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Research paper

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

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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.

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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.

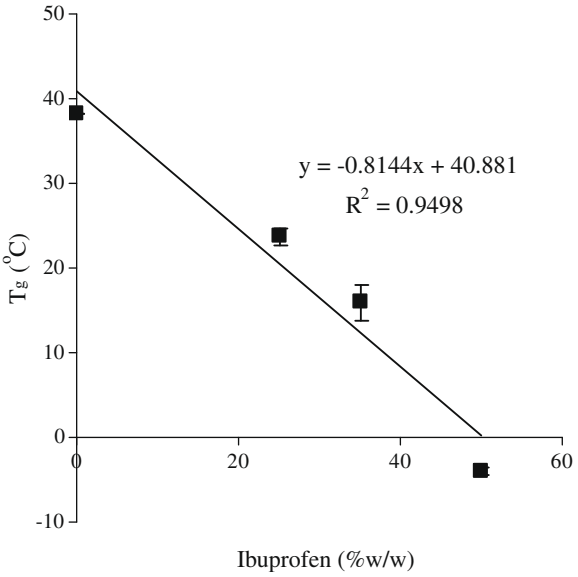

Fig. 1. The effect of ibuprofen concentration on T_g of Kollidon SR extrudates at 70 °C processing temperatures. T_g as a function of ibuprofen concentration was represented.

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).

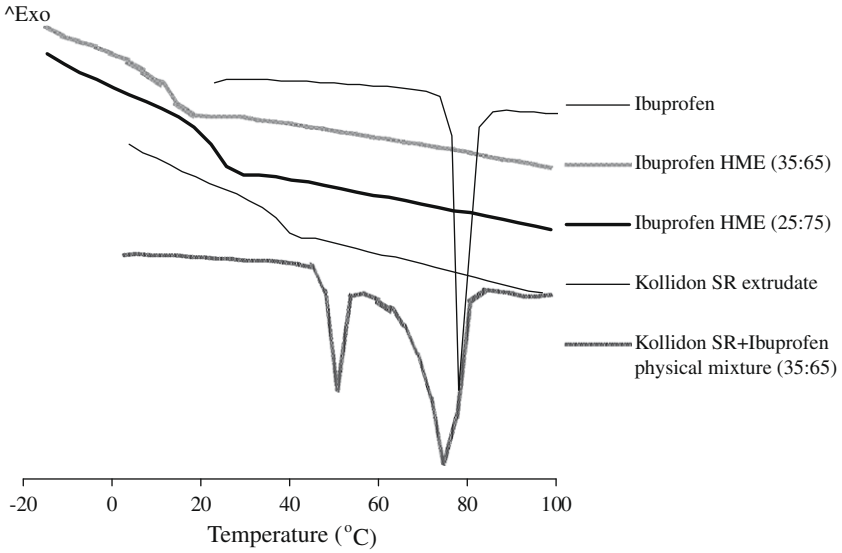

Fig. 2. DSC thermograms of ibuprofen, Kollidon® SR extrudates, physical mixture of ibuprofen and Kollidon® SR (in drug:polymer ratio 35:65), ibuprofen extrudates (in drug:polymer ratios 35:65 and 25:75) prepared at 70 °C

and 80 °C. The samples were removed from the medium at predetermined time intervals (2, 4, 6 and 8 h) and carefully blotted with tissue paper to remove excess water from the surface. The weight change due to the water uptake and leaching of the polymer and additives was then determined. The percentage of water uptake was calculated as follows:

$$\text{Water uptake } (\%) = \frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \times 100$$

2.6. In vitro drug release

The drug release was determined using the USP XXVI rotating paddle method (900 ml phosphate buffer pH 7.4 USP XXVI; 100 rpm; 37 °C; $n = 3$) (Vankel VK 800, Vankel Industries, Edison, NJ, USA). At predetermined time intervals, samples were withdrawn (3 ml, no medium replacement) and assayed spectrophotometrically at 226 nm and 272 nm for ibuprofen and theophylline, respectively (UV-2101 PC, Shimadzu Scientific Instruments Inc., Columbia, MD, USA).

