

IDENTIFICATION OF CRITICAL FORMULATION VARIABLES FOR OBTAINING METOPROLOL TARTRATE MINI-TABLETS

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Abstract

The aim of this experimental work was the obtaining of mini-tablets with 3 mm diameter containing metoprolol tartrate as active ingredient. They can be used either as pediatric medication or adult medication after further coatings, in order to obtain modified release mini-tablets.

The mini-tablets were prepared using an eccentric tableting machine after a fluid bed granulation of the components. The dosage form with proper pharmaceutical and physico-chemical properties: no sticking, uniformity of weight and content uniformity in required limits, as well as desired immediate release of the drug was obtained. The formulation with these properties contained: 20% of the active drug, lactose as filler for fluid bed granulation, Cellactose 80 as extra granular diluent, as well as magnesium stearate and Compritol as lubricants.

Rezumat

Scopul acestei lucrări experimentale a fost obținerea unor minicomprimate cu diametrul de 3 mm, conținând ca substanță activă metoprolol tartrat. Aceste minicomprimate pot fi folosite atât în pediatrie, cât și ca medicație pentru adulți, după acoperirea ulterioară cu filme polimerice în vederea obținerii de minicomprimate cu cedare prelungită.

Minicomprimatele au fost preparate folosind o mașină de comprimat cu excentric după o granulare în pat fluidizat a componentelor. S-au obținut minicomprimate cu proprietăți fizico-chimice corespunzătoare: fără lipire, uniformitatea masei și uniformitatea conținutului în limitele cerute, cedarea imediată, dorită a substanței medicamentoase. Formularea cu aceste proprietăți conține: 20% substanță activă, lactoză monohidrat - excipient pentru granularea în pat fluidizat, Cellactose 80- excipient diluant extragranular, stearatul de magneziu și Compritol ca lubrifianți.

Keywords: fluid bed granulation, mini-tablets, metoprolol tartrate, formulation variables

Introduction

Mini-tablets are tablets having a diameter equal to or smaller than 2-3 mm [12]. Mini-tablets have numerous advantages over larger single unit tablets in terms of flexibility during the formulation development and therapeutic benefits to patients [9]. Mini-tablets have also some advantages

over other multi-particulates like pellets: for their production standard equipment is used; the tableting process is shortly comparative with drug layering in the pelletization procedure. Additional benefits of mini-tablets include excellent size uniformity, regular shape and smooth surface, offering an easily coating substrate either for immediate release or modified release purposes [13].

Mini-tablets can be used as a potential new formulation for pediatric oral drug delivery [17]. In pediatric use mini-tablets present many benefits over orally administrated liquids, including the delivery of an accurate dose without any manipulation before administration and the opportunity of dose flexibility (for different patient ages and weights) through administration of multiple mini-tablets [6].

Like other multi-particulate technologies, mini-tablets can be either filled in hard capsules or placed in sachets for an easy administration [13].

The objective of this work was to identify critical formulation and process variables, in order to obtain mini-tablets with a diameter of 3 mm, containing metoprolol tartrate. The aim of obtaining these minitabets is using them either as pediatric medication or adult medication after further coatings, in order to obtain modified release mini-tablets.

Metoprolol tartrate is a powder with poor flow and compaction properties due to its low bulk density, electrostatic charge, as well as sticking tendency and in consequence it is an active pharmaceutical very difficult to work with [14]. A direct compression of this substance in the powder form was not possible. In general, a good flow can be achieved by increasing the particle size of the powders [3, 10, 18]. The wet granulation process was chosen to obtain granules which are suitable in mini-tablets manufacturing. In the case of mini-tabletting, due to the small diameter of the dies, the big particle size of the granules can lead to interrupted flow through the small orifices [11, 12]. According to the previous works, the material processed by the fluid bed granulator is finer, more free-flowing than the materials processed by conventional wet granulation [15].

