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RESEARCH PAPER

Effects of Cellulose Derivatives and Additives in the Spray-Drying Preparation of Acetaminophen Delivery Systems

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ABSTRACT

Microcrystalline cellulose (MCC), sodium carboxymethylcellulose (NaCMC), hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), and ethylcellulose (EC) were used for the production of time-controlled acetaminophen delivery systems using a spray-drying technique. The influence of factors such as polymer concentration, inlet temperature, and drug/polymer ratio were investigated. The product yields were a function of the type and concentration of the polymer, with the highest values being reached from feeds containing 1% MCC and EC. Parameters of 1% polymer concentration and an inlet temperature of 140°C gave rise to optimal processing conditions. Using these parameters, the influence of some adjuncts, such as polyethylene glycol 6000 (PEG 6000), dibutyl sebacate (DBS), polyvinylpyrrolidone (PVP), and carboxylic acids such as citric acid (CA), phthalic acid (PA), succinic acid (SA), tartaric acid (TA), and oxalic acid (OA), on the spray-drying process was evaluated. Of the additives tested, PVP (with MCC), DBS (with EC), and PEG 6000 (with NaCMC) induced yield decreases from 70% to 49%, 66% to 39%, and 37% to 17%, respectively. As for carboxylic acids (with NaCMC), similar or better performances of 43%, 45%, 47%, and 49% were obtained with SA, OA, PA, and TA, respectively. Dissolution studies in pH 1 dilute HCl and pH 6.8 phosphate buffer dissolution media showed

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that formulations consisting of 1% polymer with a drug/polymer ratio of 1/1 exhibited the slowest drug release, with the spheroids coated with NaCMC and HEC showing the longest $T_{50\%}$ *values (with 45 and 53 min at pH 1 and 49 and 55 min at pH 6.8, respectively). Slightly better sustained drug release in pH 6.8 dissolution medium was reached, showing the following trend: HEC > NaCMC > MCC > EC > HPMC. Concerning the additives, the trends in dissolution* $T_{50\%}$ *of drug revealed TA > SA > CA > OA > PVP > PA > DBS in acidic pH 1 dissolution medium and PVP > OA > TA > SA > PA > CA > DBS in phosphate buffer at pH 6.8.*

INTRODUCTION

Polymers capable of forming a film over the surface of drying droplets are often included in formulations for spray-drying to produce microparticles. This is primarily due to their spray-coating properties and ability to achieve prolonged drug release. Various polymers, especially cellulose derivatives such as sodium carboxymethylcellulose (NaCMC), hydroxypropylmethylcellulose (HPMC), and ethylcellulose (EC), were used as coating materials in the preparation of microparticulate systems by spray-drying technique (1–3). Polyols and carboxylic acids have been used as plasticizers in the preparation of drug solid forms, and their effects on microencapsulation by spray-drying have been studied (2,4,5).

The objectives of this study was to assess the application of polymers such as HPC (hydroxypropylcellulose), HEC (hydroxyethylcellulose), MCC (microcrystalline cellulose), EC, NaCMC, and HPMC for the preparation of prolonged-release formulations by spray-drying and to evaluate the effects of adjuncts: polyethylene glycol 6000 (PEG 6000), polyvinylpyrrolidone (PVP), dibutyl sebacate (DBS), and carboxylic acids (citric acid [CA], phthalic acid [PA], succinic acid [SA], tartaric acid [TA], and oxalic acid [OA]) on the spray-drying process. The efficiency of these materials was tested by dissolution studies in pH 1 and pH 6.8 media.

