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분무건조와 용매증발을 이용한 Kollidon VA 64에 포접된 아세클로페낙의 개선된 용출 거동

양재원 · 박진영 · 이천중 · 김혜민 · 이현구 · 장나금 · 고현아 · 조선아 · 양대혁* · 강길선†
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Improved Dissolution Behavior of Aceclofenac Loadings with Kollidon VA 64 Using Spray Drying and Rotary Evaporation Process

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초록: 난용성 약물인 아세클로페낙의 용해도를 개선하기 위해 약물과 고분자의 다른 비율을 사용하여 분무건조와 용매증발의 방법으로 Kollidon VA 64의 고체분산체를 제조하였다. 아세클로페낙을 포접하는 고체분산체의 형태학적, 물리화학적 분석을 하기 위해, 전자주사현미경(SEM), 푸리에변환 적외선분광법(FTIR), 시차주사 열량측정법(DSC) 등이 사용되었다. 포접률과 인공장액에서의 용출 거동은 HPLC를 사용하여 측정하였고, 비교를 위해 원약물과 시판제 Airtal®이 사용되었다. 이것은 두 가지 방법에 따라 개선된 용출 거동을 나타내었다.

Abstract: In order to improve the poor water solubility of aceclofenac, it was loaded into solid Kollidon VA 64 dispersion prepared by spray drying and rotary evaporation methods using different drug and polymer ratios. Morphology and physicochemical behavior of the aceclofenac loaded solid dispersions was analyzed by scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), X-ray diffractometry (XRD), and differential scanning calorimetry (DSC). Encapsulation efficiency and dissolution behavior in a simulated intestinal juice of aceclofenac in the solid dispersions was measured using HPLC and the latter was compared with that of the active pharmaceutical ingredient (API) and Airtal®. It was demonstrated that two methods could significantly improve the dissolution behavior of aceclofenac.

Keywords: aceclofenac, dissolution rate, rotary evaporation, solid dispersion, spray drying.

Introduction

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) and it is used as a pain relief and to treat inflammation.[1-3] Systematic IUPAC name of aceclofenac is 2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxyacetic acid and its molecular formula is $C_{16}H_{13}C_{12}NO_4$ with a 354.19 g/mol molecular mass in Figure 1(a).[4,5] Aceclofenac can be administered orally or topically and its estimated half-life is 4 hrs in GI tract. As an anti-inflammatory drug, aceclofenac acts as a cytokine and cyclooxygenase inhibitor in body[6,7] that can be a more advantageous therapeutically than other anti-inflammatory drugs such as indometacin and diclofenac.[8-10] Aceclofenac is available in tablet form by Airtal® (Daewoong Co., Korea).[11-13]

Aceclofenac has a poor water solubility that compromise its anti-inflammatory/biological effects and makes the development of a pharmaceutical formulation difficult.[14,15] Furthermore, it has normally not only the reduced biocompatibility

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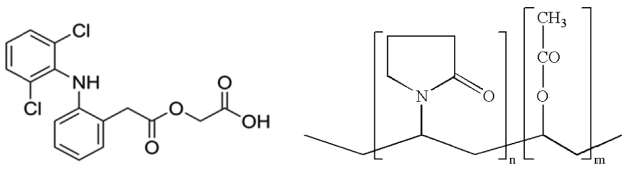

(a) (b)

Figure 1. Chemical structures of (a) aceclofenac; (b) Kollidon VA64.

but also low solubility.

The structure of aceclofenac was described in Figure 1(a). In order to improve the water solubility and the absorption of a hydrophilic drug, an appropriate drug delivery system has to be developed for a particular drug.

