

CHARACTERIZATION OF PHYSICAL PROPERTIES AND DISSOLUTION RATE OF BINARY SYSTEMS ERYTHROMYCIN STEARATE-MICROCRYSTALLINE CELLULOSE AND SPRAY DRIED LACTOSE DUE TO COMPRESSION FORCES

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ABSTRACT

Physical properties and dissolution rate of binary system erythromycin stearate (ERS): microcrystalline cellulose (MCC) and spray dried lactose (SDL) due to compression forces had been studied using X-ray powder diffraction (XRPD), differential thermal analysis (DTA), scanning electron microscope (SEM) and dissolution test. ERS:MCC and ERS:SDL with a ratio of 90:10, 80:20 and 70:30 (w/w) were compressed by hydraulic press plain flat punches with a diameter of 13 mm and compression force of 29.5 kN. The main peaks X-ray powder diffraction positions at 5.7 and 10.5° were used to calculate the values of peak broadening, crystallite size and crystal orientation using the WinPlotr. Peak broadening was calculated from the full width at half maximum (FWHM). The FWHM values of binary system became higher as the amount of excipient increased, crystallite size and intensity of X-ray diffraction decreased compared to ERS. Phase diagram of the physical mixture shows the binary system ERS:MCC and ERS:SDL has no interaction, each individually melted in accordance with the melting point. From the results of scanning electron micrograph, it was known that the MCC and SDL dispersed among ERS which plastic deformation. ERS:MCC was rougher than the ERS:SDL. Enthalpies value decreases with increased amount of ERS. The result of dissolution test showed that the dissolution rate of ERS:MCC is faster than the ERS:SDL.

Keywords: Dissolution rate, Physical properties, Erythromycin stearate, Microcrystalline cellulose, Spray dried lactose, Compression force

INTRODUCTION

Generally, tablet manufacturing process such as milling, granulation, drying and compression could transform of crystal form during the process. Interactions between drug molecules and excipient molecules can be induced by mechanical and thermal energy during the manufacturing process of pharmaceutical preparations^{1,2}.

Several solid dosage form of erythromycin stearate is known not meet the test requirements of dissolution which is some tablets have a better dissolution rate (from 89.6 to 101.0%) compared with capsule dosage form (40.4 to 44.6%)³. It could be due to the formula (composition of materials), manufacturing process or a combination of both. Compression forces on the crystal properties of erythromycin acitrate tablets affected in increasing the size of the crystals on the surface of the tablet after being given a low compression (4 kN) and also observed in all the crystal lattice⁴. The physical properties of pharmaceutical ingredients crystal and the compression force are important parameters that can affect the stability, processability and bioavailability⁵.

The level of crystallinity, crystallite size and lattice damage of some pharmaceutical ingredients (aspirin and nicotinic acid) correlated with compression force. Dissolution properties of pharmaceutical preparations that were influenced by the level of crystallinity has been widely reported but only a few have reported that compression force can affect the level of crystallinity⁶ and also the interaction between active ingredients and excipients. Interaction between erythromycin-PEG 6000 and erythromycin transformation can occur in the presence of heat⁷.

ERS which is compressed with different compression force indicated the occurrence of plastic deformation and also sintering (loss of surface boundary due to incorporation of particles)⁸. From further studies on the influence of compression force on the mixture ERS:PEG-6000 1:1 (w/w) with the compression force of 14.7 kN using SEM micrograph, erythromycin stearate showed molecularly dispersed among the matrix of PEG-6000⁹.

Microcrystalline cellulose (MCC) is a purification of cellulose depolymerization that serves as a binder or filler in the formulation of tablets and capsules that can be used with wet granulation method or direct compression. Spray dried lactose (SDL) consists of

crystalline lactose monohydrate crystals and some amorphous to enhance compactibility. Both materials are commonly used as filler material in the manufacture of direct compression tablets¹⁰.

In this research the physical properties and dissolution rate of binary system erythromycin stearate (ERS):microcrystalline cellulose (MCC) and spray dried lactose (SDL) due to compression forces was studied.

MATERIALS AND METHODS

Materials

Erythromycin stearate was procured from PT.Kimia Farma, Jakarta, Indonesia, microcrystalline cellulose (MCC) was obtained from Asahi Chem.Co, Kansei, Japan and spray dried lactose (SDL) was obtained from DMV-Fonterra Excipients GmbH & Co, Germany.

