Original Paper

Study of the Oral Formulation of Metoprolol - the Release from Prolonged Release Formulations

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ABSTRACT: The purpose of our study was to realize some pharmaceutical forms with extended release of Metoprolol, included in hydrophilic metocel or carbopol media (10%, 20% and 30% hydrophilic polymer), and to test the kinetic of Metoprolol release of these formulations in two distinct phases: 60 minutes in hydrochloric acid 0.1 N (simulating the gastric environment), and four hours in phosphate buffer solution pH 6.8 (simulating the intestinal environment). From the obtained data, it was found that for metocel forms the rate of Metoprolol release was much lower than the carbopol forms. It is well known that the kinetics of drug release from hydrophilic matrix is controlled by diffusion, as long as the hydrated polymer remains intact. Therefore, we found a linear relationship between the quantity of released drug and time's square root, which shows that Higuchi's equations, valid for explaining the release from insoluble matrix, can by also applied to hydrophilic matrix.

KEYWORDS: Metoprolol, extended release (ER), dissolution test, carbopol, metocel.

Introduction

Making pharmaceutical prolonged release formulations is a continuous search in pharmaceutical research because they offer some advantages such as:

-Elimination of fluctuations in plasma levels of drugs, with particular importance when administering drugs that have a narrow therapeutic concentration range; examples of drugs classes that fit in this category are: anticonvulsants, cardiac tonics, antibiotics, antiarrhythmics, and so on;

-Known release rate over a longer period of time;

-Extension of the administered dose action duration for substances with short half-life;

-Improvement in patients' compliance with the drug dosing regimen;

-Reduction of adverse effects both locally and systemically.

On the other hand, research in this direction is quite difficult because the designed formulations must be controlled in much more detail in order to identify opportunities to avoid disadvantages of long-acting pharmaceutical systems such as:

-Risk of overdose if the dose is higher than the conventional formulations;

-Extension of accidental toxicity or undesirable side effect;

-Action reproducibility due to the action of gastric contents emptying;

-Little or no efficacy if the drug is not absorbed by the intestinal mucosa;

-Difficulty in dosage adjustment for certain cases of intervariability in pharmacokinetics;

-Inflexibility of dosing regimen;

-Higher cost that the one for conventional formulations.

-The dissolution tests for these formulations have two main objectives:

-The control of product variability between batches;

-Predicting the release of the "in vivo" pharmaceutical formulation active principle (compound, substance); and especially,

-Getting assured that a good release ("dumping") of a large quantity of the active principle (compound, substance) is not possible

It is well known that the drug substance release kinetics of the hydrophilic matrices is controlled by diffusion as along as the hydrated polymer remains intact. A linear relationship was found between the amount of drug substance release and the square root of time. This indicates that Higuchi's equations valid for explaining the release from insoluble matrices can be applied also for hydrophilic matrices.

There are two types of matrix systems that control the dissolution: soluble matrix systems and insoluble matrix systems. The soluble matrix systems assure a prolonged release by the slow dissolution of the matrix. In the case of insoluble matrix systems, the release occurs as the liquid enters the matrix, dissolves the drug substance and the solution diffuses through the pores of the matrix filled with liquid.

Metoprolol is a substance which belongs to the I BCS class (high solubility and permeability) and is considered the classic model for the development of in vitro-in vivo correlations. Some countries accept the bioequivalence for products containing metoprolol based only on the results obtained from in vitro release tests.

This paper proposes the development of extended release formulations of metoprolol included in the metocel or carbopol hydrophilic environments and the kinetics testing of the release of metoprolol contained in these formulations.

Materials and methods
The dissolution test

The dissolution test was divided into two distinct stages: the first stage was the testing of the active substance release after holding it for 60 minutes in 0.1 N hydrochloric acid (simulated gastric environment) and the second stage was holding the tablets for four additional hours in 6.8 pH phosphate buffer solution (simulated intestinal environment) and the evaluation of the release profile of metoprolol contained in tablets during this time.

