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# Development and characterization of nifedipine-amino methacrylate copolymer solid dispersion powders with various adsorbents

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ABSTRACT

Solid dispersions of nifedipine (NDP), a poorly water-soluble drug, and amino methacrylate copolymer (AMCP) with aid of adsorbent, that is, fumed silica, talcum, calcium carbonate, titanium dioxide, and mesoporous silica from rice husks (SRH), were prepared by solvent method. The physicochemical properties of solid dispersions, compared to their physical mixtures, were determined using powder X-ray diffractometry (PXRD) and differential scanning calorimetry (DSC). The surface morphology of the prepared solid dispersions was examined by scanning electron microscopy (SEM). The dissolution of NDP from solid dispersions was compared to NDP powders. The effect of adsorbent type on NDP dissolution was also examined. The dissolution of NDP increased with the ratio of NDP:AMCP:adsorbent of 1:4:1 when compared to the other formulations. As indicated from PXRD patterns, DSC thermograms and SEM images, NDP was molecularly dispersed within polymer carrier or in an amorphous form, which confirmed the better dissolution of solid dispersions. Solid dispersions containing SRH provided the highest NDP dissolution, due to a porous nature of SRH, allowing dissolved drug to fill in the pores and consequently dissolve in the medium. The results suggested that solid dispersions containing adsorbents (SRH in particular) demonstrated improved dissolution of poorly water-soluble drug when compared to NDP powder.



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## 1. Introduction

The oral drug administration is the most preferred route of drug delivery due to convenience, patient adherence and rational production investment of oral solid dosage forms. After oral ingestion, the drug must be liberated and then solubilized in gastrointestinal (GI) fluid before it can be absorbed and has a systemic effect. Poor solubility of drug in GI medium generally leads to low dissolution rate and insufficient bioavailability [1,2]. The selection of suitable formulation is of great significance in the development of successful product for oral administration of poorly water-soluble drugs. Several formulation approaches can be used to improve the bioavailability of poorly water-soluble drugs. The most common method of increasing dissolution rate is to reduce the size of solid drug particles, which leads to an increased surface area available for dissolution [3]. The dissolution rate can also be increased by inducing salt formation or prodrug synthesis, which the new chemical entity has better solubility profiles but the same pharmaceutical activity after absorption in systemic [4,5]. Another common method of improving bioavailability for the poorly soluble drugs is to prepare an amorphous formulation allowing faster drug dissolution in comparison to its corresponding crystalline form. Solid dispersion is known as one of the effective methods for preparing amorphous solids and can be used for enhancing dissolution rate of poorly water-soluble drugs [6]. The mechanism of dissolution enhancement of solid dispersions can be explained by the transformation of a stable crystalline drug into a less stable amorphous state, a reduction in drug particle size and an increase in wettability and solubility of drug surrounded by hydrophilic carriers, such as polyethylene glycol, hydroxypropylcellulose and polyvinylpyrrolidone [1,2,7].

Amino methacrylate copolymer (AMCP) is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It can be dissolved in gastric fluid up to pH 5.0 and swelled above pH 5.0. Previously, AMCP was used as a carrier for solid dispersions, for example, chlordiazepoxide-AMCP solid dispersions [8]. It was observed that all AMCP-based solid dispersion formulations produce higher dissolution rate than the physical mixtures and the pure chlordiazepoxide. Li et al. [9] prepared solid dispersions of curcumin using AMCP as a matrix carrier by simple solution mixing method. They found that the solubility of curcumin was increased by forming curcumin-AMCP solid dispersions. Nevertheless, the prepared solid dispersions of AMCP tend to be sticky or tacky, resulting from the intermolecular interaction of eutectic composition between drug and polymer [10]. This leads to a decrease in the yield of solid dispersions and results in inconvenience handling in the subsequent manufacturing process.

Recently, adsorbents (e.g., fumed silica (FS), magnesium aluminum silicate, etc.) have been extensively applied as carriers in fabrication of solid dispersions to improve dissolution of poorly water-soluble drugs [11]. In general, adsorbents are used when there is a need to add a liquid or semisolid ingredient in the formulation; adsorbents are capable of sorbing the liquid component onto the dry powder. Most commonly used adsorbents in pharmaceuticals are anhydrous calcium phosphate, kaolin, magnesium carbonate, magnesium silicate, magnesium oxide, starch and silicon dioxide. By using the adsorbents, the melt of solid dispersion could be adsorbed in the pores and/or rough surface of absorbents, thus improving powder flowability and compressibility for further manufacturing processes [7,12–14].