Necessarily, it needs to look for application in drug delivery system, including absorption enhancer as hydrophilic drug(s) an appropriate drug delivery system has to be applied. For example, drug delivery methods include micronization, amorphous crystallization, solid dispersion, self-microemulsifying drug delivery system (SMEDDS), salt formulation, micellar aggregation and mixed grinding.[16-18] Amongst these methods, solid dispersions of a lipophilic drug dispersed in a polymeric carrier be prepared using either spray drying (SD) or rotary evaporation (RE) methods.[19-21]

It commonly means that SD technique is a method to raise the temperature for evaporation and to disperse a drug into a polymer.[22,23] This polymer plays a role as the carrier, which loads a drug perfectly. It is easy to move for absorption in the body because amorphous was generated.

To enhance dissolution properties *in vitro* or *in vivo,* SD is often used as controlled the dissolution rate. Also, it was seen as the different dissolution rate respectively in detail, depending on composition, proportion and crystallinity. RE technique is a method to evaporate the solvents under rotation and the reduced pressure.[24] Because of low pressure, boiling point would decline, which is easy to evaporate the solvent. Unless the solvent is eliminated completely, it could remove the solvent under high vacuum.

In this study, Kollidon VA 64[25,26] was used as a polymeric carrier of aceclofenac to prepare solid dispersions.

Kollidon VA 64 is a white or yellowish powder and has a molecular weight of 45000 to 70000. It's composed of polyvinyl pyrrolidone (PVP) and polyvinyl acetate (PVA), with Figure 1(b) in a ratio of 6:4. It is mostly used as dry binder, granulating agents and film-forming agents using the physical mixture method. The Kollidon VA 64 could be dissolved in all hydrophilic solvents including water, ethanol, isopropanol, methylene chloride, glycerol and propylene glycol *etc*.

In this study, P407 is a hydrophilic non-ionic surfactant.[27,28] There were most of the common uses of P407 because of its surfactant properties. Compared to just general poloxamer, P407 is mostly used in cosmetics by dissolving oily ingredients in water.[29]

The dissolution behavior was evaluated using HPLC. It was employed in the second fluid (the simulated intestinal juice pH 6.8). In comparison to dissolution, Airtal® was used for the control group. Also, active pharmaceutical ingredients (API) were progressed in comparison with it. The analysis could be characterized by scanning electron microscopy (SEM), Fourier transformation infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffractometer (XRD). The changes of crystallinity and structure explained salt generation of hydrogen bonds between drug and polymer.

In this study, the purpose is that the bioavailability and dissolution rate could be well improved. Also, the number of oral administration could be reduced owing to efficiency.

Experimental

Materials. Aceclofenac was purchased by Masung Company (Korea) as a model drug in this study. Kollidon VA 64 and Poloxamer 407 (BASF, Ludwigshafen, Rheinland-Pfalz, Germany) was prepared for hydrophilic polymer. Also, P407 was used as a surfactant. Airtal® (Daewoong Co., Korea) was provided for evaluation. All materials and reagents prepared in this study were using a high performance liquid chromatography (HPLC) grade.

Preparation of Solid Dispersion Mixtures. In this study, the mixtures were prepared using spray dryer SD-1000 (Eyelar, Japan) with aceclofenac. The other mixtures were determined with a rotary evaporator (Eyelar, Japan). They were performed, after co-solvent of methanol completely dissolved samples. The ratios of aceclofenac, Kollidon VA 64 and P407 were written respectively in Table 1, having various amounts (1:1:0.2, 1:2:0.2, 1:3:0.2, 1:4:0.2) (w/w/w%).

The conditions of SD were performed at in-let temperature (140±5 ºC), having a pressure of about 10 kPa. The blow rate was raised until 0.30 m^3/min. Finally, pump speed was 3 mL/min. As another method, RE proceeded under temperature (65 ±5 ºC) for evaporating solvents. All the mixtures were stored in a desiccator before study and analysis.