A presentation of the dissolution is summarized in the table below:

Table 1: Parameters of the dissolution test for tablets containing prolonged release metoprolol

Dissolution parameters	
Stage I	
Equipment used	II USP (palete)
Dissolution environment	HCl 0,1 N
Volume	900 ml
Dissolution temperature	37°C
Stirring (rpm)	75 rpm
Sampling times	15, 30 ,45, 60 min
Stage II	
Equipment used	II USP (palete)
Dissolution environment	6,8 pH buffer solution
Volume	800 ml
Dissolution temperature	37°C
Stirring (rpm)	75 rpm
Sampling times	60, 120, 180, 240 min
Detection	UV, 274 nm

Tested formulations

Six different products containing 100 mg metoprolol tartrate were formulated. Three formulations contained various concentrations of carbopol and the other three contained various concentrations of metocel to ensure prolonged release of the active substance.

The analytical method

The quantitative analysis of released metoprolol was performed by determining spectrophotometric absorbance of the samples at the wavelength corresponding to maximum absorption of metoprolol, which was 275 nm in simulated gastric environment.

The method validation was performed in terms of precision, accuracy and stability of the samples in compliance with the internationally accepted standards following the 2001 Crystal Gate Conference in Washington.Table 2:

Formulation mode of the six products with prolonged release containing metoprolol

Product	Delaying agent
P1	30% metocel
P2	20% metocel
P3	10% metocel
P4	30% carbopol
P5	20% carbopol
P6	10% carbopol

Results and Discussions

Release from metocel based formulations

First we observe that we have fairly large "intra-formulation" variability, i.e. between tablets of the same formulation and the same experimental batch. Considering that in force regulations impose a limitation in terms of variability, "standard deviation of the mean of any product should be less than 10% from second to the last time point", ranges above 20%

variation which can be seen with the naked eye in all three formulations in some of the points are a sign of instability and unpredictability of release kinetics. Note also that this instability refers essentially to the portion of the curve corresponding to the dissolution in neutral environment. The dissolution in acidic environment (the first hour) is much lower.

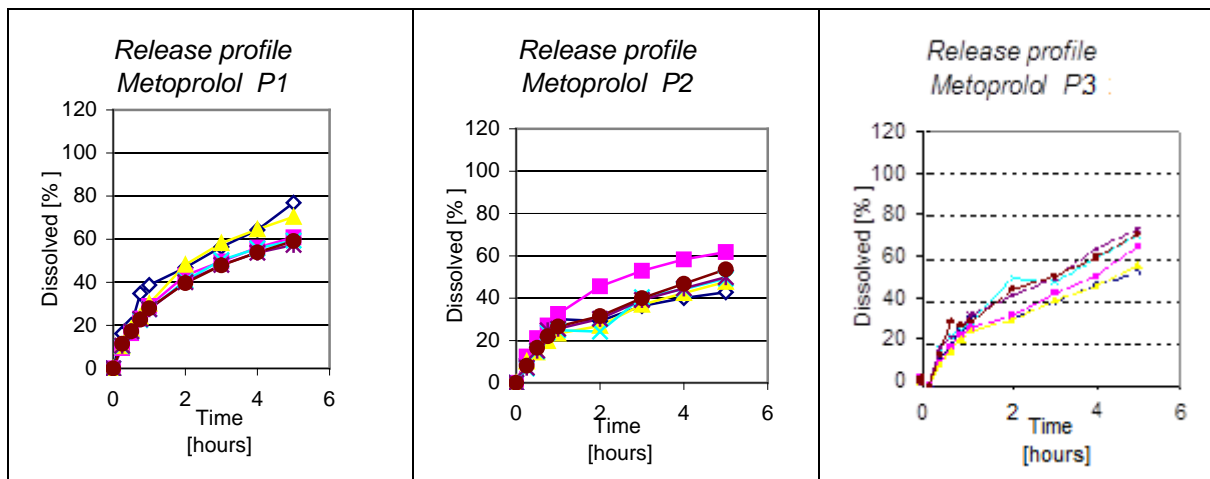We also observe that the process rate is much higher in acidic environment than in neutral environment.

Fig.1.In vitro release profile for the P1, P2 and P3 formulations

Comparison of profiles corresponding to different formulations

Examination of average dissolution profiles highlights the following aspects:

In acidic environment there are no differences between the dissolution environments for the three formulations, which are virtually identical.

