SPRAY-DRIED HPMC MICROPARTICLES OF INDOMETHACIN: IMPACT OF DRUG-POLYMER RATIO AND VISCOSITY OF THE POLYMERIC SOLUTION ON DISSOLUTION

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تم دراسة الجسيمات الدقيقة البوليمرية المحضرة بطريقة التجفيف بالبخ لتعزيز معدل ذوبان دواء إندوميثاسين بالمقارنة مع الجسيمات الدقيقة التقليدية المحضرة بطريقة ترسيب البعثرة الصلبة. وتم استخدام نسب الدواء والبوليمر ولزوجة السوائل البوليمرية كعوامل محتملة لتعزيز معدل ذوبان دواء إندوميثاسين. واستخدمت طريقة التجفيف بالبخ لتحضير الجسيمات الدقيقة باستخدام معلق مائي لدواء إندوميثاسين في محلول بوليمر هيدروكسي بروبيل ميثيل سليولوز. وتم دراسة نسب الدواء – البوليمر على معدلات ذوبان دواء إندوميثاسين في وسط معوي منشط. وتم تحليل دواء إندوميثاسين طيفياً عند 320 نانومتر. ولكل نسبة دواء – بوليمر ، تم تحضير محاليل بوليمرية منخفضة وعالية اللزوجة مع دراسة تأثيرها على ذوبان دواء إندوميثاسين. وتم التحقق من شكل الجسيمات الدقيقة بواسطة الاستجهار الضوئي. كما تم دراسة التداخل بين دواء إندوميثاسين وبوليمر هيدروكسي بروبيل ميثيل سليولوز بواسطة مقياس المسح الحراري التفاضلي ومقياس انعراج الأشعة السينية. وتم الحصول على جسيمات دقيقة كروية منفوشة لدواء إندوميثاسين باستخدام بوليمر هيدروكسي بروبيل ميثيل سليولوز. وقد لوحظ أن الجسيمات الدقيقة المحضرة بالتجفيف بالبخ زادت معدل ذوبان دواء إندوميثاسين. وقد تحققت الزيادة في معدلات الذوبان بنسب دواء إلى بوليمر تعادل 1:1 و 2:1 ، ومن المثير للاهتمام أن الانخفاض في محتوى الدواء بنسبة تزيد عن 2:1 نتج عنه انخفاض في معدلات الذوبان. وأيضاً ، وبجميع نسب الدواء – البوليمر ، أعطت المحاليل البوليمرية منخفضة اللزوجة معدلات ذوبان أعلى. ونستنتج أن جسيمات الهيدروكسي بروبيل ميثيل سليولوز الدقيقة المحملة بدواء إندوميثاسين تم تحضيرها بطريقة التجفيف بالبخ وأنه تمت دراسة احتمالية هذه الطريقة لتعزيز الذوبان. وتدل النتائج على أن ذوبان جسيمات دواء إندوميثاسين المحضرة بطريقة التجفيف بالبخ قد اعتمد على نسب الدواء – البوليمر وعلى لزوجة المحاليل البوليمرية.

Polymeric microparticles prepared by spray-drying technique were investigated to enhance the dissolution rate of indomethacin (IM) in comparison with conventional microparticles prepared by co-precipitation solid dispersion method. Drug-polymer ratios and viscosity of polymeric solutions as potential factors were used in order to enhance the dissolution rate of IM. Spray-drying technique was used for preparing of microparticles using aqueous suspension of IM in hydroxypropyl methylcellulose (HPMC) polymer solution. The effect of drug-polymer ratios on dissolution rates of IM was studied in simulating intestinal medium. IM was analyzed spectrophotometrically at λ= 320 nm. For each drug-polymer ratios, low and high viscosity polymeric solutions were prepared and their impacts on the dissolution of IM were observed. Microparticles were morphologically characterized by optical microscopy. The interaction between IM and HPMC was studied by differential scanning calorimetry (DSC) and x-ray diffractometry (XRD). Spherical fluffy microparticles of IM were obtained using HPMC. It was observed that the prepared spray-dried microparticles significantly increase the dissolution rate of IM. The increase in dissolution rates was achieved with drug:polymer ratios 1:1 as well as 1:2 and

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interestingly, the decrease in drug content in ratio exceeding 1:2 resulted in reduction in dissolution rates. Also, with all drug-polymer ratios, the low viscosity polymeric solutions gave the higher dissolution rates. In conclusion, HPMC microparticles loaded with IM were prepared by spray-drying technique and the potential of this technique to enhance the dissolution was studied. The findings indicate that the dissolution profile of IM microparticles prepared by spray-drying technique relied on drug-polymer ratios and viscosity of polymeric solutions.

