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Applications of EUDRAGIT® NM 30 D as a new Modified Release Polymer in Matrix Tablets

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INTRODUCTION

One of the most commonly used dosage forms for controlled drug release is matrix tablets [1]. They are easily manufactured by direct compression or compression of granules obtained by dry or wet granulation (high shear mixer or fluidized bed) or hot melt processes. Various hydrophilic and inert polymers can be used as matrix formers.
The objective of this study was to investigate the suitability of the new aqueous pH-independent poly-methacrylate dispersion EUDRAGIT® NM 30 D for the manufacturing of matrix tablets and to establish suitable formulations.

EXPERIMENTAL METHODS

Granulation trials were performed with fluid bed granulator, respectively high shear mixer. Theophylline was used as model for low soluble actives and Diltiazem was used as model for highly soluble drugs. Diltiazem was combined with the low soluble filler Emcompress® in order to be able to apply higher amounts of polymer in the high shear mixer granulation [2].

Materials

Diltiazem HCl (lot # DIL 808) was supplied by Lusochimica, Lomagna, Italy. Theophylline anhydrous 200M (lot # 11080) was supplied by BASF Ludwigshafen, Germany. Emcompress® (lot # E13K) was supplied by JRS Pharma, Rossenberg, Germany. EUDRAGIT® NM 30 D (lot # B 060462003) was supplied by Roehm, Darmstadt, Germany. Magnesium stearate (lot # K-300661063) was supplied by Merck, Darmstadt, Germany. Aerosil® 200 (lot # 4070813) was supplied by Degussa AG, Frankfurt, Germany.

	COMPONENTS	THEOPHYLLINE	DILTIAZEM
		%	%
Granule	Theophylline	82.4	-
	Diltiazem	-	29.0
	Emcompress®	-	53.9
	EUDRAGIT® NM 30 D [polymer]	16.6	16.6
Tablet	Mg - stearate	0.5	0.5
	Aerosil® 200	0.5	-
Total		100.0	100.0

Table 1: Formulation of the matrix tablets.

Granulation process

As EUDRAGIT® NM 30 D is an aqueous dispersion, the chosen manufacturing technology was wet granulation. Granulation trials were performed in a high shear mixer UMX-12 (A. Stephan u. Sohne, GmbH&Co., Hameln, Germany) as well as in a fluidized bed coater WSG-2 (Glatt AG, Binzen, Germany). Spraying dispersions for granulation in fluidized bed were prepared by diluting the commercial product EUDRAGIT® NM 30 D with water to 20% solids in order to ensure homogeneous distribution during granulation. For high shear mixer granulation the commercial product EUDRAGIT® NM 30 D was used directly. In all trials the amount of dry polymer used was 20% calculated on the drug respectively drug/filler amount.

Fluidized bed granulation

Granulations of Theophylline, respectively Diltiazem / Emcompress® in the fluidized bed coater were done in one step. The top spray nozzle diameter was 1.2 mm and the atomization air pressure was 2 bar. The dispersion was directly applied onto the powder. Drying was performed in the device until the exhaust air humidity was at the same level as before granulation.

High shear mixer granulation

High shear mixer granulation of Theophylline was done in one step. After passing through a 0.8 mm mesh size sieve the granules were dried for 24 hours at 40°C in a circulating air cabin. Due to the high solubility of Diltiazem and the chosen equipment which had no drying device, it was not possible to do the granulation in one step as otherwise over wetting would have happened. Approximately 260 g of polymer dispersion were added per step. The material was sieved and dried between each granulation step. The granules were finally passed through a 0.8 mm mesh size sieve and dried for 24 hours at 40°C in a circulating air cabin.

Tablets preparation and characterization

After drying, the Theophylline granules were mixed with Magnesium stearate and Aerosil® 200 in a double cone blender (ERWEKA GmbH, Heusenstamm, Germany) for 5 minutes. After granulation and drying, Diltiazem granules were mixed with Magnesium stearate in a double cone blender (ERWEKA GmbH, Heusenstamm, Germany) for 5 minutes. Bulk, tapped density and Hausner factor of the granules were tested using Pharma Test PT-TD1 (Pharmatest Apparatebau GmbH, Heinburg, Germany). Flow test, Flow through and Angle of repose were analyzed according to DIN 53916.
The compression was done on an instrumented eccentric press Korsch EK0 (Korsch, Berlin, Germany), with 11 mm punch diameter and 8.5 mm curvature radius. Compression forces of 5 to 25 kN were applied. Hardness, weight and diameter of tablets were analysed with Multicheck (ERWEKA GmbH, Heusenstamm, Germany) n = 10, PTF E Pharma Test (Apparatebau GmbH, Germany) was used for friability testing according to Ph.Eur. 5. A compression force of 15 kN was selected for dissolution test. The dissolution tests were performed according to USP 29, using Apparatus 2 (paddle) at 100 rpm in phosphate buffer pH 6.8, n = 6. Storage stability test were performed for tablets based on the fluidized bed granulation at 40°C / 75% r.h., 30°C / 65% r.h. and 25°C / 60% r.h in closed HPPE bottles.