3. Results and discussion

Kollidon® SR matrices could be successfully prepared by hot-melt extrusion up to 50% drug loading. Higher theophylline loadings resulted in processing difficulties as indicated by too high torque values because of high amounts of dispersed theophylline particles. Higher ibuprofen loadings led to a nonextrudable, low viscosity mass. The extrudates loaded with ibuprofen showed die swelling, whereas extrudates loaded with theophylline did not exhibit swelling. The die swelling was caused by the recoverable shear strain in the deformation upon leaving the die [14]. It depends on several factors such as processing conditions and the nature of the materials [15].

Ibuprofen, a low melting point drug, acts as a plasticizer for the extended release polymers ethylcellulose and Eudragit RS PO [12,16]. It also plasticized Kollidon® SR. The T_g of Kollidon® SR was inversely related to the ibuprofen content (Fig. 1). The plasticizing effect was also reflected in decreasing torque values with increasing ibuprofen concentration (Table 3). The torque values also decreased with increasing processing temperatures. Ibuprofen

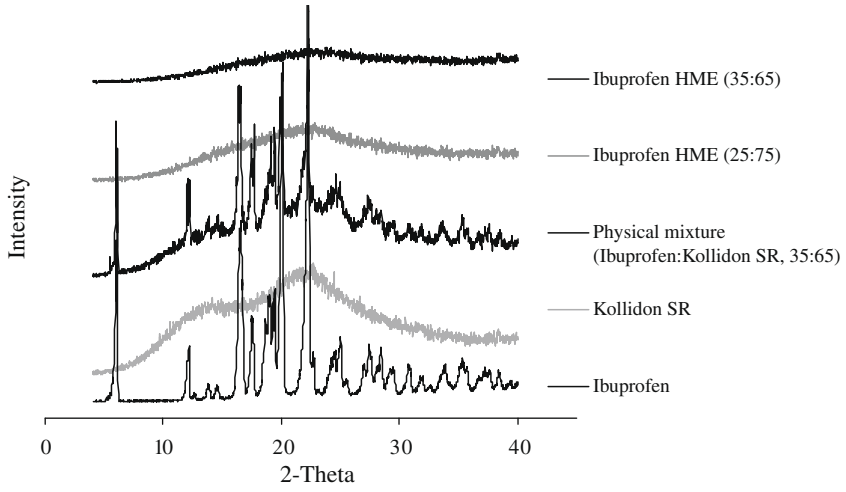

Fig. 3. X-ray diffraction patterns of ibuprofen, Kollidon® SR, and physical mixture of 35% w/w ibuprofen and Kollidon® SR, hot-melt extrudates of ibuprofen and Kollidon® SR with 25 and 35% w/w drug loading; processing temperature, 70 °C.

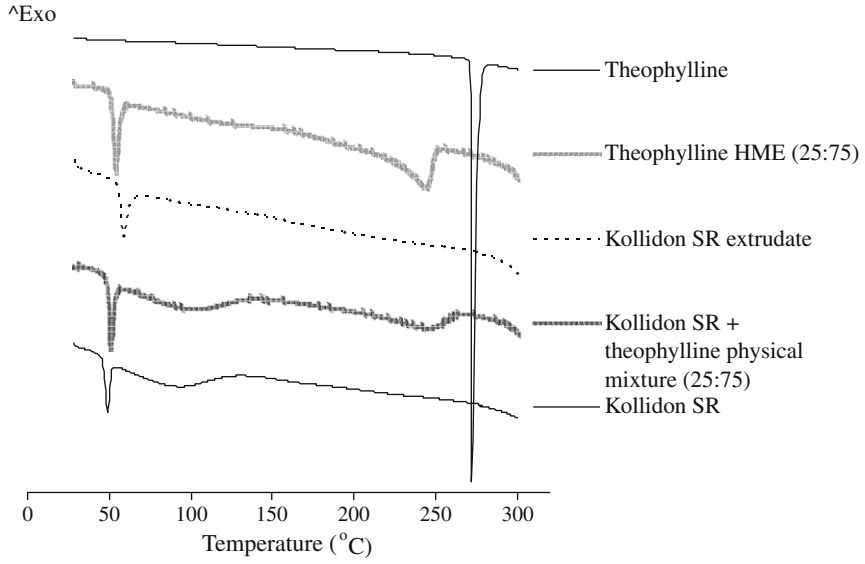

Fig. 4. DSC thermograms (first cycled) of theophylline, Kollidon® SR, Kollidon® SR extrudate, physical mixture of theophylline and Kollidon® SR, theophylline extrudates (in drug:polymer ratios 25:75) prepared at 80 °C.

