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Personalised medicine

Drug-printing by flexographic printing technology—A new manufacturing process for orodispersible films

Eva Maria Janßen[a,*], Ralf Schliephacke[b], Armin Breitenbach[c], Jörg Breitkreutz[a]

[a] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitätsstr. 1, 40225 Düsseldorf, Germany
[b] tesa SE, Technologiezentrum tesa, Quickbornstr. 24, 20253 Hamburg, Germany
[c] Labtec GmbH, Raiffeisenstr. 4, 40764 Langenfeld, Germany

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ABSTRACT

Orodispersible films (ODFs) are intended to disintegrate within seconds when placed onto the tongue. The common way of manufacturing is the solvent casting method. Flexographic printing on drug-free ODFs is introduced as a highly flexible and cost-effective alternative manufacturing method in this study. Rasagiline mesylate and tadalafil were used as model drugs. Printing of rasagiline solutions and tadalafil suspensions was feasible. Up to four printing cycles were performed. The possibility to employ several printing cycles enables a continuous, highly flexible manufacturing process, for example for individualised medicine. The obtained ODFs were characterised regarding their mechanical properties, their disintegration time, API crystallinity and homogeneity. Rasagiline mesylate did not recrystallise after the printing process. Relevant film properties were not affected by printing. Results were comparable to the results of ODFs manufactured with the common solvent casting technique, but the APIs are less stressed through mixing, solvent evaporation and heat. Further, loss of material due to cutting jumbo and daughter rolls can be reduced. Therefore, a versatile new manufacturing technology particularly for processing high-potent low-dose or heat sensitive drugs is introduced in this study.

1. Introduction

Orodispersible films (ODFs) disintegrate within seconds when placed onto the tongue. Deliberate swallowing is not mandatory for effective treatment. Therefore, ODFs are an ideal oral dosage form for paediatric and geriatric drug delivery (Breitkreutz and Boos, 2007). ODFs have gained popularity during the recent years. OTC products based on ODF technology are available in the U.S. for years. First prescription drugs with ODF formulation have entered the market recently (Hoffmann et al., 2011).

For the common way of manufacturing the active pharmaceutical ingredient (API) is added to a coating mass, which is subsequently casted onto an intermediate liner, dried, cut to final film size, removed from the intermediate liner and packaged (Hoffmann et al., 2011). The API can be dissolved or suspended within the polymer solution. The API is stressed by the used solvents, the high-shear mixing process and the subsequent drying step (Dixit and Puthli, 2009; Goel et al., 2008; Hoffmann et al., 2011). Unstable APIs may be affected by mixing and drying. The realisation of a homogeneous distribution of the API within the film might be difficult, especially if high-potent drugs at low doses are used. Using the solvent casting approach a huge film on a jumbo roll is produced first, which is afterwards cut to daughter rolls and later to final film size. During this cutting step API containing waste is produced. The properties of the coating mass like i.e. viscosity or density are affected by the properties and the amount of the processed APIs. The quality of the coating mass is critical for a successful film casting. Therefore, the formulation of the coating mass often has to be adjusted for each new API and each new dose strength.

Aim of this work was to cast a drug-free ODF and to add the API at the end of the process to the drug-free ODF by using an industry-relevant printing technique. Printing on pharmaceutical dosage forms is commonly used for labelling and counterfeit protection i.e. of capsules and tablets. Screen printing and pad printing methods were used for the loading of transdermal patches with API, but especially pad printing is limited by the low production speed (Anhäuser and Klein, 1988; Nick et al., 1984). Three-dimensional printing was also used for the production of layered oral dosage forms (Katstra et al., 2000; Rowe et al., 2000). Voura et al. (2011) introduced 'printable medicines' for the manufacturing of medicinal products for personalised medicine: the API is printed onto a carrier, which is rolled up and inserted into a capsule. Sandler et al. (2011) used inkjet printing for the precise deposition of APIs on different paper substrates, which can be inserted into a capsule. Inkjet printing was also used for the preparation of personalised-dose oral films made from edible paper, a solid starch-based

* Corresponding author. Tel.: +49 211 8114220; fax: +49 211 8114251.
E-mail address: e.m.hoffmann@uni-duesseldorf.de (E.M. Janßen).

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material (Buanz et al., 2011). Nevertheless, inkjet printing is still not suitable for high-throughput industrial production. Further, the printing of suspensions is only feasible with a very low particle size (Pardeike et al., 2011).

The idea of adding the API to an ODF by spraying, impregnating or dipping was already mentioned in the first patents on ODFs (Deadman, 1964). Nevertheless, the idea has never been fully transferred into practise in a satisfactory way. The challenge of API printing onto ODFs is to avoid film disintegration or rupturing during the printing process and to maintain the fast dissolving properties.

In the present study flexography printing technology was investigated for the manufacturing of ODFs. Printing results were compared to ODFs manufactured by the conventional solvent casting method. Tadalafil and rasagiline mesylate served as model drugs with different physicochemical properties.

2. Materials and methods

2.1. Materials

The excipients for ODF processing were hypromellose (HPMC) in Pharmacoat 606 (Shin-Etsu, Tokyo, Japan) or Methocel E5 (Dow Wolff Cellulosics, Bomlitz, Germany) quality, crospovidone (Kollidon CL-M, BASF, Ludwigshafen, Germany) and glycerol (Caesar & Loretz, Hilden, Germany). Purified water was used as solvent.

