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Research paper

Development and characterization of extended release Kollidon® SR mini-matrices prepared by hot-melt extrusion

Işık Özgüney [a,b,*], Duangratana Shuwisitkul [a], Roland Bodmeier [a]

[a] College of Pharmacy, Freie Universität Berlin, Berlin, Germany
[b] Faculty of Pharmacy, Department of Pharmaceutical Technology, University of Ege, İzmir, Turkey

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ABSTRACT

Kollidon® SR as a drug carrier and two model drugs with two different melting points, ibuprofen and theophylline, were studied by hot-melt extrusion. Powder mixtures containing Kollidon® SR were extruded using a twin-screw extruder at temperatures 70 and 80 °C for ibuprofen and 80 and 90 °C for theophylline. The glass transition temperature (T_g) and maximum torque were inversely related to ibuprofen concentrations, indicating its plasticizing effect. The results of differential scanning calorimetry (DSC) and X-ray diffraction analysis showed that ibuprofen remained in an amorphous or dissolved state in the extrudates containing drug up to 35%, whereas theophylline was dispersed in the polymer matrix. The increase in amounts of ibuprofen or theophylline in the hot-melt extrudates resulted in the increase in the drug release rates. Theophylline release rate in hot-melt extruded matrices decreased as the extrusion temperature increased. In contrast, a higher processing temperature caused the higher ibuprofen release. This was a clear indication of the plasticizing effect of ibuprofen on Kollidon® SR and a result from water uptake. Theophylline release rate from hot-melt extrudates decreased with increasing triethyl citrate (TEC) level because of the formation of a denser matrix. By adding of Klucel® LF as a water-soluble additive to the hot-melt extruded matrices, an increase in ibuprofen and theophylline release rates was obtained.

1. Introduction

Hot-melt extrusion (HME) is a commonly used process in the plastics industry. Speiser [1,2] and Hüttenrauch [3] adapted this process to pharmaceutical dosage forms. In recent years, HME has been evaluated for the preparation of various drug delivery systems, including granules, tablets and transdermal and transmucosal systems. The advantages of HME are: (1) organic solvent-free process; (2) fewer processing steps in only one equipment; (3) no requirements for good compressibility of active ingredients or excipients; (4) good drug content uniformity due to intense mixing and agitation; and (5) improved bioavailability through drug solubilization or dispersion at the molecular level [4,5].

The drug release is primarily controlled by the type and concentration of thermoplastic polymer, other excipients (e.g., plasticizers) and the processing conditions (e.g., temperature).

Several polymers (ethyl cellulose, hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose, polyethylene glycol, polyethylene oxide, polyvinyl acetate, acrylic polymers) have been investigated as release-controlling carriers for oral drug delivery systems prepared by HME [6–8]. De Brabander et al. [6] developed ethyl cellulose hot-melt extrudates for oral extended release. The properties of hot-melt extrudates containing polyvinyl acetate were reported by Zhang and McGinity [7]. A mixture of a poorly water-soluble drug, indomethacin, Eudragit® RD 100 and triethyl citrate (TEC) was prepared using HME. The drug release rate was increased by the addition of Pluronic® F68, Eudragit® L 100 or Eudragit® S 100 [8]. In addition to the release-controlling polymer, other additives, such as plasticizers, are often necessary to properly fabricate oral dosage forms prepared by HME. All components must be thermally stable at the processing temperatures [9].

In the present study, sustained-release Kollidon® SR mini-matrices for oral delivery were developed by HME. Kollidon® SR is an extended release excipient based on polyvinyl acetate and polyvinylpyrrolidone (8:2) and is used in matrix tablets prepared by direct compression or wet granulation [10,11]. The application of this polymer using HME has not been described in the literature.

In this study, ibuprofen and theophylline were used as low and high melting point model drugs (78–80 °C [12] and 270–274 °C [13]). The influence of the type of drug and drug loading, excipients (plasticizer, hydrophilic additives) and different process conditions on extrudability and release and thermal properties of the Kollidon® SR extrudates were investigated.

* Corresponding author. Faculty of Pharmacy, Department of Pharmaceutical Technology, University of Ege, 35100 Bornova, İzmir, Turkey. Tel.: +90 232 3434000x5132; fax: +90 232 3885258.
E-mail addresses: isik.ozguney@ege.edu.tr, isik.ozguney@gmail.com (I. Özgüney).

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Table 1
Formulations of matrices containing ibuprofen used for the present study.[a]

Component	Formulations					
	1	2	3	4	5	6
Ibuprofen	25	35	50	25	35	35
Kollidon SR	75	65	50	52.5	45.5	55.25
Klucel LF	–	–	–	22.5	19.5	9.75

[a] All quantities are percentage (w/w).