Materials and methods

Apparatus. Laboratory fluidized bed system Strea 1 (GEA-Aeromatic, Switzerland); tablet press EK-0 (Korsch, Germany); DIN sieve set (VEB MLW, Germany); oscillator mill FGS with sieve 0.6 mm (Erweka Germany); friability tester type TA (Erweka Germany); powder flow tester type GTB (Erweka Germany); tablet hardness tester (Pharmatest PTZ-E, Germany); dissolution apparatus (Erweka DT800, Germany); spectrophotometer UV-Vis (Agilent 8453, SUA) .

Materials. Metoprolol tartrate was received as a gift from Microsin, Romania; polyvinylpyrrolidone – PVP K 30 (BASF Germany); Lactose monohydrate–Pharmatose 200M (DMV-Fonterra, Netherlands); pregelatinised starch–Starch 1500 (Colorcon UK); co-processed excipient - Cellactose 80 (Meggler, Germany), was a gift from Pharmachemicals GmbH, Hamburg; Spray-dried lactose–FlowLac100 (Meggler, Germany), magnesium stearate (Mallinckrodt, USA); silicon dioxide–Aerosil 200 (Degussa), Glyceryl behenate-Compritol 888 ATO (Gattefosse, France).

Methods.

Granule preparation. Granulation process was performed in a fluid bed system Strea 1 (Aeromatic, Switzerland). The different granulation formula and the variable working conditions are presented in Table I and Table II.

Table I
Fluid bed granulation formulations

Composition (quantities in %)	Formulation no.		
	1	2	3
Metoprolol tartrate	51.5	51.5	51.5
Lactose monohydrate	44.9	29.4	13.9
Pregelatinized starch	0	15.5	31.0
Povidone K30*	3.6	3.6	3.6

* aqueous solution 10%

Table II
Fluid bed granulation process parameters

Process parameters	Formulation no.
	1, 2, 3
Preheating time, (min.)	2
Charge load (g)	161.74
Nozzle diameter, (mm)	0.8
Spraying rate (g/min)*	3.244
Atomizing pressure	1
Fan air (m ³ /min)*	3- 4
Spraying time, (min)	18
Inlet air temperature, (°C)	68-73
Outlet air temperature, (°C)	33-40
Drying temperature (°C)	65
Bag filter shaking time, (sec)	7

The obtained granules were milled in an Erweka FGS oscillator mill (sieve 0.6 mm).

Blend preparation for compression. In order to improve tableting properties of metoprolol granules, the extra granular ingredients were added for obtaining the blend for compression (Table III).

Table III
Minitablets composition

Composition (quantities in %)		Formulation no.						
		1 A	1B	1C	1D	2A	2B	3
IG	Metoprolol tartrate	33.36	33.36	20.00	20.00	33.36	20.00	33.36
IG	Lactose monohydrate	29.00	29.00	17.38	17.38	19.00	11.38	9.00
IG	Pregelatinized starch	-	-	-	-	10.00	6.00	20.00
IG	Povidone K30*	2.34	2.34	1.40	1.40	2.34	1.40	2.34
EG	FlowLac 100	31.80	28.80	54.72	-	31.80	54.72	31.80
EG	Cellactose 80	-	-	-	54.72	-	-	-
EG	Colloidal silicon dioxide	1.00	1.00	1.00	1.00	1.00	1.00	1.00
EG	Magnesium stearate	2.50	2.50	2.50	2.50	2.50	2.50	2.50
EG	Compritol 888ATO	-	3.00	3.00	3.00	-	3.00	-

IG- intra-granular ingredient, EG-extra-granular ingredient

* aqueous solution 10%;

In the formulation no., 1,2, 3 represents fluid bed granulation formulation (Table I), and A,B,C or D means the different extra granular composition for the same granule

Determination of blend and tablets characteristics

Particle size distribution of the blend was performed using dry sieving method with a set of 6 sieves: 600, 500, 400, 315, 200 and 125 μm (for 100 g of blend) [7]. Granule mean diameter (Md) and variation coefficient (CV) were calculated according to equations (1), (2) and (3):

$$Md = \frac{\sum n_i x_i}{N} \quad (1), CV = \pm \frac{SD}{Md} \times 100 \quad (2), SD = \pm \sqrt{\frac{\sum n_i x_i^2 - (\sum n_i x_i)^2 / N}{N - 1}} \quad (3)$$

where N is the frequency and SD is the standard deviation.

