THE INFLUENCE OF SOME DILUENTS ON THE RELEASE OF METOPROLOL TARTRATE FROM PROLONGED RELEASE MATRIX TABLETS

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ABSTRACT

Scope: The objective of this study was to formulate, to optimize and prepare some prolonged release matrix type tablets with metoprolol tartrate, in order to obtain a stable product, containing appropriate doses of active ingredient.

Materials and methods: For this, active substances was included in hydrophyllic matrix, using 20% hydroxypropyl methylcelullose polymer (Metolose 60SH-4000), in order to ensure a prolonged release with diferent fillers in same concentration as: lactose (Tabletosse 80), microcrystalline cellulose (Avicel PH102) and pregelatinized starch (Starch 1500). The tablets were prepared by direct compression. As gliding and lubricant agents there were used magnesium stearate and fumed silica (Aerosil).

Results-discussion: The prepared tablets where characterized from the point of view of the pharmaceutical properties: weight uniformity, mechanical strength, friability and in vitro dissolution behavior.

Conclusions: These tests show that the formulation has lead to adequate tablets with metoprolol tartrate. The study of the effect of the filler on a metoprolol formulation tablets at 20% Metolose 60SH-4000 level concluded that filler solubility had a limited effect on release rate.(1) The release profiles showed a decrease of about 5-7% after 6h, as the filler was changed from lactose to microcrystalline cellulose then to pre-gelatinized starch.The delay is due to the formation of links between pre-gelatinized starch polymer- hydroxypropylmethyl-celullose polymer and they affect the properties of the gel layer around the tablet with the effect on release. Addition of soluble fillers enhanced the dissolution of soluble drugs by decreasing the tortuosity of the diffusion path of the drug. Also, the presence of swelling insoluble filler like microcrystalline cellulose changed the release profile to a small extent due to a change in swelling at the tablet surface.

INTRODUCTION

Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level. It is necessary that many patients can benefit from drug intended for chronic administration by maintaining plasma levels within a safe and effective range.

Matrix system is the release system, which prolongs and controls the release of drug that is dissolved or dispersed. A hydrophilic matrix tablet is the simplest method of fabricating an extended release (ER) or sustained release (SR) solid oral dosage form. A typical matrix system consist of a drug, one ore more water – swellable hydrophilic polymers, excipients such as fillers or binders, a flow aid (glidant) and a lubricant. Also other ingredients may be included to improve or optimize the release and the stability of the formulation system such as surfactants, buffering agents, stabilizers, solubilizers. The method to manufacture the matrix tablet is similar to conventional tablet formulation: granula-

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tion, blending, compression and coating. The most widely method is direct compression because is low-cost method.

Hydroxypropil metilcellulose (HPMC) is one of the commonly used hydrophilic polymer for developing matrix tablet because it works as pH-independent gelling agent. Swelling as well as erosion of the polymer occur simultaneously and contribute to overall release of drug.(2)

Formulations of oral sustained release dosage forms for highly water-soluble drug has always been a difficult task, because the release it is at a high rate and cause problems dues to toxic concentration. But it is a challenging task to formulate a suitable tablet dosage form for sustained action of highly water-soluble drugs.

Metoprolol is a cardio-selective beta-blocker and it is used in the management of hypertension, angina pectoris, and cardiac arrhythmias, myocardial infarction and heart failure. The half-life of metoprolol is stated to 3-4 hours.

Metoprolol tartrate, the active ingredients, with its incomplete oral bioavailability, short half life, and multiple daily dosing is appropriate for a formulation in an extended release dosage form. It is a white crystalline powder with high aqueous solubility and high permeability throughout gastrointestinal tract.(3)

The objective of this study was to formulate100 mg metoprolol tartrate tablets with prolonged release, in order to obtain a stable product, containing appropriate doses of active ingredient.

The formulation of prolonged-release metoprolol tablets was based on o hydrophillic matrix. The product was manufactured by direct compression, using hydroxypropylmethylcellulose as polimer matrix former, used in 20% concentration. It is quoted in the literature that a minimal concentration of 15-17% of polymer is enough to generate a hydrophyllic matrix. In formulation of matrix tablets was used different types of diluents (lactose, microcrystalline cellulose and pre-gelatinized starch), in same proportions, in order to ensure a prolonged release and show the influence of those of rate to release of drug. Also other ingredients like magnesium stearate and fumed silica were used as gliding and lubricant agents.

Three formulations with 100 mg of metoprolol were developed. (Table 1).

The purpose of the formulations was:

– to ensure an adequate density of the mix subjected to direct compression,
– to ensure an adequate flow of the mix by using a combination of lubricants,
– to ensure an optimal dissolution profile, the drug being relesed by diffusion and errosion.

