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Nano-suspension coating as a technique to modulate the drug release from controlled porosity osmotic pumps for a soluble agent

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ABSTRACT

In controlled porosity osmotic pumps (CPOP), usually finding a single solvent with a capability to dissolve both film former (hydrophobic) and pore former (hydrophilic) is extremely challenging. Therefore, the aim of the present investigation was to tackle the issue associated with controlled porosity osmotic pump (CPOP) system using nano-suspension coating method. In the present study 4-Amino pyridine was used as a highly water soluble drug. In this method, a hydrophilic pore former (sucrose or mannitol) in nano range was suspended in polymeric coating solution using ball-mill. The performance of the prepared formulations was assessed in terms of D_{12h} (cumulative release percent after 12 h), Dev_{zero} (mean percent deviation of drug release from zero order kinetic), t_L (lag time of the drug release) and RSQ_{zero}. The results revealed that gelling agent amount (HPMC E_{15LV}) in core and pore former concentration in SPM had crucial effect on SPM integrity. All the optimised formulations showed a burst drug release due to fast dissolving nature of the pore formers. Results obtained from scanning electron microscopy demonstrated the formation of nanopores in the membrane where the drug release takes place via these nanopores. Nano suspension coating method can be introduced as novel method in formulation of CPOPs.

1. Introduction

In recent years, novel drug delivery systems (NDDS) have gained great attention due to providing sustained and constant drug release. Among NDDS, per oral controlled release (CR) systems including matrices, reservoirs and osmotic devices allocated the foremost market segment because of their advantages over others delivery systems [1]. On the other hand, the drug release from other delivery systems can be affected by the presence of food, pH and other physiological factors. The independency of these factors to a large extent in the case of osmotic systems is considered as advantages [2,3].

Osmotic pumps devices can be very useful for delivery of drugs, particularly for drugs with short biological half-life which requires frequent consumption during 24 h [4]. Many different systems have been developed based on the principle of osmotic pressure and some of these systems have reached the market. Elementary osmotic pump (EOP) [5–7], sandwiched osmotic tablet system (SOTS) [8], push-pull systems (PPOP) [9–12], controlled porosity osmotic pumps (CPOP) [13,14], tablet in tablet (TNT) cores [15], Asymmetric membrane capsule for osmotic drug delivery [12,16], osmotic systems made by swellable-core technology [17] and swellable elementary osmotic pump(SEOP) [18,19] can be noted. An EOP device principally consists of an osmotically active core covered by a semipermeable membrane (SPM) generally composed of cellulose acetate as film former and a small orifice drilled by laser beam or mechanical drills [2,20]. Controlled porosity osmotic pumps (CPOPs) are very simple forms of osmotic systems which the delivery orifice is formed by the incorporation of a water-soluble component in the membrane [21,22]. Thus, there is no need for sophisticated equipment for drilling of SPM. Other advantages of this system over EOPs are the drug release occurs from

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the entire surface of the membrane consequently decreasing the chance of pore-blocking which generally leads to release stop or system cracking. Once the tablet exposes to the aqueous media, the hydrophilic component dissolves and produces microscopic holes in SPM for release of drug solution [23,24]. The main polymer in (CPOP) construction is a hydrophobic polymer to form a semi-permeable membrane which is completely insoluble in water such as cellulose acetate or cellulose acetate butyrate [25]. Liquid coating (solvent system) should be an organic solvent such as acetone with low polarity or a combination of non-polar solvents in order to solve this polymer [23]. Due to the very low water solubility of these polymers even a small amount of water in the composition of the coating liquid cannot be used. The other main ingredients used in the formulation of semi-permeable membrane for this kind of osmotic systems are pore formers that after exposing the tablet to aqueous solutions (dissolution medium) can produce pores to release the drug [24]. Therefore, these materials should have high water solubility leading to the drug release in aqueous media instantly.

Technical problem in the preparation of these tablets is simultaneously dissolving lipophilic film former and hydrophilic pore formers in one solvent system. Using highly water soluble materials as pore formers in the SPM composition can result in reduction of the lag time of drug release from CPOP systems and increasing amount of released drug from CPOPs. Since the used pore formers with high solubility in water have a low solubility in acetone-ethanol solvent thus in the present study an attempt was made to employ nano-sized pore former solid particles suspended in a polymer solution to tackle the release issue. The micro-sized pore former particles suspended in polymeric solution has already been applied in our research lab [26], but in the present study, the authors have focused on employing nano-sized pore former to control the porosity of the membrane in osmotic systems.