The determination of the flow rate was performed using the powder flow tester type GTB (Erweka) [7]. It was measured the necessary time for 10 g of powder to pass through a funnel with 3 mm diameter.

The pharmaceutical characteristics of the tablets were determined by the officinal methods: average mass and mass uniformity, content uniformity, hardness, friability [5,7,19], assay - UV method at 274nm [4,5] and dissolution test [16, 19].

Results and discussion

In the initial formulation phase, several different diluents and lubricants were used, in order to find the most suitable formulation from the technological point of view. In the fluid bed granulation, the starting material has to present different properties, like a small particle size, a narrow particle size range, a low density [15]. The influences of the two intragranular fillers, in different ratio and different extra-granular composition (different type and concentration of diluents and lubricants, and different active drug amount in the final blend) on the properties of granule and mini-tablets were evaluated.

1. Evaluation of the influence of different formulation factors on the blend properties

Evaluation of the process factors influence on the particles of the blend mean diameter and its variation coefficient

Particles of the blend can be characterized physically by mean diameter and particle size distribution [3, 18, 20]. Very good quality blend have a particle size distribution within a narrow range, which is proved by a minimum average variation coefficient (CV) [10, 20]. In Table IV there are presented the mean diameter and variation coefficient obtained for all the tested formulations.

Table IV
Properties of the blend for compression

Formulation Number. (according to Table III)	Mean diameter (μm)	CV (%)	Flow rate mg/sec
1A	225.78	39.1	9.39
1B	225.62	39.2	9.39
1C	153.22	60.5	12.3
1D	177.89	54.4	10.39
2A	207.27	56.2	9.45
2B	175.77	52.1	11.56
3	187.26	55.1	9.52

By comparing the formulations 1A, 2A and 3 (only the quantity of filler for granulation is different- see table III) it can be observed that the effect of introducing and increasing the content of pregelatinized starch is decreasing the mean diameter due to the decrease in granule growth (Table IV). The important changes in mean diameter values were obtained either by using different percentages of extragranular diluent (FlowLac100 in formulation 1A, 1B, 1C or 2A, 2B -see table III) or by using extra-granular

diluents with different characteristics (FlowLac100 versus Cellactose 80, formulation 1C versus 1D - see Table III) [1, 8].

Evaluation of the formulation factors influence on blend flowability properties. In Table IV there are also presented the results of the flow rate through the funnel for all the formulations. According to the results obtained, the flow velocity through the funnel with 3 mm diameter is inversely correlated to the mean particle size: the finer the granules, the higher the velocity of flow.

2. Evaluation of the formulation factors influence on the mini-tablets characteristics

Evaluation of the formulation factors influence on the uniformity of weight

In table V there are presented the characteristics of the mini-tablets for all formulations.

Table V
Mini-tablets Characteristics

Form. no.	Average weight (mg)	Uniformity of weight limits (%)	Stickin g	Hardness (N)	Friability (%)
1A	25.9	25.9 ± 8.4%	3	25-35	0.09
1B	25.6	25.6 ± 8.76%	2	25-35	0.08
1C	24.75	24.75 ± 6.55%	1	22-34	0.08
1D	25.1	25.1 ± 4.38%	1	30-40	0
2A	25.2	25.2 ± 10.29%	3	25-40	0.1
2B	25.5	25.5 ± 3.92%	2	30-40	0.07
3	25.3	25.3 ± 12.33%	3	25-45	0.12