Key words: Indomethacin, hydroxypropyl methylcellulose, spray drying, dissolution rate

Introduction

Spray drying is a well known technique in food industry, and is used to dry solutions such as milk. Spray drying, also, has been used in pharmaceutical industry since the early of 1940s (1) for drying heat-sensitive materials, increase the solubility of poorly water-soluble drugs, masking the taste, enteric coating, improving the flow properties in tablet production and coating of some drugs or drug microencapsulation. The main advantages of spray drying in microencapsulation are one step processing, low cost, absence of organic solvent, ease of working in sterile conditions and scale up, preparing of fine particles with no granular, and the possibility of secondary formulation in suspensions, capsules or tablets (2).

Indomethacin (IM) is a drug widely used as non-steroidal anti-inflammatory, with inherently poor-dissolution rate in water (3). Many efforts have been conducted to enhance solubility and dissolution of IM using different methods such as solid dispersion (4), complex formation with certain polymers (5, 6) and cyclodextrin (7), incorporation of buffers (8), using of adsorbents (9), and spray drying (10).

Hydroxypropyl methylcellulose (HPMC) is the most commonly used hydrophilic polymer to modify the release of some drugs due to its versatility, safety and compatibility with many drugs (11). The HPMC can take up and retain large amount of water, which influence the physical and chemical properties of the polymer and drug release profile (12).

The objective of the present study is to utilize spray drying technique for preparing IM-HPMC microparticles to enhance the dissolution of indomethacin. The influence of drug:polymer ratio as well as viscosity of polymeric solution on the dissolution profile of IM was studied. Comparison in the release profiles of IM from microparticles prepared by co-precipitation solid dispersion and spray drying methods was conducted. The microparticles were characterized by differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) to detect either possible drug-carrier interactions or any possible incompatibilities as well as to study the crystallinity of IM on the microparticles.

Material and Methods

Materials:

Indomethacin (IM) was purchased from Sigma (St.Louis, MO, USA). Hydroxypropyl methylcellulose (HPMC, K100) was kindly donated from DOW (Midland, MI, USA). All other chemicals and solvents used were of pharmaceutical grade.

Methods:

A. Preparation of drug- polymer suspension for spray drying:

The HPMC was dissolved in boiled water and then it was immediately cooled down to form a clear solution according to the producer preparation method (DOW comp. Midland, MI, USA). Indomethacin was dissolved in ethanol and this ethanolic solution was added slowly to the polymeric solution to form 10 % v/v ethanol solution in water. Indomethacin:HPMC ratios were adjusted in the preparations to give 1:1, 1:2 and 1:4. To study the effect of the viscosity of the polymeric solution on dissolution rates, each IM:HPMC ratio was prepared in either low or high viscosity polymeric drug suspension (table 1).

B. Preparation of indomethacin microparticles by spray drying technique:

All batches of microparticles were prepared by spray-drying using Buchi 190 mini spray drier (Büchi Labortechnik AG, Germany) with 0.5mm nozzle. The IM-HPMC suspension was fed to the nozzle via peristaltic pump (spray flow rate of 16 ml/min.). The suspension was sprayed as atomized droplets by the force of the compressed air (air flow rate of 4 pound per square inch). The solvents in the

droplets were evaporated in drying chamber by the blown hot air (inlet air temperature of 160 ^{o}C and outlet air temperature of 90 ^{o}C). The dried product was collected in collection vessel. The particle size fraction which passed through 250 µm sieve (Endocott Sieve Ltd, London, UK) and retained up 90 µm sieve was used in this study.