Methods

Physical mixture ERS:MCC and ERS:SDL with a ratio of 90:10, 80:20 and 70:30 (w/w) was compressed using hydraulic press with a diameter of 13 mm flat punches and a compression force of 29.5 kN, equivalent to 3,000 kgf (Graseby-Specac, Germany). Characterization is done by X-ray powder diffraction (XRPD), differential thermal analyzer (DTA), scanning electron microscope (SEM) and dissolution studies.

X-ray Powder Diffraction Studies

X-ray powder diffraction patterns were obtained using a X-ray diffractometer (Philips X'Pert, Netherland) with CuK α radiation (1.54 Å), at 40 kV, 30 mA, passing through a nickel filter with a divergence slit (0.5°), antiscattering slit (0.5°), and receiving slit (0.15 mm). Scanned at a rate of 2.4°/min, over the 2 θ range of 5-40°. Obtained diffractograms were analyzed with Winplotr diffraction software.

Peak Broadening

Peak broadening was calculated using the Full Width at Half Maximum (FWHM)⁴. Data presented in graphical form between the ratio of the ERS:SDL and ERS:MCC (X axis) and FWHM (2 θ) Y axis.

Crystallite size

Crystallite size calculated using the Scherrer's equation:

$$D = k \lambda / \beta \cos \theta$$

where k varies from 0.89 to 1.39, but the assumption of $k = 1$, wavelength of X-rays $\lambda = 0.1541$ nm and β is integral breadth⁴. Data was presented in graphical form between the ratio of the ERS:SDL and ERS:MCC (axis X) and crystallite size (Y axis).

Preferred orientation of crystals

Preferred orientation is seen from the intensity of diffraction peaks⁴ at $2\theta = 5.7$ and 10.5° . Data was presented in graphical form between the comparison of ERS:SDL and ERS:MCC (X axis) and intensity (Y axis).

Differential Thermal Analysis Studies

Differential thermal analysis was performed on a differential thermal analyzer (Metler Toledo FP 85, Switzerland). ± 5 mg of a mixture of ERS:SDL and ERS:MCC with various comparisons were heated in hermetically sealed aluminum pans with a heating rate of $10^\circ\text{C}/\text{min}$. Heating performed at a temperature of 50 - 250°C .

Scanning Electron Micrograph

ERS, SDL, MCC raw surface material and fracture surface structure of ERS, ERS:SDL and ERS:MCC tablets were observed with scanning electron microscope (SEM) JEOL, JSM-840A, Japan Electron Optics Limited, Japan with magnification of 1000 and 500 times.

Dissolution Studies

The dissolution of ERS:SDL and ERS:MCC was determined using a dissolution apparatus (ERWEKA DT 7000, Germany) in the 900 ml of phosphate buffer pH 6.0. The paddles were rotated at 100 ± 1 rpm and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$ ¹¹. A 7 ml aliquot was withdrawn at appropriate time intervals (filtered, diluted with dissolution medium) and replaced with a 7 ml of fresh dissolution medium after each sampling to maintain the constant volume. The amount of erythromycin was determined spectrophotometrically at 236 nm. Erythromycin concentration was calculated and expressed as percentage of erythromycin dissolved from the mean of three determinations.

RESULTS AND DISCUSSION

The result of characterization using XRPD on the tablet surface of ERS:SDL, ERS:MCC and ERS powder was showed in Figures 1 and 2. From that XRPD diffractogram, FWHM can be calculated. FWHM is a measurement of peak width ($x_2 - x_1$) in half of intensity height ($1/2 F_{\text{max}}$)¹². The effect of compression force on the FWHM values was calculated from the surface of the tablet as shown in Figure 3. The two peaks at $2\theta = 5.7^\circ$ and 10.5° described that the crystal lattice of sample have a different direction. On the surface of the ERS tablet, compression force of 29.5 kN may increase FWHM value in the direction of the lattice on the amount of SDL and MCC by 20%, then decreases in the amount of 30% (Figure 3). Increasing value of FWHM was due to the compression force and heat so that crystallites adjacent to one another. Crystallite may be broken and filled the space between the crystallites so that the crystal lattice increased. A widening of the diffraction peak is influenced by crystallite size and crystal lattice damage. In paracrystallite theory, a crystallite size of less than 1000 \AA , will lead to widening and broadening of diffraction peaks which was independent to scattering angle. Damage of crystal lattice also produces widening of the peak with increasing scattering angle^{5,6}. On a larger excipient composition (30%) broken crystallites were separated by the excipient. Separation force of MCC was higher than the SDL because the MCC was formed from longer monomer than the SDL which only consists of short-chain monomers.

