated: P3 formulation containing 20% HPMC, P4 formulation containing 30% HPMC and P5 formulation having 40% hydrophilic polymer (20% HPMC and 20% CMC). The drug released profiles after 1 hour seem to be parallel and equidistant, the amount released being inversely proportional with the polymer content. In the case of P3 formulation, the drug released after 1 hour was greater than 37% being over the specified limit, which prevents dose dumping. The increasing of polymer content to 30 or 40%, determined release less than 25%. The drug released after 4 hours varied between 36 and 59% and after 6 hours, between 49 and 70%.

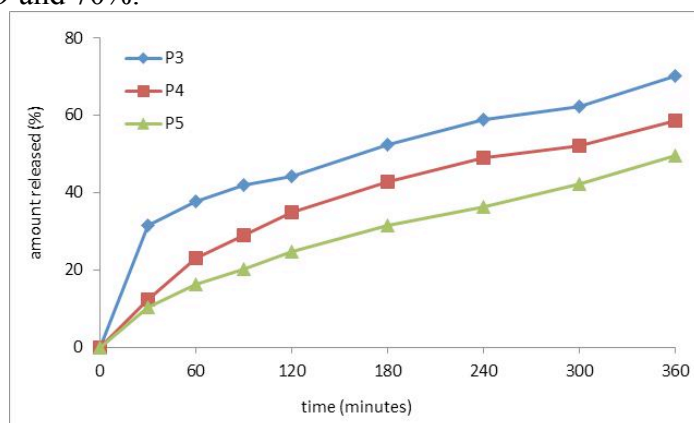


Figure 2

The influence of type and proportion of polymer on the *in vitro* dissolution profiles of metoprolol tartrate

In the case of formulation P3, the addition of different type and quantities of excipients such as lactose, microcrystalline cellulose, starch or calcium phosphate, determined a significant decrease of drug released. As it can be seen from figure 3, the reduction of the released amount (P6, P2, P1) was more than 15% for the entire interval of sampling: 20-23% amount

released after 1 hour (compared with 37%), 40-46% after 4 hours (compared with 58%) and 54-56% after 6 hours (compared with 70%).

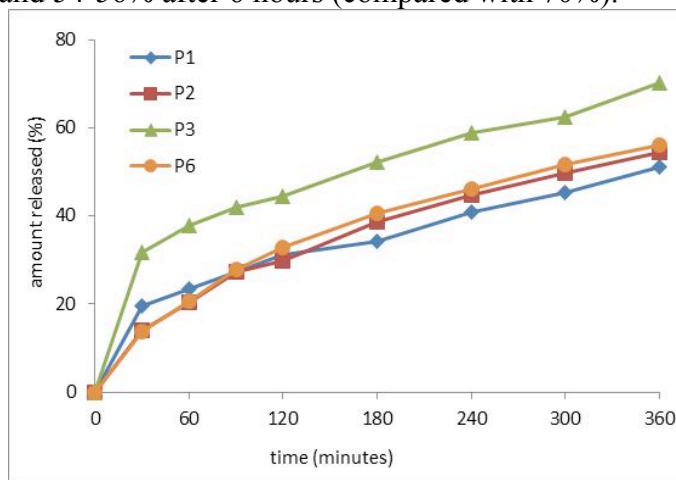


Figure 3

The influence of the type and proportion of excipients on the *in vitro* dissolution profiles of metoprolol tartrate

The technique of preparation, direct compression (P4 formulation) or wet granulation (P7 and P8 formulations), was another factor which could affect the *in vitro* release of metoprolol tartrate from extended release tablets. The comparative analysis of the *in vitro* dissolution profiles revealed a distinct kinetic mechanism and a significant impact on the amount released (Figure 4).

