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Investigation of Ethylcellulose in the Preparation of Theophylline Extended Release Inert Matrix Tablets

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PURPOSE

Ethylcellulose (EC) is commonly used in the formulation and manufacture of extended release (ER) pharmaceutical solid dosage forms, using barrier membrane (film coating) technologies. The application of ethylcellulose as a release retardant binder in ER inert matrices has also been reported in the literature.[1,2,3,4]

The objective of this study was to investigate the influence of EC particle size and molecular weight on drug release from inert matrices containing a sparingly water soluble drug, theophylline. The influence of varying the polymer concentration, filler choice and compression force on drug release was also evaluated.

METHODS

Dry Powder Blending and Characterization

Theophylline (TP) (33.0 – 50.0% w/w) was mixed with EC (ETHOCEL™ premium ethylcellulose polymers, Standard) (FP) 10 or 100 cP10.0 - 50.0% w/w inclusion, with or without a filler (lactose or microcrystalline cellulose; 32.8 - 55.8% w/w), followed by addition of silicone dioxide (0.5% w/w) and magnesium stearate (1.0% w/w) in an 8-quart V blender (Patterson-Kelley Co., USA). The formulation details of the inert matrix are shown in Table 1. The bulk and tapped densities were assessed using a VanKel density tester (Varian Inc., USA). The relative gravimetric flow rates were measured using a SOTAX FT300 flowability tester (SOTAX, USA). The true density of each ingredient was evaluated using a Helium Pycnometer (Micrometritics AccuPyc 1330, USA).

Table 1. Theophylline Inert Matrix Formulations

Ingredient	% Composition				
	ECNF	ECL1	ECL2	ECM1	ECM2
Theophylline anhydrous (Spectrum Chemical, USA)	49.48	32.98	32.98	32.98	32.98
ETHOCEL™ (IFF, USA)	49.47	32.98	9.85	32.98	9.85
Fast-Flo Lactose (EMD Chemical Inc., USA)		32.98	55.83		
Emcocel 90M (JRS Pharma LP, USA) or Microcel MC-200 (Blanver, Brazil)				32.98	55.83
CAB-O-SIL M5-P (Cabot Corporation, USA)	0.50	0. 50	0. 50	0.50	0.50
Mg. St. (Mallinckrodt Chemical Inc., USA)	1.00	1.00	1.00	1.00	1.00

Note: ETHOCEL grades used in this study were: ETHOCEL 10FP, 100FP, Standard 10 or 100; Formulations ECM1 or ECM2 contain Emcocel 90M with EC Std. or Microcel 200 (B) with EC FP.

Tablet Preparation and Characterization

The inert matrix tablets were prepared in a Piccola 10-station rotary tablet press (RIVA, Argentina) at 30 rpm and compression forces of 5 – 30 kN, or by a single-punch MTCM-1 manual tablet press (Globe Pharma, USA) at compression forces between 5 - 15 kN (standard round concave, 9.52 mm and 304.5 mg). The Piccola was utilized for formulations with good powder flow, while the manual press (mp) was used for formulations with poor powder flow. A total of 20 different tablet compositions were produced. Tablet weight, breaking force, diameter and thickness were measured using a Multicheck tablet tester (Erweka, Germany). Theophylline release was tested in a VK 7010 dissolution unit (Varian, USA), USP II with sinkers, 100 rpm using 1000 mL of purified water at 37°C ± 0.5°C. An on-line dual beam UV-Visible spectrophotometer Cary 50 (Varian, USA) with quartz flow cells of 1.0 mm path length was used for the detection of theophylline at a wavelength of 272 nm.