MATERIALS AND METHODS

Materials

Acetaminophen (acetaminophen USP fine powder, Mallinckrodt, Chesterfield, UK) was used as the model drug. The polymers were MCC (Vivapur® PH101, Rettenmaier and Söhne, Ellwangen, Germany), EC (Aquacoat® ECD 30, Seppic, Paris, France), NaCMC (Blanose® cellulose gum 7LF, Hercules, Rueil-Malmaison, France), HEC (Natrosol® EFEP, Hercules), HPMC (5cp, SK&F Laboratories, Pessac, France), HPC (Klucel® 250, Hercules). Plasticizers used in this study were PEG 6000 (Hoechst, Frankfurt, Germany), DBS (Fluka Chemika, St. Quentin Fallavier, France), PVP (Kollidon® 30, BASF, Ludwigshafen, Germany), and carboxylic acids, including SA (Merck, Darmstadt, Germany), PA (Merck), OA (Prolabo, Paris, France), TA (Aldrich-Chemie, St. Quentin Fallavier, France), and CA (Carlo Erba, Val de Reuil, France).

Preparation of Feed

Acetaminophen and polymer in mass ratios of 10:1 and 1:1 were dissolved (with NaCMC, HPMC, HEC, HPC) or suspended (with MCC and EC) in distilled water, with a constant drug content of 1% in the feed. The polymer was first hydrated and mixed in about 250–300 ml of distilled water. While mixing, the drug was added, and the solution was made up to 500 ml. For the formulations containing additives, a drug/polymer mass ratio of 1:1 was used, while the quantity of plasticizer added was function of the mass of polymer involved (Table 1).

Spray-Drying Technique

The solution or suspension feeds were stirred continuously while being spray-dried with a Büchi 190 mini spray-dryer (Büchi Laboratoriums Tecnik AG, Flawil, Switzerland). The operating parameters were set as follows: inlet temperature 140°C or 160°C; spray flow 700 NL/hr; atomizing air pressure 1 kgf/cm^2; feed pump setting 4 ml/min. A 0.5-mm nozzle was used throughout the experiments. Spray-dried products were collected and kept away from rehydration until further tests.

Scanning Electronic Microscopy Studies

Spray-dried products were coated under argon atmosphere with gold/palladium and examined under an electron microscope (Hitachi S 4000, Tokyo, Japan).

Table 1

Production Yields of Acetaminophen Microparticles from Aqueous Feeds at Inlet Temperature 140°C

Polymer		Drug/Polymer	Plasticizers		Yields
Type	Concentration	Ratio	Type	(%[a])	(%)
HPC	0.1	10/1			29
HPC	1	1/1			3
HEC	0.1	10/1			54
HEC	1	1/1			16
HPMC	0.1	10/1			27
HPMC	1	1/1			8
MCC	0.1	10/1			44
MCC	1	1/1		0	70
MCC	1	1/1	PVP	3	49
EC	1	1/1	DBS	0	66
EC	1	1/1	DBS	5	39
EC	1	1/1	DBS	10	0
EC	1	1/1	DBS	24	0
NaCMC	0.1	10/1			44
NaCMC	1	1/1		0	37
NaCMC	1	1/1	PVP	3	37
NaCMC	1	1/1	PEG 6000	30	17
NaCMC	1	1/1	Succinic acid	30	43
NaCMC	1	1/1	Phthalic acid	30	47
NaCMC	1	1/1	Oxalic acid	30	45
NaCMC	1	1/1	Tartaric acid	30	49
NaCMC	1	1/1	Citric acid	30	48

Control spray-dried raw acetaminophen; HPC, hydroxypropylcellulose; HEC, hydroxyethylcellulose; HPMC, hydroxypropylmethylcellulose; MCC, microcrystalline cellulose; EC, ethylcellulose; NaCMC, sodium carboxymethylcellulose; PVP, polyvinylpyrrolidone; DBS, dibutyl sebacate; PEG 6000, polyethylene glycol 6000.

[a] Expressed on the basis of the mass polymer used.

Film Formation Studies

Films were cast from aqueous feeds prepared as described above. Aliquots (20 ml) of sample feeds were poured into glass petri dishes and dried in a preheated oven at 140°C for 3 hr (3,5). The resulting films were observed under a light microscope (Nikon optiphot PFX, Garden City, NY) and a binocular microscope (Nikon SMZ 10A, Japan).