Calculation of Encapsulation Efficiency (EE). The 5 mg

Table 1. Formulation of Aceclofenac Solid Dispersions Using Spray Drying and Rotary Evaporation Method

Batch No.	Ratios (drug : polymer)	Drug	Polymer (carrier)	Surfactant	Encapsulation efficiency (%)
		Aceclofenac	Kollidon VA 64	P407	
SD[a] 1	1 : 1	1	1	20%	87.6
SD[a] 2	1 : 2		2		90.9
SD[a] 3	1 : 3		3		99.1
SD[a] 4	1 : 4		4		99.4
RE[b] 5	1 : 1		1		94.1
RE[b] 6	1 : 2		2		98.0
RE[b] 7	1 : 3		3		98.1
RE[b] 8	1 : 4		4		99.3

[a]Solid dispersion prepared by spray drying method. [b]Solid dispersion prepared by rotary evaporation method.

aceclofenac was dissolved in 20 mL methanol among solvents. The amounts of prepared mixture using solid dispersion including 5 mg aceclofenac are different depending on ratios between drug and polymer. It is filtered using a 0.45 μm PTFE filter (Tokyo Roshi Kaisha, Ltd., Japan). Encapsulation efficiency of solid dispersions was measured by HPLC. Encapsulation efficiency (EE) was defined by the actual drug loading of the prepared solid dispersions. The equation was as follow:

$$EE\% = \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100 \quad (1)$$

Morphology of Spray Drying and Rotary Evaporator. The morphology characterization of aceclofenac and Kollidon VA 64 was observed by SEM (LV-SEM, S-3000N, Hitachi Co, Japan). SEM images were described respectively, depending on ratios between the drug and polymer in Figure 2. Samples were placed on a carbon fiber tape. They were coated with platinum-palladium during 100 sec under argon gas at twice at 30 mA. The samples were observed at 15.0 kV.

Crystalline Analysis by XRD and DSC. The crystallinity of aceclofenac, Kollidon VA 64, Airtal® according to solid dispersions was analyzed by PXRD (MAX 2500 X-ray diffractometer, Rigaku, Japan). The step size is 0.02°. The pattern range of angle is from 5° to 50°. Scan speed is at 4°/min. It runs at 30 mA, 40 kV.

The thermal behavior was performed by DSC 4000 (Perkin Elmer, Inc, Japan). The amounts of approximately from 5 to 10 mg were weighed into aluminum pans and crimped by aluminum caps. The samples were initially cooled down to -20 °C. Then, it has heated at a rate of 30 °C/min up to 200 °C under nitrogen purge.

Structural Analysis by FTIR. FTIR (Perkin Elmer, Waltham, Massachusetts, USA) was used to analyze prepared solid dispersions, aceclofenac and Kollidon VA 64. Measurements were performed from 4000 to 650 cm^{-1}. The amounts of mixtures in ratios of KBr : sample (100 : 1) are put in transparent disk.

Dissolution Studies. The dissolution of aceclofenac as a pure substance besides Kollidon VA 64 and solid dispersions was prepared in a dissolution apparatus type dissolution tester (DST-610, Fine Sci, Instr, Korea), using the paddle method (USP II method). The test was executed at 37±0.5 °C with paddle rotation speed of 50 rpm. The ball was filled in the dissolution medium (the simulated intestinal juice at pH 6.8) with amounts of 900 mL. The capsules were filled with prepared pellets of solid dispersion. At the predetermined time intervals, the 1 mL sample was withdrawn from dissolution medium and was replaced with the same amounts of prepared medium.

API as pure substance and Airtal®, in addition to RE and SD in solid dispersions were performed in the same prepared medium. Each of 1 mL samples was extracted at 5, 10, 15, 30, 45, 60, 90, 120, 240, and 360 min. To confirm error or fluctuation, all tests were conducted at thrice. As the same methods, samples were filtered through a 0.45 μm PTFE filter. They were analyzed by HPLC.

HPLC Conditions. The dissolution analysis was carried out by NS-4000 HPLC system and NS-6000 autosampler (Futecs, Korea). The condition of wavelength as UV detection is 282 nm. The column is used as ProntoSIL SH C_{18} (250×4.6 mm, 5 μm) Bischoff chromatography.