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Dissolution profiles were characterized using the Higuchi square root of time relationship:[5] $Q = k\ t_{1/2}$, where Q is amount of dissolved drug (mg), k is release rate constant (mg/hour$^{1/2}$), and t is dissolution time (hour). The porosities of theophylline inert matrix tablets were calculated using the equation:

$$\varepsilon = (1 - \frac{P_{cal}}{P_{true}}) \times 100$$

$$P_{cal} = \frac{M_{tablet}}{V_{tablet}}$$

where P is tablet porosity (%), P_{cal} is calculated tablet density (g/mL), P_{true} is true density (g/mL), M_{tablet} is tablet weight (g) and V_{tablet} is tablet volume (mL).

RESULTS

Dry Powder Properties

Formulations containing EC FP grades exhibited lower bulk / tapped densities than those with EC standard grades, and the subsequent Carr's index values were higher for EC FP grades vs. standard grades. The SOTAX flow results of the formulations are shown in Figure 1. The formulations containing EC 10FP showed poorer flow (0.4 – 4.1 g/sec) than those with EC standard (3.7 – 6.9 g/sec).

Figure 1. SOTAX Flow of Formulations ECNF, ECL1, ECL2, ECM1 & ECM2

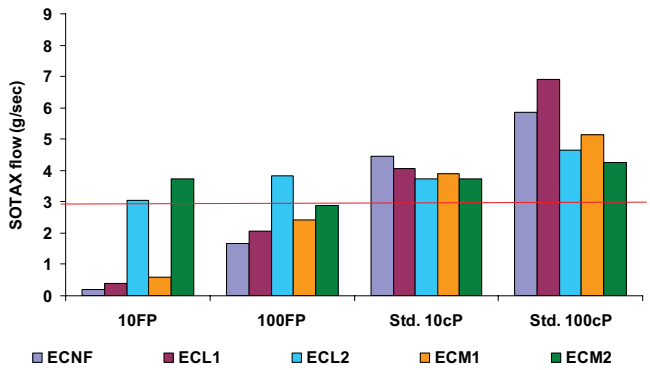

Figure 2. Dissolution Profiles of Theophylline from EC Inert Matrices (no filler) (TP/EC = 1:1 ratio, Compression Force: 10kN)

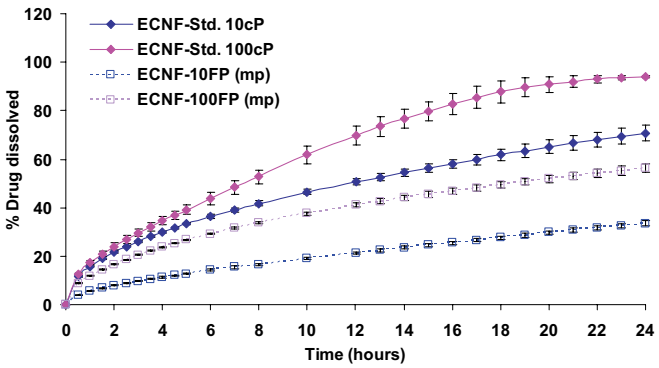

Figure 3. Dissolution Profiles of Theophylline Tablets (ECL1) (TP / EC / FF Lactose = 1:1:1, Compression Force: 10 kN)

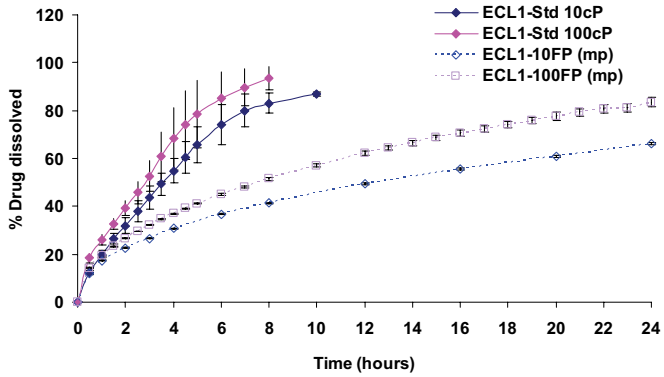

Figure 4. Dissolution Profiles of Theophylline Tablets (ECM1)(TP / EC / MCC = 1:1:1, Compression Force: 10 kN)

