Application of Surelease® in Preparation of Theophylline Extended Release Inert Matrix Tablets by Spray Granulation

APPLICATION DATA SUMMARY

- Surelease®, aqueous ethylcellulose dispersion, was investigated as a wet granulation agent in the preparation of theophylline extended release, inert matrix tablets.
- The influence of filler type (lactose monohydrate, microcrystalline cellulose, or dicalcium phosphate) on tablet properties and drug release is reported.
- The results of this study indicate that Surelease, in combination with the proper choice of filler, can be successfully used at relatively low levels to modulate drug release in ER inert matrices.

INTRODUCTION

Ethylcellulose (EC) has been widely used as a barrier membrane or binder, to prepare pharmaceutical oral modified release dosage forms. The aqueous dispersion of ethylcellulose, for example Surelease has been utilized to manufacture modified release multiparticulates for filling into capsules and single unit tablets or soft-gel capsules through film coating applications.[1] In addition, the use of aqueous ethylcellulose dispersion as a release retardant binder for the manufacture of inert matrices has been reported. Surelease® enhanced the compaction characteristics of drug,[3, 4] and the drug release mechanism from those inert porous matrices was by diffusion.[2, 3, 4]

The objective of this study was to investigate the application of Surelease as a wet granulation agent (release retardant binder), using theophylline anhydrous as a model drug, in the preparation of extended release (ER) inert matrix tablets. The manufacturing process of wet granulation and tableting will be discussed, as well as the effect of filler choice.

METHODOLOGY

Dry powder screening and blending

The composition of theophylline ER matrices is shown in Table 1. Theophylline anhydrous (TP) and fillers were passed through an ASTM #30 mesh (600 µm), and then mixed in an 8-quart V blender (Patterson-Kelley Co., USA) at 26 rpm for 10 minutes.

Table 1. Formulation of theophylline ER inert matrices

Ingredients	Functionality	% Composition			
		EC-1	EC-2	EC-3	EC-4
Theophylline anhydrous (Spectrum Chemicals)	API	44.0	44.0	44.0	44.0
Surelease E-7-19050 (Dry solids, Colorcon, Inc.)	Polymer network former	11.0	11.0	11.0	11.0
Lactose monohydrate (EMD Chemical Inc.)	Soluble filler	44.0	-	-	22.0
Microcrystalline cellulose (MCC) (Emcocel 50M, JRS Pharma LP)	Insoluble filler	-	44.0	-	22.0
Dicalcium phosphate (DCP) (DI-TAB, Rhodia Inc.)	Insoluble filler	-	-	44.0	-
Silicon dioxide (Cab-O-Sil M-5P, Cabot Co.)	Flow aid	0.5	0.5	0.5	0.5
Magnesium stearate (Mallinckrodt Chemical Inc.)	Lubricant	0.5	0.5	0.5	0.5

Granule preparation and characterization

The powder blends were granulated using a Glatt GPCG-3 fluid bed (Glatt Air Techniques, USA) by top spraying. Prior to application, Surelease was diluted from 25% w/w with deionized (DI) water to 15.0% w/w. Process parameters for fluid bed granulation are shown in Table 2. The resulting granules were dried in the Glatt at 40ºC for 5 minutes. The dried granules were analyzed for bulk and tapped density using a VanKel density tester (Varian Inc., USA), flowability using a SOTAX FT300 flowability tester (SOTAX, USA), particle size distribution (Hosokawa sonic sifter L3P, USA) and loss on drying (LOD) by an IR moisture balance (Denver Instrument, Model: IR-200, USA).

Table 2. Process parameters for theophylline fluid bed granulation*

Fluid Bed Equipment: Glatt GPCG-3	Top spraying
Nozzle size (mm)	1.2
Atomization pressure (bar)	1.5
T_{inlet} (ºC)	65 – 90**
T_{bed} (ºC)	42
T_{outlet} (ºC)	40 – 41
Spray rate (g/min)	30
Spray time (min)	30

* Process parameters are shown for a batch size of 2.0-2.5 kg and were based on typical Surelease coating parameters. Operating condition may vary depending on batch size/equipment.

** Inlet temperature was adjusted so as to maintain product bed temperature in the range of 40-41ºC.

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Tablet preparation and characterization

Silicon dioxide and magnesium stearate were mixed and screened through an ASTM #40 mesh (600 μm), then blended with dried granules in an 8-quart V blender (Patterson-Kelley Co., USA) at 26 rpm for 2 minutes. The final granule mixtures were compressed at 5 - 20 kN using an instrumented 10-station rotary tablet press (RIVA, Argentina) at 30 rpm using standard round 9.52 mm concave tooling. The average tablet weight of all formulations was maintained at 303.0 ± 6.0 mg. All the compositions exhibited low ejection forces (85-140 N) as shown in Table 3.

