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E. S. D.

Referencia: Expediente No. 07-116.475
Solicitud de Patente de Invención titulada: "formulaciones de un inhibidor de SRC/ABL"

Solicitante: Bristol-Myers Squibb Company

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 223 DEL 17 DE JUNIO DE 2011, OFICIO NO. 09788 (EXAMEN DE FORMA)

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término legal:

Solicitud de suministro de información (artículo 46)

En atención a lo expresado en el auto 09788 del 17 de junio de 2011 me permito presentar los documentos solicitados según la siguiente relación:

1. International Journal of Pharmaceutics, Volume 31, Issues 1-2, July 1986, page 175-177 .
2. International Journal of pharmaceutics, Volume 31, Issues 1-2, July 1986, page 55-64.

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3. Niazi, Sarfarez K "Appendix: Coating Solution, Pharmaceutical Manufacturing Formulations: Compressed Solid Product, Volume 1 (2004), pp. 267-279

4. Li et al., "The role of intra – and extragranular microcrystalline cellulose in tablet dissolution", Pharmaceutical Development and Technology, 1(4): 1996, pp 343-355

5. Bohuis et al,; "Improvement of dissolution of poorly soluble drugs by solid deposition on a super disintegrant. II. The choice of superdesintegrants and effect of granulation" European Journal of Pharmaceutical Sciences, 5 (1997), pp 63-69.

En virtud de lo anterior, solicito que se acepten las razones expuestas en el presente documento y en consecuencia, se otorgue el privilegio de patente de invención para el invento que se tramita en este expediente.

Atentamente,

ÁLVARO CORREA ORDOÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281
anexo. copia de los 5 documentos mencionados.

International Journal of Pharmaceutics, 31 (1986) 175–177
Elsevier

IJP 01034

The solubility parameters of some cellulose derivatives and polyethylene glycols used in tablet film coating

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(Received January 16th, 1986)
(Accepted February 3rd, 1986)

Key words: solubility parameter – cellulose derivatives – polyethylene glycols

Summary

The solubility parameters of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate and the polyethylene glycols of molecular weight 200–6000 $g \cdot mol^{-1}$ have been calculated using group molar attraction constants. The calculated values are, with the exception of those calculated using the group molar attraction constants given by Small (1953), in close agreement with those observed experimentally.

A knowledge of the compatibility characteristics and solubility of polymers and plasticizers used in film coating is important in the optimization of both the film formulation and the processing conditions (Rowe, 1984). In this respect polymer scientists have tended to use the solubility parameter approach based on the regular solution theory of Hildebrand and Scott (1950) who defined the solubility parameter (δ) of a substance as the square-root of its cohesive energy density or energy of vaporization per unit volume. Although it is relatively easy to directly measure the solubility parameter of volatile substances, the method is not applicable to non-volatile polymers. Solubility parameters for these materials can only be determined indirectly by studying polymer–solvent interactions which are assumed to be a maximum when the solubility parameter of the polymer is equal to the solubility parameter of the solvent. These methods, which usually involve viscosity or polymer swelling measurements, can be laborious and time consuming and a more rapid approach is sometimes necessary. In this respect, it is possible to calculate the solubility parameter of a polymer from its molecular structure from the summation of the group molar attraction constants (F) present in the molecule using the formula:

$$\delta = \frac{\Sigma F}{V}$$

where V is the molar volume of the polymer (Small, 1953).

This approach has been applied in this work to both the cellulose derivatives and polyethylene glycols used in tablet film coating.

The film formers studied were ethyl cellulose and hydroxypropyl cellulose (EC and HPC; Hercules Powder Co., Wilmington, DE, U.S.A.); hy-

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droxypropyl methylcellulose and hydroxypropyl methylcellulose phthalate (HPMC and HPMCP; Shin-Etsu, Chemical Co., Tokyo, Japan) and cellulose acetate phthalate (CAP; Eastman Chemical Products, Kingsport, TN, U.S.A.). The polyethylene glycols (PEG) with nominal molecular weights of 200, 400 600, 1000, 4000 and 6000 $g \cdot mol^{-1}$ were obtained from BDH Chemicals, Poole, U.K. Densities of the cellulose derivatives were determined using helium pycnometry (model 930, Beckman Instruments, Glenrothes, Fife, Scotland). The number average molecular weights of the polyethylene glycols were determined using gel permeation chromatography with tetrahydrofuran as carrier solvent. The solubility parameters for the cellulose derivatives were calculated by dividing the sum of the group molar attraction constants for one representative structural unit by the molar mass of that unit and multiplying by the polymer density. Those for the polyethylene glycols were calculated from the entire molecule. The group molar attraction constants were obtained from tables given by Small (1953), Hoy (1970) and van Krevelen and Hoftyzer (1976).

The results together with experimental data from the literature are given in Table 1. It can be seen that, for the cellulose derivatives for which experimental data are available, there is good agreement between the solubility parameter calculated using the group molar attraction constants given by Hoy (1970) and van Krevelen and Hoftyzer (1976) and that determined experimentally. However, the solubility parameters calculated using the group molar attraction constants given by Small (1953) are much smaller. This discrepancy is due, in the main, to the somewhat arbitrary molar attraction constant assigned by Small to the hydroxyl group present in relatively

TABLE 1

CALCULATED SOLUBILITY PARAMETERS TOGETHER WITH LITERATURE EXPERIMENTAL DATA FOR THE CELLULOSE DERIVATIVES AND POLYETHYLENE GLYCOLS (DATA AT 25°C UNLESS STATED)

	Solubility Parameter ($MPa^{\frac{1}{2}}$)			
	Small	Hoy	van Krevelen	Literature
EC	16.1	19.0	20.6	19.4–19.7 (Kent and Rowe, 1978) 21.1 (Burrell, 1975)
HPMC	16.1	21.5	24.4	20.7–25.6 (Aulton et al., 1985)
HPC	17.0	21.1	24.9	21.7–23.6 (Roberts and Thomas, 1978)
HPMCP	17.2	22.4	26.4	–
CAP	21.7	24.1	27.2	–
PEG 200	19.1	20.2	26.1	23.7 (Vaughan, 1985)
PEG 400	18.4	20.2	23.1	18.0 [a] (Takamiya et al., 1959) 23.2 (Vaughan, 1985)
PEG 600	18.0	19.7	22.5	20.5 [b] (Kawakami et al., 1976)
PEG 1000	19.1	21.5	23.4	20.1 [b] (Kawakami et al., 1976)
PEG 4000	18.9	21.1	22.5	19.4 [b] (Kawakami et al., 1976) 23.7 (Otozai and Tohyama, 1976) 22.1–24.6 [c] (Burrell, 1975)
PEG 6000	18.8	21.2	22.4	23.7 (Otozai and Tohyama, 1976)

[a] Measured at 100°C.
[b] Measured at 67.3°C.
[c] Mid range values for poorly, moderate and strongly hydrogen bonding solvents.

large numbers in all the polymers (348 $MPa^{\frac{1}{2}} \cdot cm^3 \cdot mol^{-1}$ the sum of 205 for the hydrogen and 143 for the ether oxygen) compared to those constants determined by Hoy (462 $MPa^{\frac{1}{2}} \cdot cm^3 \cdot mol^{-1}$) and van Krevelen and Hoftyzer (754 $MPa^{\frac{1}{2}} \cdot cm^3 \cdot mol^{-1}$). Tables comparing the constants determined by all these workers are given in Barton (1983). The high values for the solubility parameters calculated for cellulose acetate phthalate are consistent with those observed for the closely related cellulose acetate polymer (27.1–27.8 $MPa^{\frac{1}{2}}$ — Burrell, 1975).

A similar explanation to the one given above can be used for the differences between the solubility parameters calculated for the polyethylene glycols but here the discrepancy is not so marked since there are only two hydroxyl groups per molecule. The effect of these hydroxyl groups on the solubility parameter will decrease with increasing molecular weight, hence the slight decrease in the calculated solubility parameters with increasing molecular weight consistent with that observed in practice (Kawakami et al., 1976; Otozai and Tohyama, 1976; Vaughan, 1985). The distinct break in the trend occurring between PEG 600 and PEG 1000 is due to the simple fact that the former is a liquid and the latter is a solid and that different density values were used in the calculations — 1.12 $g \cdot cm^{-3}$ for the liquid polyethylene glycols and 1.20 $g \cdot cm^{-3}$ for the solid polyethylene glycols. The effect of variable density is the reason for the relatively low values of the solubility parameter determined by Takamiya et al. (1959) and Kawakami et al. (1976) since both groups of workers made measurements in excess of the melting points of the solid polyethylene glycols. If the calculated solubility parameters are corrected for the changes in density at these temperatures (1.09 $g \cdot cm^{-3}$ at 67.3°C and 1.06 $g \cdot cm^{-3}$ at 100°C) then the agreement between the calculated and observed values is much better.

