Investigation of Aqueous Ethylcellulose Dispersion in Extended Release Metformin Inert Matrices

ABSTRACT SUMMARY:

In the present study, Surelease®, aqueous ethylcellulose dispersion (Colorcon Inc., USA), was used to formulate metformin HCl extended release (ER) inert matrix tablets by fluid bed granulation. All the formulated tablets showed extended drug release properties. The formulation offered the flexibility to modulate the drug release rate by altering the amount of Surelease used during granulation.

INTRODUCTION:

There has been recent interest in formulating extended release oral dosage forms using inert matrix systems, due to their ease of manufacturing and as an alternative to hydrophilic matrices.[1] Ethylcellulose is commonly used in oral solid dosage forms. It has been used as a binder, a controlled release barrier coating, and as a controlled release matrix in direct compression.[2-3] The use of Surelease as a release retardant binder for the manufacturing of inert matrices has also been reported.[4-5] The objective of the present study was to investigate the applications of Surelease as a release retardant binder in tablet formulations of metformin HCl, a freely soluble drug, applied via fluid bed granulation. Metformin HCl release rates from high and low dose extended release (ER) inert matrices (compressed from Surelease granuled formulation) were studied.

EXPERIMENTAL METHODS:

The compositions of the inert matrices are shown in Table 1. Granulation was performed using a high (F2) or low (F1) amount of Surelease. Metformin HCl was screened through an ASTM #30 mesh sieve (600 µm), and then fluid bed granulated using a Glatt GPCG-3 fluid bed (Glatt Air Techniques, USA) by top spray. Prior to application,

Surelease (25% w/w) was diluted with deionized (DI) water to 15% w/w. Process parameters for fluid bed granulation are shown in Table 2. The dried granules were assessed for bulk and tapped densities using a VanKel density tester (Varian Inc., USA), relative gravimetric flow rates using a SOTAX FT300 flowability tester (SOTAX, USA), particle size distribution (Hosokawa sonic sifter L3P, USA) and loss on drying (LOD) by a moisture balance (Model: IR-200, Denver Instrument, USA). Granules were blended with silicon dioxide, lubricated with magnesium stearate, and were compressed at 5-20 kN using an instrumented 10-station rotary tablet press (PICCOLA, RIVA, Argentina) at 30 rpm. Both granulations (F1 and F2) were compressed at tablet weights of 303 mg and 1000 mg, using 9.52 mm standard round concave tooling and 19.05 mm X 9.27 mm caplet tooling, respectively. Tablet weight, breaking force, diameter and thickness were measured

with an automated tablet tester (Multicheck, Erweka, Germany). Tablet friability was measured using a VanKel friability tester (Varian Inc., USA) after 100 revolutions at 25 rpm. Drug release was measured in a USP compliant bath (VK 7000, Varian, USA), apparatus II with sinkers, 100 rpm using 1000 mL of DI water as dissolution media at 37°C ± 0.5°C. A uv-visible spectrophotometer (Agilent, USA), operated at a wavelength of 233 nm, was used for detection of metformin HCl. Deionized water was used as reference.

Dissolution profiles were characterized using the Higuchi square root of time relationship6: Q = k t1/2, or power law equation4: Q = ktn, where Q is amount of dissolved drug, k is release rate constant, n is the release exponent, and t is dissolution time.

Table 1. Formulation of Metformin HCl ER Inert Matrices

Ingredients	**% Composition (w/w)**	
	F1	F2
Metformin HCl (Medilom. Co.)	66.0	56.6
Surelease NG E-7-19050 (Colorcon, Inc.) (on dry basis)	33.0	42.4
Silicon dioxide (Cab-O-Sil M-5P, Cabot Co.)	0.5	0.5
Magnesium stearate (Mallinckrodt Chemical Inc.)	0.5	0.5
Total	100.0	100.0

Table 2. Process Parameters for Fluid Bed Granulation

Fluid Bed: Glatt GPCG-3	Top spray
Batch size (kg)	2.5
Nozzle size (mm)	1.2
Automization pressure (bar)	1.5
Inlet air volume (cfm)	51 – 79
T_{inlet} (ºC)	80 – 90
T_{bed} (ºC)	43 – 46
T_{oulet} (ºC)	39 – 41
Spray rate (g/min)	20

RESULTS AND DISCUSSION:

Surelease granulated formulations exhibited good powder flow as indicated by the low Carr's Index and higher Sotax flowability values (Table 3). The average particle size of granules ranged from 200-300 μm (max. 675 μm). Increasing the amount of Surelease in the granulation resulted in lower tablet hardness irrespective of the total tablet weight or tooling used (Table 4 and Figure 1). Tablet hardness improved with increasing compression force, until a threshold was reached at a compression force of 15 kN (Figure 1). All the tablet formulations exhibited low friability values (Table 4).