Table 1: Various Formulations and Characteristics of Indomethacin Microparticles

Formulation	IM: HPMC Ratio	IM %	HPMC%	Yield %	EE %	Viscosity cp
F1:1 HV	1:1	0.5	0.5	21.1	52 ± 2.1	12 ± 1.15
F1:1 LV	1:1	0.25	0.25	25.5	54 ± 2.1	8 ± 0.6
F 1:2 HV	1:2	0.5	1	20.3	50 ± 2.5	24 ± 1.8
F 1:2 LV	1:2	0.25	0.5	24.4	45 ± 1.9	12 ± 1.15
F1:4 HV	1:4	0.5	2	21.3	54 ± 2.3	130 ± 2.3
F1:4 LV	1:4	0.25	1	25.9	44 ± 1.8	24 ± 1.8
SD 1:1	1:1	0.5	0.5	-	-	-
SD 1:2	1:2	0.5	1	-	-	-
SD 1:4	1:4	0.5	2	-	-	-
PM 1:1	1:1	0.5	0.5	-	-	-
PM 1:2	1:2	0.5	1	-	-	-
PM 1:4	1:4	0.5	2	-	-	-

F= spray drying product, HV= high viscosity, LV = low viscosity , SD = solid dispersion, PM = physical mixture, EE= entrapment efficiency

C. Preparation of indomethacin microparticles by co-precipitation solid dispersion:

Solid dispersions containing IM and HPMC in different ratios (1:1, 1:2, 1:4 drug: polymer) were prepared employing solvent evaporation technique (13). The weighed drug and polymer were dissolved in the least amount of ethanol. The organic solvent was removed by evaporation at room temperature with the aid of gentle stirring. The dried mass was pulverized. The particle size fraction which passed through 250 µm sieve and retained up 90 µm sieve was used in this study. The samples were kept in a desiccator till further investigation. Physical mixtures of IM and HPMC were prepared in the same ratios as in solid dispersion by gentle mixing for the drug and polymer in a mortar.

D. Morphology of IM-HPMC microparticles:

The morphology of the microparticles was studied and photographed using biological microscope model DN-200M (Novel, China) equipped with digital camera connected to PC set with imaging software. The microparticles were dispersed with liquid paraffin in a microscope slide and samples were observed microscopically.

E. Drug content:

The drug content of the microparticles was determined spectrophotmetrically (♧ =320 nm). The HPMC microparticles (50mg) loaded with IM were dissolved in 15 ml of phosphate buffer (pH=7.4) under sonication. The solutions were filtered and the amount of IM was measured. Preliminary studies showed that dissolved polymer didn't interfere with IM absorbance at 320 nm.

F. Differential scanning calorimetry:

Differential scanning calorimetry studies were done using Universal V4.1D TA Instrument (Q100, TA Instruments, Delaware, USA) and they were carried out under the following conditions: sample weight 3-5 mg, scanning speed 10 ^{o}C / min, in the 20-300 ^{o} C temperature range. Indium was used as standard.

G. Powder X-Ray Diffraction:

Powder X-ray diffraction patterns of the prepared spray dried, solid dispersion and physical mixture samples were carried out using a wide-angle X-ray diffractometer (Siemens D-500, Bruker AXS, Coventry, UK). The instrument was operated in 2-

Theta scale. The angular range was 5° to 40° 2θ and counts were accumulated for 1 second at each step.

H. Viscosity measurement:

The viscosity of the prepared polymer solutions at concentrations 0.25, 0.5, 1 and 2% w/v was determined (table1) using Brookfield DV+II model RV viscometer (Brookfield Engineering Laboratories Inc, Middleboro, USA).

I. Dissolution study:

Dissolution measurements were carried out in a USP dissolution test apparatus (Caleva Ltd., Model 85T, Philips, UK). The dissolution profiles of IM from microparticles were studied in phosphate buffer (pH=7.4). The drug-loaded microparticles containing 25 mg of IM were placed in a rotating basket (50 ± 1 rpm) filled with 500 ml of the dissolution medium, thermostated at 37 ± 0.4 °C. At schedule time intervals, the samples (5 ml) were withdrawn and replaced immediately with fresh medium. The samples were filtered and assayed spectrophotmetrically at 320 nm for drug content. It should be noted that the influence of particle size on dissolution rate was minimized by the use of relatively similar particle sizes in all studied patches. The dissolution experiments were conducted in triplicate and the means of the absorbance were calculated. The time required for 50% of the drug to be dissoluted (T_{50} %) was calculated graphically and was used as comparison parameter in dissolution studies.

