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Research paper

Application of failure mode and effects analysis in quality by design approach for formulation of carvedilol compression coated tablets

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ABSTRACT

Compression coating technique has been used in formulation of chronotherapeutic drug delivery systems with pulsatile carvedilol release with polyethylene oxide as controlling release agent. FMEA, risk analysis tool, was applied within Quality by Design approach with aim to detect process and formulation parameters affecting the carvedilol release profile from compression coated tablets. It gives Risk Priority Numbers (RPNs) for each failure mode. Also, using experimental designs, statistical significance of the formulation parameters influence was estimated. High RPNs in case of the lag time as critical quality attribute (CQA) was obtained for polymer molecular weight, compression of coat and low concentration of sodium chloride. For percent of released carvedilol from coated tablets (Q), second CQA, RPNs were high for low concentration of sodium chloride, sodium starch glycolate and crospovidone, polymer molecular weight and also for compression of the tablet coat. Experiments performed according to experimental plans, showed statistically significant influence of Polyox® WSR N60K and sodium chloride concentration on lag time, and concentration of polymer, sodium chloride, mannitol and type of superdisintegrant on Q. These studies demonstrate that FMEA may be a useful tool for Formulation by Design of compression coated tablets.

1. Introduction

1.1. Pulsatile drug delivery systems

Chronopharmaceutic systems are a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy [3,13,22]. Pulsatile drug delivery systems have fulfilled requirements posted in front of the chronotherapeutics. These systems show drug release suddenly after well-defined lag time or time gap, according to circadian rhythm of disease states. No drug is released from the device within this lag time [4,11].

Carvedilol is a non-selective β-blocker indicated in the treatment of mild to moderate congestive heart failure, hypertension and myocardial infarction. It can be used in formulation of chronotherapeutic systems and compression coated tablets [1,17].

1.2. Compression coating technique

Compression coating, press-coating or dry coating is an old technique. In general, a press-coated tablet consists of an inner core tablet and an outer coat. The outer layer surrounds the inner core, and therefore selection of the outer layer materials has a significant impact on the performance of the tablet, including the coating's mechanical strength, drug release characteristics, and tablet stability [2,11]. Drug delivery systems based on press-coating technique have been proposed for delayed, pulsatile, and programmable release of the drug (carbamazepine, acetaminophen, chlorpheniramine maleate [15], sumatriptan succinate [7,8]). Schematic design for preparing press-coated tablets is shown in Fig. 1.

1.3. Quality by design

Development of compression coated tablets involves formulation of the tablet core, in order to obtain pulsatile drug release and, furthermore formulation of outer coat to provide predetermined lag time. Different types of excipients are included in formulation of the fast disintegrating or modified release tablet core, such as

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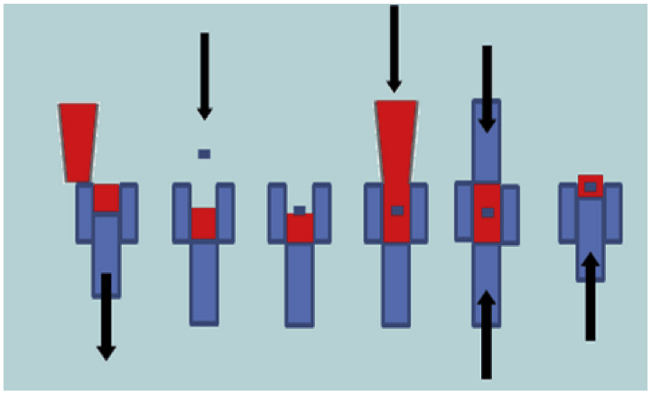

Fig. 1. Graphical representation of the press-coating process.

superdisintegrants (sodium starch glycolate, sodium carboxymethyl cellulose, and cross-linked polivinil pyrrolidone [8]), and osmotic excipients (sodium chloride [12], mannitol [16,20]). Press-coated tablets may be modified to provide different release patterns, by varying the drug distribution and type of polymers used in the core and outer coat. Polymers which are often used are cellulose derivatives (hydroxypropyl methyl cellulose, hydroxypropylcellulose, hydroxypropyl methyl cellulose acetate succinate, and ethyl cellulose), polysaccharides (guar gum, pectin, behenic acid), polyethylene oxides (PEO), waxes etc.