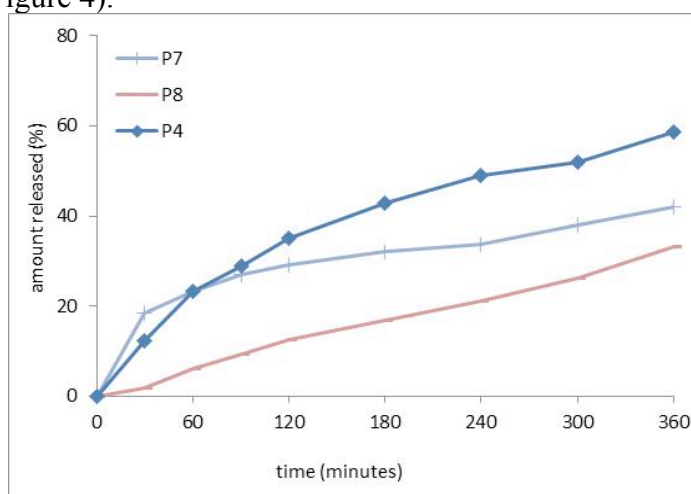


Figure 4

The *in vitro* dissolution profiles of metoprolol tartrate prepared by direct compression or wet granulation

The dissolution tests of metoprolol tartrate from modified release tablets were performed using peak vessel, which prevented the cone effect and assured a different hydrodynamic profile compared with the classical one. The dissolution profiles were similar, with the same rank order for the amount released, increasing from P8 to P3 formulation (Figure 5). Nevertheless, it has to be noted that the fractions released were at least 10% greater in the case of peak vessels, probably due to a more intense peripheral erosion of the matrix (Figure 6).

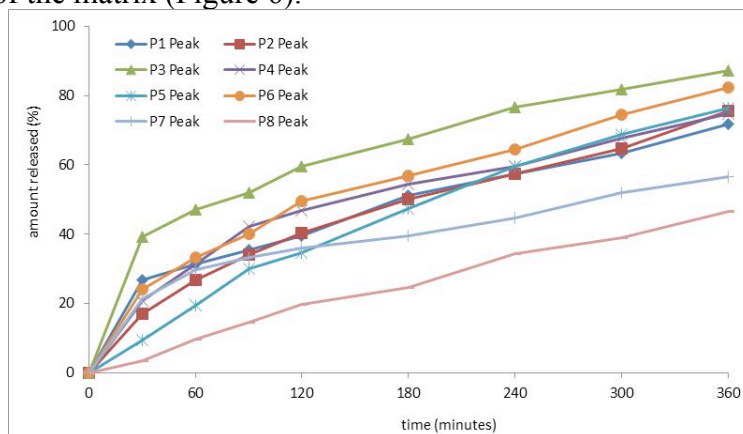


Figure 5

The dissolution profiles of metoprolol tartrate from extended release tablets, in the case of peak vessel

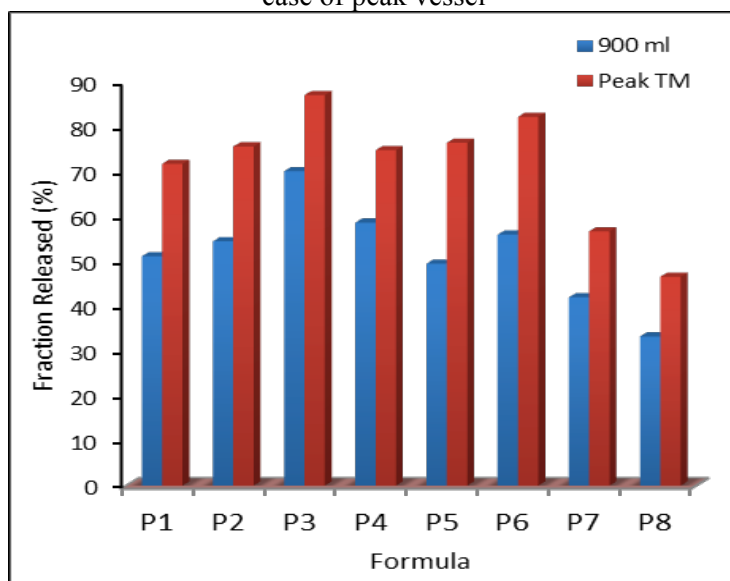


Figure 6

Comparative fraction released using two types of dissolution vessels

Conclusions

Several sustained drug delivery systems containing metoprolol tartrate were prepared based on hydrophilic polymers, using wet granulation and direct compressions techniques. The experimental formulations were subjected to a set of pharmacotechnical and *in vitro* release tests. The swelling pattern and dissolution profiles indicated that the type of polymer and its concentration represent critical factors that control the delivery rate. The hydration and consecutive diffusion across gel barrier are the limiting steps, metoprolol being a high permeability drug and class I standard for the biopharmaceutical classification system.

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