Average crystallite size ERS was decreased by increasing amount of SDL and MCC up to 20% (Figure 4). X-ray diffraction is very sensitive to changes in the atomic arrangement in the long ranges in crystalline materials. Diffraction peaks become plainer and less

intensive if there is a decrease of crystal size and continuity of atomic fields. If there is a decrease in crystal size, then field of planar atomic length scale also continuously decrease which can be seen from the increase in FWHM of diffraction peaks¹³. Crystal orientation or texture can be defined as a condition in which the distribution of crystal orientation is non-random. The change of maximum diffraction intensity can be explained with this crystal orientation. The strength of the orientation of crystallites will increase with increasing compression force¹⁴. Influence of compression force on the crystal orientation on the surface of erythromycin tablets acitrate has been studied². Crystal orientation can be seen from the intensity of diffraction peaks at 2θ specific. The results of this study indicate that the intensity of X-ray diffraction ERS was decreased by increasing the amount of SDL and MCC at a compression force of 29.5 kN (Figure 5). It indicates that the crystal orientation ERS was random and this can caused deterioration in the bonding force between ERS molecules. Increasing the amount of SDL and MCC does not give significant differences between SDL and MCC.

Phase diagram between ERS:SDL (Figure 6) and ERS:MCC (Figure 7) within all ratio showed no interaction between both substances. Each substance melted in accordance with their melting point. Enthalpy value of ERS:SDL and ERS:MCC binary systems decreased by the increase of excipient amount (Tables 1 and 2).

Scanning electron micrographs of ERS, SDL, MCC raw materials, ERS, SDL, MCC tablets and ERS:SDL (70:30 w/w) and (H) ERS:MCC (70:30 w/w) with compression force 29.5 kN showed that the SDL was dispersed in melted ERS, also in ERS:MCC binary system (Figure 8. A-H). The scanning electron micrographs showed a clear visual impression of the particles, while the XRPD analysis gave information about the substructure of particles, crystals and crystallites. This dispersion is similar with research that has been done before where the ERS with pressure 4.9 kN caused lamellar structure or sintering (loss of surface boundary due to incorporation of particles)⁸. This is typical characteristic of the ERS properties. The character of sintering and this dispersion will affect the process ERS solid dosage forms. ERS:MCC tablets have a rougher surface and showed the presence of pores larger than ERS:SDL tablets.

ERS dissolution profile on ERS:SDL and ERS:MCC binary systems with various weight ratios in pH 6.8 phosphate buffer media showed in Figure 9. Dissolution Efficiency (DE) at the time of 120 minutes of ERS:SDL (90:10), (80:20) and (70:30) were 8.2, 8.7 and 12.2% respectively and ED of ERS:MCC (90:10), (80:20) and (70:30) were 31.9, 63.4 and 66.3% respectively. ED value indicates that the dissolution rate of ERS:MCC was better than the dissolution rate of ERS:SDL. This is due to the ability to avoid the formation of lamellar structure that is better than the MCC compared with SDL which caused the contact between the dissolution media with ERS was better. SDL theoretically more soluble in water compared with the MCC, but because its structure is tighter will inhibit contacts of dissolution media to ERS.

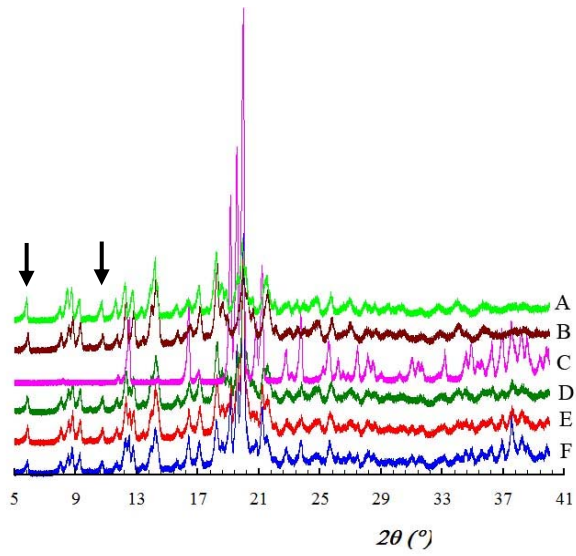


Fig. 1: X-ray diffractograms of A. ERS powder, B. ERS tablet, C. SDL powder D. ERS:SDL (90:10) E. ERS:SDL (80:20) and F. ERS:SDL (70:30) compressed with 29.5 kN

