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POROUS PELLETS – A POSSIBILITY TO OBTAIN A MODIFY RELEASE FOR METOPROLOL SALTS

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ABSTRACT
This study have the objective to obtain porous pellets consisting in a mix of HPMC (hidroxypropylmethylcellulose) and xanthan gum or alginates salts or carrageens salts, and calcium salts soluble in water as gelling agent.
This pellets after the removal of the calcium ions via extraction with water was evaluated by loading techniques to incorporate metoprolol salts by two techniques: fluid bed and immersing in a drug solutions.
The pellets obtained by extrusion and spheronisation was characterized from residual content in calcium ions, friability and drug loading.
The pellets obtained can be used as carriers from metoprolol salts (succinates and tartrate).
The drug loading studies have shown that immersing the pellets in a drug solution are able to deposit metoprolol salts inside.
Using fluidized bed coating no drug was found inside the porous pellets.
Key words: alginates salts, carrageens salts, and calclium salts soluble in water gelling agent, extrusion, hidroxypropylmethylcellulose, metoprolol salts (succinates and tartrate), spheronisation, xanthan gum.

INTRODUCTION
The drug delivery systems disperse freely in the gastrointestinal tract, and this action contributes to maximum drug absorption, reduced peak plasma fluctuations, and less side effects (2, 4, 6, 9).

Multiparticulate drug delivery systems, such as pellets, are used frequently because they offer therapeutic advantages over single unit dosage.

Furthermore, pellets also allow the formulator to modify the drug release by coating the pellets, and a mixture of pellets with different release characteristics can be used to obtain the desired release profile (1, 5, 6, 10, 15).

The objective of this study was to develop porous pellets that allow the incorporation of large drug fraction (deposited inside the porous structure or layered on the surface of pellets) (2, 9, 11, 14).

Pellets consisting in a mix of HPMC (MethocelÒ) and xanthan gum or alginates salts or carageenan salt, and calcium salts soluble in water (calcium acetate) were manufactured and after the removal of the calcium ions via extraction from porous pellets were obtained (17, 18).

Their potential as drug carriers was tested by loading the pellets with drugs.

Two techniques were evaluated as loading techniques to incorporate drugs into the porous pellets:

1. fluid bed layering and
2. immersing the pellets in a drug solution.

Fluidized bed layering is the most commonly used technique to load pellets with drug.

Pellets are fluidized in the fluidized bed system and a drug solution or suspension is sprayed on the pellets (9, 10).

Soaking the pellets in a drug solution is the simplest method to incorporate drugs into the pellets.

The drug are dissolved in a appropriate solvent and pellets are soaked in the solution for a certain time period (3).

MATERIALS AND METHODS
Hydroxyproylmethylcellulose (HPMC, MethocelÒ),

Xanthan gum, alginates salts and carageenan– this four hydrocolloids were obtained as a gift samples from Applied Research and Investment Co. (CCAI), Bucharest, Romania

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 samples from S.C, Magistra C&CS R.L.-Romania

Calcium acetate was from Merck^{R}

MANUFACTURING OF POROUS PELLETS
Calcium acetate was sieved on CISA Sieve (Spain) for 5 minutes and the sieve fraction < 125 μm was collected.

The mix of HPMC (MethocelÒ) with and xanthan gum or alginates salts or carageen and calcium acetate fraction < 125 μm were dry mixed (20:10:70, w/w) in a mixer (UMA-Pharmag, Germany) (Table 1.)

Subsequently, 40 % (w/w) water was added to the mixture and the wet mass was granulated for 10 minutes.

Extrusion was performed using a single screw extruder (Caleva model 25, England) at 50 rpm, equipped with a 1 mm perforated screen.

The extrudates were spheronized on a spheronizer (Caleva model 120, England) with a cross-hatched friction plate, operating at 1000 rpm with a residence time of 5 minutes.

The pellets were oven-dried at 40^0 C in a Memmert oven (Germany), followed by sieving whereby the 250 μm pellet fraction was collected.

The calcium ions was removed from the pellets by aqueous extraction: 50 g pellets were placed on to a 500 mL bottle top filter Gooch 0.22 μm, the filter was placed on a 2 L flask and connected to a vacuum pump.

A sample of 2 L of water was poured on to the filter in steps of 250 mL to extract the calcium acetate fraction.

Later, the pellets were oven-dried at 40^0 C.

The composition of the pellets **Table 1.**

Ingredient of the pellets (g%)	Batch code		
	MX	MA	MC
Methocel R	20	20	20
Xanthan gum	10	-	-
Alginates salts	-	10	-
Carageens salts	-	-	10

PELLETS EVALUATION

Residual Ca^{+2}

To determine the residual Ca^{+2} ions content after extraction, the amount of Ca^{+2} ions in the porous pellets was quantified using a volumetric method (see below).

A sample of 10 g of porous pellets were soaked in 100 mL demineralized water and after disintegration of the pellets, using a magnetic stirrer (Heidolph MR 3001K, Germany) and centrifugation (Janetzky, Poland) at 2500 x g, the Ca^{+2} concentration in the supernatant was determined by a volumetric method (titration with EDTA- sodium in the presence of murexide at pH less 12) (Table 2).

The mean value of three samples of each batch were calculated.

The friability

The friability was determined by placing 10 g pellets (P_s) in an abrasion wheel (Friabilator VanKel – US) together with 200 g glass beads, diameter 4 mm.