In neutral environment the profiles are significantly different, but these differences don't seem to be correlated with the metocel concentration. Thus, dissolution curve corresponding to 10% metocel concentration is between the 20% curve and that of 30%.

Changing the release environment leads also to a significant change of the curve shape, the time change (one hour) is a point of discontinuity of the derivative.

Profiles are approximately linear: a line during the first hour (corresponding to the release in acidic environment) and another line with lower slope which corresponds to dissolution in neutral environment. If we extend the first line at 2 hours we get a double dissolution rate (60%) than what was actually achieved in 2h (30%).
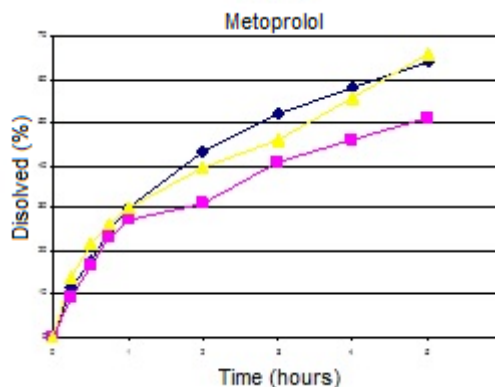

Fig.2.Average in vitro release profiles for formulations containing metocel

Formulations containing carbopol:

The dissolution curves for 4 tablets of each of the three carbopol based formulations are presented in fig.3. Dissolution rate is higher in acidic environment, but the difference in rate between the dissolution in acidic environment and dissolution in neutral environment is lower so we have a smooth transition from one range to another.

A significant difference from metocel based formulations is that the "retardation" effect depends on the concentration of carbopol. When performing a brief review it can be seen that the three curves are significantly different - they are respecting the retardant concentrations hierarchy. As the concentration increases the release rate and degree are decreasing
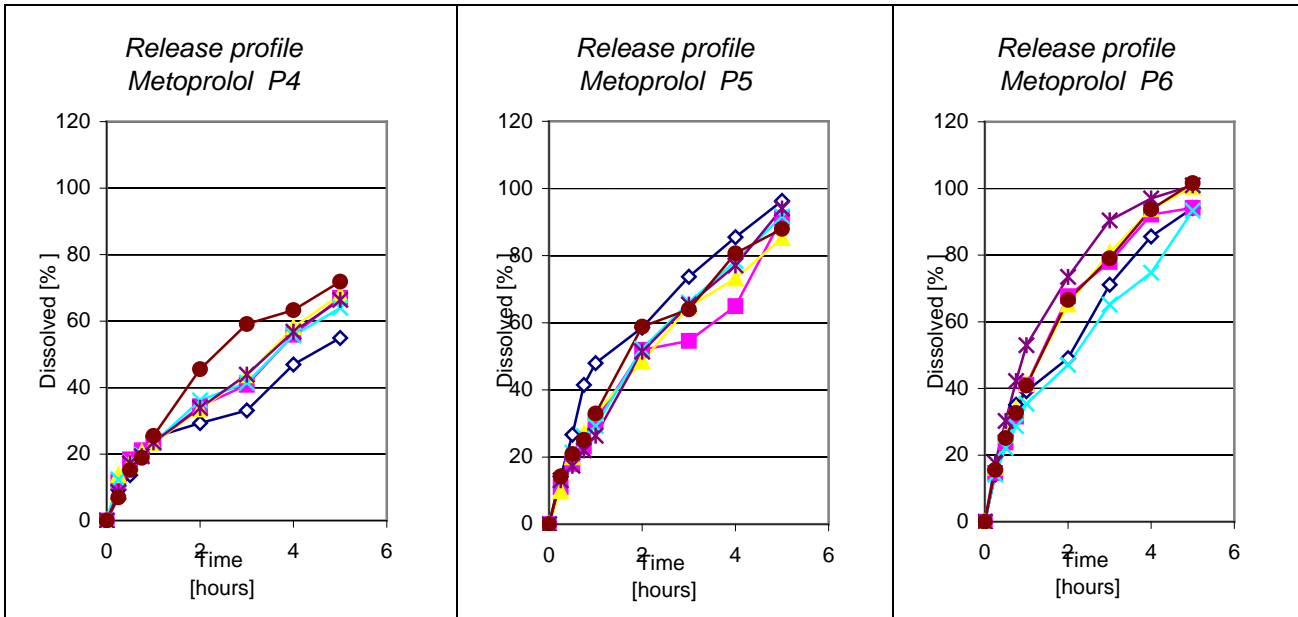
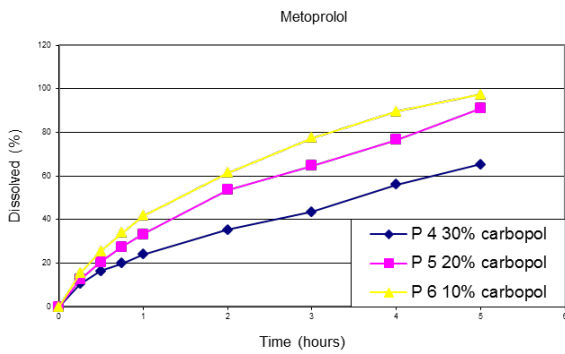**Fig.3.Dissolution curves for the P4, P5 and P6 formulations**