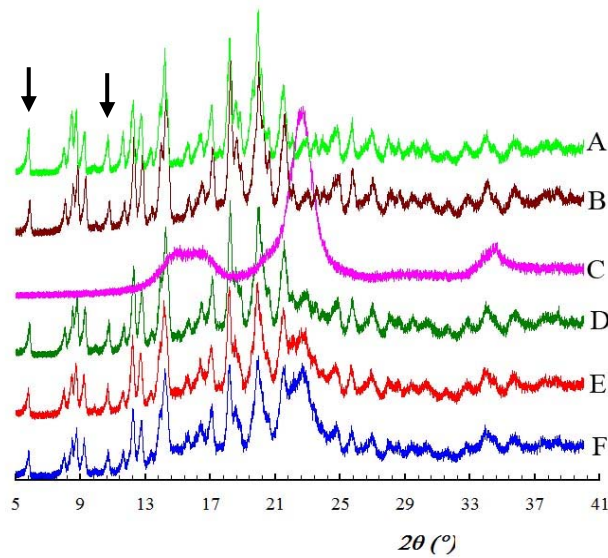


Fig. 2: X-ray diffractograms of A. ERS powder, B. ERS tablet, C. MCC powder D. ERS:MCC (90:10) E. ERS:MCC (80:20) and F. ERS:MCC (70:30) compressed with 29.5 kN

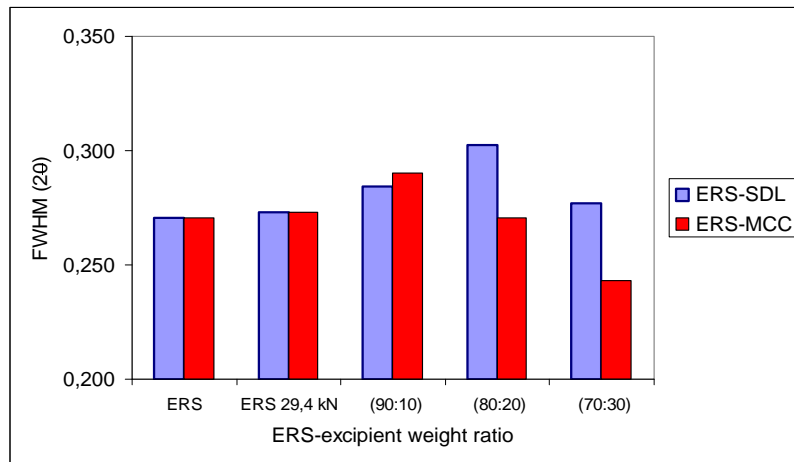


Fig. 3: FWHM from mean of two peaks with different ERS-excipients weight ratio

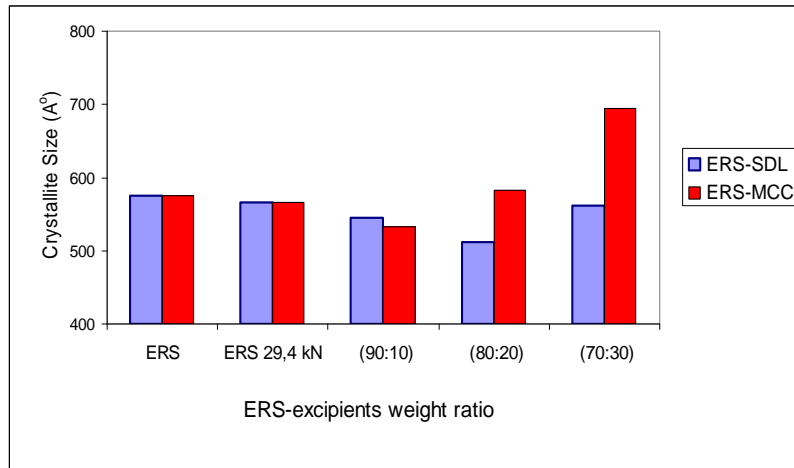


Fig. 4: Crystallite sizes from mean of two peaks with different ERS-excipients weight ratio