The pellets were subjected to falling shocks at a rotational speed of 25 rpm for 10 minutes.

Later, the fine pellets were removed by sieving through a 250 μm sieve for 5 minutes (2 mm amplitude).

The fraction above 250 μm (F_a) was used to calculate the friability (Table 2) using the following equation:

$$Friability\ (\%) = [(F_s - F_a)/F_s] \times 100$$

The mean value of three samples of each batch were calculated.

Pellets characterization **Table 2**

	MX (n=3)	MA (n=3)	MC (n=3)
Residual Ca^{+2} (g % calcium acetate)	3.8	4.75	5.2
Friability (%)	0,98	1,05	0.945

DRUG LOADING

To incorporate drugs into pellets were used two techniques:

1. immersing the pellets into a drug solution
2. fluid bed layering

Method 1: 1 g of porous pellets (n = 3) was added to 100 mL of metoprolol tartrate or metoprolol succinate solution (10 % and 20 % w/v).

After 30 minutes, 6 hours and 12 hours, the pellets were separated using a sieve (250 μm) and then oven-dried at 40^0 C

Method 2: aqueous coating solutions containing 1 % or 2 % metoprolol tartrate or succinate (w/v) were prepared.

A sample of 2 L of each coating solution was sprayed on the pellets (batch size 100 g) in a fluid bed (MiniCoater/Drier 2, Caleva - England).

The operating condition while coating were set a 20 g / min spray rate, 2 atm. atomization pressure, at 40^0 C outlet temperature, and 2 hours process time.

Coating efficiency

The coating efficiency was calculated on the basis of the theoretical amount of metoprolol tartrate or succinate layered on the pellets.

For the determination of loading yield (mg drug/g pellets), the pellets were crushed, placed in water and stirred for 30 minutes, followed by centrifugation.

The amount of drug in the supernatant was determinated using UV spectrofotometry (Caspec 330 M UV/Vis Spectrofotometer, England) (Table 3).

The mean value of three samples of each batch were calculated.

RESULTS AND DISCUSSION

Most of the calcium acetate fraction was removed during the aqueous extraction as analysis of the porous pellets using the volumetric method determinate the residual calcium acetate content is less 6 %, respectively 5.2 %, 4.75 and 3.8 depending on the formulation approached (Table 2).

Although almost of 65 % calcium acetate is removed from the porous pellets by extraction and therefore by extension their porosity was approximate 65 %.

Despite their high porosity, the porous pellets were sufficiently strong to withstand the friction forces during handling as the friability was below 0,1 % (Table 2).

Two drug loading techniques were tested for drug deposition in the porous structure of the pellets.

Metoprolol salts, the model drug used, have a very good solubility in the solvent used.

After soaking the porous pellets for 5 minutes in a 10 % (w/v) metoprolol tartrate or metoprolol succinate solution the drug load was around 100.4 to 112.5 mg / 100 g pellets and around 198.8 and 249.8 mg / 100 g pellets for solution 20 % (w/v) metoprolol tartrate or metoprolol succinate (Table 3).

Increasing exposure time to 2 hours leads to the amount of drug deposited on the pellets up to 543.3 to 543.2 mg /100 g pellets for metoprolol tartrate and up to 580.9 to 660.5 mg / 100 g pellets (Table 3).

Drug loading

Table 3

		Immersing method (n=3) -coating solution-						Fluid bed layering (n=3) -coating solution-	
		10 % (w/v)			20 % (w/v)			1 % (w/v)	2 % (w/v)
		30 min	6 h	12 h	30 min	6 h	12 h	2 hours	2 hours
MX	*Metoprolol succinate* (mg/100g pellets)	112.5	151.2	260.4	249.8	300.3	580.9	0.96	1.96
	Metoprolol tartrate (mg/100g pellets)	118.4	146.9	249.3	232.4	298.7	566.3	0.84	1.85
MA	*Metoprolol succinate* (mg/100g pellets)	111.8	148.4	255.9	220.6	312.3	660.5	0.958	1.99
	Metoprolol tartrate (mg/100g pellets)	120.3	139.2	235.8	212.3	311.3	623.8	0.856	1.84
MC	*Metoprolol succinate* (mg/100g pellets)	98.8	121.6	196.2	200.4	245.1	553.2	0.80	1.86
	Metoprolol tartrate (mg/100g pellets)	100.4	119.3	168.4	189.8	230.2	543.2	0.74	1.78

Regarding the mix of MethocelÒ and hidrocolloids, the pellets obtained with xantham gum and Methocel present the best porosity, the amount of drug deposited is the most (Table 3).

Layering pellets with a drug solution using fluid bed coating was also examined for drug loading because this techniques is commonly used for loading inert spheres with drug.

The coating efficiency after 2 hours with 1 % and 2 % solution of metoprolol tartrate or metoprolol succinate leads to a coated of the pellets approximately 1 % or 2 %.

The absence of the drug inside the pellets was probably due to limited penetration of the drug solution within the pellets as most of the water evaporated once the droplet was distributed on the pellet surface.

In this case the mix MethocelÒ and hydrocolloids no influence the amount of drug deposited on the pellets.

CONCLUSION

Porous pellets manufactured by extraction of residual calcium ions from the mix of MethocelÒ:Hydrocolloids can be used as drug carriers from metoprolol salts.

The drug loading studies have shown that immersing the pellets in a drug solution are able to deposit metoprolol salts inside the porous pellets.

By using fluidized bed coating on the other hand, no drug was found inside the porous pellets.

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