The mobile phase was manufactured owing to methanol : 0.02 M KH_2PO_4 (65:35). The flow rate is 1.0 mL/min and injection volume is 100 μL. Standard solutions using the way that aceclofenac was dissolved in methanol were manufactured.

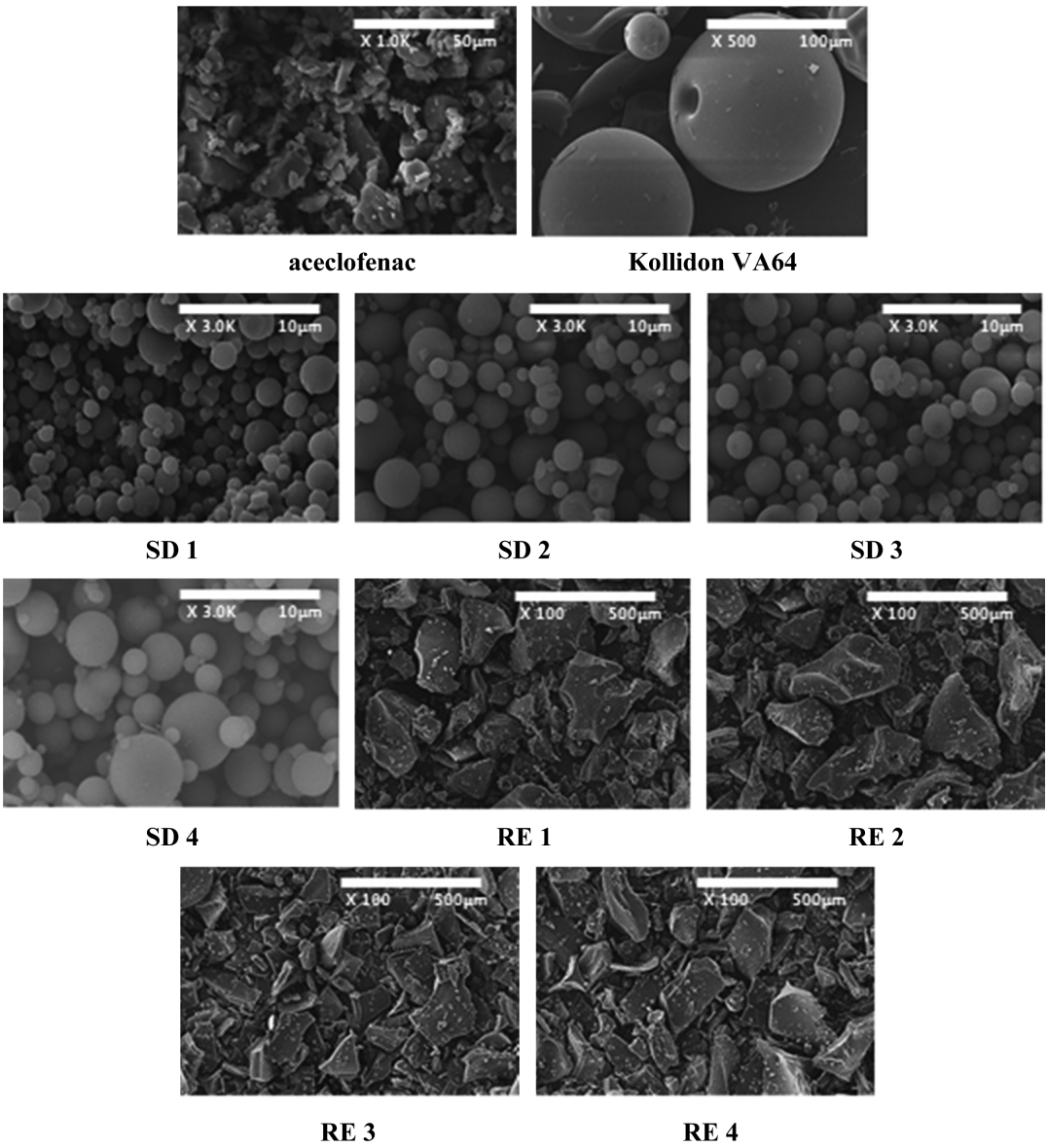

Figure 2. Surface morphologies of aceclofenac, carrier, SD 1~4, and RE 1~4.