In our preliminary study, the solid dispersions composed of nifedipine (NDP), AMCP and FS were developed (at ratios of NDP:AMCP:FS = 1:0.5–4:0–1) [15]. With no FS, gelatinous mass of solid dispersions was obtained. The free-flowing powder was achieved when inert FS was added. The results from dissolution test revealed poor and slow dissolution of pure NDP. On the other hand, solid dispersions with low amount of AMCP (i.e., the ratios of 1:0.05:1, 1:1:1 and 1:2:1) showed an improved drug dissolution. Nevertheless, the dissolution profiles of these solid dispersions resulted in slow release with drug dissolution about 20–30% after 2 h. The enhanced drug dissolution was observed when high amount of AMCP (at a ratio of NDP to AMCP of 1:4) was used, regardless of the addition of adsorbent [15]. However, the influence of the type of adsorbents on drug dissolution has not been investigated in details. Therefore, in this research, the powder form of solid dispersions was developed using various types of adsorbents. Solid state characterization, i.e., powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM), was performed. The influence of NDP:AMCP:adsorbent on drug dissolution was also evaluated.

## 2. Materials and methods

### 2.1. *Materials*

NDP was purchased from Xilin Pharmaceutical Raw Material Co., Ltd. (Jiangsu, China). AMCP (Eudragit® E) and FS (Aerosil® 200) were received from Evonik Industries (Hanau, Germany). Mesoporous silica from rice husks (referred to as SRH) was prepared by depolymerization at high temperature, as described in previous report [16]. Simulated gastric fluid USP without pepsin (SGF) was prepared by dissolving 2 g of sodium chloride and 7 mL of hydrochloric acid with distilled water to make a total volume of 1000 mL of solution. All other chemicals used in this study were of pharmaceutical grade and used as received without further purification.

### 2.2. *Preparation of NDP-AMCP solid dispersions with adsorbents*

Solid dispersions of NDP and AMCP with various adsorbents were prepared by solvent method. NDP (1 g) and various amounts of AMCP were dissolved in sufficient amount of methylene chloride to obtain a clear solution, and various amounts of different adsorbents were then added to obtain uniform suspensions. After mixing, the solvent was removed at ambient temperature (25 °C). The solid dispersion obtained was dried at 40 °C in a vacuum oven for 24 h. In this study, the adsorbents investigated were FS, SRH, titanium dioxide ($TiO_2$), calcium carbonate ($CaCO_3$), and talcum. The NDP, AMCP and adsorbent ratios were 1:0.5:1, 1:1:1, 1:2:1, 1:4:1 and

1:4:0. Physical mixtures (PM), at the same ratios to solid dispersions, were also prepared by physical mixing the accurately weighed amount of NDP, AMCP and adsorbent thoroughly using a vortex mixer until homogeneous mixture was obtained. All samples were kept in desiccator until further study.

### 2.3. Characterization

#### 2.3.1. Moisture content determination

Moisture content of solid dispersions was carried out with moisture analyzer (model MA45, Sartorius, Germany). Solid dispersions (approximately 2 g) were placed in a ventilated oven at 105 °C until reaching a constant weight [17]. Then, the moisture content was calculated by the following equation.

$$\text{Moisture content}\,(\%) = \left(\frac{(W_m - W_d)}{W_d}\right) \times 100 \quad (1)$$

where $W_m$ is the moist weight (g) and $W_d$ is the dry weight (g).

#### 2.3.2. Determination of flow properties

Angle of repose was performed on fixed and free of vibration base. The powder layer after falling from the funnel was retained [18]. The symmetrical cone of powder was built up under the funnel. Angle of repose ($\alpha$) was determined from measuring the height of the cone powder and diameter of base by the following equation.

$$\tan(\alpha) = \frac{height}{0.5\ base} \quad (2)$$

Compressibility index and Hausner ratio were also determined by tapping the powder in cylinder [18]. The equations use the unsettled apparent volume ($V_o$) and the final tapped volume ($V_f$) of the powder after tapping the sample until no further volume changes occur in measuring cylinder. Compressibility index and Hausner ratio were determined by Equations (3) and (4), respectively.

$$\text{Compressibility index} = 100 \times \left[\frac{V_o + V_f}{V_o}\right] \quad (3)$$

$$\text{Hausner ratio} = \frac{V_o}{V_f} \quad (4)$$

#### 2.3.3. DSC analysis

The DSC analysis was carried out using differential scanning calorimeter (model Sapphire, Perkin Elmer, Germany). About 2–3 mg of samples were accurately weighed, placed in an aluminum pan and sealed with an aluminum lid. Sample was heated from 25 to 200 °C at a heating rate of 10 °C/min.

#### 2.3.4. PXRD analysis

The PXRD experiments were performed using a powder X-ray diffractometer (model Miniflex II, Rigaku Co., Japan) at 30 kV, 15 mA over the range of 5–45° 2θ at the scanning speed of 4 degrees/min using $CuK_\alpha$ radiation wavelength of 1.5406 Å.

