EXCIPIENTS' INFLUENCE ON THE RATE AND EXTENT OF DISSOLUTION OF POORLY SOLUBLE DRUGS.

Nuguru, K.[1], Giambattisto, D.[1] and Al-Ghazawi, A.[2]
[1] EM Industries Inc., 7 Skyline Drive, Hawthorne, NY-10532
[2] Merck Ltd., Poole, Dorset, BH15 1TD, UK

PURPOSE

To evaluate the influence of the excipient type on the dissolution of poorly soluble drugs.

INTRODUCTION

Soluble excipients are known to improve the dissolution of poorly soluble drugs (1).
In our study, we set out to evaluate a spray-dried, DC-grade mannitol against other excipients (soluble and insoluble) for its ability to achieve better dissolution profiles for poorly soluble actives.
Spray-dried Mannitol was selected because of its chemical stability and inertness as well as its overall tabletting properties (2).
A direct compression method is preferred over a wet granulation because of the way in which the active is presented to the dissolution medium (3).
For this study, actives such as Ibuprofen, Phenytoin and Calcium carbonate were chosen as the model drugs due to their poor solubility in water (4).

MATERIALS & METHODS

Raw materials:
SDM: Parteck™ M200, Spray-dried Mannitol (Merck KGaA, Darmstadt, Germany)
GRM: Mannogem™ Granular, Granulated Mannitol (SPI Polyols Inc., New Castle, DE)
MCC: Emcocel® 90M, Microcrystalline cellulose (Penwest Pharmaceuticals Co., Patterson, NY)
Ibuprofen (Albermarle Corp., Baton Rouge, LA)
Phenytoin (Spectrum Quality products Inc., New Brunswick, NJ)
Calcium carbonate (Merck KGaA, Darmstadt, Germany)
Magnesium stearate (Merck KGaA, Darmstadt, Germany)
Instruments:
P.K.® Twin Shell dry blender® (Patterson Kelley Co., East Stroudsburg, PA)
Kilian LX 28 A Tablet Press (Kilian & Co. Inc., Horsham, PA)
AIM-TPM (Metropolitan Computing Corp., East Hanover, NJ)
VanKel Hardness Tester (VanKel Industries Inc., Cary, NC)
VanKel Dissolution Tester (VanKel Industries Inc., Cary, NC)
VanKel Disintegration Tester (VanKel Industries Inc., Cary, NC)
Solubility Data (4):
Ibuprofen: Relatively insoluble in water, readily soluble in organic solvents.
Phenytoin: Practically insoluble in water, 1 in 60 ml of alcohol, 1 in 30 ml of acetone, soluble in alkali hydroxides.
Calcium carbonate: Practically insoluble in water, soluble in dilute acids.
Formulas:
Ibuprofen tablets:

Ibuprofen	200 mg	(22.2%)
Excipient	691 mg	(76.8%)
Magnesium stearate	9 mg	(1%)

Phenytoin tablets:

Phenytoin	50 mg	(25%)
Excipient	148 mg	(74%)
Magnesium stearate	2 mg	(1%)

Calcium carbonate tablets:

Calcium carbonate	400 mg	(40%)
Excipient	590 mg	(59%)
Magnesium stearate	10 mg	(1%)

Procedure:
Active and 50% of the excipient were blended for 4 minutes.
Rest of the excipient was added and mixing was continued for an additional 4 minutes.
Magnesium stearate (pre-sieved) was then added and blended for 4 minutes.
Tabletting was performed using 9/16 " S.S. concave, bevel edged punches (Elizabeth Carbide of North Carolina Inc., Lexington, NC) .
Tablet press speed was set at 30 rpm.
Tablet properties such as hardness, dissolution etc. were determined.
Dissolution tests were performed as per USP monograph corresponding to the individual active.

RESULTS

Rate and extent of dissolution varied depending upon the type of active and excipient used (Figures-1, 2 & 3).
For calcium carbonate (Figure-1), the amount dissolved (in 30 minutes) was higher for SDM formulation (97.9% ± 4.6) than for MCC formulation (82.5% ± 3.5) and GRM (78.1% ± 1.3).
Rate of dissolution was also higher for SDM formulation (98.9% ± 5.2 in 10 minutes) than MCC (67.7% ± 4.6 in 10 minutes) and GRM (74.5% ± 1.0 in 10 minutes).
The dissolution of Ibuprofen (Figure-2) was comparable for all 3 materials.
The extent of Phenytoin (Figure-3) dissolved in 30 minutes was similar for MCC (85.2% ± 0.6) and SDM (91.0% ± 3.2) while GRM showed significantly lower results (5.6% ± 0.8 dissolved in 30 minutes). The rate of dissolution was different between the 3 materials (86.0% ± 1.0, 57.9% ± 1.2 and 1.8% ± 0.4 released in 10 minutes for MCC, SDM and GRM respectively).
Table-1 summarizes the key dissolution test parameters and dissolution data obtained for each of the active ingredients.
Disintegration times were also determined and are presented in Figure-4.

CONCLUSIONS

In this study, it was observed that the excipient type influences the rate & extent of dissolution of the active.
Inclusion of a soluble excipient in the formulation may aid in readily presenting/exposing the active to the dissolving medium and thus increase its rate and extent of dissolution.
Additionally, by virtue of its porous structure, SDM generally performed better than GRM in this aspect and exhibited comparable results to MCC.
In general, dissolution profiles followed the same pattern as the disintegration times.