Results and Discussion

Observation of EE in Solid Dispersion. The percentage EE of solid dispersion in accordance with eq. (1) was given by Table 1 for each composition studied. The EE for SDs and REs was found to be more than 87%. The drug contents of in RE 1 and RE 2 were slightly higher than SD 1 and SD 2. However, the results of SD 3 and SD 4 were the similar to the results of RE 3 and RE 4. Depending on the amounts of polymers, EE also was different overall. It was reported that it gave an opportunity for interaction between polymer as carrier and limited drug closely.[30]

Morphology Observation. Aceclofenac had rod-shape and in size from 30 to 50 μm in Figure 2. Kollidon VA 64 had sphere-shape and was normally 100 μm. The magnification of SD adjusted ×3.0 K, whereas magnification of RE adjusted ×100 because the size of SD was smaller than RE. Indicating that spray drying technology employed in this study caused efficient, down to the microscale, the smooth and round SD granules were formed. And in comparison with SD 1, lots of Kollidon VA 64 was observed in SD 4. The surface of RE did not observe initial sphere-shape of Kollidon VA 64. It was reported that the drug loadings and the process also investigated to gain better understanding of the effect of polymers

with physical state.[19]

Crystalline Analysis by XRD. The intrinsic peaks of aceclofenac were observed by test in Figure 3(a). Significantly, as can be seen, aceclofenac sample was a higher crystalline content. On the other hand, Kollidon VA 64 was in the amorphous form. From SD 1 to SD 4, the peaks appear amorphous. The crystalline content of aceclofenac attributed to the polymer transforming the solid dispersion into amorphous form.