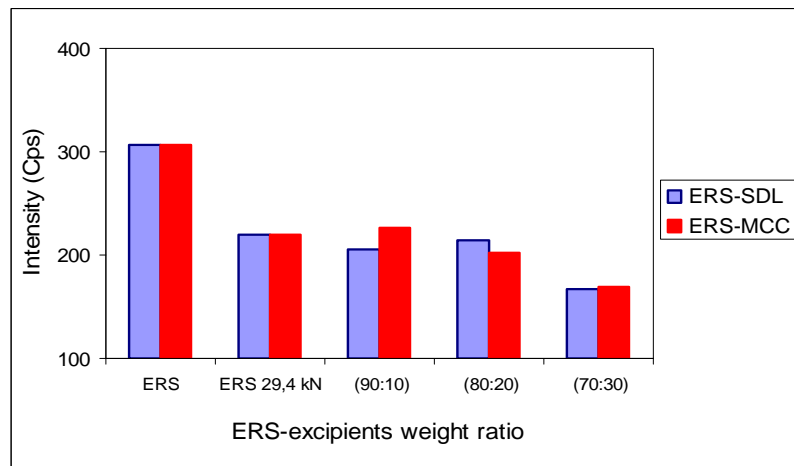


Fig. 5: Intensities from mean of two peaks with different ERS-excipients weight ratio

Table 1: Thermograms data physical mixture of ERS:SDL with various weight ratio

Excipient Rasio	Endo 1 C / J/g	Endo 2 C / J/g
SDL	-	219.7 / 48.5
ERS:SDL (1:9)	107.8 / 3.16	221.2 / 90.3
ERS:SDL (3:7)	110.6 / 13.2	220.1 / 64.4
ERS:SDL (5:5)	110.6 / 31.9	216.8 / 21.7
ERS:SDL (7:3)	111.5 / 37.3	214.9 / 28.7
ERS:SDL (9:1)	111.4 / 48.9	215.3 / 6.28
ERS	112.8 / 52.0	-

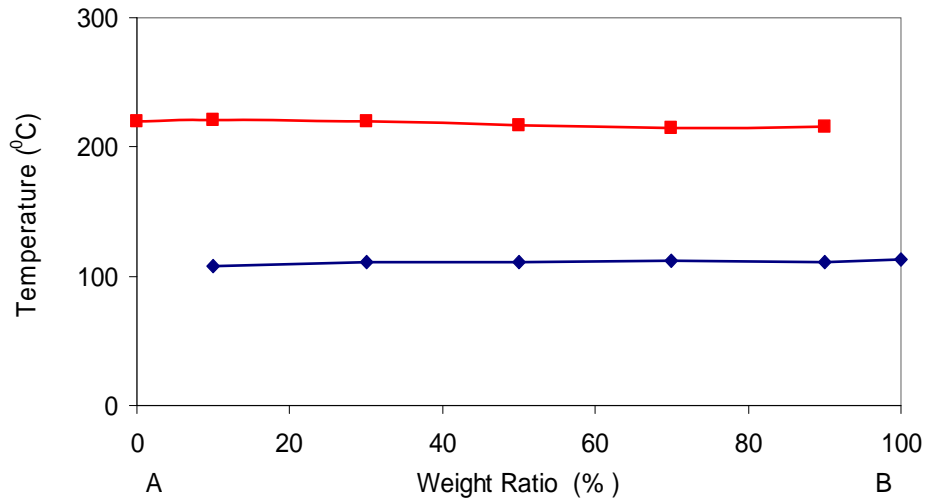


Fig. 6: Phase diagram of binary system ERS:SDL prepared with weight ratio

A. SDL 100% and B. ERS 100 %

Table 2: Thermograms data physical mixture of ERS:MCC with various weight ratio

Excipient Rasio	Endo 1 C / J/g	Endo 2 C/ J/g
MCC	-	142.1/ 74.3
ERS:MCC (1:9)	110.7/ 4.29	147.6/ 87.4
ERS:MCC (3:7)	111.6/ 14.3	146.7/ 64.4
ERS:MCC (5:5)	112.7/ 25.6	145.8/ 20.8
ERS:MCC (7:3)	111.1/ 37.7	161.8/ 24.7
ERS:MCC (9:1)	111.8/ 54.4	159.3/ 38.9
ERS	112.8/ 52.0	-

