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Investigation of a Directly Compressible Hypromellose Matrix Formulation for a Low Dose, Practically Insoluble Drug

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Introduction

The objective of this study was to investigate a direct compression (DC) extended release (ER) tablet formulation of a low dose, practically insoluble drug using hypromellose (HPMC, Methocel*).

HPMC is extensively used in the formulation of extended release matrix systems. The rate of drug release is mediated by a hydrated gel layer on the surface of the matrix. Critical factors impacting drug release from these matrices include HPMC polymer type & concentration, drug solubility, choice of fillers, tablet size and polymer/drug ratio[1].

Indapamide, a low dose thiazide type diuretic which is practically insoluble in water, was chosen as the model drug. The primary benefit of an ER preparation of Indapamide is that a lower dosage is needed to maintain a uniform blood plasma concentration and therefore provides uniform clinical effect[2].

An initial formulation was generated using the HyperStart® formulation service[3], and compared to a reference product, Natrilix® SR table. The effects of filler types was investigated.

Methodology

The particle size of the Indapamide (Calao Srl, Italy) was measured using laser scattering technique (Malvern Mastersizer). The mean particle size was 13.54 microns.

500g formulations containing 0.75% w/w drug, 38.68% w/w HPMC (Methocel K15MCR), 0.50% fumed silica (Aerosil® 200)) and 0.5%w/w magnesium stearate (Peter Greven) were prepared. Two different fillers were used at 59.75%w/w i.e. spray-dried lactose (FastFlo®) or microcrystalline cellulose (Avicel® PH102).

Table 1. Formulations Used in this Study

Materials	**Concentration (% w/w)**	
	A*	B
Indapamide	0.75	0.75
HPMC K15M CR	38.68	38.68
Lactose	59.57	-
Microcrystalline cellulose	-	59.57
Fumed silica	0.50	0.50
Magnesium stearate	0.50	0.50

*Formulation generated using HyperStart

Mixing procedure for low dose active drug:

1. Drug and a portion of the filler were pre-blended in a Diosna high shear granulator for 5 minutes (impeller speed = 200 rpm and chopper speed = 500 rpm).

2. The rest of the filler (pre-screened with fumed silica through a 500 µm mesh) was added to the Diosna bowl and mixed for 5 minutes at the above conditions.

3. The HPMC was then added and blended for an additional 5 minutes at the above conditions.

4. Finally, magnesium stearate was added and the formulation was mixed for a further 1 minute at an impeller speed of 400 rpm.

A tap density tester (Sotax, UK) was used to measure the bulk and tapped densities of the blends.

200 mg tablets containing 1.5 mg drug were manufactured using direct compression on an instrumented 10 station rotary tablet press (Piccola, Riva, Argentina) fitted with 7mm standard concave tooling, at 20 rpm. Tablet ejection force was measured.

Dissolution testing was performed according to the USP monograph <711> for indapamide tablets4. A USP compliant Vankel dissolution bath fitted with Apparatus I (basket method) at 100 rpm was used. The dissolution medium was 900ml of 0.05M phosphate buffer (pH 6.8). Samples were taken over a 24 hour time period and analysed by HPLC.

Tablet content uniformity tests were carried out according to the USP monograph <905> for indapamide tablets[4]. Tablet mechanical strength was determined using an automated tablet tester (Schleuniger, Germany) and friability tester (Copley, UK).

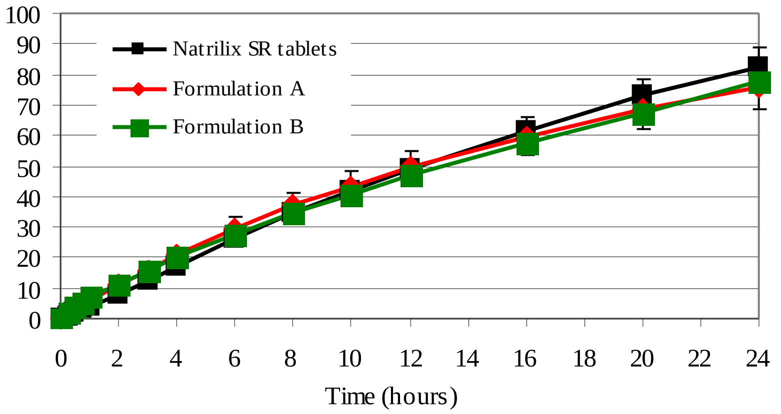
Results and Discussion

Table 2. Physical Properties of the Tablets

Formulations	A	B
Bulk density	0.52	0.43
Tapped density	0.69	0.58
Carr's Index (%)	25.0	26.0
Ejection force (N)	136.6 ± 3.6	50.3 ± 2.3
Compression force (kN)	12.9 ± 0.3	4.7 ± 0.2
Diameter (mm)	7.0 ± 0.0	7.0 ± 0.0
Thickness (mm)	4.8 ± 0.0	5.1 ± 0.0
Weight (mg)	204.0 ± 0.0	204.5 ± 1.5
Breaking force (kN)	11.4 ± 0.3	12.2 ± 0.5
Friability (%)	0.1	0.3
Content uniformity (%)	95.0 ± 0.9	96.9 ± 1.0

All mixtures showed acceptable flow characteristics. Formulation A containing lactose required a higher compression force (12.9 kN) to obtain tablets with the required breaking force. Low tablet ejection values were seen for both formulations (A: 136.6 and B: 50.3N). Robust physical properties were attained for all matrix tablets and content uniformity values were within the USP limits (Table 2).

Figure 1. Drug Dissolution Profiles



Drug release profiles were compared using F2 metric test[5,6]. An F2 value between 50 and 100 indicates similarity between two dissolution profiles. The HyperStart formulation A was compared to the reference product and an F2 value of 70 was obtained indicating similarity. Formulations A and B were compared to assess the effect of filler type on the release profiles; an F2 result of 83.5 indicates that changing the filler type did not affect drug release behaviour from these matrices.

The release profiles were analysed using the power law model to determine drug release mechanism[7].

$$Mt/Minf = ktn$$

An n value of 0.5 indicates diffusion and a value of 1.0 indicates erosion control. Values of 1.014, 0.834 and 0.771 were obtained for Natrilix SR, formulations A and B, respectively. These values indicated that erosion was the primary mechanism of drug release from all these formulations.

Conclusions

Extended release matrices containing the low dose, practically insoluble drug, indapamide were successfully manufactured by direct compression. Tablets with good physical characteristics, weight and content uniformities, reproducible and desired drug release profiles were successfully produced in both formulations A and B. The choice of filler did not significantly affect the drug release profile in this study.

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