#### 2.3.5. SEM observation

The surface morphology of solid dispersions, raw materials and physical mixtures was observed by using a scanning electron microscope (model Maxim-2000, CamScan Analytical Ltd., England), under accelerating voltage of 15 keV. Samples were fixed on SEM stub with double-sided adhesive tape and then coated in a vacuum with thin gold layer before investigation.

### 2.4. Dissolution test

The dissolution of NDP from samples (equivalent to 10 mg of NDP) was performed in 900 mL SGF, pH 1.2, at 37 ± 0.5 °C using USP dissolution apparatus II (model DT70, Erweka, Germany) with paddle rotation speed of 50 rpm. Samples were withdrawn from the dissolution vessels at 5, 10, 15, 30, 60, 90 and 120 min and passed through 0.45-μm nylon filter and then analyzed by high performance liquid chromatography (HPLC; model Jasco PU-2089 plus quaternary gradient inert pump, and a Jasco UV-2070 plus multi wavelength UV–vis detector, Jasco, Japan) at a wavelength of 235 nm using ACE® (4.6 × 250 mm) column. The system was operated under isocratic flow at 1 mL/min using a mobile phase consisting of water:acetonitrile:methanol; 50:25:25 (v/v), filtered through a 0.45-μm membrane filter, and degassed in a sonicator bath before used. Sample injection volume was 20 μL. Data were collected and analyzed by ChromNav program (Jasco, Japan). The experiments were conducted in triplicate.

### 2.5. Statistical analysis

Analysis of variance (ANOVA) and Levene's test for homogeneity of variance were carried out using SPSS version 10.0 for Windows (SPSS Inc., USA). *Post hoc* testing ($P < 0.05$) of multiple comparisons was performed by either the Scheffé or Games-Howell test depending on whether Levene's test was insignificant or significant, respectively.

## 3. Results and discussion

### 3.1. Physicochemical characterization of solid dispersions

By using solvent method with the aid of adsorbent, the fine particles of all solid dispersion formulations were obtained. The moisture content of all solid dispersion formulations ranged from 2% to 6%. A small amount of water (<6%) in the formulation is beneficial as it can inhibit drug recrystallization; the polymer that is used as solid dispersion carrier can also act as barrier to crystallization [19]. The angle of repose of all solid dispersion formulations was in the range of 40°–50° that were manufacturing satisfactorily [18], as shown in Table 1. The formulations containing FS and SRH (at a ratio of 1:2:1) and $TiO_2$ (at a ratio of 1:0.5:1) showed an excellent flow (angle of repose was in the range of 25°–30°) while those containing FS (at ratios of 1:0.5:1 and 1:4:1) showed a good flow (angle of repose was in the range of 31°–35°). The values of compressibility index and Hausner ratio also showed a similar trend; the solid dispersions using $CaCO_3$ (at ratios of 1:0.5:1 and 1:2:1) and $TiO_2$ (at a ratio of 1:0.5:1) illustrated a passable flow character, but other formulations were good and excellent in flow properties [18].

The crystallinity of NDP in solid dispersions was investigated by using PXRD. Fig. 1 shows the PXRD patterns of pure NDP, AMCP, adsorbents and solid dispersions containing

**Table 1 – Moisture content and flow properties of solid dispersion formulations ($n$ = 3).**

| Formulations | | Moisture content ± SD (%) | Angle of repose ± SD (degree) | Compressibility index ± SD (%) | Hausner ratio ± S.D. |
|---|---|---|---|---|---|
| Composition | Ratio | | | | |
| NDP:AMCP | 1:4 | 3.67 ± 0.50 | 37.69 ± 1.68 | 12.84 ± 1.81 | 1.15 ± 0.04 |
| NDP:AMCP:$CaCO_3$ | 1:0.5:1 | 2.01 ± 0.12 | 37.65 ± 2.30 | 29.06 ± 1.78 | 1.41 ± 0.04 |
| | 1:2:1 | 3.00 ± 0.17 | 44.64 ± 3.29 | 21.25 ± 1.68 | 1.27 ± 0.03 |
| | 1:4:1 | 3.95 ± 0.20 | 43.68 ± 4.71 | 20.20 ± 0.34 | 1.25 ± 0.01 |
| NDP:AMCP:FS | 1:0.5:1 | 4.75 ± 0.13 | 31.30 ± 3.62 | 15.46 ± 2.09 | 1.18 ± 0.03 |
| | 1:2:1 | 4.37 ± 0.68 | 25.64 ± 2.03 | 11.62 ± 1.37 | 1.13 ± 0.06 |
| | 1:4:1 | 5.57 ± 0.40 | 34.47 ± 1.03 | 5.98 ± 1.48 | 1.06 ± 0.02 |
| NDP:AMCP:$TiO_2$ | 1:0.5:1 | 3.94 ± 0.27 | 28.39 ± 1.12 | 28.89 ± 2.70 | 1.42 ± 0.14 |
| | 1:2:1 | 3.19 ± 0.28 | 36.20 ± 0.67 | 15.37 ± 2.46 | 1.18 ± 0.03 |
| | 1:4:1 | 3.42 ± 0.30 | 37.40 ± 1.61 | 18.89 ± 1.92 | 1.23 ± 0.03 |
| NDP:AMCP:talcum | 1:0.5:1 | 3.20 ± 0.25 | 35.19 ± 5.43 | 17.31 ± 1.81 | 1.22 ± 0.13 |
| | 1:2:1 | 4.16 ± 0.25 | 34.75 ± 1.84 | 19.91 ± 1.56 | 1.25 ± 0.10 |
| | 1:4:1 | 5.51 ± 0.33 | 41.67 ± 2.69 | 5.98 ± 1.48 | 1.06 ± 0.02 |
| NDP:AMCP:SRH | 1:2:1 | 3.35 ± 0.50 | 30.71 ± 5.09 | 18.10 ± 3.30 | 1.22 ± 0.05 |
| | 1:4:1 | 4.73 ± 0.79 | 33.18 ± 1.76 | 10.00 ± 0.00 | 1.11 ± 0.00 |