A total of 4 different tablet compositions were produced (Table 3). Tablet weight, breaking force, diameter and thickness were measured with an automated Multicheck tablet tester (Erweka, Germany). Tablet friability was measured using a VanKel Friabilator at 100 revolutions, 25 rpm (Varian Inc., USA). Theophylline release was tested in a VK 7010 dissolution unit (Varian, USA), USP II with sinkers, at 100 rpm using 1000 mL of deionized water at 37 ± 0.5°C. An on-line dual beam UV-Visible spectrophotometer (Model Cary 50 Tablet, Varian, USA), fitted with quartz flow cells of 1.0 mm path length, was used for the detection of theophylline at a wavelength of 272 nm.

Table 3. Effect of compression force on the ejection forces of theophylline inert matrices

Compression Force (kN)	5	10	15	20
	Ejection Force (N)			
EC-1 (Lactose)	101.56	108.06	115.83	122.70
EC-2 (MCC)	101.30	100.06	100.39	103.03
EC-3 (DCP)	99.53	115.57	129.11	140.35
EC-4 (Lactose + MCC)	85.26	87.5	88.58	90.43

Data analysis

Release exponent (*n*) and release rate constant (*k*) were calculated by fitting the dissolution data to the Power Law equation[4]:

$$Q = k \times t^n \qquad \text{Equation 1}$$

Where *Q* is the fractional amount released at time *t*, *k* is the kinetic constant, and *n* is the release exponent.

RESULTS AND DISCUSSION

Granule properties

The particle size distributions of granules are shown in Figure 1. Dried granules had consistently small particle sizes < 500 μm, and the granule sizes were in the rank order of MCC < DCP < lactose + MCC < lactose, which corresponded to the average particle size of the fillers (MCC: 50 μm, DCP: 150 μm, lactose: 150 μm).

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Figure 1. Particle size distribution of dried theophylline granules

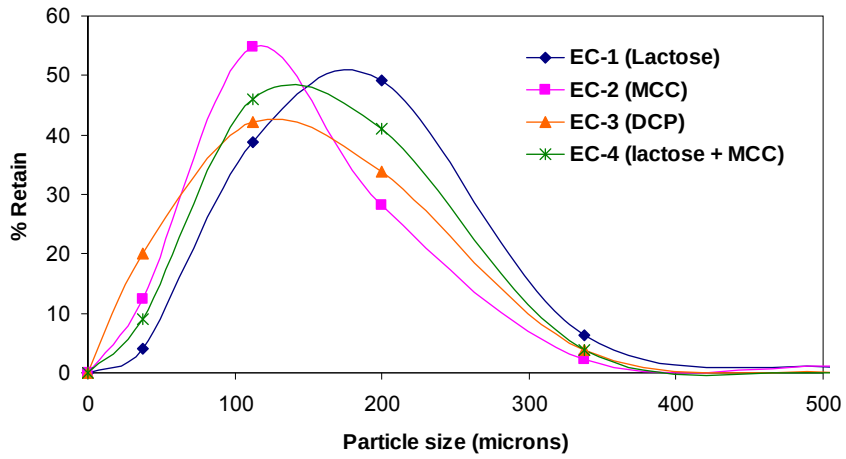

Table 4. Physical properties of theophylline granulations

Formulation #	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Sotax flow (g/sec)	LOD (%)
EC-1 (lactose)	0.39	0.46	16.00	6.27	0.47
EC-2 (MCC)	0.29	0.37	23.00	3.35	1.37
EC-3 (DCP)	0.60	0.71	14.70	7.50	1.00
EC-4 (lactose + MCC)	0.32	0.41	22.00	5.43	1.13

As shown in Table 4, the bulk and tapped density of granules were in the order of DCP > lactose > lactose + MCC > MCC. All granules exhibited low Carr's index values (14.70 – 23.00 %) indicating good-fair flow properties. Measurement of flow using Sotax flowability tester also indicated good powder flow (3.35 – 7.50 g/sec). Dried granules had LODs in the range of 0.47 – 1.37 (% w/w).

Tablet properties

Compression of the granules produced robust tablets, breaking force increased with compression force (Figure 2). Tablet hardness was in the order of MCC > (MCC + lactose) > lactose > DCP, and all tablets had good breaking strengths and met generally accepted solid dosage requirement. The consistent physical properties of theophylline tablets are shown in Table 5. Tablet weight ranged from 300.3 – 303.6 mg, and tablet diameter was in the range of 9.45 – 9.51 mm. Tablet thickness was in the order of (MCC + lactose) ~ MCC < lactose < DCP. All tablets exhibited very low friability (0.02 – 0.11 %).

