International Journal of Pharmaceutics 519 (2017) 220–229

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Simulation and evaluation of rupturable coated capsules by finite element method

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ARTICLE INFO

Article history:
Received 9 October 2016
Received in revised form 30 December 2016
Accepted 12 January 2017
Available online 18 January 2017

Keywords:
Coated capsules
Finite element method
Mechanical properties
Swelling pressure
Burst behavior
Pulsatile drug release

ABSTRACT

The objective of this study was to simulate and evaluate the burst behavior of rupturable coated capsules by finite element method (FEM). Film and coated capsules were prepared by dip-coating method and their dimensions were determined by stereomicroscope. Mechanical properties of the film were measured by tensile test and used as material properties of FEM models. Swelling pressure was determined by restrained expansion method and applied to the internal surface of FEM models. Water uptake of coated capsules was determined to study the formation of internal pressure. Burst test and *in vitro* dissolution was used to verify the FEM models, which were used to study and predict the coating burst behavior. Simulated results of coating burst behavior were well agreed with the experiment results. Swelling pressure, material properties and dimensions of coating had influence on the maximum stress. Burst pressure and critical L-HPC content were calculated for burst prediction and formulation optimization. FEM simulation was a feasible way to simulate and evaluate the burst behavior of coated capsules.

1. Introduction

Various technologies of time-dependent pulsatile capsules have been proposed for chronodelivery drug delivery systems (DDSs). A colon-specific pulsatile capsule based on an impermeable capsule and a highly methoxylated pectin/lactose plug was reported (Huang et al., 2013). The lag time was determined *via* plug erosion and could be regulated by varying the lactose content. A three-pulse capsule based on multi-layered tablets inside was developed (Li et al., 2008). The lag time could be modulated by adjusting the HPMC/lactose ratio and the drug release rate could be improved by adding a separating layer. A multiple-pulse capsule based on high frequency energy transmission systems was developed (Gröning et al., 2008). Delayed and pulsed release profiles were obtained when the high frequency field was activated discontinuously.

Pressure-controlled coated capsules based on a burst mechanism were promising pulsatile DDSs. They could be easily prepared on a large scale using conventional coating machine (Hu et al., 1998), although coating burst process should be strictly monitored and controlled. Up to now, pulsatile DDSs based on hard gelatin capsules and soft gelatin capsules have been developed (Bussemer et al., 2003a; Bussemer and Bodmeier, 2003b). Lag time was adjusted over a broad range by varying the composition and amount of coating layer and swelling layer. Compared to hard gelatin capsules, soft gelatin capsule-based systems showed shorter lag times, suggesting that inside core had effect on coating bust. Recently, novel techniques, such as injection molding (Macchi et al., 2015) and 3D printing (Melocchi et al., 2016) were applied to modulate the onset of drug release from capsules. Although texture analysis had been used to investigate the mechanical properties of hard gelatin capsule shells (Mei et al., 2006), little

Abbreviations: FEM, finite element method; DDSs, drug delivery systems; MT, metoprolol tartrate; L-HPC, low substituted hydroxypropyl cellulose; EC, ethylcellulose; TEC, triethyl citrate; DCP, dicalcium phosphate; T_{df}, thickness of dry film; T_{wf}, thickness of wet film; C_e, expansion coefficient; L_{w0}, initial length of wet film; W_{w0}, initial width of wet film; T_{w0}, initial thickness of wet film; F_t, load in tensile test; L_w, displacement in tensile test; ΔL_w, elongation at break; ΔW_w, shrink of width at break; σ, stress; ε, stain; σ_b, tensile stress at break; ε_b, tensile strain at break; E_t, elastic modulus; ν, Poisson's ratio; D_s, diameter of Plexiglas die; F_s, swelling force; P_s, swelling pressure; P_{smax}, the maximum swelling pressure; Q_w, water uptake; M_0, weight before water absorption; M_t, weight after water absorption; σ_1, the maximum principal stress; P_b, burst pressure; $C_{L\text{-}HPC}$, critical L-HPC content for burst.

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http://dx.doi.org/10.1016/j.ijpharm.2017.01.027
0378-5173/

information of burst mechanism and simulation of coated capsules had been revealed.

Finite element method (FEM) was a useful tool for burst simulation. It has been widely used in the field of Biomechanics and Engineering Structures. Balloon expandable stent in a realistic coronary artery was simulated by FEM (Zahedmanesh et al., 2010). Application of pressure with restraining elements was found to be an efficient approach to accurately predict the stress-strain field in the vessel wall following full stent expansion and recoil. Upheaval buckling of offshore pipeline buried in clay soil was simulated by FEM (Nazari et al., 2015). The proposed models showed good prediction and could be used to improve the design and risk assessment of buried pipeline under thermal loading. The stress distributions of plastic bottles for burst pressure test and top load test were simulated by FEM (Daver and Demirel, 2012). The structural simulation studies were validated by experimental findings and used for process optimization. Recently, our study demonstrated that FEM could be used to simulate and evaluate the burst behavior of coated tablets (Yang et al., 2016a).