different adsorbents. From the PXRD patterns, NDP showed a high crystallinity with characteristic diffraction peaks at 11.9°, 19.6° and 24.1° [20]. No sharp peak was observed for AMCP, indicating that the polymer was in amorphous form [20]. From the PXRD patterns of adsorbents, FS and SRH were in amorphous form while talcum, $TiO_2$ and $CaCO_3$ were present in crystalline form. Their physical mixtures still showed intrinsic crystalline peaks of NDP. The PXRD pattern of solid dispersions of NDP and AMCP at a ratio of 1:4 showed characteristic peaks of NDP but the intensity and number of NDP peaks were reduced, suggesting a decrease in drug crystallinity. For the solid dispersions of NDP and AMCP with adsorbents at a ratio of 1:4:1, no characteristic peak of NDP was observed. It is expected that NDP was molecularly dispersed in the matrix of polymer and adsorbent [21,22]. However, the solid dispersions of NCP, AMCP and adsorbent at a ratio of 1:2:1 showed characteristic crystalline peaks of NDP. This is probably due to the insufficient amount of AMCP to form

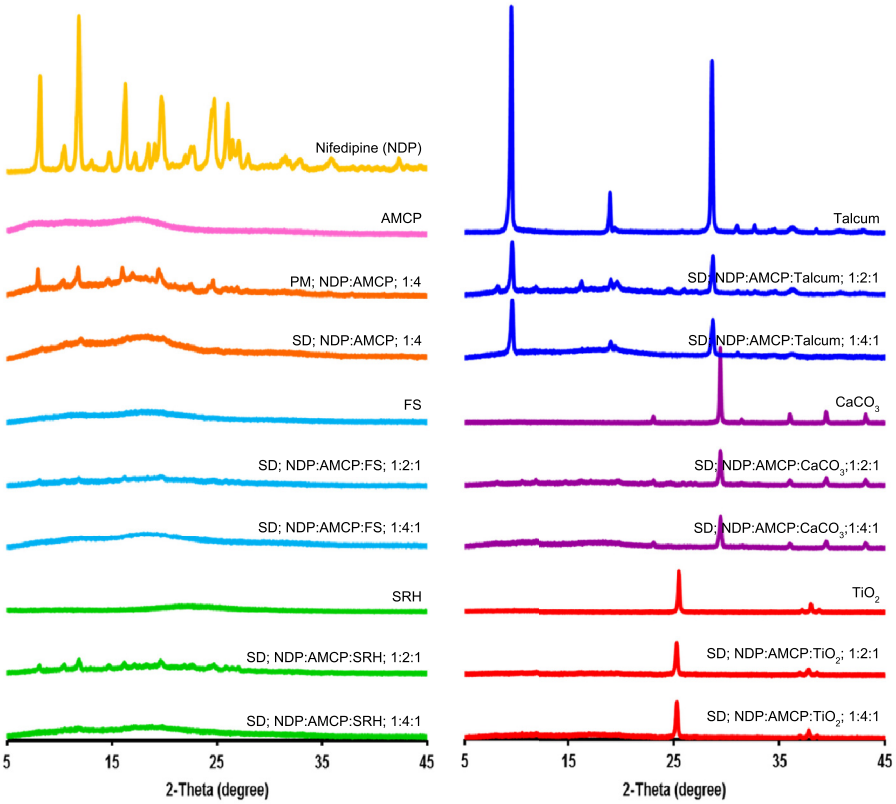


**Fig. 1 – PXRD patterns of pure NDP, AMCP, adsorbents and solid dispersions containing different adsorbents.**

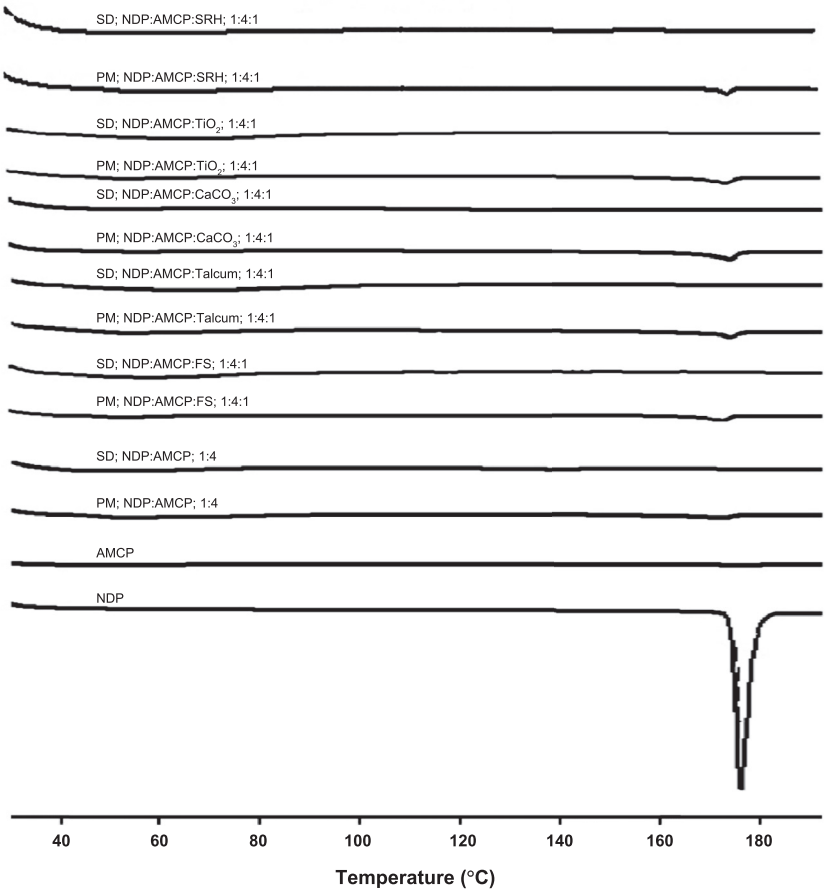


**Fig. 2 – DSC thermograms of pure NDP, AMCP, adsorbents, their physical mixtures and solid dispersions.**

homogeneous solid dispersion. Decreasing of the ratio of AMCP (i.e., to 1:1:1 or 1:0.5:1) increased the intensity of diffraction peak of NDP (data not shown).