2. Materials and methods

2.1. Materials

4-Amino pyridine (purity >99%) was obtained from Merck Chemicals (Germany). Cellulose acetate with 40% acetyl groups (Fluka, Switzerland) was used as film former polymer (SPM). Hydroxypropyl methylcellulose (HPMC E_{15LV}) (Colorcon, England) was used as water-swellable polymer and gelling agent. Polyethylene glycol (PEG) 200 (Pharmaceutical grad) and castor oil (Pharmaceutical grade; Merck, Germany) were used as plasticizer. Avicel PH101 (Blanver, Korea) was used as compressibility enhancer. Other material such as acetone (HPLC grade), absolute ethanol (HPLC grade), talc (purity 98%) and lactose monohydrate (Pharmaceutical grade) were purchased from Merck Company (Germany). Sucrose and mannitol (Pharmaceutical grade; Merck, Germany) were used as a solid pore former in formulation of SPM with different percentages. Sucrose was applied as osmotically active agent in core tablet formulation.

2.2. Preparation of core tablets of osmotic systems

4-Amino pyridine powder was micronized by jet mill (Fritsch FE80N, Germany) before using in tableting process. Drug powders along with other core ingredients were mixed thoroughly for 10 min by mortar and pestle. Then the mixture was compressed into biconvex tablets using a single tablet press (Korsch, Germany) with 9 mm diameter oval biconvex punches. The final weight of each tablet was kept at 465 mg in order to have a similar volume and surface area for the tablets. All of the core formulations contained 20 mg 4-Amino pyridine. The hardness of all prepared tablets was adjusted in the range of 6–8 Strong Cobb.

2.3. Coating of core tablets

The prepared core tablets were coated with a coating suspension containing cellulose acetate, castor oil, PEG200 and nano-suspended sucrose or mannitol in acetone/ethanol mixture (90:10) employing dip coating technique. In this technique, the cores were fixed with micro-drill (micro drill diameter was around 350 μm and held by a hand piece) and floated into coating suspension for 5 s with a gentle horizontal rotation and drying at room temperature. This step was repeated several times until the intended membrane thickness (125 ± 10 μm) was achieved. Micro-drills were pulled out from the coated tablets by rotating hand piece and the created micro pore was sealed by small amount of coating solution. The same condition was maintained during coating of all tablets and thickness of membrane was periodically checked using digital micrometer (Mitotoyo, Japan) with high accuracy (0.001 mm). Cellulose acetate (6 g) and plasticizers namely, castor oil (3%w/v), and PEG200 (2%w/v) were dissolved in 100 ml of coating liquid. Due to poor solubility of sucrose in this solvent mixture and preparing nano-suspension, the sucrose particles was suspended in the acetone/ethanol mixture (90:10 v/v) inside the ball-mill chamber (Retsch® PM100, Germany). The volume of the chamber was 25 ml containing 8 balls with 10 mm diameter. The sample was ground for 3 h at 350 rpm, and at 10 min intervals a diverse rotation was applied.

During dip coating process the coating suspension was continuously stirred to maintain a good uniformity while using in the process. The core and SPM compositions for different formulations are presented in Table 1.

2.4. Particle size analyzing

The particle size of sucrose and mannitol particles suspended in acetone/ethanol mixture after grinding in ball-mill was measured using Shimadzu-Japan (SALD-2120) and the results are demonstrated in Fig. 1.

2.5. Scanning electron microscopy (SEM)

SEM images were prepared from selected and blank formulations using Tescan (Czech Republic) apparatus with different magnifications after exposing the tablets to the aqueous media in order to assess the size and shape of pores formed by dissolving the pore formers in SPM structure. Prior to assessment with acceleration voltage of 15.0 kV, the samples were prepared on aluminum stubs and coated with gold using sputter gold coating method.

2.6. In vitro *release test*

In vitro release studies were carried out using a dissolution apparatus II paddle method (Erweka DT-6 R, Germany), set at 100 rpm (rotating speed) and 900 ml distilled water maintained at 37 ± 0.1 °C. At different time intervals (5, 10, 15, 45 min and 1, 1/5, 2, 4, 6, 8, 10, 12, and 24 h) 5 ml of the dissolution medium were withdrawn and analyzed spectrophotometrically (UV spectrophotometer, Shimadzu Mini 1240, Japan) at 260.8 nm. The withdrawn dissolution medium was instantly replaced by the same volume of the fresh medium. The release test was performed at least for 3 tablets and the corresponding mean and standard deviations (SD) were calculated.