J. Statistical analysis:

One-way analysis of variance (ANOVA) and t-test were performed using Statgraphics plus 2 software to compare the mean values of T_{50} % for all formulations. Multiple Range Test (Fisher's least significant difference procedure, LSD) was used to determine which means are significantly different from other. The level of confidence was 95%.

Results and discussions

Indomethacin is a poorly water soluble drug and many studies have been conducted to enhance its solubility and its dissolution rate (3-10). Spray drying technique has been used in the present study to enhance IM dissolution rate. The effect of viscosity of the polymeric solution and drug polymer ratio on the release profile of IM microparticles prepared by spray drying technique was examined.

The HMPC microparticles containing IM have been prepared by spray drying technique. The IM-HPMC microparticles appeared to be white-fine fluffy powder. Under optical digital microscopy, the microparticles appeared spherical and no unencapsulated IM particles were observed. The surface of microparticles appeared to be engraved as shown in Fig 1. These engraved surfaces would increase the surface area and may consequently enhance the dissolution of IM. The theoretical drug loading in the microparticles ranged from 20% to 50% (w/w). The entrapment efficiency ranged from 44 ± 1.8 % to 54 ± 2.3 % and the yield ranged from 20.3% to 25.9%. Drug:polymer ratios 1:1, 1:2, and 1:4 were used as selected ratios for spray drying as well as for experimental controls (i.e. solid dispersion and physical mixture).

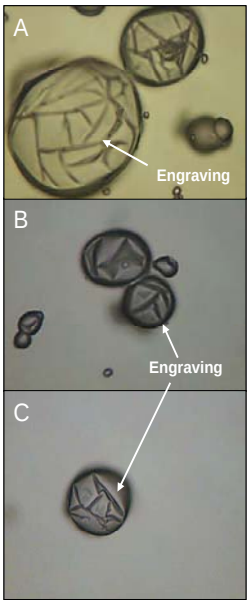

Figure 1. Morphology of IM-HPMC microparticles prepared by spray drying and observed by digital optical microscopy (X40). The different micro-particles used were: (A &B) F 1:4 LV, (C) F 1:4 HV.

The thermal behavior of microparticles prepared by spray drying and solid dispersion techniques as well as the 1:4 physical mixture in comparison with thermograms of both pure IM and HPMC K-100 is illustrated in Fig 2. The DSC-thermogram of pure IM (Fig 2-A) shows sharp endothermic peak at 160° C, corresponding to its melting point (Fig 2-A).

Also, physical mixture (Fig 2-E) exhibits a single melting peak at 160° C due to the melting of IM. No melting endotherm was recorded in the DSC curves of HPMC microparticles containing IM (1:4 ratios) prepared by spray drying for the low and high viscous polymeric solutions (Fig 2-C and 2-F) as well as the one prepared by solid dispersion (Fig 2-D). This indicates that the drug is present in non-crystalline state in the microparticles. Alternatively, this result might be explained in terms of formation of an amorphous form of drug due to spray drying and solid dispersion processes. It has been known that transforming the physical state of the drug to amorphous state leads to a high-energy state and high disorder, resulting in enhancing solubility and faster dissolution (14). Also, results mean that HPMC used in the study doesn't interfere with IM or make any shift in the melting peak.

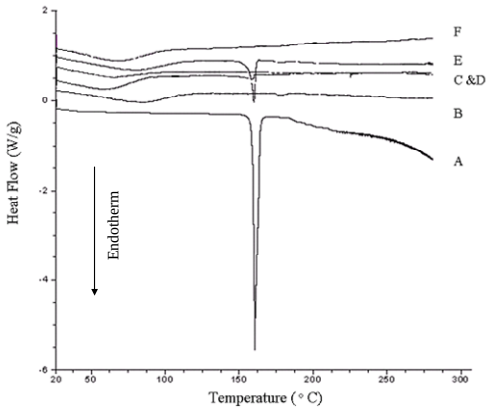

Figure 2. DSC thermograms of indomethacin micro-particles. drug alone (A), HPMC (B), F 1:4 HV (C), 1:4 SD (D), 1:4 PM (E), F 1:4 LV (F)