In conclusion it can been seen that the use of group molar attraction constants, especially those given by both Hoy (1970) and van Krevelen and Hoftyzer (1976) provides a rapid and realistic value for the solubility parameters of both the cellulose derivatives and polyethylene glycols used in tablet film coating.

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International Journal of Pharmaceutics, 31 (1986) 55–64
Elsevier

IJP 01026

An evaluation of the interaction and plasticizing efficiency of the polyethylene glycols in ethyl cellulose and hydroxypropyl methylcellulose films using the torsional braid pendulum

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(Received October 21st, 1985)
(Modified version received January 19th, 1986)
(Accepted January 23rd, 1986)

Key words: polyethylene glycols – ethyl cellulose – hydroxypropyl methylcellulose – plasticizing efficiency – torsional braid pendulum

Summary

The plasticizing efficiency of the polyethylene glycols when added to both ethyl cellulose and hydroxypropyl methylcellulose films has been evaluated by measuring the glass transition temperatures of formulations using the torsional braid pendulum. Compared to hydroxypropyl methylcellulose, where there was a significant reduction in the glass transition temperature with increasing concentration for all the polyethylene glycols, the effect in the case of ethyl cellulose was relatively small. In both cases the plasticizing efficiency of the polyethylene glycols decreased with increasing molecular weight with the high molecular weight solid members exhibiting phase separation. The experimental data was compared with predicted values using simple models based on the additivity of free volume. Agreement was limited to the systems where the plasticizer and polymer were compatible and no phase separation occurred.

Introduction

Film formers such as the cellulose ethers, ethyl cellulose and hydroxypropyl methylcellulose are now used extensively in the film coating of solid dosage forms. One commonly used method of modifying the properties of these polymers and enhancing their film-forming properties is by the addition of plasticizers. Plasticizers may be defined as low molecular weight substances, ideally of low volatility, which increase the flexibility of the macromolecules hence producing films which are softer, more pliable and often tougher with a subsequent improvement in their resistance to mechanical stress. The most commonly used plasticizers in tablet film coatings include the phthalate esters, polyethylene glycols of molecular weight 200–6000 $g \cdot mole^{-1}$, propylene glycol, glycerol and castor oil in concentrations varying from 5% to 30% by weight of the polymer (Rowe, 1984). Several methods have been suggested for evaluating the efficiency of a plasticizer with respect to the tablet coating requirements including intrinsic viscosity measurements (Entwistle and Rowe, 1979), mechanical strength testing (Entwistle and Rowe, 1979; Porter, 1980; Aulton et al., 1981), incidence of stress-induced defects (Rowe and Forse, 1981) and glass transition measurements (Entwistle and Rowe, 1979; Porter and

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Ridgway, 1983; Rowe et al., 1984; Okamafe and York, 1985; Sakellariou et al., 1985) or softening temperature (Masilungan and Lordi, 1984).

In the present work a dynamic mechanical technique, torsional braid analysis (TBA), recently applied in the determination of the thermomechanical properties and glass transition temperatures of the cellulose derivatives (Sakellariou et al., 1985) has been used to study the plasticization of both ethyl cellulose and hydroxypropyl methylcellulose by a series of polyethylene glycols with molecular weights from 200 to 6000 $g \cdot mole^{-1}$. The application of several free volume models and equations for the prediction of the properties of the plasticized film formers has also been investigated and discussed with respect to the deviations from the free volume theory.

Materials and Methods

The film formers studied were ethyl cellulose (EC — Grade N50, Hercules Powder Co., Wilmington, DE, U.S.A.) and hydroxypropyl methylcellulose (HPMC — Pharmacoat 606, Shin-Etsu Chemical Co., Tokyo, Japan). The plasticizers were a series of polyethylene glycols (PEG, BDH Chemicals, Poole, U.K.) with nominal molecular weights 200, 400, 600, 1000 and 6000 $g \cdot mole^{-1}$. Molecular characterization of the polyethylene glycols using both gel permeation chromatography with tetrahydrofuran as the carrier solvent and vapour pressure osmometry suggested that the materials, as supplied, were effectively monodispersed. All materials were used as received.

The apparatus used to provide the thermomechanical spectra of the systems studied has been fully described elsewhere (Rowe et al., 1984; Sakellariou, 1984; Sakellariou et al., 1985). The glass braids used in this study were prepared by first removing the size by heating in an oven at 500°C for 1 h followed by immersion in a 10 or 15% w/v solution of the formulation dissolved in solvent mixture consisting of equal parts by volume of dichloromethane and methanol. Braids containing the equivalent of 5, 10, 15, 20, 30 and 40% polyethylene glycol (concentration expressed as a weight percentage of the polymer) were dried to constant weight in an oven at 40–70°C. The thermomechanical spectra produced were analyzed as described previously (Sakellariou et al., 1985). The transition width was assessed from the damping/temperature curves where $W_{R\sqrt{2}}$ is the ratio of the area under the logarithmic decrement peak at half power height divided by the peak height.

Results and Discussion

Plasticization of the ethyl cellulose

Incorporation of the polyethylene glycols into ethyl cellulose films brought about considerable changes in the thermomechanical behaviour of the polymer. A typical example of the effect of polyethylene glycol 200 on ethyl cellulose is shown in Fig. 1a and b, while the relevant data of all the systems studied are listed in Table 1. In all cases there is one main transition recorded at a temperature close to the glass transition temperature of the pure polymer. Since this transition moved to slightly lower temperatures with increasing polyethylene glycol concentrations it was assigned to the plasticized polymer. In all the systems studied, with the exception of the unplasticized polymer, there was a broad plateau occurring at temperatures varying between 50 and 80°C. Although the damping level of this plateau increased with increasing polyethylene glycol concentration, no relationship could be established between either the shape or maximum damping and the grade of the polyethylene glycol. Osterwald et al. (1982) reported a similar behaviour for polyethylene glycol 6000 dispersed in hydroxypropyl methylcellulose phthalate interpreting it as an extended melting peak. However, it must be stated, that although the solidification point for the 6000 grade lies within this temperature region, those of the lower molecular weight grades occur at much lower temperatures. Since the plateau is present for all the grades of the polyethylene glycols it can be postulated that this may be due to domains of molten or rubber-like polyethylene glycol dispersed within the polymer matrix. Incorporation of the 6000 grade tended to produce a relatively narrow transition unaffected by concentration whereas the

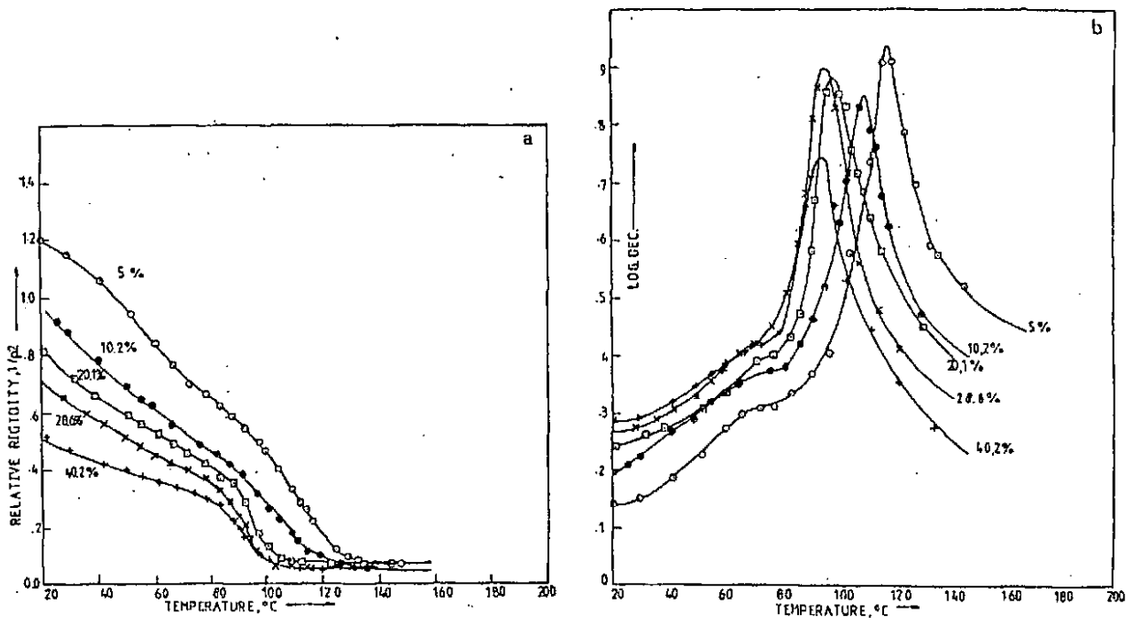

Fig. 1. The thermomechanical spectra of ethyl cellulose plasticized with polyethylene glycol 200. (a) relative regidity; (b) logarithmic decrement.