Dissolution Studies

Drug release profiles from the spray-dried microparticles were obtained by the paddle rotating dissolution apparatus. Samples placed into a sealed sachet were immersed in 900 ml deaerated 0.1 M HCl or pH 6.8 phosphate buffer maintained at 37°C ± 0.5°C, with the rotating paddle set at 50 rpm. Aliquots of samples (10 ml) collected at regular intervals, over a period of 3 hr, were assayed spectrophotometrically at 244 nm (UV-240, Shimadzu, Kyoto, Japan). Two replicates were carried out for each batch, and the mean of measurements was computed.

RESULTS AND DISCUSSION

The preparation of acetaminophen microparticles by aqueous spray-drying, using polymers such as MCC and cellulose ethers, was carried out. The results reported in Table 1 display a comparison of the type and concentration of polymers and the drug/polymer ratio in spray-drying production of microparticulate systems. In terms of production yield, the highest values were reached from

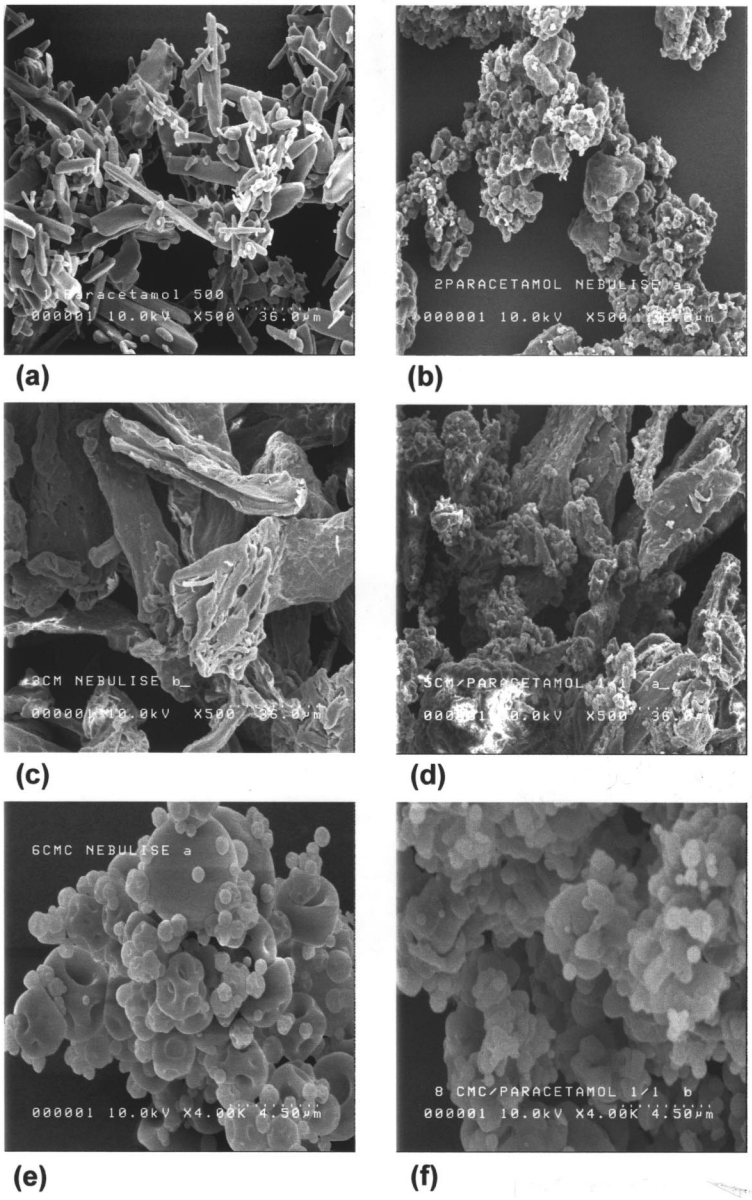

Figure 1. SEM photographs of (a) raw acetaminophen; and spray-dried particles of (b) acetaminophen, (c) MCC, (d) acetaminophen/MCC, (e) NaCMC, and (f) acetaminophen/NaCMC.