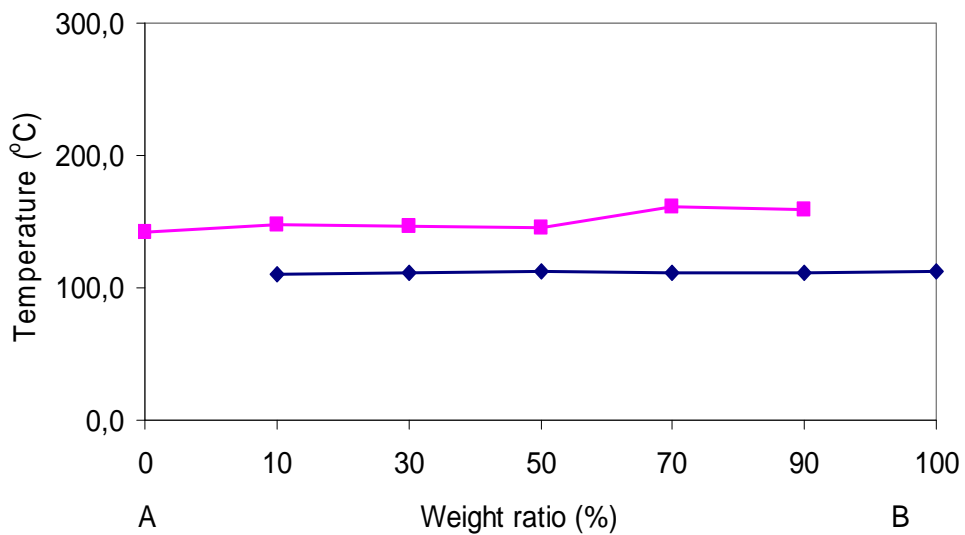


Fig. 7: Phase diagram biner system ERS:MCC prepared with weight ratio A. MCC 100% and B. ERS 100 %

