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MATRIX TABLETS WITH METOPROLOL SALTS BASED ON NATURAL HYDROPHILIC COLLOIDS SUCH AS ALGINATES, CARRAGGENS AND XANTHAN GUM

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Abstract: Hydrophilic matrix tablets comprising metoprolol salts (succinate and tartrate). and hydrophilic natural colloids such as carrageens, alginates and xanthan, were obtained by direct compression on a single station tablet press, in order to obtain a modified release of the drug.
The influence of the natural polymer, the polymer ratio on the compresibility of the tablet and their influence on in vitro release of the active substance, were studied.
The tablets were evaluated for weight uniformity, drug content, hardness and friability.
The study demonstrated that it is possible to fabricate modified release tablets of metoprolol salts hydrophylic natural colloids such as carrageens, alginates and xanthan gum and the drug release was found to be dependent on the ratio and type of the matrixing agents.

Key words: alginates, carrageens, drug release, hidroxypropyl methyl cellulose (HPMC), hydrophylic natural colloids, metoprolol ((+)-1-(isopropyl) amino)-3-[p-(2-methoxyethyl)]-2-propanolol) succinate or tartric salt and xanthan gum.

INTRODUCTION

Metoprolol ((+)-1-(isopropyl) amino)-3-[p-(2-methoxyethyl)]-2-propanolol) succinate or tartric salt is a selective beta-adrenergic receptor bloker useful in the treatment of hypertension, angina and heart failure (5, 14).

The matrix-type formulation developed to obtain a sustained or prolonged release of active substances have been broadly studied in the past decades [1, 6].

Natural hydrophilic colloids such as carraggeens, alginates and xanthan, were often used as a pharmaceutical excipient, as a matrix former [1, 4, 6].

The influence of the different content of carraggeens, alginates and xanthan, on the compactibility/compressibility (using the hardness determinations and the friability test) and their influence on the drug release was studied.

The purpose of this study was to prepare hydrophilic matrix tablets with metoprolol salts and, to see if the hydrophylic natural colloid such as carageenan, alginate and xanthan gum content influences the metoprolol release from the matrix.

MATERIALS AND METHODS

Materials

Metoprolol succinate salt was extracted with ethylic alcohol from tablets with metoprolol succinate from AstraZeneca AB-Sweden bought on the market and,

Metoprolol tartaric salt were obtained as a gift sampels from S.C, Magistra C&CS R.L.-Romania

Hydrocolloids were obtained as a gift sampels from CCAI, Bucarest, Romania

Preparation of the Hydrophilic Matrix Tablets

Hydrophilic matrix tablets were manufactured using direct compression, and batch size of 100 tablets were produced for each formulation that was manufactured.

The hydrocolloids themselves or their mixture were dry blended with metoprolol salt in a 1 L bowl of blender (Erweka, Germany) using a speed of 100 rpm for the main impeller for 10 minutes.

Thereafter 1 % (w/w) magnesium stearate and 0,5 % (w/w) colloidal silica were added and the blend mixed at the same speed for 3 minutes.

The blend were transferred to a feed hopper and tablets were compresed on single punch tablet press (Triowin, China) tooled with 10 mm flat-faced round punches to a uniform wight of 500 mg.

The total weight of the tablet was 500 mg.

A summary of the unit composition of the batch that were manufactured is shown in Table 1.

Table 1.- Metoprolol salts Matrix Tablets formula

Igredients (mg/cpr.)	Batch code							
	XT	AT	CT	XS	AS	CS	AmHT	AmHS
Metoprolol succinate	-	-	-	95	95	95	-	95
Metoprolol tartaric	100	100	100	-	-	-	100	-
Xanthan gum	392.5	-	-	397.5	-	-	397.5	397.5
Alginates	-	392.5	-	-	397.5	-		
Carraggens	-	-	392.5	-	-	397.5		
Magnesium stearate	5	5	5	5	5	5	5	5
Colloidal silica	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mixture of the hydrocolloid ratio							1:1:1	1:1:1

Evaluation of matrix tablets

- Hardness determination – was effectuated using the Tablet Hardness Tester (VanKel -200, USA) in accordance with Romanian Pharmacopoeia 10th Ed. and European Pharmacopoeia
- Friability – was conducted using a VanKel Friabilator (USA) in accordance with Romanian Pharmacopoeia 10th Ed.
- Average weight – determination by weight of 10 tablets on Mettler Toledo balance: Table 2 shown the results of the determination

The average value of hardness was obtained from 10 measurements of each sample, and that one of tablet friability from three measurements (Table 2).

The mean values of 10 determinations for each formulation are shown in Table 2 and the following figures.

