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Preparation and characterization of gastrointestinal wafer formulations

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ABSTRACT

Many active pharmaceutical ingredients (API) have a very poor or highly variable bioavailability after oral administration. One possibility to overcome this problem might be found in the application of mucoadhesive dosage forms like gastrointestinal wafers. However, a currently unsolved challenge is the control of the adhesion of the wafer to the intestinal mucus. One suggested solution might be the combination of gastrointestinal wafers and expanding systems. Such a combination requires thin and elastic wafers which are further characterized by an unidirectional drug release. In this study gastrointestinal, twolayered wafers containing a water-insoluble backing layer and a drug-loaded, mucoadhesive layer were fabricated by casting solvent technique. The backing layer consists of Ethocel™ Standard 10 Premium and the mucoadhesive layer was prepared using a mixture of Methocel™ E15 Premium LV, polyvinyl alcohol and Macrogol 400. The wafers were characterized regarding their appearance, mechanical properties and dissolution profiles as well as the influence of backing layer thickness on drug transfer and their ability of unidirectional drug release. The wafers with backing layer thickness of 500 µg Ethocel™/cm² presented adequate mechanical properties, a drug transfer about 73% and unidirectional drug release.

1. Introduction

Many active pharmaceutical ingredients (API) have a very poor and/or highly variable bioavailability after oral administration. Reasons are for example low mucosal permeability, a narrow absorption window at particular regions of the gastrointestinal tract (GIT), variable transit times, various fluid volumes, lack of stability in the gastrointestinal environment resulting in a decomposition prior to its absorption and low concentration of API in gastrointestinal contents (Bhasakaran et al., 2012; Dressman and Reppas, 2000; Hens et al., 2016, Koziolek et al., 2015, Tao and Desai, 2005). Additionally, physiological properties are of relevance. For example mucus thickness ranges from 50 to 450 µm (median 200 µm) and is influenced by hormonal, paracrine and neural stimulation as well as by inflammatory reactions and acids (Allen et al., 1993; Khutoryanskiy, 2011). One strategy to overcome these problems is the usage of mucoadhesive dosage forms like intestinal wafers. Wafers are defined by the U.S. Food and Drug Administration (FDA) (2009) as "a thin slice of material containing a medicinal agent". Due to their drug release rates and disintegration times, wafers can be classified into rapid disintegrating, meltaway and sustained release wafers. Rapid disintegrating wafers disintegrate within 30–60 s and result in immediately drug release, whereas meltaway wafers stick to the mucosa, disintegrate within 5–30 min and form a gelatinous, mucoadhesive depot at application site. Sustained release wafers are characterized by disintegration times of several hours and a continuous drug release, ideally zero order kinetics (LTS Lohmann Therapie-Systeme, 2010). After swallowing intestinal wafers have the potential to adhere to gastrointestinal (GI) mucosa because of their mucoadhesive properties. Due to the close contact between wafer and mucosa, a high drug concentration gradient is created, resulting in a high drug flux at the absorbing tissue, which is well supplied with blood. These conditions support presumably drug absorption into systemic circulation and enhance oral bioavailability (Andrews et al., 2009; Bernkop-Schnürch, 2005; Boddupalli et al., 2010).

However, a challenge is the loss of control over the dosage form after swallowing. It cannot be guaranteed that the wafers adhere in the intended region of the GIT and in the desired way. Especially using multilayered wafer, it cannot be influenced which side of the wafer adhere to the mucus layer and the underlaying epithelial layer. One suggested solution might be the combination of

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intestinal wafers with expanding systems which can control adhesion process. Such expanding systems are described in the patent of Bogdahn et al. (2015) and consist of a shell, an expansion mechanism and a wafer. The shell could be a custom-designed, gastroresistent capsule, which were swallowed and release the wafer after triggering by pH value, pressure or a composition of a fluid surrounding the shell. The expansion mechanism is selected from the group comprising mechanical expansion system, gas driven expansion system, compressed foam or compressed tissue. The wafer is packed in the shell for example lumped together, collapsed, folded or rolled (Bogdahn et al., 2015). The wafers need specific properties for combination with expanding systems. They have to be thin, elastic and folding resistant. Furthermore, an unidirectional drug release profile is required. The aim of this study was to prepare and characterize rapid disintegrating intestinal wafers which can be combined with an expanding system and are characterized by an unidirectional drug release profile.

2. Material and methods

2.1. Formulation of wafers

Wafers were produced by a casting solvent technique and consisted of a water-insoluble backing layer of Ethocel™ Standard 10 Premium (ethyl cellulose, EC) (Colorcon Limited, United Kingdom) and a drug-loaded, mucoadhesive layer.