Figure 2. The influence of compression force and filler choice on hardness of theophylline ER inert matrix tablets (n = 20)

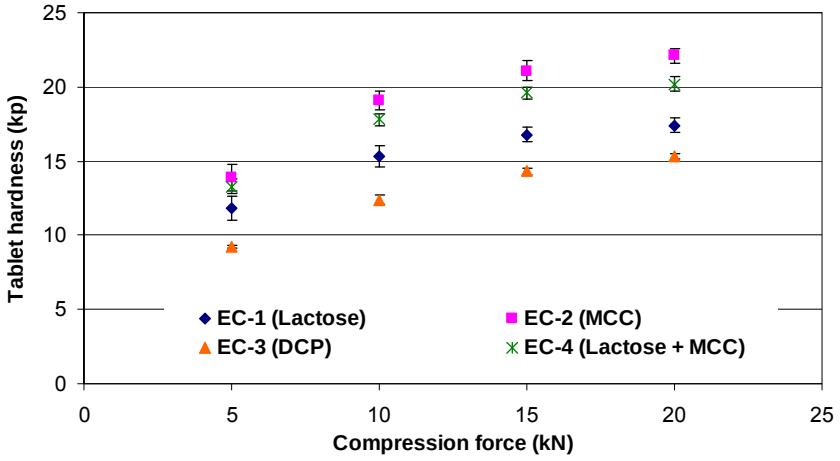

Table 5. Theophylline ER tablet physical properties (prepared at compression force of 15 kN, n = 20)

Formulation #	Tablet weight (mg)	Tablet thickness (mm)	Tablet diameter (mm)	Tablet hardness (kp)	Friability (%)
EC-1 (lactose)	300.30 ± 4.50	3.84 ± 0.03	9.50 ± 0.02	16.80 ± 0.50	0.07
EC-2 (MCC)	303.60 ± 4.30	3.92 ± 0.04	9.45 ± 0.04	21.10 ± 0.70	0.02
EC-3 (DCP)	301.70 ± 0.60	3.57 ± 0.01	9.51 ± 0.02	14.30 ± 0.20	0.11
EC-4 (lactose + MCC)	303.10 ± 2.40	3.85 ± 0.02	9.47 ± 0.01	19.60 ± 0.40	0.04

Drug release

The theophylline release profiles are shown in Figures 3 A-D. Tablets containing lactose as filler showed minimum influence of compression force on drug release profile (Figure 3A). However, tablets containing DCP, MCC or the (lactose + MCC) mixture as filler showed slower drug release with increasing compression force, until a threshold compression force of 15 – 20 kN was reached (Figures 3B, 3C and 3D). This effect could be attributed to the nature of these excipients and their mode and extent of deformation during tableting and its effect on tablet porosity. As seen in Figures 3 A-D, extended drug release was obtained with all fillers investigated in this study, and order of release rate was lactose < DCP < MCC ~ (lactose + MCC) at similar dry Surelease levels (11% w/w). Tablets containing lactose or DCP stayed intact, while those containing MCC or the (MCC and lactose) mixture split in the middle of the band during dissolution testing, which could be attributed to the capillary effect of MCC leading to migration of dissolution media into the inert matrix resulting in crack formation, splitting and subsequent faster drug release (Figures 3 & 4).

The drug release mechanisms of tablets compressed at 15 kN are shown in Figure 4 and Table 6. All dissolution profiles showed good fit to the Power law equation. The drug release from ER inert matrix tablets containing lactose (n = 0.42) or DCP (n = 0.47) was Fickian diffusion control, while those with MCC (n = 0.63)

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or (MCC + lactose) mixture (n = 0.57) showed anomalous (Non-Fickian) transport. Table 6 also shows that the time taken for 50% drug release ($T_{50\%}$) from theophylline inert matrices was in the order of lactose > DCP > (lactose + MCC) > MCC.

Figure 3. The influence of compression force and choice of filler on theophylline inert matrices: (A) EC-1 (lactose); (B) EC-2 (MCC); (C) EC-3 (DCP); (D) EC-4 (lactose + MCC)