DSC measurements were performed to study the physical state of NDP. The DSC thermograms of pure NDP, AMCP, adsorbents, their physical mixtures and solid dispersions are shown in Fig. 2. The melting transition of NDP appeared at 173.6 °C. The physical mixture of NDP and AMCP without or with adsorbent showed a small endothermic peak, which corresponded to NDP. The DSC thermogram of solid dispersion of NDP and AMCP at a ratio of 1:4 showed no melting peak of NDP, even though the peaks derived from NDP were observed in PXRD. Thermograms of solid dispersions containing adsorbents, prepared at a ratio of 1:4:1, showed the absence of NDP melting peak, suggesting that NDP was completely soluble in the liquid phase with AMCP [21]. However, in case of the solid dispersions at the ratios of 1:0.5:1, 1:1:1, 1:2:1, a small melting peak of NDP was observed (data not shown), suggesting that crystalline NDP still remained, at least to some extent [15]. These results supported the PXRD analysis; the crystallinity of NDP depended on the ratio of polymer in solid dispersions.

The morphology of solid dispersions was studied by scanning electron microscopy (SEM). SEM images of NDP, AMCP, physical mixture of NDP and AMCP, and solid dispersion of NDP:AMCP at a ratio of 1:4 are depicted in Fig. 3. The SEM analysis showed that NDP powder consisted of a mixture of small and large rectangular crystals. AMCP consisted of rough surface crystals. The physical mixture containing NDP and AMCP particles revealed rough surface particles, which may be due to presence of NDP powder onto surface of AMCP. SEM image of binary solid dispersions containing NDP and AMCP at a ratio of 1:4 showed some rough surface particles. It is likely that NDP was thoroughly mixed and dispersed within polymer carrier with the loss of little crystallinity [22,23], which was confirmed in the PXRD and DSC studies.