aqueous suspensions containing 1% MCC and EC. At a lower concentration level (i.e., 0.1%), the experiments with MCC yielded a drop to 44% of microparticle production. Conversely, aqueous solution feeds containing only 0.1% of polymer such as NaCMC, HEC, HPMC, and HPC gave rise to higher values when compared with data yielded with solutions containing 1% polymer. Thus, of the polymers used in this study, the overall data yielded showed the following trend: MCC > EC > HEC > NaCMC > HPMC > HPC, with the optimal polymer concentration being 1% with MCC and EC and 0.1% with polymers including HEC, NaCMC, HPMC, and HPC.

Inlet temperature appears as an essential parameter in the spray-drying process. Thus, with MCC, an increase of inlet temperature resulted in a decrease of production

yield, from 44% to 37% and 70% to 46% from suspension feeds containing 0.1% and 1% MCC, respectively. This decrease is due to the loss of smaller-size microparticles in the exhaust of the spray-dryer. This is consistent with earlier data reported by Giunchedi and Conte (6). An increase of inlet temperature had a great effect in reducing the size of microspheres. As for NaCMC, solution feeds containing a polymer concentration of 0.1% showed a slight yield decrease, from 44% (at 140°C) to 42% (at 160°C), while at a polymer concentration of 1%, 160°C inlet temperature was not fit for the implementation of the process. An NaCMC concentration increase from 0.1% to 1% led to a highly viscous feed solution. Atomizing viscous solutions results in the formation of large liquid droplets that dry inadequately (3), resulting in a loss of product in a filmlike deposit that forms on the drying chamber wall and cyclone collector. In addition, viscous solutions processed at 160°C inlet temperature tended to reduce the spray nozzle efficiency. In terms of production yield, this study revealed parameters of 1% polymer concentration and an inlet temperature of 140°C as optimal processing conditions. These parameters were applied to study the effects of additives (namely, PVP, DBS, PEG 6000, and carboxylic acids including SA, PA, OA, TA, and CA) on the preparation of spray-drying microparticles.

The drug/adjuncts compatibilities were tested by casting films from feed samples intended for further spray-drying experiments. Films were observed for their properties, including texture, cracking, and opacity. With EC, the film containing acetaminophen had a smooth texture and was homogeneous with no cracking aspect. The use of DBS gave rise to modifications (i.e., rough texture and cracking aspect), predicting a low capacity to retard drug release. As for NaCMC-containing film, the presence of acetaminophen gave a clear, smooth, and cracked film, whereas the NaCMC itself showed a good and uniform film. In the presence of carboxylic acids, NaCMC solutions gave rise to films with smooth texture with TA and SA, whereas a rough texture was observed with PA. Both PA and SA gave rise to opaque films.

The role of these additives in the spray-drying process is quite variable (Table 1). Thus, the incorporation of 3% PVP gave rise to a decrease in product yields with MCC, while with NaCMC polymer, no alteration of production of spray-dried products was found. The use of DBS (with EC) or PEG 6000 (with NaCMC) led to a decrease in production yields from 66% to 39% and 37% to 17%, respectively. Furthermore, the spray-drying process performed from EC suspension feeds containing various levels of 5, 10%, and 24% DBS showed that a concentration exceeding 5% was not fit for the implementation of the spray-drying process. Better performance was obtained with carboxylic acids, with the highest production yield being obtained with TA (49%), compared with the 37% yield from NaCMC solution without plasticizer.