MATERIALS AND METHODS

As materials we have used:

– Metoprolol tartrate, powder (Microsin, Romania),
– Hydroxypropylmethylcellulose – Metolose 60 SH-4000 (Shin-Etsu,Japan),
– Lactose – Tabletose 80 (Meggle),
– Microcrystalline cellulose – Avicel PH102 (Novachem,Wuhan),
– Pre-gelatinized starch – Starch 1500 (Colorcon),
– Colloidal silicone dioxide – Aerosil 200 (Evonik Industries),
– Magnesia stearate (Faci Spa.,Italia)

Table 1. Formulations of prolonged-release tablets with metoprolol

INGREDIENTS	F1	F2	F3	%	Role in formulating
Metoprolol tartrate	100	100	100	16,67	Active substance
HPMC (Metolose 60SH-4000)	120	120	120	20	Matrix – forming substance
Lactose (Tabletose 80)	362	-	-		Diluent
Microcrystalline cellulose (Avicel PH102)	-	362	-		Diluent
Pregelatinized starch (Starch 1500)	-	-	362		Diluent
Fumed silica (Aerosil 200)	12	12	12	2	Glidant
Magnesia stearate	6	6	6	1	Lubricant
Total weight	600	600	600	-	-
tartrate (mg/tab)					

The stages of the manufacture process were as follows:

– the preparation of the materials (drying, powdering, sieving),
– the preparation of the compression mix: metoprolol tartrate, colloidal silicone dioxide and a part of the hydrophyllic polymer are homogenised for 10 minutes, the rest of the excipients is added (the remaining amount of polymer, lactose – F1, microcrystalline cellulose – F2, pre-gelatinized starch – F3) and the homogenisation is continued for 10 minutes; Magnesium stearate was added in the mixture and then are homogenised for 5 minutes and sieved,
– the tableting was performed on a IMA KILIAN SYNTHESIS 300 rotating tableting press, with dye and punches with a diameter of 12 mm lenticular, not inscribed).

The tablets were tested immediately after manufacture and after 6 months, determining the organoleptic characteristics, weight uniformity, mechanical resistance, friability, metoprolol tartrate content and the release characteristics of the tablets.

The equipment used for the quality control determination were:

- for the determination of the mechanical resistance: Erweka TBH 30 MB apparatus and the method described in the Eur. Ph. 6th edition;
- for the determination of friability: Vankel friabilator and the method described in the Eur. Ph. 6th edition;
- the determination of the release of metoprolol tartrate from the tablets: using the USP apparatus II, Pharma Test according to USP 28. (6)

The test was performed in 900 ml of phosphate buffer (pH 6.8) with temperature maintained at 37,0 ± °C while the stirring speed was maintained at 100 rpm. Aliquots of 5 ml were colected at 0,5, 1, 1,5, 2, 2,5, 3, 4, 5, 6, hours and equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. All the samples were diluted suitably, filtered and analized directly at 275 nm using UV-VIS spectrophotometer. All the release studies were conducted in triplicate and the mean value were plotted versus time.

Results and discussions

The resulting tablets have a smooth surface, white colour, round shape, a 12 mm diameter, 600 mg weight and a content of 100 mg metoprolol tartrate. Based on the results, it can be stated that the formulations are adequate regarding the provisions of the Romanian Pharmacopoeia Xth edition and the Eur. Ph. 6th edition for weight uniformity, friability, mechanical resistance and disintegration. (Table 2) (4,5)

Table 2. Physical properties of tablets

Formulation	Weight variation (mg)	Diameter (mm)	Friability (%)	Hardness (kg/cm²)
F1	600±6	12,5±0,11	0,60	6
F2	600±3	12,2±0,04	0,52	7
F3	600±5	12,4±0,06	0,75	5

The most relevant test for the prediction of the in vivo effect is the dissolution test. Results of this test indicate that the dissolution is influenced by the type of diluents in the matrix. The dissolution behavior of metoprolol tartrate from matrix tablets containing different types of diluents is illustrated in Figure 1.

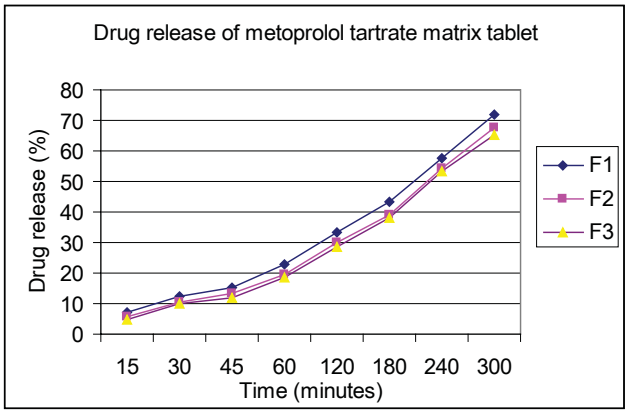

Figure 1.Dissolution profile release of metoprolol tartrate from matrix tablets of different excipients (lactose – F1, microcrystalline cellulose – F2, pre-gelatinized starch – F3)

Results revealed a difference in drug dissolution behavior between tablets with lactose and those with microcrystalline cellulose and pre-gelatinized starch. These tests show that the formulation has lead to adequate tablets with metoprolol tartrate.

Conclusions

The study of the effect of the filler on a metoprolol formulation tablets at 20% Metolose 60SH-4000 level concluded that filler solubility had a limited effect on release rate. Lactose with higher solubility will soon release the active substance from tablet. The release profiles showed a decrease of about 5-7% after 6h, as the filler was changed from lactose to microcrystalline cellulose then to pre-gelatinized starch. The delay is due to the formation of links between pre-gelatinized starch polymer – hydroxypropylmethylcelullose polymer and they affect the properties of the gel layer around the tablet with the effect on release. Addition of soluble fillers enhanced the dissolution of soluble drugs by decreasing the tortuosity of the diffusion path of the drug. Also, the presence of swelling insoluble filler like microcrystalline cellulose changed the release profile to a small extent due to a change in swelling at the tablet surface.

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