SEM images of adsorbents, physical mixture of NDP, AMCP and adsorbents and solid dispersions containing NDP, AMCP and adsorbents at a ratio of 1:4:1 are shown in Fig. 4. In this study, different adsorbents with different surface areas were investigated, that is, FS (surface area 200 $m^2/g$) [20], talcum (surface area 2.41–2.42 $m^2/g$) [24], $TiO_2$ (surface area 9.90–10.77 $m^2/g$) [25], $CaCO_3$ (surface area 6.21–6.47 $m^2/g$) [26] and SRH (pore volume 0.95 $cm^3/g$ and surface area 129.30 $m^2/g$) [16,27]. The physical mixture of NDP, AMCP and adsorbents showed the presence of NDP in the crystalline form. It is also easy to recognize the particles of adsorbents in the mixtures. As seen in Fig. 4, the SEM images of solid dispersions revealed the existence of irregular particles with several microscopic cracks and crevices, which could provide additional surface for deposition of drug particles. Drug molecules seem to be dispersed within the carrier matrix of the solid dispersions. These observations provided the evidence of solid dispersion formation by converting crystalline drug to amorphous form. In addition, the re-arrangement of adsorbents could

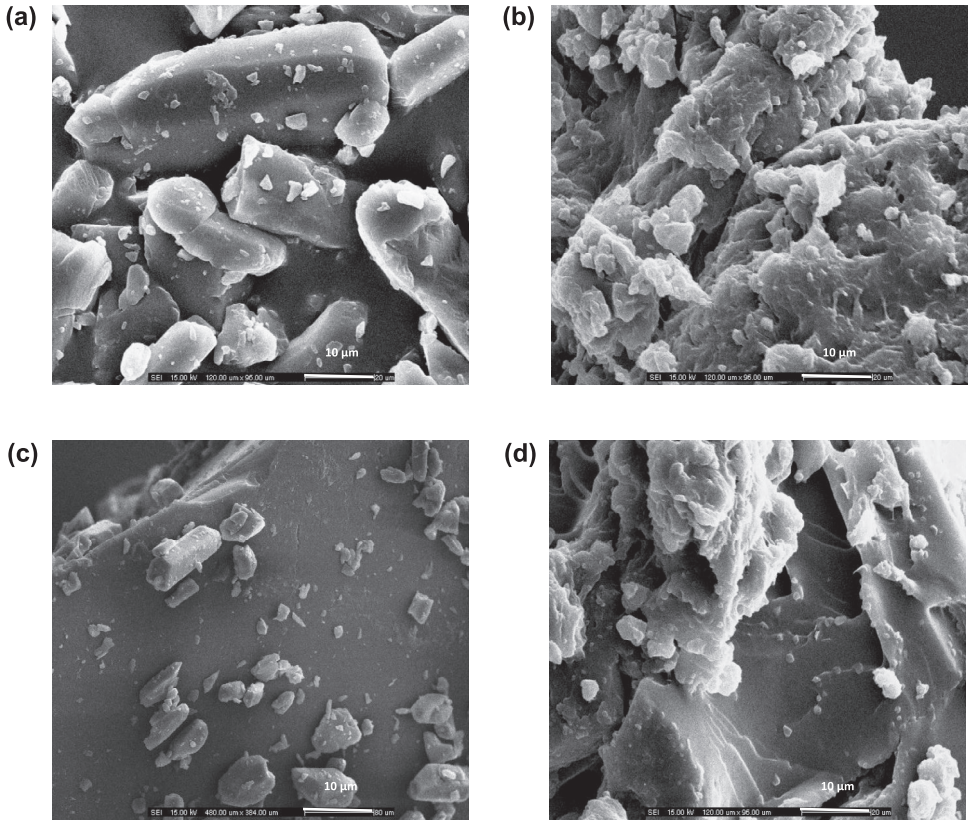


**Fig. 3 – SEM images of (a) NDP, (b) AMCP, (c) physical mixture of NDP and AMCP, and (d) solid dispersion of NDP:AMCP at a ratio of 1:4.**

physically separate NDP-AMCP solid dispersions and prevent aggregation [28].

### 3.2. *Dissolution study*

The *in vitro* dissolution studies were performed for all solid dispersions and NDP powders. Fig. 5 illustrates the dissolution profiles of NDP, in SGF, from solid dispersions containing various adsorbents and NDP powder. The dissolution of NDP powder was considerably low. The cumulative amount of drug dissolved at 20 min was only 1.3% (Fig. 6). In general, the NDP dissolution from solid dispersions markedly increased when compared to NDP powder. It might be due to presence of amorphous form of NDP [29], reduction of particle size [30], enhancement of wetting of drug particles, and/or localized solubilization by the hydrophilic carriers. Similar observations have been reported for solid dispersions of naproxen in polyethylene glycol (PEG) 4000, PEG 6000, and PEG 20000 [31]. PEG may enhance the solubility of NDP in solid dispersion by reducing the hydrophobic interaction of drug.