RESULTS AND DISCUSSION

General properties of granules
Theophylline granules

Theophylline granules manufactured in fluidized bed, have a porous structure therefore bulk and tapped density are with an average of approximately 0.33 and 0.40 g/ml very low. However the Hausner factor is with approximately 1.2 still on a good level. Granules of Theophylline made in the high shear mixer had higher density and a Hausner factor of approximately 1.2 too. These flow properties indicate that the formulations are suitable to be processed on common tablet presses.

	THEOPHYLLINE		DILTIAZEM	
	FB	HSM	FB	HSM
Bulk density (g/mL)	0.33	0.53	0.65	0.69
Tapped density (g/mL)	0.40	0.63	0.76	0.80
Flow test (s/100mL)	n.m.	13.01	12.04	14.43
Angle of repose (°)	n.m.	35.1	32.3	36.2
Hausner factor	1.21	1.19	1.17	1.16

Table 2: Analytical characterization of the granules (average values). (n.m.=not measurable, FB=Fluidized bed, HSM=High shear mixer)

Diltiazem granules

Granules of Diltiazem resulting from both, the fluidized bed and high shear mixer show almost identical bulk and tapped density. A Hausner factor between 1.16 and 1.17 as well as overall good flow properties indicate that the formulations with the highly soluble active are suitable to be processed on common tablet presses.
In case of the high shear mixer granulation four times intermediate drying was done as otherwise the powder mixture would have become too wet.

In general the granules manufactured by fluid bed granulation showed lower tapped and bulk density. This is a common difference as fluid bed granules are fluffier with a higher porosity. In case of the lower soluble Theophylline the differences are higher and therefore do affect the flow test. In case of the low soluble Theophylline an advantage concerning flow properties was seen for the high shear mixer granulation. In case of the highly soluble Diltiazem an advantage concerning processability was seen for the fluidized bed granulation.

General properties of tablets

Table 4 shows that irrespective of the manufacturing process all Theophylline and Diltiazem formulations showed good compressibility with excellent hardness values of the manufactured tablets. Due to the higher porosity the fluidized bed granules resulted in tablets with higher hardness than the high shear mixer granules. In both cases increase of the compression force up to 25 kN leads to an increase of hardness. Thus an over pressing does not occur. The low deviations in weight, low friability and high hardness values indicate good compressibility.

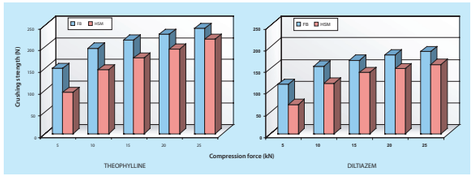

Figure 1: Crushing strength of Theophylline and Diltiazem matrix tablets. (FB=Fluidized bed, HSM=High shear mixer)

	THEOPHYLLINE		DILTIAZEM	
	FB	HSM	FB	HSM
Weight (mg)/rel SD (%)	402.6/ 0.71	409.8/ 0.41	491.6/ 0.43	518.0/ 0.62
Density (g/mL)	2.27	2.29	2.67	2.53
Hardness (N)/Rel SD (%)	216.0/ 2.3	175.0/ 6.4	169.3/ 16.7	141.0/ 3.0
Friability (%)	0.35	0.42	0.04	0.21

Table 3: Analytical characterization matrix tablets (average values) compression force 15kN. (FB=Fluidized bed, HSM=High shear mixer)

Dissolution test
Theophylline tablets

The release profile of Theophylline tablets made from high shear mixing granules show a slightly faster release compared to the fluidized bed granulation. Strong sustained release profiles with 30 - 40% drug release after 8 h were achieved irrespective of the manufacturing process in both cases.