TABLE 1

THERMOMECHANICAL DATA FOR THE POLYETHYLENE GLYCOL/ETHYL CELLULOSE SYSTEMS

PEG grade	Concentration (% w/w)	T_g (°C)	$\Delta_{20°C}$	Δ_{max}	$W_{R\sqrt{1}}$ (°C)
200	5.0	118	0.145	0.940	8.4
200	10.2	110	0.200	0.855	7.8
200	20.1	99	0.245	0.880	9.4
200	28.6	96	0.260	0.895	6.8
200	40.2	95.5	0.275	0.745	10.5
400	5.6	124	0.110	0.835	8.8
400	9.5	118	0.135	0.845	7.2
400	15.0	113	0.205	0.725	8.3
400	19.0	111	0.165	0.715	7.7
600	5.0	125	0.105	0.900	4.5
600	10.0	120	0.175	0.805	4.1
600	14.7	117	0.215	0.810	7.1
600	19.7	116	0.215	0.815	8.6
1000	5.1	127	0.100	0.930	4.9
1000	10.1	127	0.135	0.900	8.2
1000	15.3	127	0.135	0.905	10.2
1000	20.2	127	0.145	0.985	12.3
6000	4.99	129	0.120	1.045	3.5
6000	9.98	129	0.120	1.005	3.5
6000	15.0	129	0.120	0.010	3.7
6000	19.0	123	0.200	1.005	3.5

lower molecular weight grades exhibited wider transitions which tended to broaden further with increasing concentration. The maximum logarithmic decrement decreased with increasing polyethylene glycol concentration for all grades of the plasticizer although the extent of the depression was considerably less with the higher molecular weight grades.

The variation of the glass transition of the ethyl cellulose with both molecular weight and concentration (Table 1) best describes the plasticizing efficiency of the polyethylene glycols. It can be seen that the efficiency of these materials in lowering the glass transition temperature of the ethyl cellulose decreases with increasing molecular size with the two higher members of the series hardly causing any appreciable change. This effect is probably due not only to molecular size, which would affect the diffusion of the molecules into the ethyl cellulose matrix, but also the effective molar concentration of the hydroxyl groups on the polyethylene glycol molecule since this would certainly decrease dramatically on increasing the molecular weight of the plasticizer.

Plasticization of hydroxypropyl methylcellulose

Typical examples of the thermomechanical behaviour of hydroxypropyl methylcellulose plasticized with polyethylene glycol 200 and 6000 are shown in Figs. 2a, b and 3a, b, while the relevant data for all the systems studied are given in Table 2. A relatively broad transition was recorded in both the logarithmic decrement and relative rigidity curves. Since the position of the maximum logarithmic decrement was shifted to lower temperatures with increasing polyethylene glycol concentration this was assigned to the plasticized polymer. A number of samples exhibited a shoulder before the glass transition temperature at approximately 40°C and extending to approximately 80°C analogous to the plateau region seen on the ethyl cellulose systems. Although the level of the maximum damping of this shoulder was proportional to the polyethylene glycol concentra-

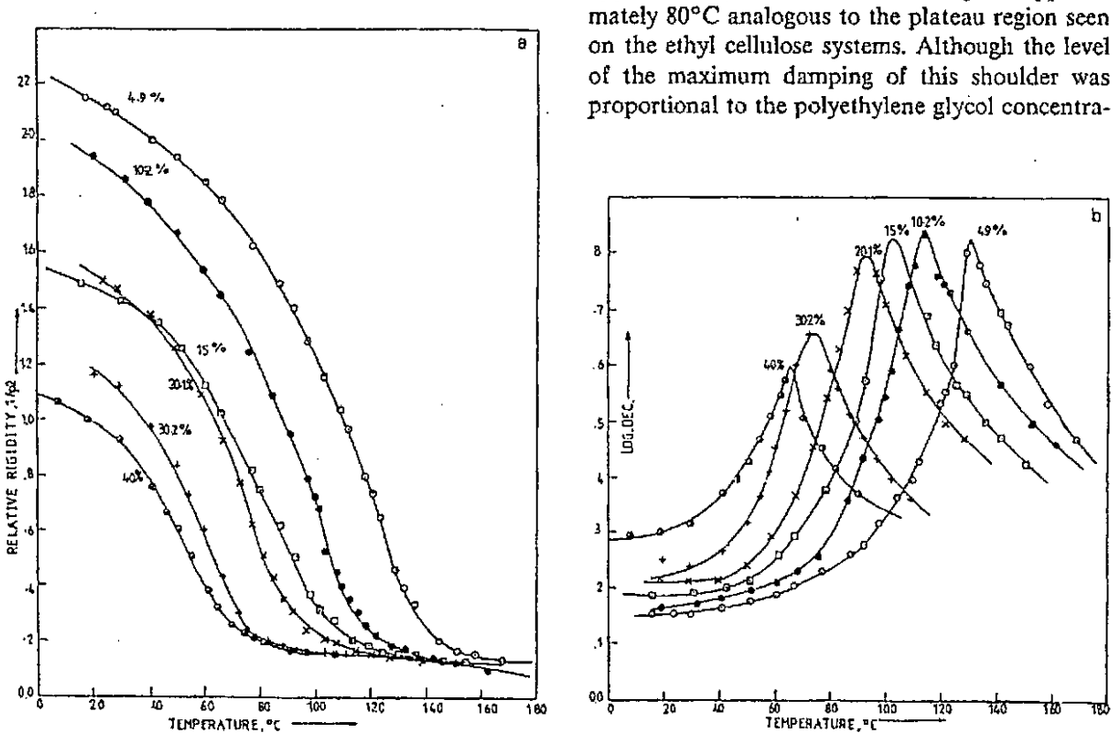

Fig. 2. The thermomechanical spectra of hydroxypropyl methylcellulose plasticized with polyethylene glycol 200. (a) relative rigidity; (b) logarithmic decrement.

TABLE 2

THERMOMECHANICAL DATA FOR THE POLYETHYLENE GLYCOL/HYDROXYPROPYL METHYLCELLULOSE SYSTEMS

PEG grade	Concentration (% w/w)	T_g (°C)	$\Delta_{20°C}$	Δ_{max}	$W_{R\sqrt{2}}$ (°C)
200	3.7	136.5	0.115	0.760	6.5
200	4.9	130.5	0.150	0.830	8.3
200	7.5	121	0.135	0.740	6.2
200	10.2	114	0.160	0.645	7.7
200	12.6	108.5	0.160	0.690	7.6
200	15.0	103	0.190	0.830	11.8
200	20.1	93	0.215	0.795	14.6
200	30.2	74.5	0.230	0.660	15.1
200	40.0	66	0.290	0.600	16.1
400	4.8	136.5	0.115	0.825	9.4
400	10.0	119	0.120	0.665	14.0
400	13.0	111	0.140	0.645	9.5
400	20.0	99	0.170	0.590	13.8
400	28.0	90.5	0.190	0.616	16.3
400	39.0	83	0.240	0.560	21.7
600	4.9	138	0.100	0.695	12.1
600	11.7	119	0.135	0.617	10.4
600	15.0	115	0.175	0.670	19.1
600	19.8	104.5	0.175	0.537	20.0
600	29.3	96	0.150	0.575	14.5
600	39.6	86	0.180	0.590	26.4
1000	5.0	139	0.09	0.710	13.9
1000	8.8	131	0.125	0.660	14.0
1000	14.6	122	0.145	0.630	16.8
1000	19.0	115	0.150	0.685	21.6
1000	36.2	105.5	0.215	0.460	25.1
6000	5.0	155	0.100	0.830	10.1
6000	10.3	154	0.160	0.766	10.1
6000	14.5	153	0.120	0.805	9.8
6000	20.3	152	0.130	0.740	15.8

tion, there was no relationship with molecular size. The level of the maximum logarithmic decrement decreased with increasing polyethylene glycol concentration indicating an appreciable interaction between the polymer and the plasticizer. Polyethylene glycol 6000 showed a depressed tendency for such an effect indicating a poorer interaction. Although there was scatter in the determination of the peak width, it did tend to increase with plasticizer concentration for all but the polyethylene glycol 6000. From both the logarithmic decrement and relative rigidity curves, it was possible to investigate the compatibility limits for phase separation of the plasticizer in the film (Table 3). This suggests that there is a definite relationship between the molecular weight of the polyethylene glycol and its interaction with the polymer. The limits are similar to those reported by Okamafe and York (1985) and were confirmed by producing films and observing them for any signs of blushing indicating migration of the plasticizer.