The NDP dissolution profiles of solid dispersions containing $TiO_2$ and talcum were similar, about 60% of NDP dissolved within 1 h. This may be due to the low surface area of $TiO_2$ and talcum. Although FS is an investigated adsorbent with the highest surface area, the NDP dissolution was not much improved. It is probable that the aggregation of solid dispersions containing FS occurred, similar to that reported in previous study [20]; the gelation of silicon dioxide formed a barrier that may retard drug dissolution from the formulations using FS. The percentage of NDP dissolved from solid dispersions containing $CaCO_3$ was significantly higher than that from NDP powder ($P < 0.05$) and solid dispersions containing $TiO_2$, talcum and FS ($P < 0.05$). In fact, $CaCO_3$ can be solubilized in acid condition (pH 1.2) and then generates the $CO_2$ gas. The $CO_2$ gas generated in the particles can facilitate disintegration, due to generation of pressure within the particles, and then faster drug dissolution. Additionally, the improved dissolution of solid dispersions containing $CaCO_3$ may result from the increased surface area after liberation of $CO_2$ gas. Interestingly, the percentage of NDP dissolved from solid dispersions containing SRH provided the highest NDP dissolution. This may be due to the fact that SRH has a porous nature, allowing dissolved drug to enter and fill in the pores of SRH during the preparation process [16,27]. These results were also supported by the study of Takeuchi and coworkers [12] who developed solid dispersion particles of indomethacin with different types of silica, nonporous (FS) or porous silica (Sylysia® 350), by using spray-drying method. They found that the drug dissolution from solid dispersion particles with porous silica was faster than that with FS [12].

The percentage of NDP dissolved from solid dispersions at 20 min was significantly higher than that of NDP powder ($P < 0.05$) (Fig. 6). Also, the percentage of drug dissolved at 20 min from solid dispersions containing higher amount of AMCP (i.e., NDP:AMCP:adsorbent ratio of 1:4:1) was significantly higher than those containing lower amount of AMCP ($P < 0.05$). For solid