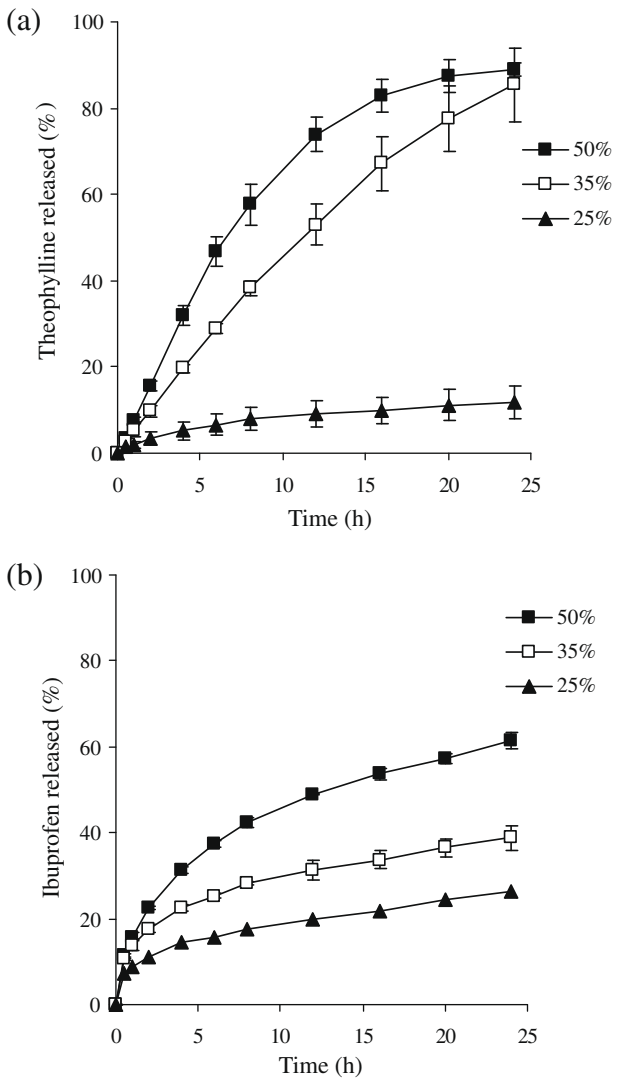

Fig. 5. The effect of drug loading (given in the figure) on the drug releases from Kollidon SR hot-melt extruded mini-matrices (a) theophylline; processing temperature, 80 °C and (b) ibuprofen; processing temperature, 70 °C.