EXCIPIENTS' INFLUENCE ON THE RATE AND EXTENT OF DISSOLUTION OF POORLY SOLUBLE DRUGS.

Nuguru, K.[1], Giambattisto, D.[1] and Al-Ghazawi, A.[2]
[1] EM Industries Inc., 7 Skyline Drive, Hawthorne, NY-10532
[2] Merck Ltd., Poole, Dorset, BH15 1TD, UK

REFERENCES

Handbook of Pharmaceutical Excipients, 3rd edition; Edited by Kibbe, A.H. American Pharmaceutical Association, Washington, D.C. and Pharmaceutical Press, London, UK, 2000.

Nuguru, K. et al., Suitability of DC-Mannitol as an excipient for direct compression of tablets (AAPS, 1999).

"Hands-on" post graduate course in tablet technology by the Dept. of Pharm. Sciences, Univ. of Tennessee; (October 1999).

The Merck Index, 11th edition, Edited by Susan Budavari, Merck & Co., Inc., Rahway, NJ-1989.

Table-1. Summary of key dissolution parameters & dissolution data for different actives evaluated.

Dissolution conditions for Calcium Carbonate: 900 ml of 0.1 N HCl (pH ~ 1.2); Apparatus-2 at 75 rpm			
n = 3	SDM	MCC	GRM
% Dissolved in 10 min.	98.9% ± 5.2	67.7% ± 4.6	74.5% ± 1.0
% dissolved in 30 min.	97.9% ± 4.6	82.5% ± 3.5	78.1% ± 1.3
Dissolution conditions for Ibuprofen: 900 ml of pH 7.2 phosphate buffer; Apparatus-2 at 50 rpm			
n = 3	SDM	MCC	GRM
% Dissolved in 10 min.	79.3% ± 4.0	84.3% ± 6.0	80.6% ± 2.7
% dissolved in 30 min.	83.7% ± 0.9	90.1% ± 2.0	81.0% ± 2.5
Dissolution conditions for Phenytoin: 900 ml of 0.05 M Tris buffer (pH ~ 9.0); Apparatus-2 at 100 rpm			
n = 3	SDM	MCC	GRM
% Dissolved in 10 min.	57.9% ± 1.2	86.0% ± 1.0	1.8% ± 0.4
% dissolved in 30 min.	91.0% ± 3.2	85.2% ± 0.6	5.6% ± 0.8

Figure-1. Dissolution profile of Calcium carbonate from different DC-formulations

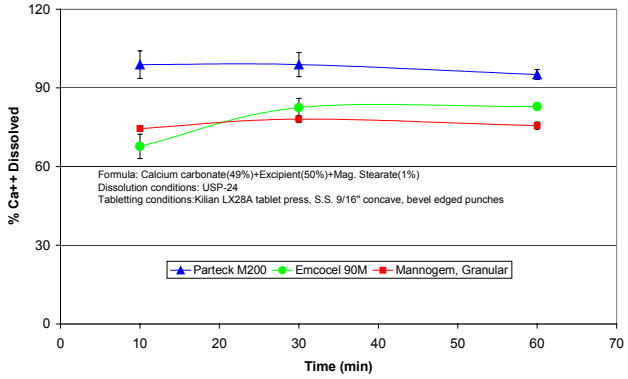

Figure-2. Dissolution profile of Ibuprofen from different DC-formulations

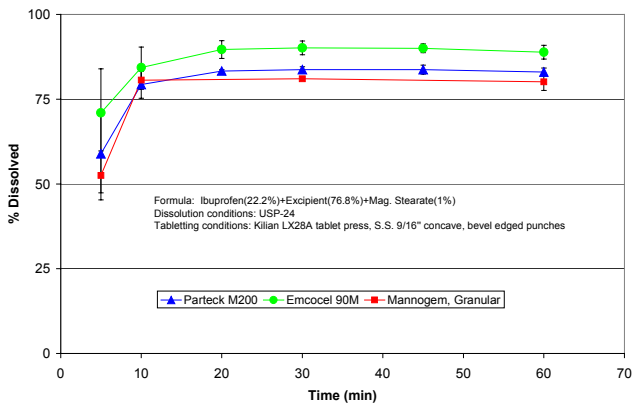

Figure-3. Dissolution profile of Phenytoin from different DC-formulations

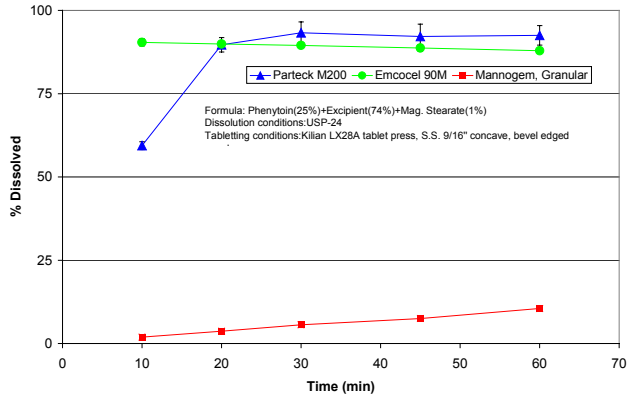

Figure-4. Disintegration Times for various DC-formulations containing different APIs