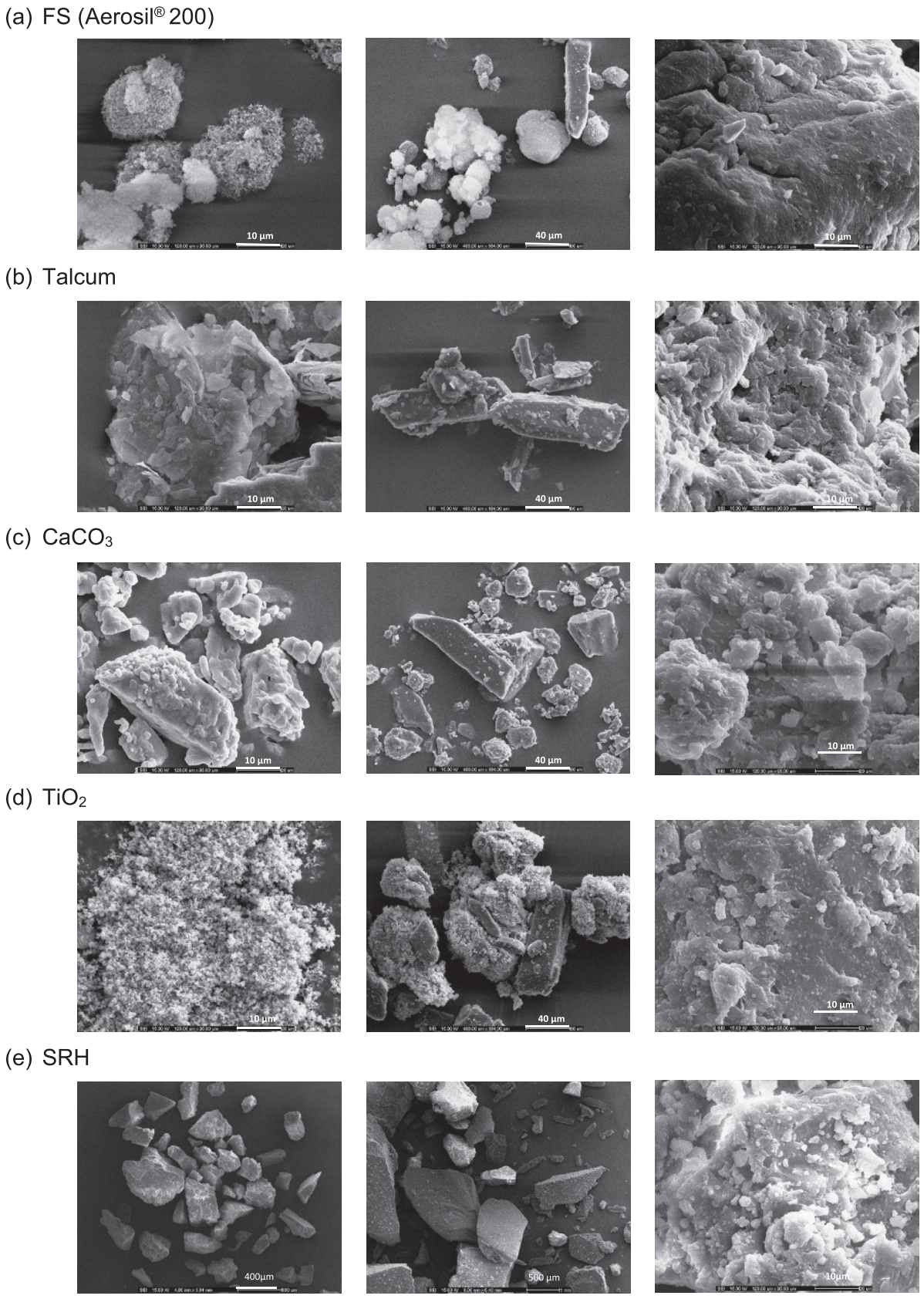


**Fig. 4 – SEM images of adsorbents (left column), physical mixture of NDP, AMCP and adsorbents (middle column) and solid dispersions containing NDP, AMCP and adsorbents at a ratio of 1:4:1 (right column). The adsorbents investigated are (a) FS, (b) Talcum, (c) $CaCO_3$, (d) $TiO_2$ and (e) SRH.**

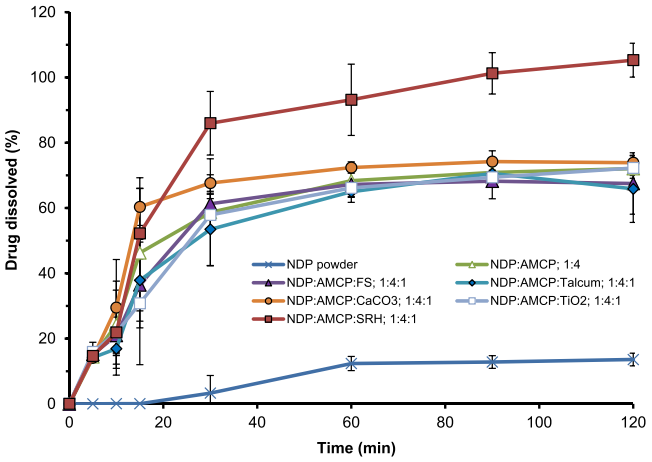


**Fig. 5 – Dissolution profiles of NDP from solid dispersions containing various adsorbents and NDP powder ($n = 3$).**

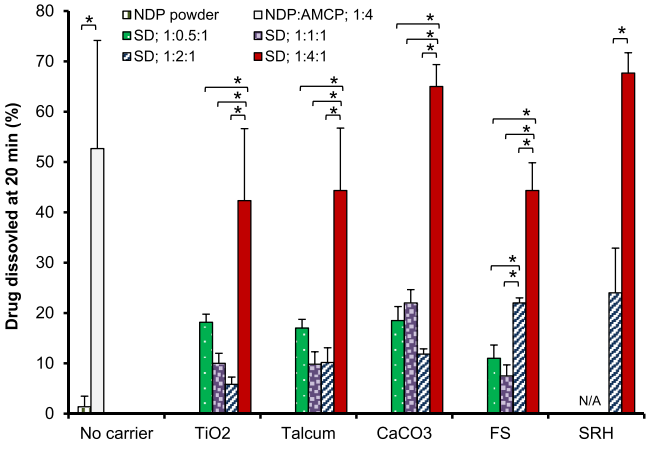


**Fig. 6 – NDP dissolved, at 20 min, from NDP powder and solid dispersions containing different adsorbents and different ratios of NDP:AMCP:adsorbent ($n = 3$).**

dispersions containing FS, NDP dissolution at 20 min increased significantly ($P < 0.05$) when the amount of AMCP increased. Using other adsorbents, at the lower amount of adsorbents (i.e., at the ratios of 1:0.5:1–1:2:1), the NDP dissolution at 20 min was not statistically significantly different ($P > 0.05$).

## 4. Conclusion

Solid dispersions of a poorly water-soluble drug (i.e., NDP) were successfully prepared by solvent method using AMCP with the aid of adsorbents. An improved dissolution of NDP has been attributed to changes in crystal structure, which were demonstrated by the results of DSC and PXRD studies. Furthermore, the free-flowing powder and enhanced dissolution behavior were obtained by addition of selected adsorbents (FS, SRH and calcium carbonate).

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