However, FEM simulation of coated capsules was different from that of coated tablets, and the major difficulties may lie in two aspects. Firstly, compared to the compacted tablet cores, coated capsules had low density substrate prepared by particle filling. The internal swelling pressure could not be measure using devices for compacted specimen (Yang et al., 2016a; Tang et al., 2011). Considering the significant influence of dry density on swelling pressure (Lee et al., 2012; Kaufhold et al., 2015), a novel device for capsules was necessary for detection precision. Secondly, the capsule coatings were non-uniform, so precise description of cap/body joint was not an easy task.

The aim of this work was to explore the potential of FEM to simulate the burst behavior of coated capsules. Pulsatile coated capsules was prepared with Metoprolol Tartrate (MT) as model drug, Low Substituted Hydroxypropyl Cellulose (L-HPC) as swelling polymer and Ethylcellulose (EC) as rupturable coating. The internal swelling pressure of capsules was determined by a self-made device, while the dimensions of coating was observed using stereomicroscope. The resulted FEM models were validated by burst test and used to evaluate the burst behavior.

2. Materials and methods

2.1. Materials

EC Std.20 was kindly donated by Shanghai Colorcon Coating Technology Co., Ltd. (Shanghai, China). Triethyl citrate (TEC) was obtained from Fengyuan Tushan Pharmaceutical Co., Ltd. (Anhui, China). Glycerol and ethanol were of all reagent grades and purchased from Huipu Chemical & Apparatus Co., Ltd. (Hangzhou, China). MT was supplied by Apeloa JiaYuan Pharmaceutical Co., Ltd. (Zhejiang, China). L-HPC was purchased from Shin-Estu Chemical Co., Ltd. (Japanese). Dicalcium phosphate (DCP) was purchased from Huzhou Zhanwang Phamacetical Co., Ltd. (Zhejiang, China). Gelatin capsules (#2) were obtained from Red Star Capsule Co., Ltd. (Shanghai, China).

2.2. Preparation of capsules and film

EC (6.0%, w/v) dissolved in a mixture solution of ethanol and glycerol (200 mL/5.5 g) was used as coating solution. TEC was added as plasticizer at a ratio of 5.0% (w/v) based on EC weight. Polymer film was produced by a dip-coating process (Bhatt and Kumar, 2016). Glass microscope slides used as molds were dipped into the coating solution, withdrawn at a speed of 7.0 mm/s and then air-dried completely. This process was repeated four times, and the obtained dry film was cut into rectangular specimens (40.0 mm × 15.0 mm) for use. Wet film was prepared by immersion dry film into purified water for 4 h.

MT (5.5%, w/w), L-HPC and DCP were mixed and manually filled into gelatin capsules (460 mg each) to prepare uncoated capsules. Uncoated capsules were fixed with rubber rods using cyanoacrylate adhesive, dipped into coating solution, withdrawn at a speed of 2.0 mm/s and then air-dried completely. As listed in Table 2, coated capsules (C_1–C_{16}) were prepared by dip-coating uncoated capsules with different L-HPC content (15, 20, 25 and 30%) for different times (2, 3, 4 and 5).

2.3. Dimensions of film and capsules

The thickness of dry film (T_{df}) and wet film (T_{wf}) were determined using an electronic micrometer. Expansion coefficient (C_e) of the film was calculated according to Eq. (1). Uncoated capsules and coated capsules were observed by stereomicroscope (SK2610A, Saikedigital, China) at certain magnification. Dimensions of uncoated capsules were determined by stereomicroscope with Microking measuring system V2.0. Coated capsules were cut and the thickness of dry coatings at different position was measured using an electronic micrometer. The thickness of wet coating at different position was calculated *via* C_e.

$$C_e(\%) = T_{wf}/T_{df} \times 100 \quad (1)$$

2.4. Mechanical properties of polymer film

Mechanical properties of wet film were measured using a texture analyzer (TA -XT plus, Stable Micro System Ltd, UK)

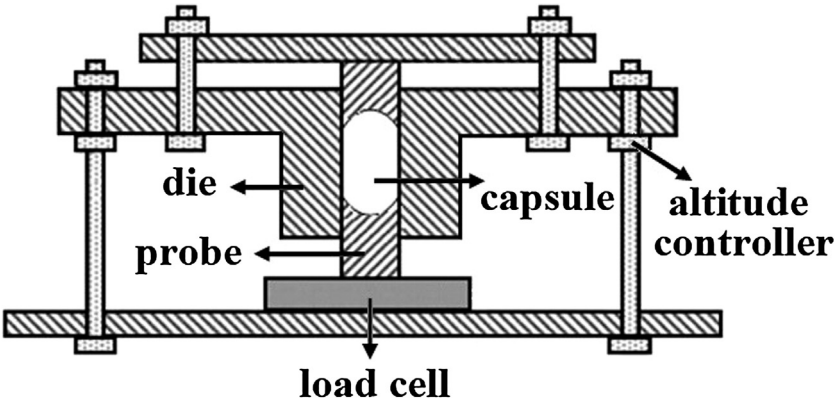

Fig. 1. Schematic diagram of the self-made device for swelling pressure of capsules.