The ink ingredients were hydroxylpropylcellulose (HPC) in Klucel EXF quality (Ashland Aqualon, Wilmington, USA) and brilliant blue (Ilperfund, Goch, Germany). Ethanol was used as solvent.

Tadalafil (Matrix Laboratories, Hyderabad, India) and rasagiline mesylate (Amino Chemicals, Marsa, Malta) were used as model drugs.

All other chemicals were of analytical grade.

2.2. Manufacturing of ODFs with API by solvent casting method

Conventional ODFs prepared by solvent casting were produced in lab scale. HPMC (13.88%) and glycerol (4.16%) were dissolved in water and mixed with constant stirring. The amount of solvent in the final coating mass was 76.41%. Crospovidone (4.66%) was added and stirred until a homogenous coating mass was formed. Vacuum was applied to remove air bubbles. Tadalafil or rasagiline mesylate were added at a ratio of 0.89%. The coating mass was casted onto a polyethylene terephthalate intermediate liner with a wet thickness of 400 μm and a casting speed of 6 mm/s using an Erichssen film applicator 509/1 (Erichssen, Hemer, Germany). The ODF were dried at room temperature over night and cut into final film size of 2 cm × 3 cm.

2.3. Manufacturing of drug-free ODFs

HPMC (14%) was suspended in hot water (80 °C). The mixture was cooled down under constant stirring while HPMC was dissolving. The amount of solvent in the final coating mass was 77.1%. Crospovidone (4.7%) and glycerol (4.2%) were added and stirred until a homogenous coating mass was formed. Vacuum was applied to remove air bubbles. The coating mass was casted onto a polyethylene terephthalate intermediate liner with a coating speed of 25 mm/s using the coating machine LBA 16 (Pagendarm BTT, Hamburg, Germany) equipped with a comma blade. The applied mass was 65 g/m^2. Coating width was 340 mm. The film was dried in an oven with four heating-zones (40 °C, 60 °C, 75 °C and 80 °C) and rolled up to a jumbo roll. The jumbo roll was afterwards cut into daughter rolls with a width of 2 cm, which is the width of the final ODF, and a length of up to 100 m.

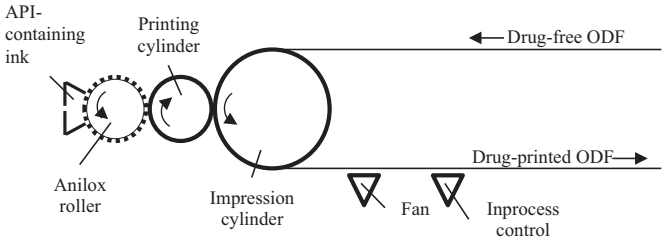

Fig. 1. Schematic overview of Flexography technology.

2.4. Flexographic printing of API-containing ink

HPC (5%) was dissolved in ethanol and mixed under constant stirring. Solvent concentration was 84.5% in the final ink. Rasagiline mesylate (10.0%) and the blue colourant (0.5%) were added and stirred until a homogenous ink has been formed.

To reduce tadalafil particle size (x_{99} < 50 μm), an aqueous suspension with 8.33% HPC and 16.67% tadalafil was passed five times through a three-roller-mill. The resulting paste was casted onto a polyethylene terephthalate intermediate liner and dried at 50 °C until loss on drying was <1%. The dried mass was mixed with ethanol obtaining an ink suspension with 5% HPC and 10% tadalafil. Finally, 0.5% blue colourant was added.

Flexographic printing technology was used for ink printing on ODFs (Fig. 1). It is an offset, rotary printing process. The ink was metered by an anilox roller. The anilox roller had a capacity of either 11.71 cm^3/m^2 or 80 cm^3/m^2. Fig. 2 shows micrographs of the two different geometries of the anilox roller cells. Excessive ink was removed by a doctor blade system. The ink was transferred from the anilox roller to the printing cylinder. After unrolling the daughter roll the drug-free film was passed through the printing cylinder and the impression cylinder, so that the ink was transferred onto the ODF. Subsequently, the solvent was removed by a fan and the film was rolled up again. A F.P.100/300 flexographic printing machine (Saueressig, Vreden, Germany) was used for printing at a speed of 16 m/min. The printing process was repeated for up to four times. Finally, the printed films on daughter rolls (2 cm width) were cut

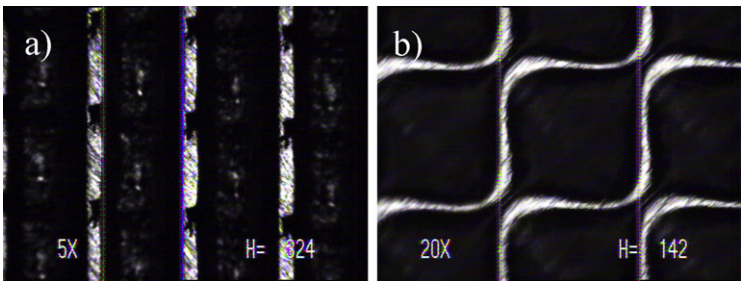

Fig. 2. Micrographs of anilox rollers: (a) 80 cm^3/m^2, 5× magnification; and (b) 11.71 cm^3/m^2, 20× magnification.