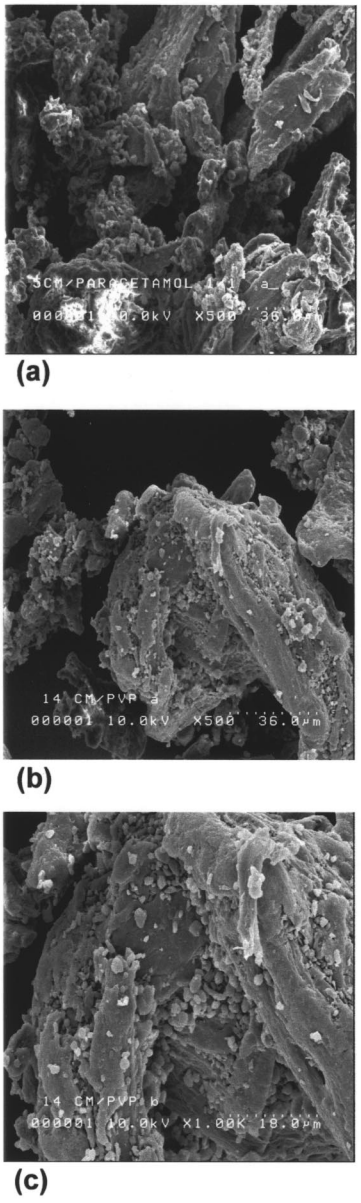

Figure 2. SEM photographs of spray-dried (a) acetaminophen/MCC × 500, (b) acetaminophen/MCC/PVP × 500, and (c) acetaminophen/MCC/PVP × 1000 systems.

Scanning electron microscopy (SEM) showed that the spray-drying process induces changes in microparticulate

Table 2

Acetaminophen Release from Microparticles Obtained by Spray-Drying Technique from Polymer Aqueous Systems with Drug/Polymer Ratios of 1/1 and 10.1

Spray-Dried Formulation	Drug/Polymer Ratio	$T_{50\%}$ (min)		T_{max} (min)	
		pH 1	pH 6.8	pH 1	pH 6.8
Raw acetaminophen		3	4	14	27
Control		6	13	45	60
HEC	10/1	14	20	90	105
HEC	1/1	53	55	>180	>180
HPMC	10/1	11	10	90	75
HPMC	1/1	20	22	105	150
MCC	10/1	15	11	90	90
MCC	1/1	30	32	>180	>180
MCC + PVP	1/1	41	116	>180	>180
EC	1/1	12	25	120	135
EC + DBS	1/1	10	17	85	85
NaCMC	10/1	28	17	>180	90
NaCMC	1/1	45	49	>180	>180
NaCMC + PVP	1/1	34	60	>180	>180
NaCMC + succinic acid	1/1	53	48	>180	>180
NaCMC + phthalic acid	1/1	35	48	>180	>180
NaCMC + oxalic acid	1/1	45	83	>180	>180
NaCMC + tartaric acid	1/1	70	52	>180	>180
NaCMC + citric acid	1/1	47	45	>180	>180

Control spray-dried raw acetaminophen; HEC, hydroxyethylcellulose; HPMC, hydroxypropylmethylcellulose; MCC, microcrystalline cellulose; EC, ethylcellulose; NaCMC, sodium carboxymethylcellulose; PVP, polyvinylpyrrolidone; DBS, dibutyl sebacate.

size and morphology (Fig. 1). For the model drug acetaminophen, changes in particle size and crystallinity were observed. Thus, the spray-drying of raw drug consisting of long, thin, needlelike elements (Fig. 1a) gave rise to spherical microparticles and/or agglomerates (Fig. 1b). As for polymers, the spray-drying process revealed large, porous, irregularly shaped aggregates with MCC (Fig. 1c), while from NaCMC, regularly shaped smooth spherical particles were obtained (Fig. 1e). Feeds made of acetaminophen and MCC as the polymer resulted in small microspheres of drug adsorbed or encrusted into porous particles of MCC and within empty available areas (Fig. 1d). The spherical agglomerates obtained with NaCMC were much smaller and homogeneously well distributed (Fig. 1f) than in the SEM obtained without acetaminophen (Fig. 1e). The SEM photographs in Fig. 2 obtained from acetaminophen/MCC and acetaminophen/MCC/PVP indicate that the use of PVP gave rise to larger agglomerates of the flakelike elements (Fig. 2b) when compared with formulations without PVP (Fig. 2a). In addition, a 2 × observation of the SEM photographs (×1000) revealed clear adherence of the flakelike agglomerate particles after addition of PVP (Fig. 2c). With NaCMC as the polymer, the use of PVP induced the agglomeration of small pellets, whereas carboxylic acids associated with NaCMC gave rise to larger aggregates of spherical microcapsules, the largest being obtained with SA and CA.