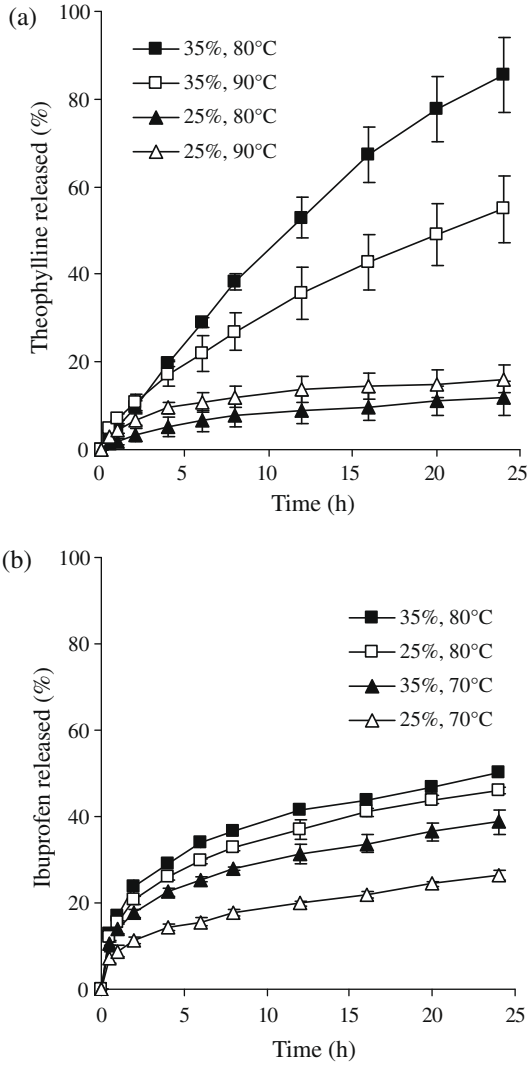

Fig. 6. The influence of hot-melt extruded temperatures (given in the figure) on the drug releases from Kollidon SR hot-melt extruded mini-matrices; drug loading, 25 and 35% w/w; (a) theophylline; processing temperature, 80 and 90 °C and (b) ibuprofen; processing temperature, 70 and 80 °C.

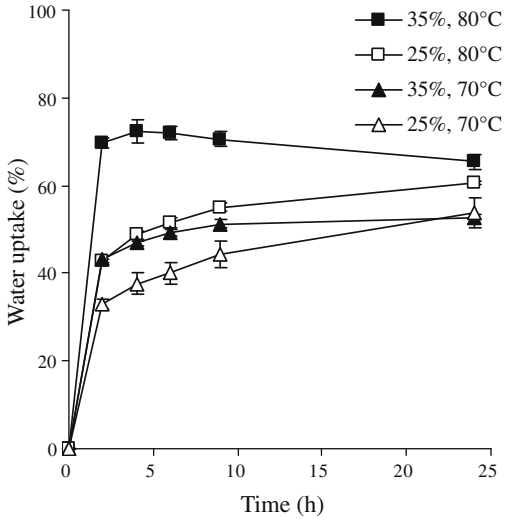

Fig. 7. Water uptake of Kollidon SR extrudates loaded with 25 and 35% ibuprofen at processing temperature, 70 and 80 °C (given in the figure).

was dissolved in the Kollidon® SR matrices as indicated by the absence of the melting endotherm or diffraction pattern in DSC and x-ray diffraction studies (Figs. 2 and 3). In contrast, theophylline was dispersed in the polymer matrix (Fig. 4). The physical state of theophylline and its effect on T_g of Kollidon SR were studied by DSC. For Kollidon SR extrudate containing 25% theophylline, the melting endotherm of theophylline was observed. No plasticizing effect of theophylline on Kollidon SR could be detected (Fig. 4).

Kollidon® SR hot-melt extruded mini-matrices maintained their original shape throughout the dissolution test. The drug release increased with increasing drug loading for both theophylline and ibuprofen (Fig. 5a and b). The big jump in theophylline release between 25% and 35% drug loading could potentially be explained with dispersed theophylline particles being isolated and not in contact within the matrix at the lower loading, resulting in a drug release primarily through the hydrated polymer matrix and not through pores created by dissolved drug particles as possibly happening at the higher loadings. Comparing the release profiles for the two drugs, ibuprofen (dissolved in matrix) was released faster at the lower loading of 25%, but slower at the higher loadings of 35% and 50% than theophylline (dispersed in matrix). The slower ibuprofen release at higher loadings could be explained by the low drug solubility. At 37 °C, the solubility of ibuprofen (6.26 ± 0.61 mg/ml) was lower than that of theophylline (13.67 ± 0.43 mg/ml) in the release medium.

The theophylline release from hot-melt extruded mini-matrices decreased with increasing extrusion temperature (Fig. 6a). The matrices probably were more dense when extruded at 90 °C than that at 80 °C. In contrast, a higher processing temperature resulted

Table 4
Influence of TEC as a plasticizer on maximum torque obtained the extrudates prepared with theophylline loading.