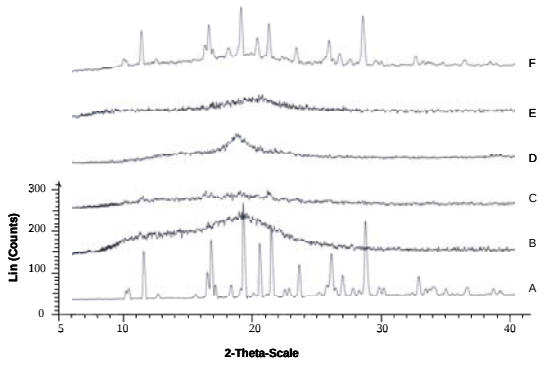

Figure 3. Powder X-ray diffraction patterns of indomethacin microparticles. drug alone (A), HPMC (B), F 1:4 HV (C), 1:4 SD (D), F 1:4 LV (E), 1:4 PM (F)

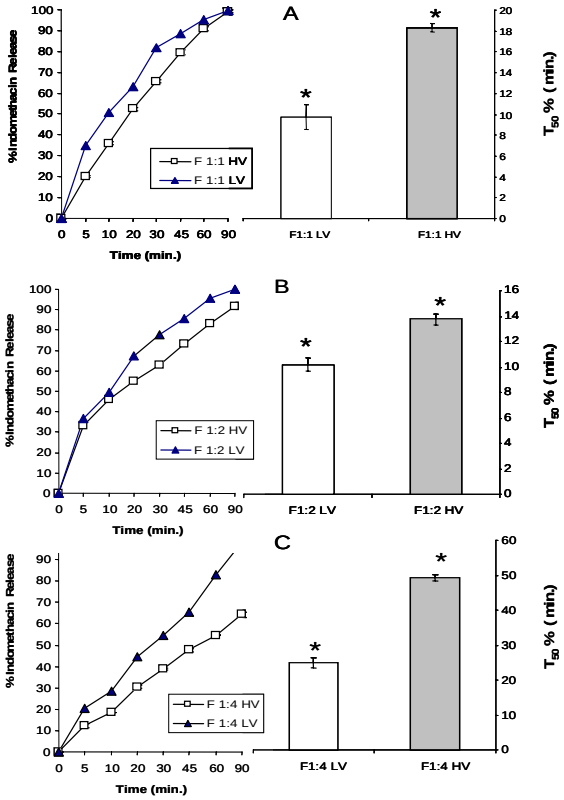

Figure 4. Dissolution profiles of indomethacin –HMPC microparticles prepared by spray drying in pH 7.4 at 37 ± 0.4 ° C. Ratio 1:1 (A), ratio 1:2 (B), ratio 1:4(C). LV stated for low viscosity polymeric solutions. HV stated for high viscosity polymeric solutions. T_{50} % is the time in which 50% of the drug released. * donates significant statistically difference between two means at $P< 0.05$.

Powder X-ray diffraction patterns of IM and HMPC are shown in Figures 3-A and 3-B, respectively. The diffractogram of pure IM revealed the presence of some characteristic form peaks which indicated the crystalline form of IM. The XRD pattern of pure HPMC was typical of amorphous substance, without any intense peak in its diffractogram being detectable. The XRD patterns of IM-HPMC microparticles (Fig. 3-C, 3-D & 3-E) revealed the absence of IM in the crystalline state, indicating the conversion of IM to amorphous form by spray drying technique which is in agreement with previous DSC results. The XRD pattern of physical mixture (Fig. 3-F) shows peaks similar to that of IM indicating that no interaction between HPMC and IM in solid state happens.