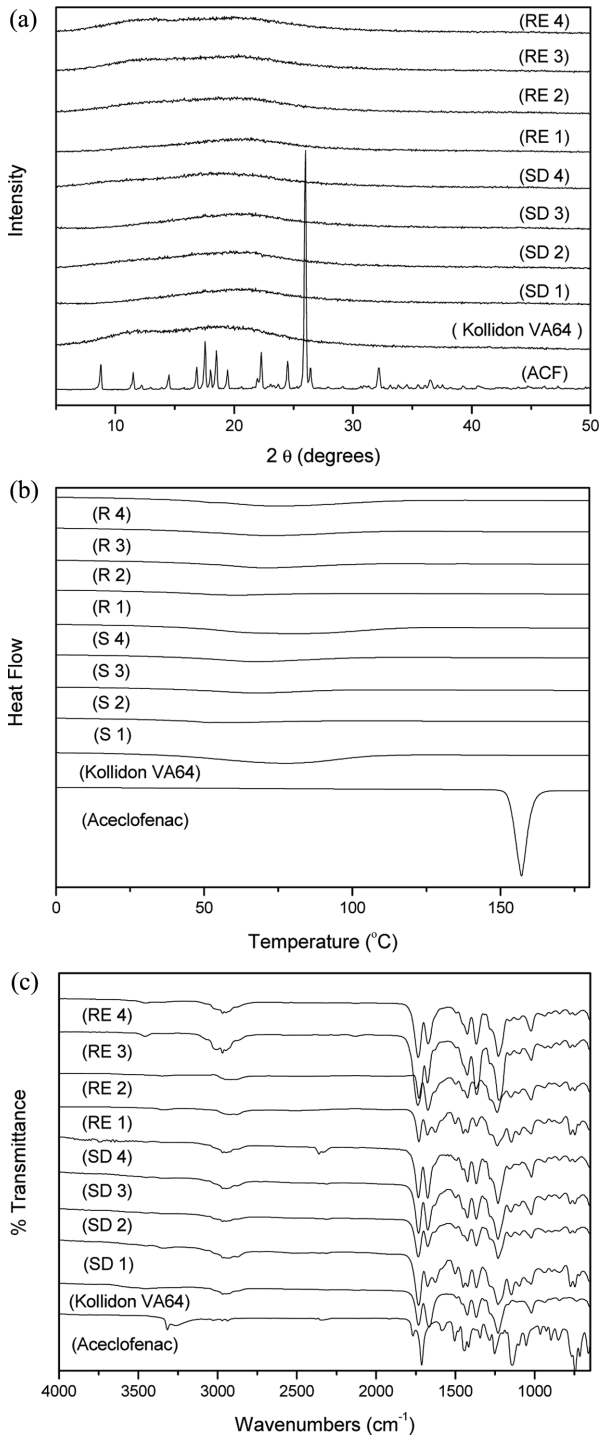

Figure 3. PXRD (a); DSC (b); FTIR (c) results of aceclofenac, carrier, SD 1~4, and RE 1~4.

Likewise, from RE 1 to RE 4, it found out that the crystallinity of aceclofenac was also reduced. Thus, all SDs and REs considered that the crystalline continued to decrease and amorphous could be formed. While both drug and polymer dissolved in solvents completely were in the liquid state, they lead to chemical interaction, in detail, which explained H-bond between drug and polymers.

Crystalline Analysis by DSC. The results of DSC with aceclofenac and solid dispersion were compared in Figure 3(b). This test also described the characterization of crystalline. Dehydration of aceclofenac occurred between 150 and 180 ºC. It seems a single endotherm on the DSC thermogram.

In this regard, this also revealed that this peak appears remarkable crystallinity of aceclofenac. All solid dispersions containing Kollidon VA 64 formed amorphous because XRD diffracttogram without aceclofenac showed no peaks.

As a result, since endotherm appeared unseen, relationship between drug and polymers allows H-bond to be persuaded.[31]

Structural Analysis by FTIR. FTIR spectra was used to evaluate the possible interactions between aceclofenac and Kollidon VA 64 in the solid state. Against Kollidon VA 64, the N-H bond peak of aceclofenac was between 3150 and 3420 cm^{-1} in Figure 3(c).

First of all, this peak of amine bond was formed at wavenumber of SDs and REs. It is noted that the peak of O-H bond at aceclofenac also appeared at between 3150 and 3420 cm^{-1} with N-H bond. There was no this peak in Kollidon VA 64. Also, The N-H bond and O-H bond showed few peaks in SDs and REs. The peaks of C=O bond appear at between 1620 and 1840 cm^{-1} throughout all samples. Moreover, the peak at 1735 cm^{-1} corresponds to the ester group presents without Kollidon VA 64. It is considered that the peaks were observable in the corresponding solid dispersion. The peak at 660 and 800 cm^{-1} represents the stretching of C-O bond in aceclofenac.

This peak of C-O bond was seen in aceclofenac, which appeared unseen in Kollidon VA 64 because it has no structure. In the result, all SDs and REs generally showed physicochemical interactions and structural change. Moreover, it confirmed that the initial chloride peak of aceclofenac has disappeared in all solid dispersions now that it was made of H-bond between a chloride group of aceclofenac and hydrogen group of Kollidon VA 64. To sum it all up, it confirmed that

the salt through the intermolecular hydrogen bond was generated between drug and polymer.[31]

Dissolution Studies. Dissolution test was conducted to confirm the release behavior of aceclofenac with Kollidon VA 64 using SDs and REs in addition to P407 in Figure 4. To begin with, The API was released by about 55% at 360 min. Overall, the cumulative release of SDs and REs besides Airtal® was more than 90% at 360 min. The T_{max} of Airtal® was approximately 120 min, which showed that the initial release normally was low. It seems to form a gentle curve because of low 4 half-life hours. The initial release of SDs was high and the T_{max} of SD 1 was 30 min in Figure 4(a). Other SDs have the T_{max} at 90 min. However, the cumulative release of SD 1 and SD 2 was 101%, compared with the 93% cumulative release of SD 3 and SD 4 in addition to Airtal®.