Table 2.- Matrix tablets characteristics

Code batch	Average weight (mg) (n=10)	Hardness (N) (n=10)	Friability % (n=20)
XT	512.5	80.9	0.37
AT	512.4	79.3	0.53
CT	512.6	63.2	Fracture of three tablets
XS	518.4	87.2	0.46
AS	518.2	83.9	0.39
CS	518.5	64.5	Fracture of three tablets
AmHT	515,5	87.2	0.27
AmHS	511.5	86.7	0,3

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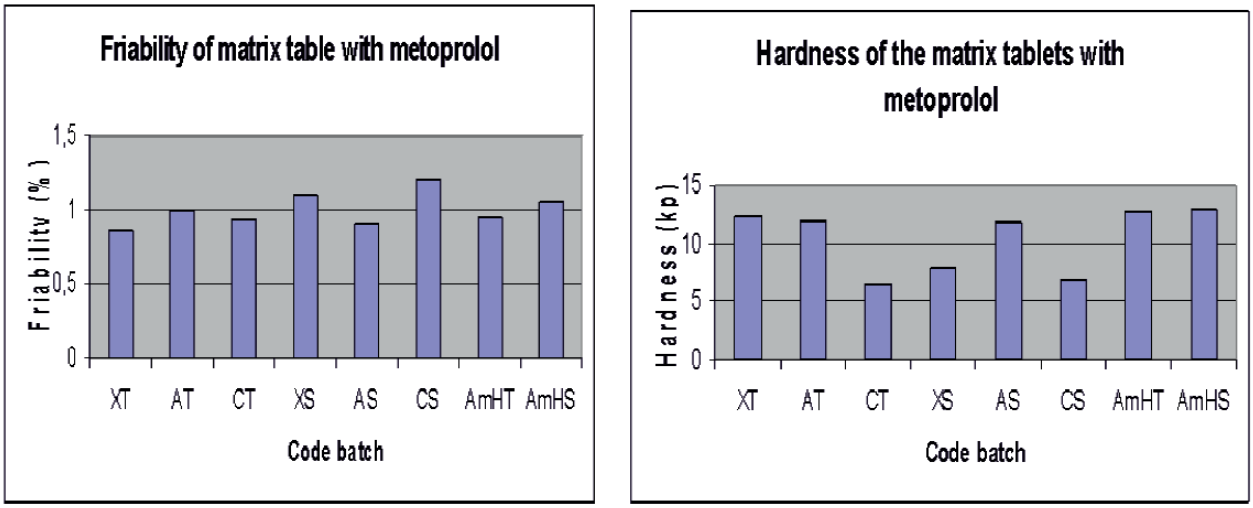

Fig. 1-Friabiliy and hardness of tablets matrix with metoprolol salts

• Determination of the drug release

The dissolution test has been carried out in accordance with Romanian Pharmacopoeia 10th Ed. and European Pharmacopoeia ed. V – method 1, using VanKel VK 7000 Dissolution Testing Station (VanKel – USA). The determination was performed under the following conditions:

- dissolution medium: phosphate buffer solution (pH 6,8)
- medium volume: 900 mL;
- temperature: 37 0,5 C;
- speed rotation: 75 rpm;
- time of assay: 12 hours.

The samples have been collected at predetermined time intervals (2, 4, 6, 8 and 12 hours) and the assay of the metoprolol has been performed under Romanian Pharmacopoeia 10th Ed. conditions.

The samples of dissolution medium (10 ml) were withdrawn up to 12 h and analyzed spectrophtometrically at 280 nm by using a Camspec 330 M UV/Visible Spectrophotometer (England).

The mean values of the 3 determinations for each formulation are shown in table 3.

Table 3.-Metoprolol - rate of the release from each formulations

Batch code	Dissolute metoprolol [%]				
	After 2 hours	After 4 hours	After 6 hours	After 8 hours	After 12 hours
XT	38.2	51.6	76.7	85.2	95.6
AT	34.6	54.8	71.6	83.1	93.0
CT	28.8	49,8	62.0	79.8	89.5
XS	23.4	58.0	73.8	86.1	95.8
AS	37.7	60.1	70.8	84,1	92.3
CS	27.1	55.8	66.8	80.3	88.7
AmHT	39,5	62.5	82.4	90.5	97.5
AmHS	40.1	63.1	81.5	90.8	98.1