Table 3. Physical Properties of Metformin HCl Granules

Formula #	Bulk density (g/mL)	Tapped density (g/mL)	Carr's Index (%)	SOTAX flow (g/sec)	LOD (%)
F1	0.58	0.66	13.01	16.18	0.30
F2	0.55	0.61	10.01	15.72	0.57

Table 4. Physical Properties of Metformin HCl ER Tablets Prepared at Compression Force of 15 kN

Batch	Hardness (kp)*	Friability (%)
F1 (303 mg)	10.5 ± 0.2	0.16
F2 (303 mg)	8.6 ± 0.1	0.15
F1 (1000 mg)	19.1 ± 0.5	0.15
F2 (1000 mg)	17.0 ± 0.4	0.17

Figure 1. Effect of Compression Force on Metformin HCl ER Tablet Mechanical Strength (n = 20)

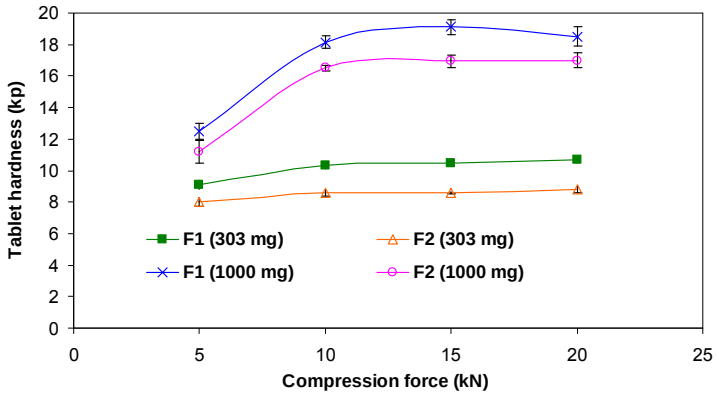
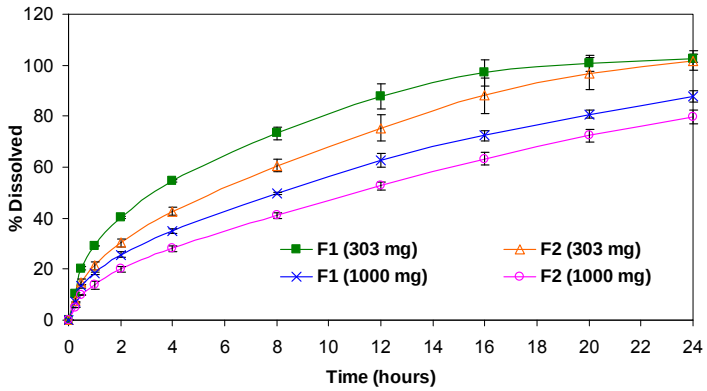


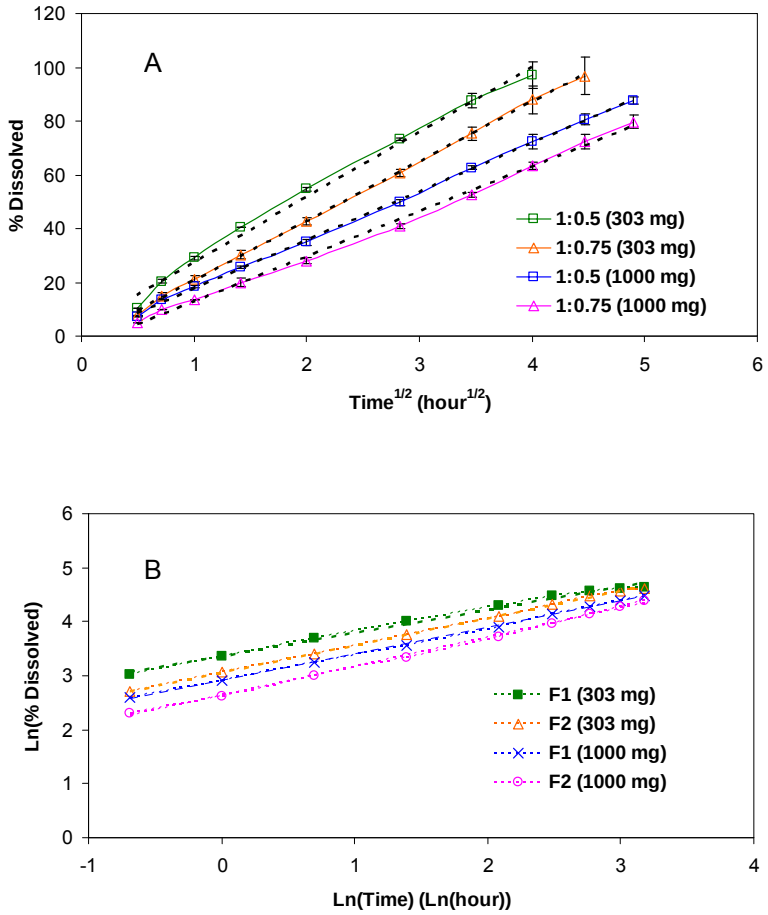
Figure 2. Dissolution Profiles of Metformin HCl ER Tablets Prepared at Compression Force of 15 kN



All tablet formulations exhibited extended release of the drug (Figure 2). The rate of drug release decreased with increasing Surelease concentration. The smaller tablets (303 mg) showed faster drug release than the larger tablets (1000 mg), which could be attributed to the high surface area to volume ratio and shorter diffusional path length of the smaller tablets. Interestingly, all inert matrix tablets stayed intact during and

after dissolution testing. The release data showed good fitting (R2 = 0.99) to both the Higuchi and power law equation indicating the mechanism of drug release by Fickian diffusion control (Figure 3A & B).

Figure 3. Drug Release Data Fitting: (A) Higuchi equation; (B) Power Law Equation. The value of n, the release exponent, ranged from 0.43 to 0.54



CONCLUSIONS:

Surelease was successfully used to granulate a freely water soluble drug (metformin HCl) and produce extended release inert matrices at high and low dose levels. Fluid bed granulation with Surelease resulted in granules with good flow properties. Inert matrix tablets with good mechanical strength and low friability were achieved at relatively low compression force. The rate of drug release decreased with increasing Surelease concentration.

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