2. Materials and methods

2.1. Materials

Kollidon® SR, ibuprofen and theophylline (BASF AG, Ludwighafen, Germany); triethyl citrate (TEC) (Morflex Inc., Greensboro, NC, USA) and hydroxypropylcellulose (Klucel® LF, Aqualon Company, Wilmington, DE, USA).

2.2. Preparation of hot-melt extruded matrices

The formulations are listed in Tables 1 and 2. A physical mixture of the ingredients was blended in a mortar for 10 min. For formulations with TEC, the plasticizer was mixed with Kollidon® SR powder followed by addition of other ingredients. The mixtures were extruded with a conical co-rotating twin screw hot-melt extruder (Minilab HAAKE Rheomex CTW5, Thermo Fisher Scientific, Karlsruhe, Germany). The torque values were recorded as a function of temperature and time. The processing parameters were extrusion temperatures, 70 and 80 °C for ibuprofen and 80 and 90 °C for theophylline; screw speed, 20 rpm and die diameter, 1.75 mm. The rod-like extrudates were manually cut into mini-matrices of length 5 mm.

2.3. Thermal analysis of the extrudates

Thermograms of ibuprofen, theophylline, Kollidon® SR extrudates with and without drug (drug:polymer ratios; 35:65 and 25:75, prepared at 70 °C, and 25:75, prepared at 80 °C for ibuprofen and theophylline, respectively) and physical mixture of ibuprofen and Kollidon® SR (35:65) were obtained by differential scanning calorimetry (Mettler DSC 821^e) and STAR® software (Mettler Toledo, Giessen, Germany) to determine the melting point or glass transition temperature (T_g). The samples (5–25 mg) were sealed in aluminum pans. All tests were run under a nitrogen atmosphere at a scanning rate of 10 °C/min over a temperature range of −20 to 100 °C.

2.4. X-ray diffraction

Wide-angle X-ray scattering measurements were carried out on a Philips PW 1830 X-ray generator with a copper anode (Cu K α radiation, λ = 0.15418 nm, 40 kV, 20 mA) fixed with a Philips PW 1710 diffractometer (Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). The radiation scattered in the crystalline regions of the samples (ibuprofen, Kollidon® SR, physical mixture and hot-melt extrudates, drug:polymer ratios of 35:65 and 25:75) was measured with a vertical goniometer (Philips PW 1820, Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). A scanning rate of 0.02° 2θ per s over the range of 4–40° 2θ was used to determine each spectrum.

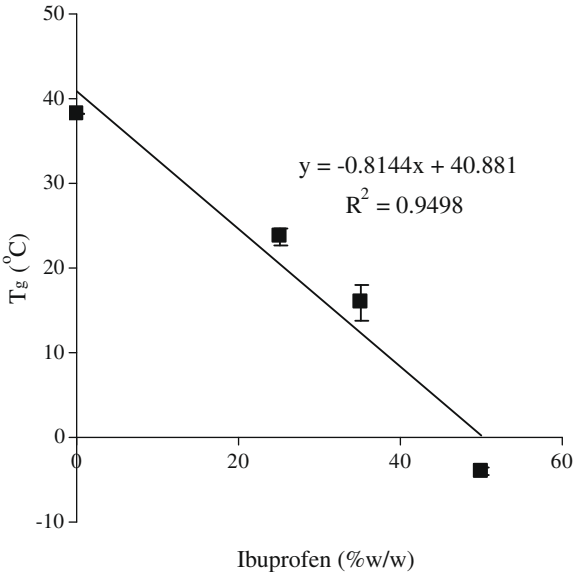

Fig. 1. The effect of ibuprofen concentration on T_g of Kollidon SR extrudates at 70 °C processing temperatures. T_g as a function of ibuprofen concentration was represented.

2.5. Water uptake of extrudates

The water uptake was measured upon exposure in phosphate buffer pH 7.4 in a horizontal shaker (GFL 3033; 100 ml, 37 °C, 70 rpm and n = 3). The water uptake study was performed with matrices containing 25 and 35% ibuprofen and prepared at 70

Table 3
Recorded maximum torque obtained from the extrudates prepared with different ibuprofen loading and processing temperatures.

Ibuprofen (% w/w)	Maximum torque (Nm) at processing temperature		
	70 °C	80 °C	90 °C
0	a	2.01	1.21
25	0.25	0.21	b
35	0.15	0.13	b
50	0.10	b	b

a = HME was unsuccessful due to over the limitation of torque.
b = The torques were not adequate to achieve the hot-melt extrudates.

Table 2
Formulations of matrices containing theophylline used for the present study.[a]

Component	Formulations									
	1	2	3	4	5	6	7	8	9	10
Theophylline	25	35	50	35	35	50	50	25	35	35
Kollidon SR	75	65	50	61.75	58.5	47.5	45	48.75	42.25	52
TEC	–	–	–	3.25	6.5	2.5	5	3.75	3.25	3.25
Klucel LF	–	–	–	–	–	–	–	22.5	19.5	9.75

[a] All quantities are percentage (w/w).