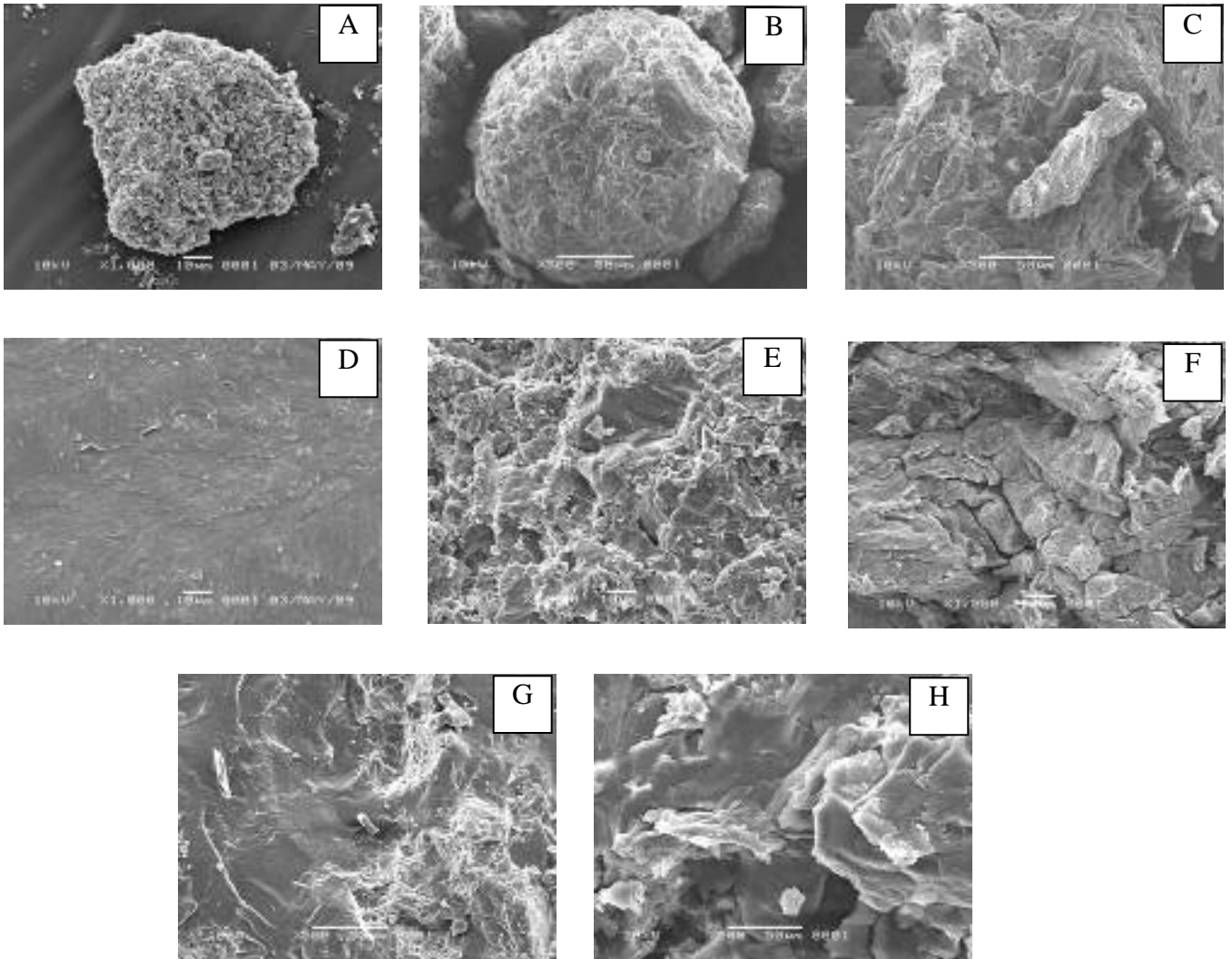


Fig. 8: Scanning electron micrographs of A. ERS, B. SDL, C. MCC raw material, D. ERS, E. SDL, F. MCC, G. ERS:SDL (70:30 w/w) and H. ERS:MCC (70:30 w/w) with compression force 29.5 kN

-- Bars: (A, D,E,F) 10 mm; (B,C,G,H) 50 mm.

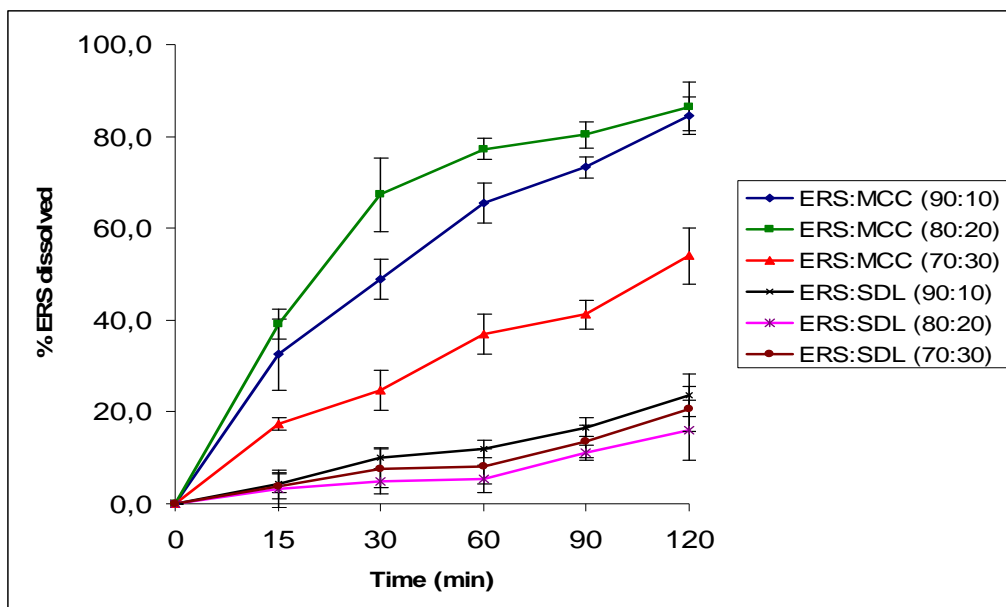


Fig. 9: Dissolution profiles ERS:SDL (90:10), ERS:SDL (80:20), ERS:SDL (70:30), ERS:MCC (90:10), ERS:MCC (80:20) and ERS:MCC (70:30), in phosphate buffer pH 6.8

CONCLUTIONS

Binary systems of ERS:SDL and ERS:MCC with 29.5 kN compression force increased ERS peak broadening (FWHM), reduced ERS crystallite size and ERS crystal orientation by the increase of excipients amount. Binary system ERS:MCC showed a rougher structure than the ERS:SDL. Binary systems of ERS:SDL and ERS:MCC with 29.5 kN compression force did not show the interaction between both ingredients. Dissolution rate of ERS in binary system ERS:MCC was faster than ERS:SDL in all ratios.

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