The variation of glass transition temperature with increasing plasticizer concentration (Table 2) shows that the plasticizing efficiency of polyethylene glycol decreases with increasing molecular weight with polyethylene glycol 6000 being virtu-

TABLE 3

COMPATIBILITY LIMITS FOR THE POLYETHYLENE GLYCOL/HYDROXYPROPYL METHYLCELLULOSE SYSTEM

PEG grade	Compatibility limit (% w/v)
200	40
400	28
600	28
1000	15
6000	10

ally a non-plasticizer for the polymer. These observations are in good agreement with both intrinsic viscosity data which showed a maximum viscosity for hydroxypropyl methylcellulose dissolved in polyethylene glycol 200 (Entwistle and Rowe, 1979) and with data on the mechanical properties of hydroxypropyl methylcellulose films plasticized with polyethylene glycols of varying molecular weight (Aulton et al., 1981).

Theoretical considerations

It is interesting to compare the experimental data with those predicted using equations relying on the additivity of the free volume of both the polymer and the diluent/plasticizer. The first equation chosen was that of Garfield and Petrie (1964) which relates the plasticizing efficiency parameter, β, of a plasticizer at a reference temperature, T, to the glass transition temperatures and thermal expansion coefficients of the polymer and plasticizer, i.e. T_{gp}, T_{gd}, α_p, α_d, respectively:

$$\text{i.e. } \beta(T) = \alpha_p(T - T_{gp}) - \alpha_d(T - T_{gd}) \qquad (1)$$

The second equation chosen was that of Kelley

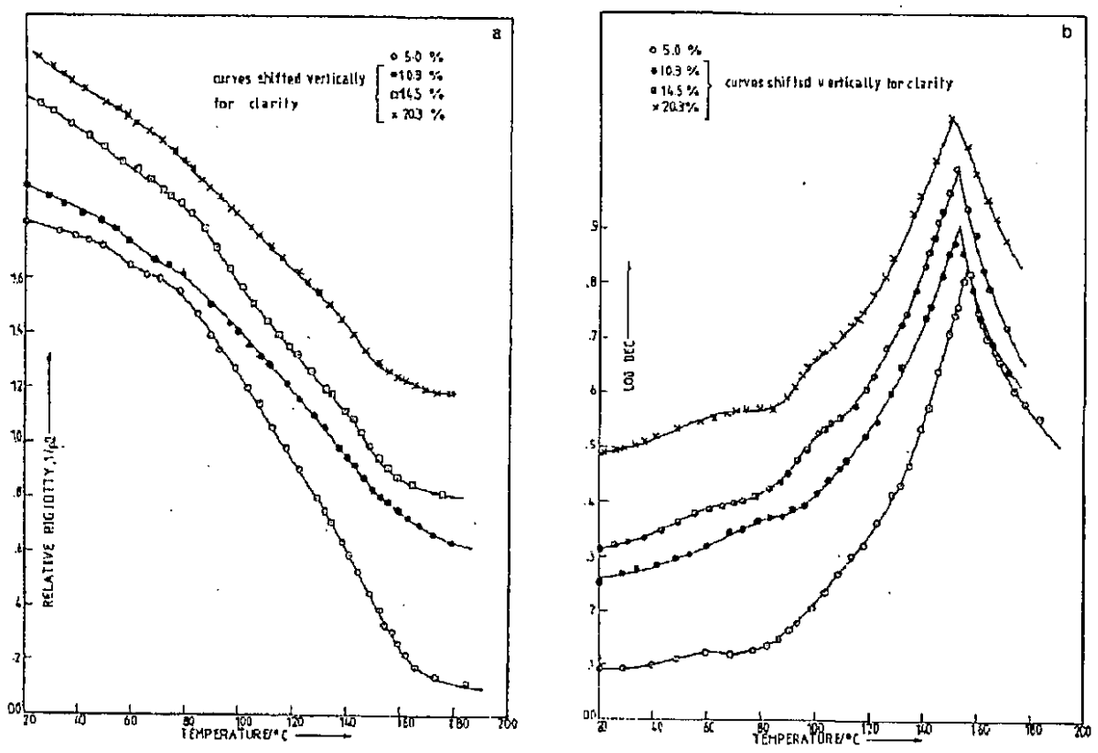

Fig. 3. The thermomechanical spectra of hydroxypropyl methylcellulose plasticized with polyethylene glycol 6000. (a) relative rigity; (b) logarithmic decrement.

and Bueche (1961) which relates the predicted glass transition temperature of the plasticized polymer, T_g, with the volume fractions of the polymer and plasticizer, V_p, and V_d respectively:

$$T_g = \frac{\alpha_p \cdot V_p \cdot T_{gp} + \alpha_d \cdot V_d \cdot T_{gd}}{\alpha_p \cdot V_p + \alpha_d \cdot V_d} \quad (2)$$

Table 5 shows values for β (using constants for the equation as given in Table 4) at two reference temperatures, firstly at the glass transition temperature of the polymer and secondly at 40°C to facilitate comparison with data produced by Fujita and Kishimoto (1958). It can be seen that the β parameters for the ethyl cellulose system are generally lower than those for the hydroxypropyl methylcellulose, decreasing with increasing polyethylene glycol molecular weight for both systems. It is interesting to note that the maximum β parameter for the ethyl cellulose system is similar to that for the hydroxypropyl methylcellulose system containing polyethylene glycol 6000 (cf. the experimental data which shows phase separation and poor interaction in these systems). Although the calculated values for the β parameter are of the expected order (0.05–0.30; Fujita and Kishimoto, 1958) they do not provide any information on the validity of the assumptions made in the derivation of the equation.

Application of the Kelley and Bueche (1961) equation does provide information of the validity of the approach by comparing predicted glass transition temperatures with experimental data. It can be seen (Fig. 4) that for hydroxypropyl methylcellulose the predicted values compare favourably with the experimental data for all plasticizer concentrations up to 15% for all the grades of polyethylene glycol studied with the exception of PEC 1000 where the concentration was reduced to 10% and of PEG 6000 where there was poor agreement at all concentrations. For ethylcellulose (Fig. 5), with the exception of the PEG 200 at concentrations below 10%, there was poor agreement in all cases. It is interesting to note that in every case where there is poor agreement the experimental curves always deviate toward higher temperatures. These observations added to the fact that poor agreement was invariably seen in systems where there were signs of phase separation would suggest the assumptions in the equation are invalid.

Further information on this point can be obtained by involving the theory of Braun and Kovacs (1965) who proposed that the introduction of an interaction constant, k, to account for the non-additivity of the free volumes of the components. From their theory it is possible to derive a modified Kelley and Bueche equation.
i.e.

$$T_g = \left[\frac{\alpha_p \cdot V_p \cdot T_{gd} + \alpha_d \cdot V_d \cdot T_{gd}}{\alpha_p \cdot V_p + \alpha_d \cdot V_d} \right]$$

TABLE 4

CONSTANTS USED IN THE PREDICTIVE EQUATIONS

	T_{gp} [a] (°C)	α_p [b] (°C^{-1})	T_{gd} (°C)	α_d [c] (°C^{-1})
Ethyl cellulose	131.5	4.8×10^{-4}		
Hydroxypropyl methylcellulose	153.5	4.8×10^{-4}		
PEG 200			−77	7.3×10^{-4}
PEG 400			−70	7.3×10^{-4}
PEG 600			−67	7.3×10^{-4}
PEG 1000			−65	7.3×10^{-4}
PEG 6000			−56	7.3×10^{-4}

[a] Sakellariou et al. (1985).
[b] Williams et al. (1955).
[c] Trade Literature, Hoechst Polyglycol Manual (1977).

TABLE 5

PLASTICIZING EFFICIENCY (β) PARAMETERS AT A — THE GLASS TRANSITION TEMPERATURE OF THE POLYMER AND AT B — 40°C

PEG grade	A		B	
	PEG/ HPMC	PEG/ EC	PEG/ HPMC	PEG/ EC
200	0.168	0.152	0.240	0.168
400	0.163	0.147	0.173	0.163
600	0.160	0.144	0.169	0.159
1000	0.156	0.139	0.166	0.155
6000	0.153	0.137	0.163	0.152