Modification of the lag time is often achieved using PEO polymers. [7] investigated compression coated tablets with Polyox WSR 205 and xanthan gum in tablet coating achieving lag time from 2 to 6 h, depending on Polyox WSR 205 concentration. [19] used Polyox WSR 303 with different channeling agents in coating formulation of compression coated tablets, and achieved lag time from 4 to 12 h. Also, [18] examined the influence of Polyox WSR 301 and 1105 on torsemide release profile. Formulations showed lag time of 6 h and as the amount of PEO was increased in the outer layer the drug release was delayed. [9] investigated compression coated floating pulsatile drug delivery systems of bisoprolol using Polyox WSR 205 and N12K. All formulations showed lag time in range from 2 to 6 h.

Considering all previously mentioned factors that can influence the drug release profile, one of the approaches to make this step of formulation easier is Formulation by Design. It represents an approach in which experiments are designed in certain manner where key independent statistically important variables can be identified. The first step is definition of the Quality Target Product Profile (QTPP) which represents perspective summary of the quality characteristics of the drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product [21]. The Quality by Design (QbD) requires process understanding and the determination of the design space, which requires identification of the principal critical quality attributes (CQAs) from basis formed in QTPP [10]. One way to optimize the use of resources in development is to use risk management methods to prioritize the variables to be studied. Risk assessment is a valuable science-based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs [5]; [6]. In case of compression coated tablets it is very difficult to formulate separately tablet core and coat, because of their complex and associated influence on the lag time and total amount of released drug. Therefore, various risk analysis tools can be used for categorization of influence of greater number of different parameters, for example the Failure Mode and Effects Analysis (FMEA).

The aim of the presented study was to evaluate the influence of the formulation (core and coat) and process parameters on the CQAs of carvedilol compression coated tablets: lag time, amount of dissolved drug from core (q) and from coated tablets (Q) applying FMEA. There are no published reports of FMEA application in the purpose of investigation of formulation and process parameters influences in compression coated systems. Also, the aim was to implement Formulation by Design concepts to investigate significance of formulation parameters of compression coated tablets with carvedilol pulsatile release using experimental design and observing lag time and Q as dependent variables.

2. Materials and methods

2.1. Materials

Carvedilol was used as a model drug and it was obtained from commercial supplier (Hemofarm, Belgrade, Serbia). Polyethylene oxides (Polyox® WSR Coagulant, Polyox® WSR 301 and Polyox® WSR N60K) were obtained from Dow Chemical Company, Charleston, USA. Direct compressible lactose (Ludipress®) was kindly donated by BASF ChemTrade GmbH, Ludwigshafen, Germany. Sodium chloride (Sigma–Aldrich, Steinheim, Germany), α-lactose monohydrate (Sigma–Aldrich, Steinheim, Germany), mannitol (PEARLITOL® 200SD, Roquette Pharma, Lestrem, France) were also used. All other ingredients were of analytical grade.

2.2. Methods

2.2.1. Preparation of tablets

Preparation of the tablet cores and compression coating process were performed on the excenter tablet press (Korsch EK0 AR 402, Berlin, Germany) considering several steps. First, the inner core of the tablet is compressed. Afterwards the tableting machine die is pre-filled with one half of the coat mass material to form a powder bed, the compressed inner core tablet is then centered in the tablet die, and remaining half of the coat mass is added. The outer coat is compressed around the inner core tablet. Tablet punch diameters used for tablet core were 6 and 9 mm, and for coated tablet were 9 and 12 mm.

2.2.2. Dissolution testing

In vitro dissolution studies were carried out in 0.1 N HCl (900 mL) at 37 ± 0.5 °C using USP dissolution apparatus type II (Erweka DT 600, Hausenstamm, Germany) for both tablet cores and compression coated tablets according to USP monograph for dissolution test for carvedilol tablets. The speed of rotation was set at 50 rpm. Aliquots of dissolution medium were withdrawn for the total period of 1 h (10, 20, 30 and 45 min) in case of tablet cores and at each 30 min time interval for compression coated tablets during the 8 h long dissolution tests. Content of carvedilol was determined by using UV spectrophotometer (Evolution 300, Thermo Fisher Scientific, Laughborough, USA) at 241 nm. Parameters for the comparison of the dissolution profiles were lag time (time within less than 5% of released carvedilol), and Q (% of released carvedilol). QTPP for carvedilol compression coated tablets is shown in Table 1.

2.2.3. Risk analysis

Failure Modes and Effects Analysis (FMEA) was used as risk analysis tool in RXpress software (Educe Global Inc., USA). Process and formulation factors (Table 2) were analyzed. In the group of core related factors, osmotic agents (sodium chloride and mannitol) and superdisintegrants (sodium starch glycolate and crospovidone) were estimated. Core compression force was considered and set on constant value for all tablet cores formulations. In the coat related factors, polymer molecular weight, and its concentration were