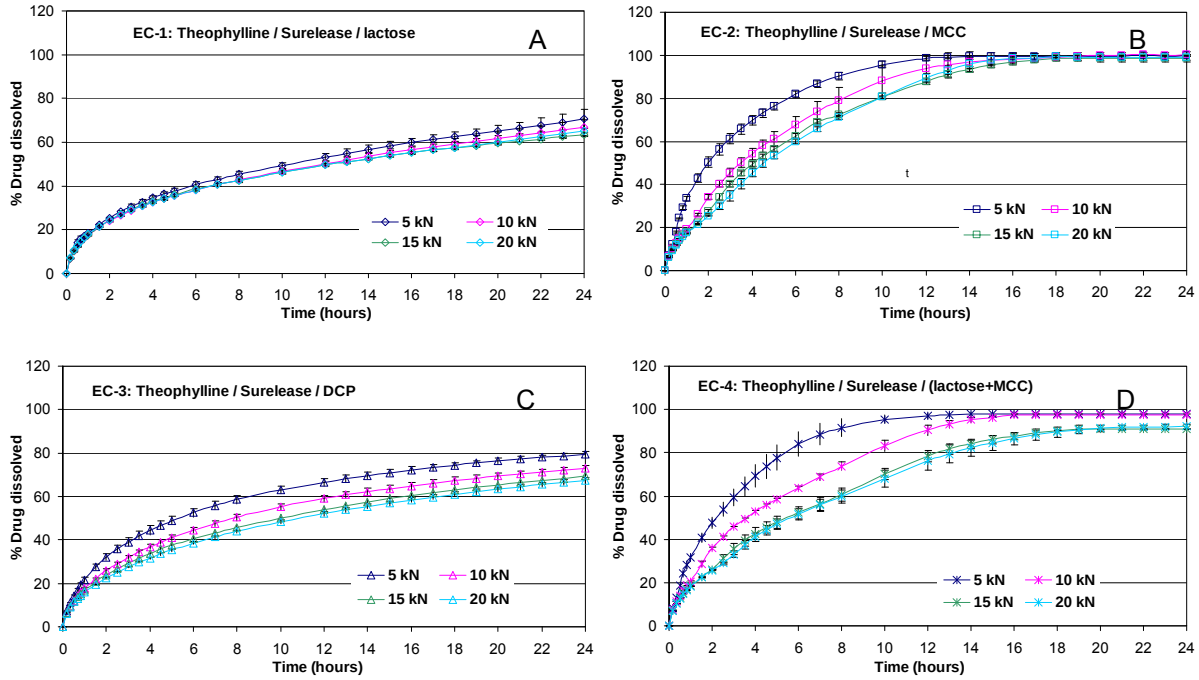

Figure 4. Drug release mechanisms of theophylline inert matrices

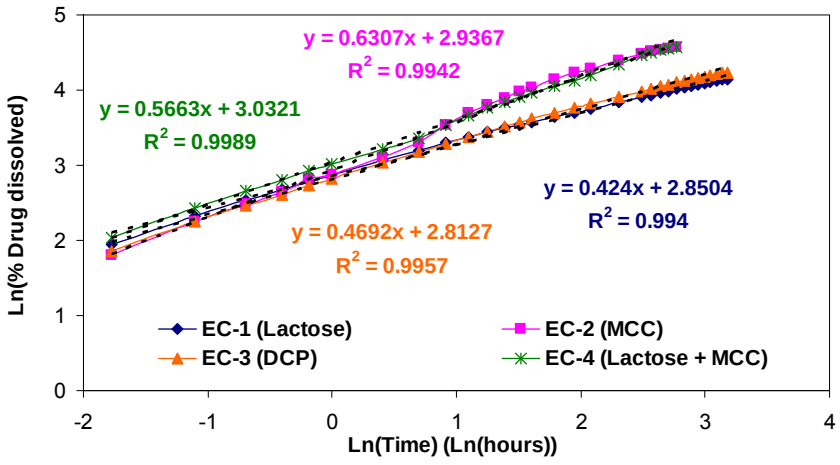

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Table 6. Dissolution profile of theophylline ER inert matrices produced at compression force of 15 kN

Formulation #	*n*	*k*	R^2	$T_{15\%}$ (hours)	$T_{30\%}$ (hours)	$T_{50\%}$ (hours)
EC-1 (lactose)	0.42	17.29	0.99	0.71	3.21	12.32
EC-2 (MCC)	0.63	18.85	0.99	0.72	2.19	4.08
EC-3 (DCP)	0.47	16.65	1.00	0.81	3.11	9.91
EC-4 (lactose + MCC)	0.57	20.74	1.00	0.66	2.40	5.47

CONCLUSIONS

The results of this study indicated that Surelease can be successfully used to modulate drug release of sparingly water soluble drugs like theophylline in ER inert matrices. Fluid bed granulation using an aqueous dispersion of Surelease at relatively low levels of polymer was used, allowing faster processing time. The resultant granulations exhibited acceptable particle size distribution and good flow properties. Matrix tablets prepared by using these granulations exhibited desirable pharmacotechnical properties. The mechanism and extent of drug release were influenced by the choice of filler (lactose, MCC, DCP, or MCC + lactose). Use of lactose or DCP as soluble and insoluble fillers respectively, is preferable in designing inert matrices of sparingly soluble drugs.

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