TEC concentration (% w/w base on polymer)	Theophylline loading (% w/w based on total amount)	Maximum torque (Nm)
0	0	2.01
	35	2.56
	50	4.79
5	0	0.43
	35	0.94
	50	3.13
10	0	0.39
	35	0.57
	50	1.80

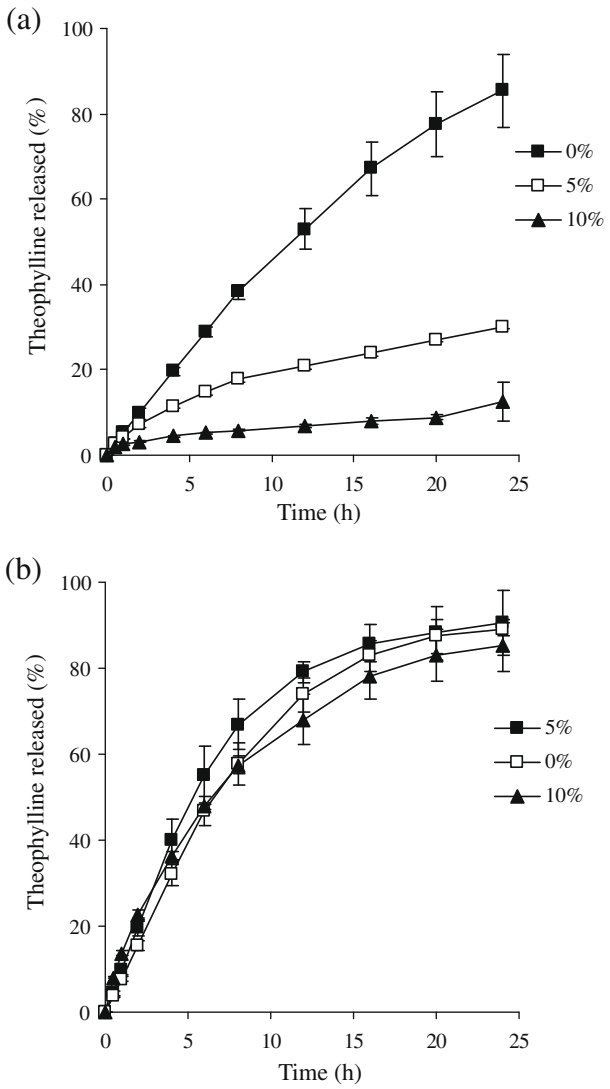

Fig. 8. The effect of TEC concentration (% w/w base on the polymer, given in the figure) on theophylline release from Kollidon SR hot-melt extruded mini-matrices. Drug loading: (a) 35% and (b) 50% w/w; processing temperature, 80 °C.

in a faster release of ibuprofen (Fig. 6b). This finding was explained by the plasticizing effect of ibuprofen on Kollidon® SR. The increase in the process temperature led to an increase in water uptake of Kollidon® SR extrudates containing ibuprofen (Fig. 7). As known, the permeability of a polymeric system for a drug strongly depends on its water content [17]. With increasing relative amount of water, the mobility of macromolecules increases and thus the free volume available for diffusion increases [18]. The plasticizing effect of ibuprofen played an important role on the water uptake and drug release.

Pharmaceutical polymers utilized in hot-melt extrusion typically require a plasticizer in order to reduce the T_g of the polymer and to facilitate the HME process [8]. The maximum torque of extrudates containing theophylline increased with increasing theophylline loading (increased resistance to the flow of dispersed drug particles) and decreased with the addition of TEC as plasticizer (Table 4). More flexible theophylline–Kollidon® SR extrudate mini-matrices were observed. As expected, the T_g of Kollidon® SR decreased with increasing TEC concentration from 38.2 °C at 0% TEC to 27.9 °C at 5% TEC and to 18.6 °C at 10% TEC. Theophylline release rate decreased with increasing TEC concentration at a drug loading of 35% because of the formation of a denser matrix