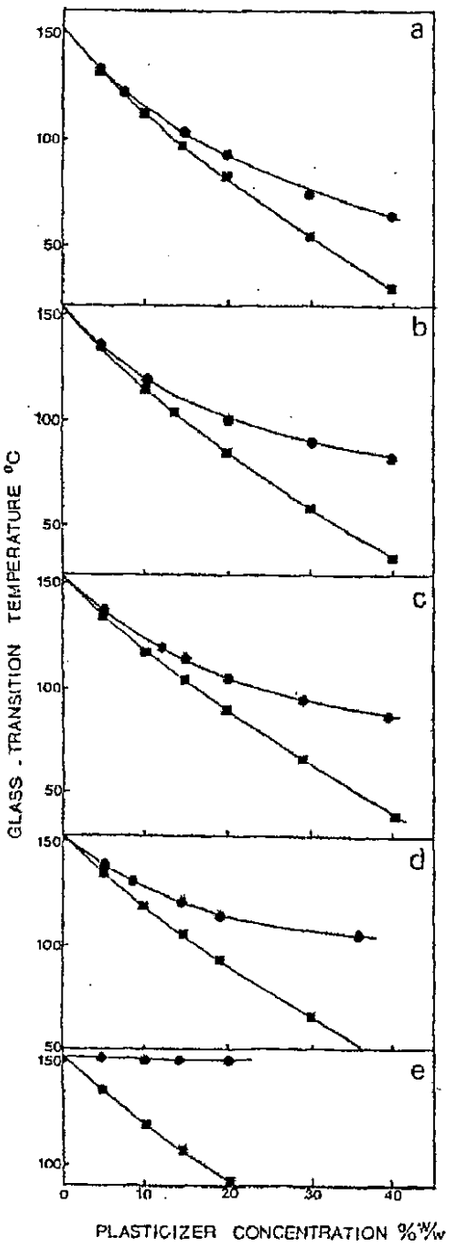

Fig. 4. The effect of concentration and grade of polyethylene glycol on the glass transition temperature of hydroxypropyl methylcellulose. (a) PEG 200; (b) PEG 400; (c) PEG 600; (d) PEG 1000; (e) PEG 6000. ●, experimental values; ■, calculated values.

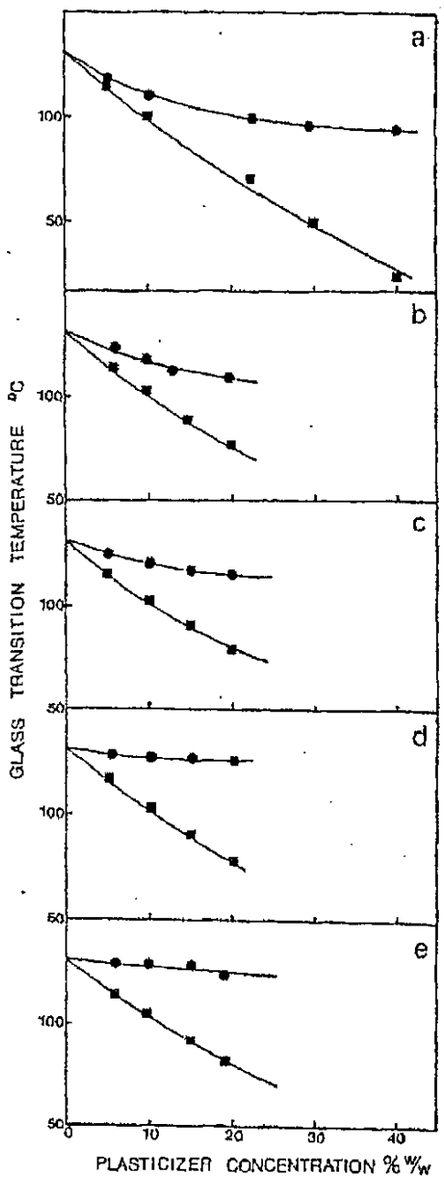

Fig. 5. The effect of concentration and grade of polyethylene glycol on the glass transition temperature of ethyl cellulose. (a) PEG 200; (b) PEG 400; (c) PEG 600; (d) PEG 1000; (e) PEG 6000. ●, experimental values; ■, calculated values.

TABLE 6

INTERACTION CONSTANTS (k) AND CORRELATION COEFFICIENTS CALCULATED FOR EQN. 3

PEG grade	PEG/HPMC		PEG/EC	
	k	Correlation coefficient	k	Correlation coefficient
200	0.1980	0.9413	0.1165	0.9036
400	0.1417	0.9517	0.1448	0.8927
600	0.1453	0.9899	0.1260	0.8725
1000	0.2070	0.9916	0.1699	0.9401
6000	0.1535	0.9924	0.1953	0.9970

$$+k\left[\frac{V_p \cdot V_d}{\alpha_p \cdot V_p + \alpha_d \cdot V_d}\right] \qquad (3)$$

According to the model proposed by Braun and Kovacs (1965), the deviation of the theoretical from the experimental data will vary linearly with the quantity $V_p \cdot V_d/\alpha_p \cdot V_p + \alpha_d \cdot V_d$ and the slope of the graph will be of the order of 10^{-2}. Table 6 summarizes the so calculated k values for both the polymers studied and it can be seen than k exceeds the expected value by a factor of 10. This implies that the non-additivity of the free volumes in the mixture is only partially responsible for the deviations in the predicted and experimental data, and that other factors are involved. Okamafe and York (1985) have suggested that the broad molecular weight distribution of the cellulose ethers might be responsible but, although such a factor would affect the recorded value of the T_g, it is unlikely that it depresses the plasticizing efficiency of the polyethylene glycols with increasing concentration. The depressed plasticizing efficiency of the polyethylene glycols above their compatibility limits must be due to their phase separation and their aggregation into small domains dispersed in the polymer matrix. Consequently the actual amount of the plasticizer dispersed at a molecular level is less than the nominal. These phase separated domains will have a specific effect on the mechanical behaviour of the films so prepared but will have little effect on their glass transition temperature.

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HANDBOOK OF Pharmaceutical Manufacturing Formulations

Compressed Solid Products

VOLUME 1

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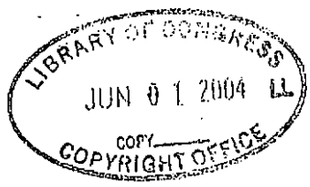
CRC PRESS

Boca Raton London New York Washington, D.C.



Library of Congress Cataloging-in-Publication Data

Niazi, Sarfaraz, 1949–
Handbook of pharmaceutical manufacturing formulations: compressed solid products / Sarfaraz K. Niazi.
p. cm.
Includes bibliographical references and index.
Contents: — v.1. Compressed solids.
ISBN 0-8493-1746-0 (alk. paper)
1. Drugs—Dosage forms—Handbooks, manuals, etc. I. Title

RS200.N53 2004
615'19—dc21

2003051451

International Standard Book Number 0-8493-1746-0
Library of Congress Card Number 2003051451
Printed in the United States of America 1 2 3 4 5 6 7 8 9 0
Printed on acid-free paper

Appendix Coating Solutions

I. INTRODUCTION

Solid dosage forms are frequently coated for varied purposes, including the following:

- Mask taste and smell
- Protect from environment
- Provide protection from gastric acid — enteric coating
- Make easy to swallow
- Provide identification
- Give aesthetic appeal
- Hide surface defects

Many types of coatings are available. Sugar coating used to be a choice coating method years ago. This was mostly replaced with film coatings, as new polymers with better film-forming properties and equipment for applying these coatings became available. Several proprietary coating formulations are also available, such as Eudragit® (http://www.roehm.com/en/rohmamerica.html), Colorcon® (http://www.roehm.com/en/rohmamerica.html), or Aquacoat® by Asahi Kasei. The advantages of using these prepacked formulations are: consistency in color matching and other considerations based on their ease of use. The basic components of a film-coating system are:

- Polymer
- Solvent
- Plasticizer
- Other ingredients
  - Antitack agent
  - Antifoam agent
  - Colorant
  - Filler/extender
  - Flavor
  - Surfactant

The following polymeric materials form the basis of the most currently available coating formulations:

- Cellulose-based
  - Cellulose acetate phthalate (CAP)
  - Hydroxypropylmethylcellulose (HPMC)
  - Hydroxypropylcellulose (HPC)
  - Hydroxypropylethylcellulose
  - Ethylcellulose
  - Methylcellulose
  - Microcrystalline cellulose and carageenan
- Methacrylic acid/methacrylate esters
  - Anionic and cationic polymers of methacrylic acid
  - Copolymers of methacrylates
  - Copolymers of acrylate and methacrylates
  - Copolymers of ethacrylate and methylmethacrylate
- Polyvinylacetatephthalate
- Shellac
- Polyvinylpyrrolidone

The choice of a coating formulation depends, to a great degree, on the purpose of the coating. For example, certain coatings from a clear coat to a multilayered coating will protect highly sensitive vitamins from oxidative degradation.

In this book, the author described several prototype formulations that can be readily adapted for the formulations provided here. The most significant aspect remains the choice of colors, which often determines the method of manufacturing the coating solutions. With a limited choice of dyes and lakes available for selection, manufacturers often use a combination of several colors and dyes, along with agents such as talc for opaqueness, to obtain the desired colors and protection levels.

Another choice often confronted by the manufacturer is whether to use an aqueous coating or an organic coating system. Both have advantages and disadvantages. Whereas organic coating provides greater protection against moisture uptake during the coating process (important for moisture-sensitive ingredients) and are easier to apply because of the fast evaporation of solvents, the problems related to environmental control of organic solvents going in the atmosphere, the need to perform solvent residue tests, and the need to have explosion-proof facilities often yields to these advantages of aqueous coating systems. In recent years, many developments in the formulation of aqueous coatings made them an almost universally accepted mode of application.