Figure 4 shows the effect of the viscosity of the HPMC polymeric solutions on the dissolution

profiles of IM microparticles prepared by spray drying. For all ratios, the lower viscous polymeric solutions, the highest IM dissolution rates were obtained. The time required for 50% of IM to be dissoluted (T_{50} %) was 9.73± 1.2 and 18.29 ± 0.4 for low and high viscous prepared formulations of 1:1 ratio, respectively (Fig 4-A). T_{50} % was 10.17 ± 0.5 and 13.73 ± 0.45 for low and high viscous prepared formulations of 1:2 ratio, respectively (Fig 4-B). T_{50} % was 24.86 ± 1.5 and 49.27 ± 0.85 for low and high viscous prepared formulations of 1:4 ratio, respectively (Fig 4-C). There is a statistically significant difference between the means of the low and high viscosity prepared formulations at the 95% level of confidence (Fig 4, right side figures). This fact can be used in common for the utilization of the high viscous polymeric solutions to retain the drug release and the lower viscous ones to enhance the drug release during preparing microparticles by spray drying process. The high difference in the dissolution of IM between the high and low viscous polymeric solutions was shown by 1:4 drug to polymer ratio (Fig.4-C). This finding can be explained by the fact that, with this ratio the percentage of the polymer is four times the percentage of the drug; thus, at this ratio the polymer retained the drug due to formation of a gel around drug particles and the effect of the viscosity was maximum.

Figure 5 represents the effect of HPMC content on IM release from microparticles. It is shown that increasing the HPMC content in the matrix decreased the fraction of IM released from microparticles prepared by spray drying (Fig. 5-A& 5-B). T_{50} % of the ratio 1:4 for the low viscosity microparticles (Fig 5-A) was 24.86 ± 1.5 and was more than that of ratio 1:1 (9.73 ± 1.2) as well as that of ratio 1:2 (10.16 ± 0.5). T_{50} % of the ratio 1:4 for the high viscosity microparticles (Fig 5-B) was 49.26 ± 0.85 and was more than that of ratio 1:1 (18.29 ± 0.41) as well as that of ratio 1:2 (13.73 ± 0.45). The microparticles with low polymer content were expected to be more porous than those with high polymer content. This might facilitate the release of the residual drug from the microparticles (15). The thickness of the hydrogel layer increases with high polymer content due to polymer swelling and forming a gel diffusion layer which retarded drug diffusion (16). This could explain the increment in the percentage release of IM between the low and the high polymer ratio. On the other hand, for the microparticles prepared by solid dispersion, the results are reversed (Fig. 5-C). With the high polymer content, the more IM was released. T_{50} % of the ratio1:1 for solid dispersion microparticles (Fig 5-C) was 14.6 ± 0.21 and was more than that of ratio 1:2 (10.36 ± 0.5) as well as that of ratio 1:4 (8.06 ± 2.8). This is in agreement with our previous publication (13) in which the release of piroxicam increased with the increment in the content of the polymer in microparticles prepared by solid dispersion. This can be explained by the fact that the drug exists as a molecular dispersion within the microparticles which means presence of the drug in solid solution. Therefore, the drug may be in solution at low drug concentrations and with the more polymer content (17).

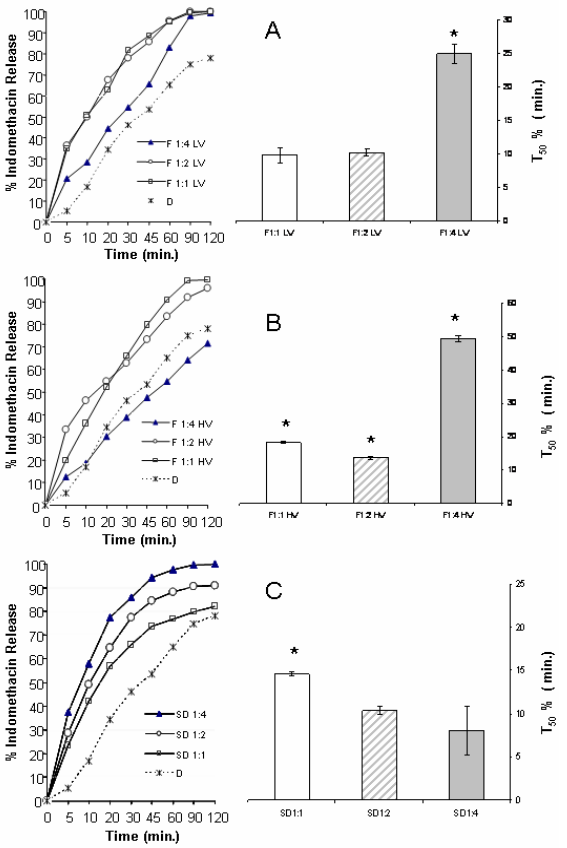

Figure 5. Dissolution profiles of indomethacin–HMPC microparticles in pH 7.4 at 37± 0.4 °C. Low viscous ratios, 1:1, 1:2, and 1:4 prepared by spray drying as well as the drug powder alone (A), high viscous ratios, 1:1, 1:2, and 1:4 prepared by spray drying as well as the drug alone (B), solid dispersion ratios 1:1, 1:2 and 1:4 as well as drug alone (C). T_{50} % is the time in which 50% of the drug released. * donates significant statistically difference between two means at $P< 0.05$.