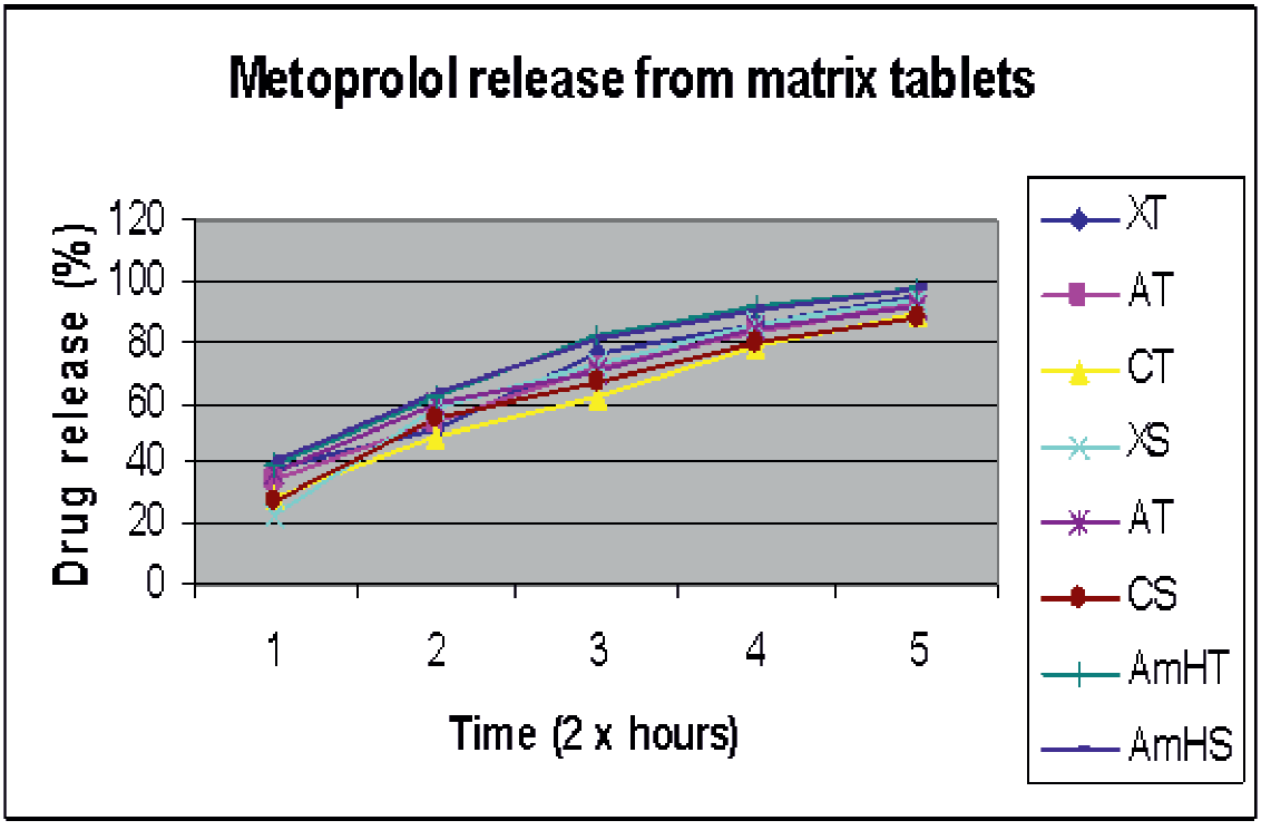

Fig.2.- Drug release from hydrophilic matrix tablets with metoprolol salts

RESULTS AND DISCUSSION

Matrix tablets characteristics

Determination of matrix tablets quality parameters is presented in table 2.

Results showed that compression process yielded tablets uniform in weight (512.5 – 518.5 mg).

Tablet hardness is ranged in narrrow interval from 7,8 – 12, to 88.9 N, with the exception of sample with carageenan (CT and CS).

For this formulation, it was not possible to achieve higher tablet hardness than 63 – 63.2 N to 64.5 N with metoprolol salts (succinate or tartric) despite using higher pressure force.

Tablet friability was in between 0.27 and 0.53 % for all samples with the exception of sample CS and CT with carrageenan when the fracture of three tablets was observed within the test.

From these results, it seems that carrageenan negatively influenced the mechanical properties of matrix tablets.

For highly soluble drugs like metoprolol salts, is neccesary a rapid rate of hydration of matixing agents because a slow polymer hydration rate may led to ,,a dose dumping" due to a quick penetration of dissolution fluid into tablet core and subsequent diffusion of drug solution.

A rapidly hydrating hydrophilic matrixing agent was chosen in the present study and this is the mix of the three hidrocolloids in ratio 1:1:1

The mix of this matrixing agents can be used to overcome the disavantages of individual matrixing agent or to achieve desired drug release pattern (8-10).

CONCLUSIONS

Important formulation factors were systematically studied for the development and fabricate modified release tablets of metoprolol xanthan gum, alginates salts and carageens and mix of this natural hydrocolloids.

The combination of matrixing agents: xanthan gum, alginates salts, carageenans overcomes disavantages of each polymer.

The drug release, and tablets characteristics was found to be dependent on the amount and type of matrixing agent.

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