II. HYDROXYPROPYL METHYLCELLULOSE (METHOCEL, HPMC) AQUEOUS COATINGS

Methocel-based coatings in an aqueous base are the most popular coating options. Two methods of making solutions are possible. If a lake is used, then alcohol is also included (see, for example, Holberry Red).

A. Brite Rose

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/l
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
0.25	4	Dye Red D&C No. 30 Lake	2.50
2.00	5	Titanium dioxide, special coating grade	20.00
QS	6	Water, purified, QS to	1 l

MANUFACTURING DIRECTIONS

Charge 250 ml of water into a suitable container, and heat to 60 to 70°C. With gentle stirring, disperse the hydroxypropyl methylcellulose onto the hot water. When the cellulose has wetted, quickly add 250 ml of cold water. Stir until the dispersion is homogenous, although the solution of cellulose may not be complete. Dissolve polyethylene glycol 8000 in 50 ml of water, and then add to the step above. Add polyethylene glycol 400 to the basic solution above. Load a suitable sized ball jar with Dye Red No. 30 Lake and titanium dioxide. Add a sufficient amount of water to cover the pigment and balls. Mill overnight or for 12 h. Other pigment reduction methods may be used to yield a particle size not above 1 μm. Add milled pigments to the base solution from the step above, and make up the volume with cold water. Use within 7 days.

B. Cherry Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/l
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
1.80	4	Dye Red FD&C No. 3 Lake	18.00
0.10	5	Dye Red FD&C No. 2 Amaranth	1.00
2.10	6	Titanium dioxide, special coating grade	21.00
QS	7	Water, purified,, (deionized) QS to	1 l

C. Geranium Rose

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/l
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
0.24	4	Dye Red FD&C No. 3 Lake	2.00
QS	5	Water, purified	1 l

D. Gloss

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/l
3.33	1	Hydroxypropyl methylcellulose 2910 15 cps	33.33
1.66	2	Polyethylene glycol 400	16.66
QS	3	Water, purified, QS to	1 l

E. Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/l
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
2.50	4	Dye Red FD&C No. 3 Lake	25.00
0.50	5	Titanium dioxide	5.00
QS	6	Water, purified, QS to	1 l

F. Moderate Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/l
6.00	1	Hydroxypropyl methylcellulose 2910 15 cps	60.00
2.00	2	Polyethylene glycol 400	20.00
2.00	3	Polyethylene glycol 8000	20.00
0.50	4	Dye Yellow FD&C No. 3 Aluminum Lake	5.00
2.50	5	Dye Red Ponceau 4R Lake	25.00
1.00	6	Titanium dioxide, special coating grade	10.00
QS	7	Water, purified, QS to	1 l

Pharmaceutical Development and Technology, 1(4), 343-355 (1996)

RESEARCH ARTICLE

The Role of Intra- and Extragranular Microcrystalline Cellulose in Tablet Dissolution

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Received November 29, 1995; Accepted August 5, 1996

ABSTRACT

The objective of this study was to examine the influence of intra- and extragranular microcrystalline cellulose (MCC) on drug dissolution from tablets made by high-shear granulation. Granulations were made in a Littleford Model W-10-B (10-liter) mixer and dried in a fluid bed dryer (Niro Inc.). A Plackett–Burman screening design and 2^3 factorial design were employed to study how drug type, MCC (intra- or extra-), filler type (lactose or dicalcium phosphate), disintegrant type (sodium starch glycolate or croscarmellose sodium) and level, proportion of magnesium stearate, and impeller speed affect tablet hardness, disintegration time, and dissolution. Two model drugs were chosen based on their solubility: metoprolol tartrate (solubility > 1000 mg/ml) and hydrochlorothiazide (solubility = 1.05 mg/ml). Tablets were compressed to the same target weight (dose) and similar tablet hardness. In some cases, dissolution testing was also carried out on the loose granules. The intra–extragranular distribution of MCC was found critical to the compactibility and initial dissolution rates from these tablets. Intragranular MCC reduced drug dissolution, the effect being most marked in the case of the slightly soluble hydrochlorothiazide. For formulations containing intragranular MCC, the granulating fluid level on tablet dissolution was also important, since an increase in fluid level resulted in slower drug dissolution from both the loose granules and the tablets compressed from them. Conversely, extragranular MCC tended to increase both dissolution rates and compactibility. It may be concluded that the appropriate distribution of MCC between and within granules may optimize both dissolution and compactibility without changing overall tablet composition.

KEY WORDS: Experimental design; Extragranular; High-shear granulation; Hydrochlorothiazide; Intragranular; Metoprolol; Microcrystalline cellulose.

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INTRODUCTION

Microcrystalline cellulose (MCC) is one of the most significant tablet excipients introduced in modern times. It functions as an excellent dry binder–filler in direct compression tablets as well as a disintegrating agent in concentrations greater than 20% (1). MCC is also widely used in wet granulations, where it helps prevent overrunning granulation end points (2). This property of MCC is extremely useful in a high-shear granulation process where end points are reached quickly. However, the properties of MCC which make it such an excellent filler also reduce its compactibility after wet granulation. In practice, it is preferable to incorporate one-half into the wet mass and the remainder into the final blend. This procedure will provide both the flexibility of granulation end point control resulting from intragranular MCC and the excellent binding and compactibility produced by dry blending of MCC after granulation.

Although the applications of MCC in direct compression and granulation have been extensively documented in the literature (3,4), its disintegrating behavior and its effect on tablet dissolution when incorporated into a wet granulation have received little attention. Unvala et al. (5) compared the dissolution of drugs from wet-granulated (planetary mixer) and directly compressed tablets containing a 5% level of either theophylline, hydrochlorothiazide, or chlorpheniramine maleate in MCC. They observed greater compactibility of the direct-compression formulations; however, there was little difference between the two methods of tableting on the drug dissolution rate. Chowhan and Amaro (6) studied the effect of the level of intragranular MCC and the volume of granulating water on the dissolution of a water-soluble drug from tablets made by high-shear granulation. They found that the rate of dissolution was inversely proportional to the level of intragranular MCC and the percent of granulating fluid. In a recent study of the high-shear granulation process for metoprolol tablets containing 20% MCC, Rekhi et al. (7,8) evaluated the influence of the granulation mode of MCC on tablet dissolution. They found that intragranular MCC slowed down drug dissolution for tablets made by high-shear granulation. Furthermore, the dissolution rate also decreased when a higher impeller speed was used.

The foregoing studies suggest that in addition to loss of compactibility, the disintegration power of MCC also may be diminished after high-shear wet granulation, thereby resulting in retarded tablet disintegration and dissolution. Given the widespread use of high-shear granulators, and of MCC as an adjunct in modern wet-granulation formulations, there is a need for a clearer understanding of this phenomenon and of how it may be influenced by drug solubility as well as various formulation and process variables. To that end, an experimental design approach was implemented to examine the influence of intra- and extragranular MCC and other variables on the dissolution of drugs representing a broad range in solubility.

EXPERIMENTAL

Materials

Two model drugs were used in this investigation: metoprolol tartrate (METOP) USP (Assia Chemical Industries Ltd., Israel) and hydrochlorothiazide (HCTZ) USP (Merck & Co. Inc., West Point, PA). Metoprolol tartrate is classified as a very soluble drug (1000 mg/ml) and HCTZ as a slighdly soluble drug (1 mg/ml) (8).

The excipients used in tablet formulations for both drugs included: microcrystalline cellulose NF (Avicel PH102®, FMC Corp., Philadelphia, PA); lactose monohydrate NF (Fast Flo®, Foremost Co., Baraboo, WI); dicalcium phosphate, anhydrous USP (Di-Tab®, Rhone Poulenc Basic Chemicals Co., Shelton, CT); povidone USP (Plasdone® K29/32, ISP Technologies, Wayne, NJ); sodium starch glycolate NF (Explotab®, Edward Mendell Co. Inc., Patterson, NY); croscarmellose sodium NF (Ac-Di-Sol®, FMC Corp. Philadelphia, PA); colloidal silicon dioxide NF (Cab-O-Sil®, Eastech Chemical Inc. Philadelphia, PA); magnesium stearate NF (Mallinckrodt Inc., St. Louis, MO).

Experimental Design

A typical tablet formulation in this study is shown in Table 1. For the sake of comparison, each formulation contained the same strength for either drug. To determine the influence of the formulation and process variables on drug dissolution and to identify the relative importance of the estimated effects and any possible two-factor interactions, two screening experimental designs were selected using Statgraphics Plus 7® (Manugistics Inc., Rockville, MD).