The effectiveness of polymers involved in the spray-drying experiments was assessed against a control product obtained from spray-drying of raw acetaminophen. To compare differences in drug release rates, indexes such as the dissolution $T_{50\%}$ and T_{max} parameters, that is, the time for both 50% and maximum (after a 3-hr experiment period) drug release from spray-dried systems, in pH 1 and pH 6.8 dissolution media were considered (Table 2).

With a drug/polymer ratio of 10/1, all the polymers used gave rise to similarly fast drug release with either pH 1 or pH 6.8 dissolution media, except NaCMC polymer, which permitted a notable $T_{50\%}$ of 28 min in acidic medium. However, when compared to dissolution $T_{50\%}$ and T_{max} values from control products, the overall formulations, even with a high drug/polymer ratio, exhibited

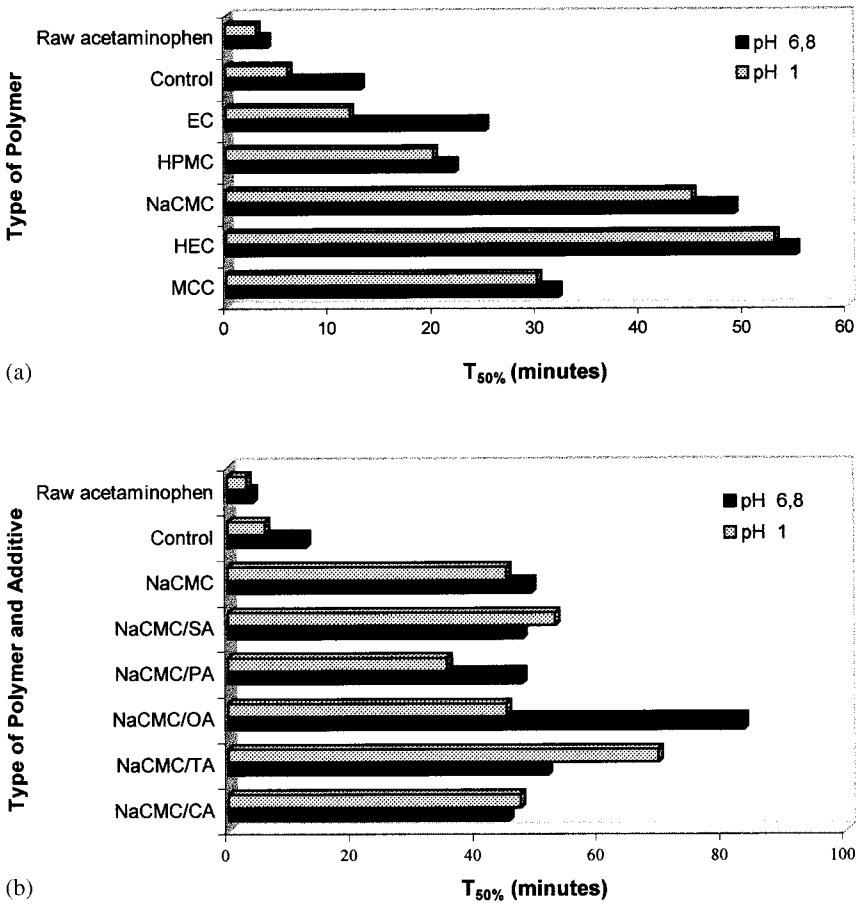

Figure 3. (a) Influence of polymers on the dissolution $T_{50\%}$ values of the spray-dried systems in acidic pH 1 and phosphate buffer pH 6.8 environments; (b) effects of carboxylic acids (SA, PA, OA, TA, and CA) on the dissolution $T_{50\%}$ values of the spray-dried systems in acidic pH 1 and phosphate buffer pH 6.8 environments.

notably retarded drug release in acidic dissolution medium.