Fig.4.Average dissolution profiles for formulations containing carbopol

The graphical representation of the released quantity at a certain moment in time depending on the concentration of carbopol reveals a surprising linear correlation as we can see in the chart below:
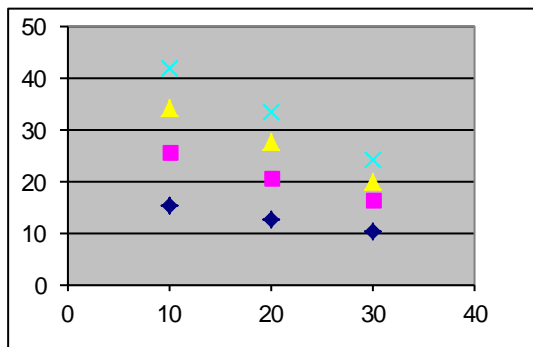

Fig.5.Relationship between the concentration of carbopol and the release of Metoprolol

Metocel – carbopol comparisons

It is noted that for the formulations containing metocel (P1, P2 and P3) the metoprolol release rate is much lower than that of formulations containing carbopol.

One aspect that should be noted is that for the first three products the differing metocel ratio does not lead to significant changes in the release rate of the active substance in the medicinal product -in 5 hours, the dissolved substance proportions are 64.00 for P1, 50.85 for P2 and 65.66 for P3. In the case of the other three formulations the amount of contained carbopol determines dramatic release changes.
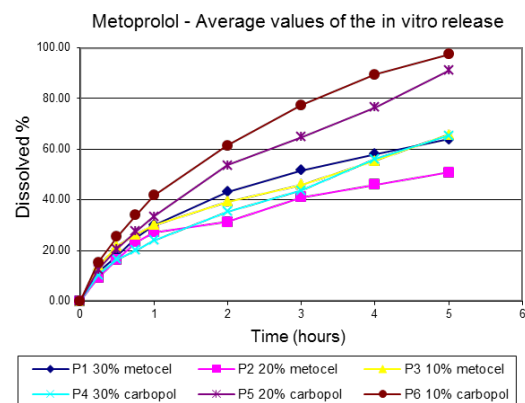

Fig.6.Average dissolution profiles for six prolonged release formulations containing metoprolol

Thus, P4 containing 30% carbopol releases in 5 hours about 65% of the active substance behaving like the P1-P3 products. In contrast, along with the decrease of carbopol amount, the

metoprolol release rate increases significantly (P5 - 91% and P6 - 97%).

Conclusions

Both metocel and carbopol ensure retardation of metoprolol, prolonging the dissolution time of 30 minutes for un-retarded products at more than 5 hours.

At similar concentrations metocel is more effective than carbopol. Metocel should be used in concentrations smaller than 10% and carbopol in concentrations larger than 30%. The effect of the two retardants is much stronger in neutral environment.

A relevant dissolution test should include an acidic release environment and a neutral release environment. The initial release in acidic environment and the following release in neutral environment bring the dissolution test closer to the physiological conditions, being more "biologically relevant".

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