Form.no.- Formulation number according to table III, 1-no sticking, 2-moderate sticking, 3- sticking

According to the European Pharmacopoeia, for a tablet weight of 80 mg or less, the weight variation should be less than 10%. The uniformity of weight is in the required limits for almost all the formulations (Table V), excepting the formulations that contain 33.34% metoprolol tartrate and 20% or 10% of Starch 1500 (Formulations 2A and 3). According to the obtained results (Table IV and Table V) the weight uniformity is related to the granule flow behavior. The good flow of the granule means uniform die filling and subsequently good weight uniformity. Although the small particle size of the formulation that contained pregelatinized starch is an advantage for flowability through small orifice, uniformity problems occur (for example formulations 2A and 3 have a lower particle size and higher flow rate versus formulation 1A). The possible explanation for this can be that during fluid bed granulation the granule growth of hydrophilic materials takes place selectively [15]. In the case of formulations 1A, 2A and 3, as the content of pregelatinized starch increases the weight uniformity is better.

Evaluation of the formulation factors influence on the tablets sticking

In Table V there is also presented the sticking tendency for all tested formulations. Almost all formulations have sticking problems excepting the formulations that contain only lactose as filler for granulation, 20% metoprolol tartrate and 2 lubricants (2.5% magnesium stearate, 3% Compritol). The argument for these results is not only the fact that metoprolol tartrate is a very sticky material, but also the die's small diameter in the compression of mini-tablets. The effect of air flow and pressure gradients, as well as the large surface in contact with the die, may lead to the development of friction forces [11]. According to the previous experiences, to keep the ejection forces in an acceptable range, higher concentration of lubricant or a combination of two lubricants is required [2,12].

Evaluation of the formulation factors on the mechanical strength and friability of the tablets

In table V there are also presented the results for hardness and friability. Considering mini-tablets as the possible coating substrate, a good hardness and less friability are required.

By comparing the 1C and 1D formulations (formulations without sticking problems), the formulation that contains Cellactose 80 (formulation 1D) has higher hardness and lower friability results than the formulation with FlowLac100 (formulation 1C). Cellactose80 is a co-processed excipient that contains lactose monohydrate (75%) and cellulose powder (25%). According to Garr and Rubinstein, the good compactibility of Cellactose is attributed to a synergetic effect of consolidation by fragmentation of lactose and plastic deformation of cellulose [8].

Evaluation of the chemical parameters for the best formulation obtained

According to the results (table IV and table V), from a technological point of view, the best formulation obtained is formulation 1D: proper granule flow, uniformity of weight in the required limits, no sticking problems, good hardness and no friability. In table VI the results of chemical parameters for formulation 1D are presented: assay for granule and mini-tablets, dissolution and content uniformity. The results indicate that formulation 1D has good pharmaceutical and physico-chemical characteristics.

Table VI
Chemical parameter evaluation- formulation 1D

Parameter	Limits	Results
Assay % for granule[5]	97-103 %	98.02
Assay % for mini-tablets [5] 10 mini-tablets contain:	95-105%	97.05
Dissolution % (By UV) [19]	*NLT 75 % of the labeled amount of Metoprolol tartrate is dissolved in 30 minutes	99.82
Uniformity of dosage units (By content uniformity)[5,7]	± 15 % of the label claim **AV ≤ 15	99.64%- 104.85% AV=4.8

*NLT= no less than; **A= average

Conclusions

It was studied the influence of the formulation factors on the characteristics of the granules obtained through a fluid bed method, and mini-tablets subsequently prepared. Powder flow and tooling lubrication have a very important influence for mini-tablets formulation.

Mini-tablets with proper physico-chemical properties (no sticking, reproducible weight and content uniformity, and desired immediate release of the drug (Table VI), were obtained when there was used: lactose as filler for fluid bed granulation, Cellactose 80 as extra granular diluent, the 20% amount of the active drug, magnesium stearate and Compritol as lubricants (Formulation 1D –Table III).

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