Plackett–Burman Design

A Placket–Burman design (Resolution III) was selected with 7 formulation and process variables and a to-

Table 1

Typical Tablet Formulation

Ingredients	Content	
	Percent	Milligrams/Tablet
Drug (METOP or HCTZ)	30.3	50
Filler (Lactose or Dicalcium Phosphate)	q.s. 100	
Microcrystalline cellulose	20	33
Povidone K29/32	3	5
Disintegrant (sodium starch glycolate or croscarmellose sodium)	2/8	3.3/13.2
Magnesium stearate	0.5/1	0.8/1.6
Colloidal silicon dioxide	0.5	0.8
Tablet weight		165

tal of 12 experiments (Tables 2 and 3). Lactose was considered as a slack factor varying from 33% to 44% in order to make up the difference between the tablet weight resulting from the prescribed ingredient levels and 165 mg. It was assumed that any changes in the responses were due to the changes in the level of the variables studied rather than the results of the consequential changes in the proportion of lactose. The measured responses included tablet disintegration time, percent drug dissolved in 10 and 30 min (Q_{10} and Q_{30}), and compression force used to target the same tablet hardness.

Table 2

Factor Levels for Plackett–Burman Design

Factor	Low	High
Drug (type)	METOP	HCTZ
MCC (% intra)	0	100
Filler (type)	Lactose	Dical
Disintegrant (type)	Sod. St. Gly.[a]	Cros. sod[b]
Disintegrant (level)	2%	8%
Impeller speed (rpm)	400	800
Magnesium stearate (%)	0.5%	1%

[a]Sodium starch glycolate.
[b]Croscarmellose sodium.

Table 3

Plackett–Burman Design

Run No.	Drug Type	Filler Type	MCC (% Intra)	Disintegrant[a]		Impeller Speed (rpm)	Magnesium Stearate (%)
				Type	%		
1	HCTZ	DiCal	0	Cros. sod.	2	400	0.5
2	HCTZ	DiCal	100	Sod. st. gly.	8	800	0.5
3	METOP	DiCal	100	Cros. sod.	2	800	1.0
4	METOP	DiCal	0	Sod. st. gly.	2	800	1.0
5	HCTZ	Lactose	0	Sod. st. gly.	8	800	1.0
6	METOP	Lactose	0	Cros. sod.	8	800	0.5
7	HCTZ	DiCal	0	Cros. sod.	8	400	1.0
8	METOP	DiCal	100	Sod. st. gly.	8	400	0.5
9	METOP	Lactose	0	Sod. st. gly.	2	400	0.5
10	HCTZ	Lactose	100	Sod. st. gly.	2	400	1.0
11	HCTZ	Lactose	100	Cros. sod.	2	800	0.5
12	METOP	Lactose	100	Cros. sod.	8	400	1.0

[a]Cros. sod., croscarmellose sodium; Sod. st. gly., sodium starch glycolate.

2^3 Factorial Design

Based on the results from the Plackett-Burman design, three of the factors—drug type, granulation mode of MCC, and filler type—were chosen for further study. A 2^3 factorial design (Resolution V) with eight experiments (Table 4) was conducted in order to identify any possible two-factor interactions. Sodium starch glycolate was used as a disintegrant. Other ingredients and variables were fixed at the low levels.

Effect of Granulation Fluid Level

The proportion of granulation fluid used for each run in the experimental designs varied depending on the formulation. It was assumed that the effect of granulation fluid level for each run is the same and negligible compared to the effect of other variables in the study. However, the effect of granulating fluid level on the drug dissolution rate for tablets containing intragranular MCC was evaluated. Selected batches (runs 2′ and 5′ of the factorial design) with only drug-type differences were chosen and granulated with different amounts of water. The percentage of water varied from 7% to 13% for run 2′ (METOP) and from 20% to 30% for run 5′ (HCTZ).

Manufacturing Procedure

A premix of the drug, lactose/dicalcium phosphate, and MCC (if any) was deagglomerated using a Comil® 197S (Quadro Engineering Inc., Millburn, NJ). The premix, intragranular disintegrant (50%) and povidone were granulated (batch size 1 kg) with distilled water in a 10-liter high-shear mixer (Model W-10-B, Littleford Bros Inc., Florence, KY), and then dried in a fluid bed dryer (Strea-1®, Niro Inc. Columbia, MD) at 60°C to a loss on drying (LOD) of <2%. The dried granulations were screened through a #18-mesh screen using an Erweka® FGS oscillating granulator (Erweka Instrument Corp., Milford, CT). Extragranular MCC (if any), disintegrant, and colloidal silicon dioxide (#40 mesh) were blended with the granulations (about 500 g of final blend) in a 2-quart V-blender (Patterson-Kelley Co., East Stroudsburg, PA) for 10 min at 34 rpm. Magnesium stearate (#40 mesh) was added into the final blend and mixed for 3 min. The final blend was compressed into tablets using an instrumented Stokes® B2 press (Stokes–Merrill Inc., Bristol, PA) with 10/32-in. round flat tooling. The tablet hardness was approximately controlled in the range of 40–50 N by varying the compression force. Selected batches were compressed at a fixed compression force of 700 kg (± 10%).

Table 4

Worksheet for 2^3 Factorial Design

Run No.	Drug Type	MCC (% Intra)	Filler Type
1′	METOP	0	Dical
2′	METOP	100	Lactose
3′	HCTZ	100	Dical
4′	HCTZ	0	Lactose
5′	HCTZ	100	Lactose
6′	HCTZ	0	Dical
7′	METOP	100	Dical
8′	METOP	0	Lactose

Evaluation of Granulations and Tablets

Physical Testing

The loss on drying of the granulations was measured using a Computrac™ moisture analyzer (Model MAX-50, Arizona Instrument Corp., Tempe, AZ) with a heating temperature of 105°C. Sieve analysis was performed using an Allen-Bradley® sonic sifter (ATM Corp. Milwaukee, WI).

Tablet weight variation, thickness, and hardness were determined.

Disintegration Time

Disintegration testing was performed on each tablet batch as described in USP XXII using the Vanderkamp® disintegration apparatus (Model W-110, Van-Kel industries Inc., Edison, NJ). Purified water was used as disintegration medium.

Dissolution Testing

The USP XXII basket (Apparatus I) assembly using a rotation speed of 100 rpm was employed (10) with 900 ml 0.1 N hydrochloric acid solution (37 ± 1°C) as the dissolution media. Six tablets were tested from each batch. The drug concentration in the solution was measured by ultraviolet absorbance at a wavelength of 272 nm (for HCTZ) and 275 nm (for METOP) using a spectrophotometer with an automatic sample cell changer (Beckman® Model 35, Beckman Instruments Inc., Fullerton, CA). Three samples of granules (each contain-

ing an equivalent of 50 mg drug and taken from the fraction retained on #25 mesh) from selected batches also were tested.

RESULTS AND DISCUSSION

A statistical analysis of the responses was performed using Statgraphics software. The analysis provides estimates of how strongly each of the experimental factors affects the responses, such as tablet disintegration time and dissolution.

To graphically evaluate the data, standardized Pareto charts (11) were used to represent the relative significance of the effects after eliminating noise factors. A p value of 0.05 was considered as the criterion for statistical significance. Analysis of variance (ANOVA) was used as an alternative tool to justify the estimated regression model.

Plackett–Burman Design

The experimental data obtained from the Plackett–Burman design are summarized in Tables 5 and 6. The geometric mean diameters of granules were obtained based on log-normal probability plots (12). The tablet disintegration and dissolution data were analyzed statistically.

Figure 1, a standardized Pareto chart for tablet disintegration, indicates that the type of drug is the single most important and also the only significant factor affecting tablet disintegration. (Note: the vertical line represents the critical t value at the 0.05 significance level.) The negative value means that the tablet disintegration time is shorter when the drug in the system is changed from metoprolol to hydrochlorothiazide. Direct observation of tablet disintegration revealed that metoprolol tablets did not disintegrate but eroded instead. The HCTZ tablets, however, disintegrate into granules rapidly. It seems that the tablets with soluble ingredients disintegrate more slowly than those with insoluble ingredients. The rapid dissolution of the soluble ingredients offsets the effect of disintegrant swelling when immersed into water. Although various proportions of disintegrant and the two types of fillers with different solubilities are used in the system, the large solubility differences in drug type appear to play a major role in determinating the tablet disintegration time.