The cumulative release of REs showed 94% at 360 min in Figure 4(b). The T_{max} of REs have the similar to SDs. Most of REs have the T_{max} between 60 and 90 min. Only RE 3 was approximately between 90 and 120 min about T_{max}.

Though Airtal® has the best euphemistic curve, T_{max} of SD 3 and RE 3 have the similar to Airtal®.

In these results, the drug release kinetics from the SDs and REs was superior to that of API. The highest cumulative release of solid dispersions could be attributed to the amorphous shape and small size, in addition, that solid dispersion improves drug to solubilize water. Also, it was because the reduced interfacial tension between the dissolution medium and the drug particles due to the presence of the polymer.

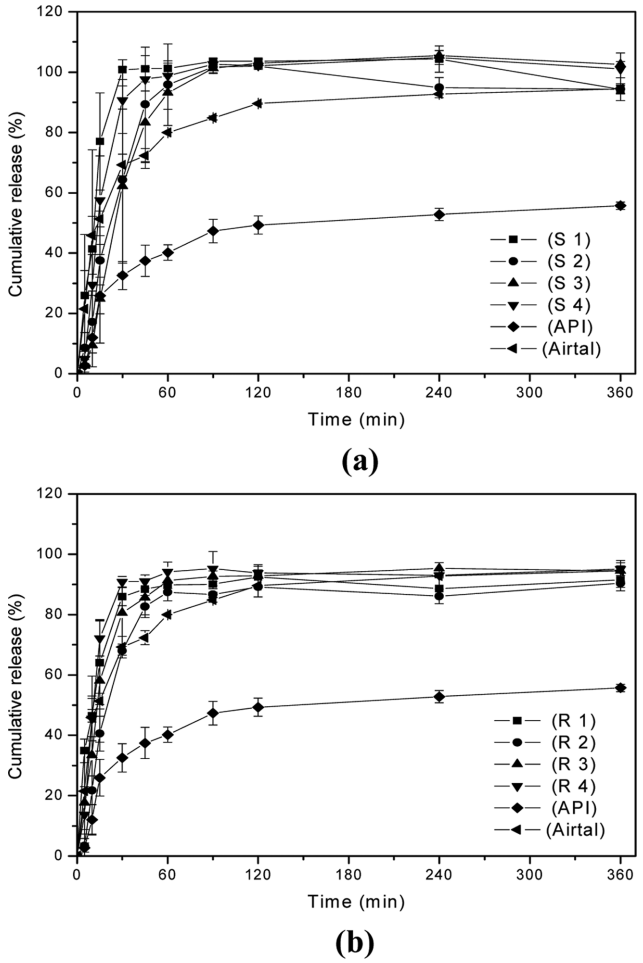

Figure 4. Release behavior of (a) SD 1, 2, 3, 4, API; (b) Airtal® in addition to RE 1, 2, 3, 4.

Conclusions

The purpose of this study was to improve the dissolution behavior of water-insoluble aceclofenac using two solid dispersions with spray drying and rotary evaporator. These solid dispersions were proved to be an effective technique for preparation of drug loading of aceclofenac with Kollidon VA 64. Also, the combination of XRD and DSC was used to explain the effect of amorphous. During the solid dispersion process, aceclofenac in the formulation was shown to convert into the amorphous form, to which be stabilized within the polymer as a carrier through non-specific intermolecular interactions. Also, the cumulative release of SDs normally remained higher than REs with P407. Compared to Airtal®, the drug release kinetics from the solid dispersion was superior to either API or simple PMs, which also was attributed to granules size reduction at the same time, the loss of crystallinity due to the presence of hydrophilic polymer.

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