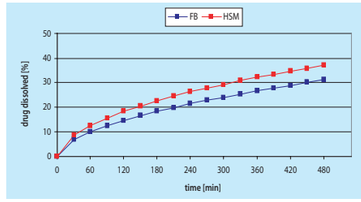

Figure 2: Release profiles of Theophylline matrix tablets, compression force 15kN. (FB=Fluidized bed, HSM=High shear mixer)

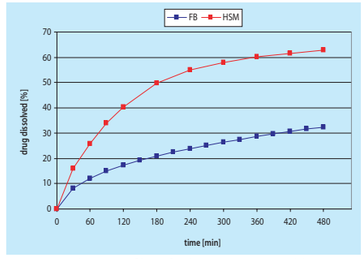

Figure 3: Release profiles of Diltiazem matrix tablets, compression force 15kN. (FB=Fluidized bed, HSM=High shear mixer)

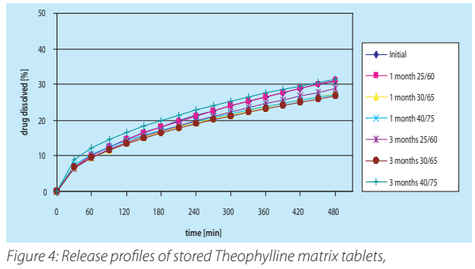

Figure 4: Release profiles of stored Theophylline matrix tablets, [Fluidized bed granules]

Diltiazem tablets

The release profile of Diltiazem tablets made of high shear mixing granules release the drug much faster compared to fluidized bed granulation, where strong sustained release profiles were achieved. This difference is caused by the solubility of the drug.

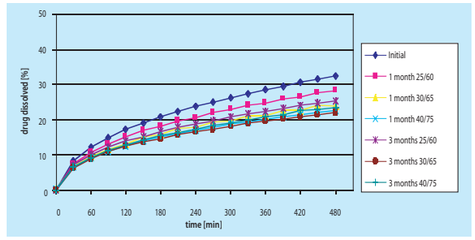

Figure 5: Release profiles of stored Diltiazem matrix tablets, [Fluidized bed granules]

Because of the longer process time and the better mixing the fluidized bed granulation in general lead to a better distribution of the polymer. This causes stronger sustained release properties, especially in case of highly soluble drugs like Diltiazem where the better distribution obviously results in a stronger effect [3].

EUDRAGIT® NM 30 D based matrix tablets of Theophylline as well as Diltiazem show good storage stability over 3 month. After a short phase of polymer relaxation which appears at 1 month testing the final release profile is reached and stable even under accelerated ICH conditions [4].

CONCLUSION

The new aqueous dispersion EUDRAGIT® NM 30 D is a very effective matrix former for low soluble drugs like Theophylline as well as for highly soluble drugs like Diltiazem. The achieved flow properties of the granules, the low deviations in weight as well as the high mechanical stability of the tablets indicate overall good processability. The resulting matrix tablets showed excellent retardation characteristics. For low soluble drugs high shear mixer granulation can be preferred because of the shorter process time. For high soluble drugs the equipment of choice should be the fluidized bed system. A high shear mixer without drying device is unfavorable as intermediate drying becomes necessary in order to avoid over wetting of the powder mixture. High shear mixers with drying devices improve processing of high water amounts. The amounts of EUDRAGIT® NM 30 D polymer which are sufficient to achieve a suitable release profile in a matrix formulation are below 20%, no matter whether a highly or low soluble drug is used. Matrix formulations with EUDRAGIT® NM 30 D show overall good stability during storage.

REFERENCES

1. Lehmann, K. (1996) Chemistry and Application Properties of Polymethacrylate Coating Systems in McGinity, J. (1996) Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. Marcel Dekker, Inc. 270 Madison Avenue, New York, 101-174.
2. Bauer, K.H., Lehmann, K., Osterwald, H.P., Rothgang, G. Coated Pharmaceutical Dosage Forms. (1998). Medpharm GmbH Scientific Publishers, Birkenwaldstr. 44, D-70191, Stuttgart
3. Gao, J., Jain, A., Motheran, R., Gray, D.B., Hussain, M.A. Fluid Bed Granulation of a Poorly Water Soluble, Low Density, Micronized Drug: Comparison with High Shear Mixer Granulation. International Journal of Pharmaceutics, 237, 2002; 1-14.
4. Rafiee-Tehrani M, Jafari-Azar Z (1998) Formulation of Theophylline Controlled Release Tablets: in Vitro/in Vivo and Stability Studies. Acta Pharmaceutica (Zagreb) 1998; 155-166.