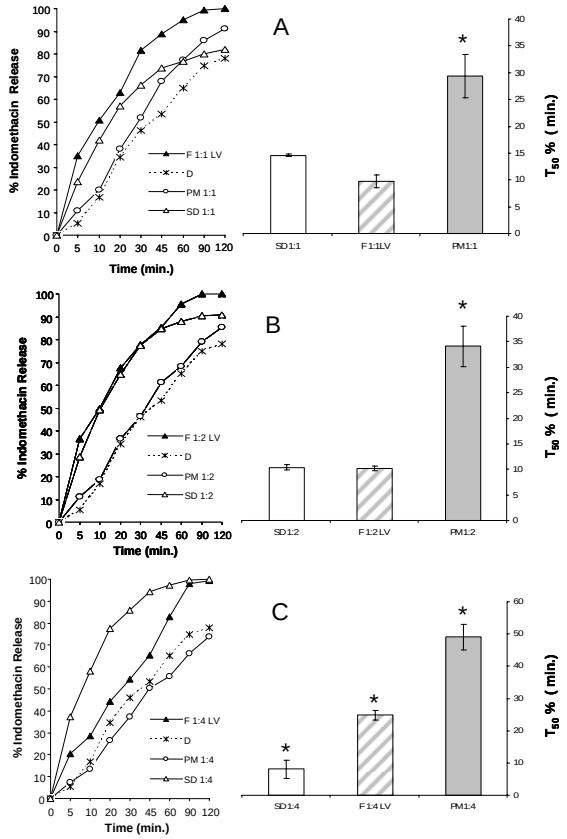

Figure 6. Dissolution profiles of indomethacin–HMPC microparticles in pH 7.4 at 37 ± 0.4 ^{o} C prepared by spray drying, solid dispersion, physical mixture and drug alone. Ratio 1:1 (A), ratio 1:2 (B), ratio 1:4 (C). T_{50} % is the time in which 50% of the drug released. * donates significant statistically difference between two means at $P< 0.05$.

Figure 6 represents the difference in IM dissolution from microparticles prepared by spray drying and solid dispersion under the same drug: polymer ratio. For ratio 1:1, T_{50} % was 9.73 ± 1.2 and 14.6 ± 0.21 for spray drying and solid dispersion, respectively (Fig. 6-A). For ratio 1:2, T_{50} % was 10.17 ± 0.5 and 10.36 ± 0.5 for spray drying and solid dispersion, respectively (Fig. 6-B). For ratio 1:4, T_{50} % was 24.86 ± 1.5 and 8.06 ± 2.8 for spray drying and solid dispersion, respectively (Fig. 6-C). For the ratio 1:1 and ratio 1:2, there was no statistically significant difference in the T_{50} % between microparticles prepared by spray drying and solid dispersion. However, there was a statistically significant difference in the T_{50} % for ratio 1:4 between microparticles prepared by spray drying and solid dispersion.

In conclusion, the potential of the spray-drying technique for preparing microparticles to enhance the solubility and dissolution of IM was investigated. The findings indicate that the release profile of IM microparticles prepared by spray-drying technique relied on drug-polymer ratios and on the viscosity of polymeric solutions. The increase in dissolution rates was achieved with drug:polymer ratios 1:1 as well as 1:2 and interestingly, the decrease in drug-polymer ratios beyond 1:2 resulted in reduction in dissolution rates. The high viscous polymeric solutions can be used to retain the drug release and the lower viscous ones can be used to enhance the drug release during preparation of microparticles by spray drying process. Also, spray drying technique produces microparticles that have release rate different from that of solid dispersion using the same drug-polymer ratio.

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