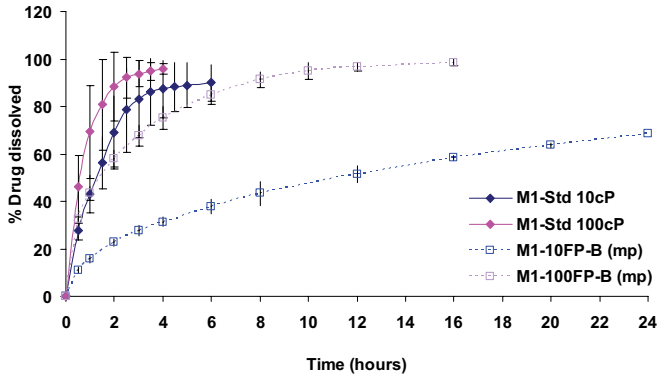

Table 2. Theophylline Inert Matrix Tablet Properties (ECL1, Compression Force: 10 kN)

Formulation #	Tablet Hardness (kp)	Porosity (%)	*k* (mg/ hr $^{1/2}$)	R^2
ECL1-10FP	28.4 ± 1.2	38	12.74	1.00
ECL1-100FP	24.0 ± 0.8	40	16.60	1.00
ECL1-10cP	12.0 ± 0.5	41	35.94	0.99
ECL1-100cP	8.1 ± 0.6	42	31.26	0.99

Tablet Physical Properties

Study results showed that tablet hardness and compressibility are in the order of EC 10FP > 100FP > Std. 10cP > Std. 100cP. The incorporation of theophylline resulted in lower tablet hardness. Lactose or MCC increased hardness of tablets containing EC standard grades, but lowered hardness of tablets containing EC FP grades. Tablets with MCC were harder than those with lactose. All formulations resulted in tablets with acceptable hardness ≥ 6.9 kp at compression force of 10 kN.

Theophylline Tablet Release Profiles

The release profiles of theophylline tablets are shown in Figures 2-4. Theophylline release rate and porosity were in the order of EC 10FP < 100FP < Std. 10cP < Std. 100cP. Drug release rate decreased with increasing EC concentration. Study results showed that EC 10FP provided sustained release

(T_{50} = 2.96 hrs) at EC concentration of 10.0% w/w. Theophylline tablets with lactose showed slower drug release than those with MCC. Theophylline inert matrix tablets of ECNF-10FP & 100FP, ECL1-10FP & 100FP, ECM1-10FP were intact after 24-hr dissolution testing, but tablets from the rest of the formulations were partially or completely disintegrated.

Tablet hardness, porosity and release constant (*k*) of ECL1 tablets are shown in Table 2. Tablets containing FP grades have lower porosity than those with standard grades, and tablets manufactured at higher compression force resulted in lower porosity than those prepared at low compression force, which may explain slower drug release observed at high compression force. Tablets containing no filler have slightly lower porosity (30 – 41%), in comparison to those containing lactose or MCC (37 – 43%). Theophylline tablets containing lactose or MCC had similar porosity at the same formulation and compression forces. Study results also showed that dissolution profiles had a good fit to the Higuchi equation and corresponding release constant (*k*) is in the order of 10FP < 100FP < Std. 10cP < Std. 100cP.

CONCLUSIONS

The results of this study indicated that ETHOCEL FP grades provided formulation advantages by yielding harder tablets, better compressibility, and slower drug release than corresponding standard grades of ETHOCEL. However ETHOCEL FP grades had poor powder flow, making it a challenge for direct compression. The theophylline inert matrix tablets containing microcrystalline cellulose are harder than those with lactose. Tablets prepared from lower molecular weight grades of ETHOCEL (10 or 10 FP) had slower drug release than tablets prepared from higher molecular weight grades (100 or 100 FP). Drug release rate decreased with increasing ethylcellulose concentration and increasing compression force. Lactose provided slower drug release than microcrystalline cellulose.

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