Firstly, the backing layer was prepared by spraying a solution of 4% (w/w) EC in acetone on the release liner according to a defined spraying scheme. Acetone was evaporated by room temperature for 15 min. Polyethylene paper (Polyslik® 111/105, Loparex, Netherlands) was used as release liner. The thickness of the backing layer was expressed as amount of EC per area. It was adjusted to 0–750 μg EC/cm^2 and was controlled by weighing.

Secondly, the drug-loaded, mucoadhesive layer was fabricated. The most suitable formulation was determined in preliminary tests (data not shown). For this purpose, different mixtures of Methocel™ E15 Premium LV (hydroxypropyl methylcellulose, HPMC) (DOW Chemical Company, USA), polyvinyl alcohol, partially hydrolyzed (MW approx. 200 000) (PVA) (Merck Schuchardt OHG, Germany) and Macrogol 400 (polyethylene glycol, PEG400) (Fagron GmbH & Co.KG, Germany) were produced, whereby the ratio of one ingredient at a time varied. Produced formulations were tested regarding their disintegration time, tensile strength, elongation at break and folding endurance. A mixture of Methocel™ E15 Premium LV, PVA and PEG400 with a ratio of 1:2:4 was chosen as most suitable formulation for drug-loaded, mucoadhesive layer. In this study fluorescein sodium (FL) (Fluka Analytical, Germany), quinine anhydrous (QN) (Sigma–Aldrich Chemie GmbH, Germany) and diclofenac sodium (Diclo) (Fagron GmbH & Co.KG, Germany) were used as model drug substances. These substances were chosen because of their different hydrophilicity/lipophilicity and various solubility in aqueous media. The final drug concentration in each wafer was 5 μg/cm^2 for fluorescein (FL), 100 μg/cm^2 for quinine (QN) and 500 μg/cm^2 for diclofenac (Diclo). Additionally, placebo wafers were produced. The compositions of all formulations are summarized in Table 1. The polymer mixture was kept overnight and centrifuged by 4400 rpm for 50 min to remove all entrapped air bubbles. Then the mixture was cast onto the dried backing layer using a mechanical film casting apparatus equipped with a vacuum suction plate and 300 μm film applicator frame (film applicator CX4, mtv messtechnik OHG, Germany). Casting speed was adjusted to 30 mm/s. The casted mixture was dried at 40 °C for 6 h and stored on release liner packed in aluminum foil at room temperature. The resulting polymer film was cut into smaller pieces and peeled off the release liner before usage.

2.2. Wafer characterization

2.2.1. Appearance

The surface uniformity of the produced wafers was visually inspected. It was rated whether the surface was homogenous, smooth, and free of holes and air pockets. Additionally, scanning electron microscopy (SEM) (Phenom™, FEI Company™, L.O.T.-Oriel GmbH & Co.KG, Germany) was used to observe surface morphology of a placebo wafer with a backing layer thickness of 500 μg EC/cm^2.

The wafer thickness was measured by a mechanical thickness dial gauge (0.01 mm capacity, Kaefer Messuhrenfabrik GmbH & Co. KG, Germany). The wafer (size 2.5 × 4 cm) was placed between to flat contact points and the thickness was read on the analog display. For each formulation the thickness of three wafers was measured on three defined spots and the average was calculated.

Finally, the mass of the wafers (size 2.5 × 4 cm) was determined using a digital balance (Sartorius GmbH, Germany).

2.2.2. Drug content uniformity

The model drug substance distribution in the produced wafers was measured to ensure uniformity. Ten samples (size 1 × 1 cm) were collected randomly from each formulation and dissolved by stirring in 10 mL distilled water using a magnetic stirrer. After complete dissolution of the drug-loaded, mucoadhesive layer of the wafer, samples were measured by fluorescence spectroscopy (Varioskan Flash, Thermo Fisher Scientific Germany BV & Co.KG, Germany) (FL λ_{ex} 490 nm, λ_{em} 513 nm and QN λ_{ex} 347 nm, λ_{em} 373 nm) or UV/vis-spectroscopy (Cary 50 Scan, Varian, Inc., Germany) (Diclo 276 nm) against calibration in the same medium. Wafers passed content uniformity test if they met requirements of the European Pharmacopoeia 8.8 (Ph.Eur. 8.8) chapter 2.09.06 content uniformity.

Table 1
Summary of produced wafer formulations using a mixture of Methocel™ E15 Premium LV, polyvinyl alcohol and Macrogol 400 with a ratio of 1:2:4, different backing layer thicknesses as well as model drug substance concentrations (EC = ethyl cellulose, FL = fluorescein sodium, QN = quinine anhydrous, Diclo = diclofenac sodium).

	Backing layer (μg EC/cm^2)	Model drug substance (μg/cm^2)		
		FL	QN	Diclo
Twolayered wafers (placebo and drug-loaded)	0	5	100	500
	300	0	0	0
		5	100	500
	400	0	0	0
		5	100	500
	500	0	0	0
		5	100	500
	750	0	0	0
		5	100	500