With a drug/polymer ratio of 1/1, polymers such as NaCMC, HEC, and MCC have the potential of being good drug carriers since drug release from spheroids showed longer dissolution $T_{50\%}$. In addition, T_{max} values reached with MCC-, NaCMC-, and HEC-microparticulate systems exceeded 180 min in both acidic and neutral media. The current study ranked EC and HPMC as less efficient polymers in terms of coating materials. Formulations consisting of 1% polymer with a drug/polymer ratio of 1/1 induced the slowest drug release, with spheroids coated with NaCMC and HEC showing the longest $T_{50\%}$ values in either pH 1 or pH 6.8 dissolution media. Slightly better sustained drug release in pH 6.8 dissolution medium was reached, showing the following trend: HEC > NaCMC > MCC > EC > HPMC (Fig. 3a).

The magnitude of the changes produced by the additives depends on the pH of the dissolution media and on the type of polymer and plasticizer (Table 2). If the use of DBS with EC polymer induced faster drug release than in samples without DBS, the incorporation of PVP in NaCMC solution resulted in an increase of dissolution $T_{50\%}$ of acetaminophen in pH 6.8 media. As for carboxylic acids, only OA gave rise to a higher value of dissolution $T_{50\%}$ of acetaminophen (83 min) in a neutral dissolution environment. The highest $T_{50\%}$ (116 min) was encountered in a pH 6.8 dissolution environment for the formulations prepared from aqueous MCC suspensions with PVP, with the maximum percentage drug released being only 58% after a 3-hr dissolution test period. In an acidic dissolution environment, TA associated with NaCMC gave rise to the slowest release. The trends in dissolution $T_{50\%}$ of drug from the formulations showed TA > SA >

CA > OA > PVP > PA > DBS in acidic pH 1 dissolution medium and PVP > OA > TA > SA > PA > CA > DBS in pH 6.8 phosphate buffer (Fig. 3b).

The findings of the current study indicate that the slow release of acetaminophen is in part due to changes in drug crystal form induced by the spray-drying as shown by SEM (Fig. 1) and confirmed with the $T_{50\%}$ obtained from both raw acetaminophen and control products (Table 2). The drug/polymer ratio exerts an influence on drug release characteristics, with varying the polymer a fundamental requirement to optimize the preparation of controlled-release products. The release of drugs results from a combination of diffusion and polymer erosion. The availability of drug from microparticulate systems depends on the degree of hydrophilicity of the polymer used. Hydrophilic polymers such as NaCMC and HEC gelled faster, resulting in the fast formation of a viscous gel barrier and prolonged drug release. An increase in polymer concentration leads to a larger barrier, consequently retarding drug release in the dissolution medium. Faster drug dissolution obtained from formulations with a drug/polymer ratio of 10/1 was due to the lack of continuous coating or a coat that was too thin.

CONCLUSION

For controlled-release polymeric systems, this study shows that NaCMC and HEC are efficient coating agents, with NaCMC being the most suitable for the spray-drying process. The spray-drying of MCC suspension leads to the formation of microspheres embedding the acetaminophen, also resulting in prolonged drug release. From the additives tested, PVP associated with MCC gave rise to the longest dissolution $T_{50\%}$ in pH 6.8 medium. Of the additives used with NaCMC, most of the carboxylic acids were revealed to be efficient plasticizers, increasing both the production yield and the prolonged drug release.

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