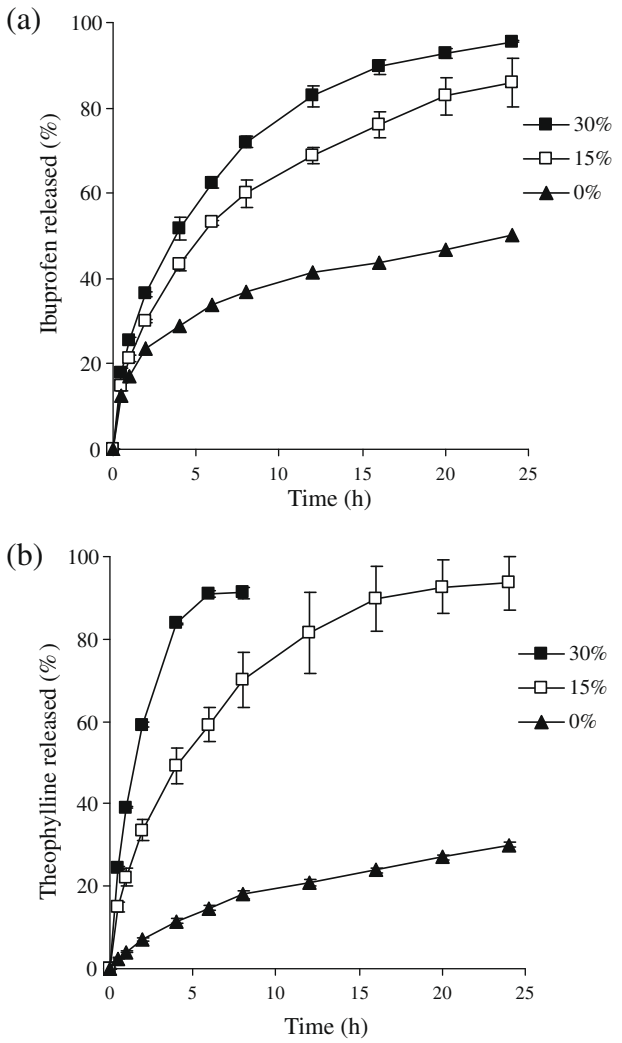

Fig. 9. The influence of Klucel LF concentration (% w/w base on the polymer, given in the figure) on drug releases from Kollidon SR hot-melt extruded mini-matrices; (a) ibuprofen and (b) theophylline; drug loading, 35% w/w; processing temperature, 80 °C.

(Fig. 8a). In contrast, TEC had no effect on theophylline release at the higher drug loading where the dispersed drug particles (50%) probably formed a complete network allowing rapid drug release (Fig. 8b).

Hydrophilic polymers are often added to extended release polymers to modify the drug release [6]. In this study, hydroxypropylcellulose (HPC) (Klucel® LF) was added as a water-soluble pore-former to modify the release of ibuprofen and theophylline. Five percent TEC was necessary to improve the processibility for the formulation loaded with theophylline. An increase of approximately 45% in the ibuprofen release and 60% in the theophylline release were achieved with incorporating 30% Klucel® LF (Fig. 9a and b). HPC leached into the dissolution medium, thus creating a more porous matrix.

Based on the results, Kollidon® SR could be processed using HME to form an oral controlled-release delivery. The drug releases over the period of a day from high drug loading as 50% w/w were achieved due to the combination of polymer properties itself and HME. The process was possibly conducted at low extrusion temperature (70–80 °C) in comparison with a process of higher T_g polymers, even though no plasticizer or other additives was added. On the other hand, high maximum torques during HME of Kollidon® SR should be taken into consideration particularly with high drug loading because of the high melt viscosity of the polymer.

4. Conclusion

Hot-melt extrusion is a useful method to prepare Kollidon® SR mini-matrix tablets for extended oral delivery. Drug loadings up to 50% could be extruded. Ibuprofen lowered the T_g of Kollidon® SR and functioned as a plasticizer in HME process. DSC and X-ray diffraction studies showed that ibuprofen was soluble or embedded as an amorphous form in Kollidon® SR up to the 35% level, whereas the solid dispersion from the extrudates containing theophylline was obtained. The increase in ibuprofen or theophylline loading for the hot-melt extrudates resulted in the increase in the drug release rates. The higher processing temperature resulted in the faster release of ibuprofen, but a slower release in theophylline. Increasing the level of TEC in the theophylline hot-melt extrudates caused the decrease of theophylline release. By the addition of Klucel® LF as pore former, faster ibuprofen and theophylline releases were achieved.

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