Figure 2 displays the relative importance of the factors affecting tablet dissolution Q_{10} and Q_{30}. The proportion of disintegrant is obviously the most significant variable affecting dissolution. The drug dissolution rate is increased when the percentage of disintegrant is increased from 2% to 8%. The increase in the level of intragranular MCC results in lower Q_{10} values. These results are in accordance with the findings of Chowhan and Amaro (6) and Rekhi et al. (7,8). The type of drug and proportion of magnesium stearate also affects Q_{30} significantly. As expected, the higher the aqueous solubility of the drug, the faster the tablet dissolution. Surprisingly, the dissolution rate is increased when the pro-

Table 5

Granulation Parameters from Plackett-Burman Design

Run No.	Granulating Fluid Level (%)	Granulation Yield (%)	LOD (%)	Geometric Mean Diameter (μm)
1	20	92	1.98	315
2	28	90	1.90	410
3	10	87	1.99	670
4	4	93	1.72	350
5	19	89	1.11	430
6	7	95	1.10	410
7	20	92	1.85	290
8	15	84	1.47	710
9	7	92	1.83	510
10	25	93	1.37	260
11	25	84	1.62	335
12	11	94	1.04	285

Table 6

Tablet Properties from Plackett–Burman Design

Run No.	Compression Force (kg)	Weight[a] (mg)	Thickness[a] (mm)	Hardness[a] (N)	Disintegration[a] (min)	Dissolution[a] Q_{10}	Dissolution[a] Q_{30}
1	600	166	2.20	44	1.74	61.2	65.7
		(1.0)	(0.02)	(2)	(0.26)	(2.25)	(2.76)
2	980	177	2.32	33	1.00	57.6	65.7
		(1.8)	(0.01)	(3)	(0.12)	(2.33)	(2.95)
3	860	177	2.35	55	22.33	39.7	96.4
		(2.6)	(0.02)	(2)	(1.03)	(1.94)	(3.20)
4	510	166	2.36	49	10.90	44.6	92.5
		(1.4)	(0.02)	(2)	(0.38)	(1.55)	(1.27)
5	650	167	2.55	42	3.29	86.9	96.6
		(1.9)	(0.02)	(3)	(0.36)	(1.35)	(0.51)
6	520	165	2.73	48	6.17	94.6	99.1
		(1.1)	(0.01)	(2)	(0.15)	(1.13)	(0.94)
7	690	175	2.31	42	1.18	86.7	93.7
		(1.7)	(0.01)	(2)	(0.10)	(1.20)	(0.77)
8	740	169	2.40	52	13.45	60.1	96.2
		(2.6)	(0.03)	(3)	(0.51)	(0.56)	(0.85)
9	380	167	2.77	45	7.24	81.5	85.2
		(1.8)	(0.01)	(4)	(0.38)	(3.16)	(0.94)
10	860	170	2.63	45	4.87	33.5	72.5
		(4.7)	(0.02)	(3)	(1.35)	(7.00)	(6.13)
11	900	171	2.54	43	4.84	38.8	62.9
		(1.1)	(0.02)	(2)	(0.37)	(1.03)	(1.93)
12	540	171	2.77	51	8.63	75.9	98.4
		(2.3)	(0.02)	(3)	(0.14)	(5.99)	(1.91)

[a]Standard deviations given in parentheses ($n = 6$ for dissolution; $n = 10$ for others).

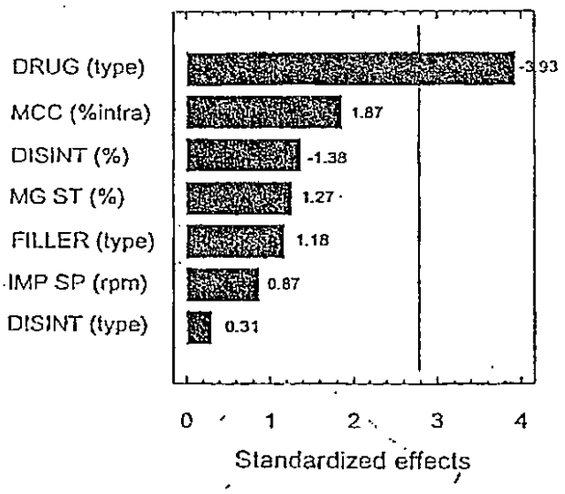

Figure 1. Standardized Pareto chart for tablet disintegration: Plackett–Burman design.

portion of magnesium stearate is increased from 0.5% to 1%. This result is in contradiction to the general rule of magnesium stearate as a hydrophobic lubricant. However, this effect may be due to magnesium stearate weakening the bonding between the granules so that the drug is released from tablets more rapidly (13). The type of filler and disintegrant, and impeller speed do not affect dissolution significantly.

Interaction Effect Between Drugs, MCC, and Fillers

The granulation and tablet properties from the 2^3 factorial design are summarized in Tables 7 and 8. Figures 3–5 show the main effects and two-factor interactions between drug type, the mode of incorporation of MCC, and filler type on tablet disintegration and dissolution. The major effects are similar to the ones from the Plackett–Burman design. The type of drug is the

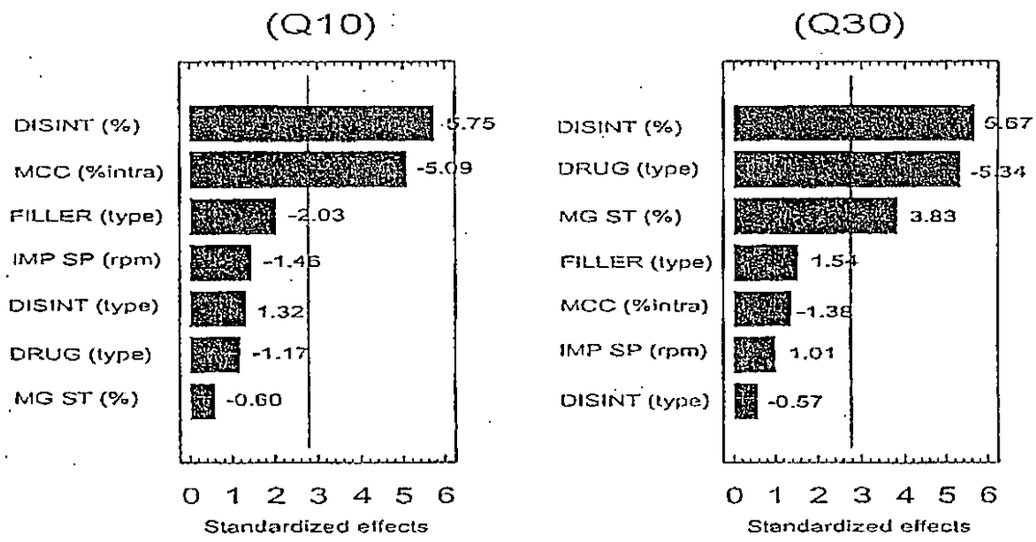

Figure 2. Standardized Pareto chart for percent drug release in 10 (Q_{10}) and 30 min (Q_{30}): Plackett–Burman design.

only significant factor affecting tablet disintegration (Fig. 3). However, the interaction between drug type and mode of MCC incorporation on tablet disintegration was nearly significant at $p < 0.05$. The interaction plot (Fig. 4) indicates that the disintegration time for METOP tablets increases dramatically when the proportion of MCC added intragranularly increases. However, the disintegration time for HCTZ tablets remains unaffected with either intra- or extragranular MCC. Q_{10} was not significantly affected by any variables studied although the method of incorporation of MCC was close to $p < 0.05$ (Fig. 5). By observation during the disintegration tests, we found that metoprolol tablets did not disintegrate but rather eroded. The tablet erosion was slower with the addition of intragranular MCC. On the other hand, HCTZ tablets disintegrated rapidly into granules for either intra- or extragranular MCC formulations. Only drug type affected Q_{30} significantly. The type of filler used had no significant effect on tablet dissolution for either drug.

Table 7

Granulation Parameters from 2^3 Factorial Design

Run No.	Granulating Fluid Level (%)	Granulation Yield (%)	LOD (%)	Geometric Mean Diameter (μm)
1′	6	92	2.0	410
2′	10	94	0.8	540
3′	30	93	1.52	350
4′	15	95	0.55	410
5′	25	93	1.37	260
6′	16	94	1.99	430
7′	8	94	1.79	350
8′	7	92	1.83	500

Table 8

Tablet Properties from 2^3 Factorial Design

Run No.	Compression Force (kg)	Weight[a] (mg)	Thickness[a] (mm)	Hardness[a] (N)	Disintegration[a] (min)	Dissolution[a] Q_{10}	Dissolution[a] Q_{30}
1′	510	172	2.48	49	10.53	40.5	97.9
		(1.9)	(0.01)	(2)	(0.57)	(1.98)	(3.25)
2′	700	166	2.64	50	18.80	43.9	96.5
		(2.2)	(0.02)	(3)	(0.51)	(3.10)	(3.72)
3′	890	169	2.22	40	0.82	42.8	61.5
		(1.3)	(0.02)	(2)	(0.09)	(1.60)	(3.09)
4′	540	168	2.65	42	1.44	74.4	78.4
		(2.3)	(0.01)	(3)	(0.26)	(2.00)	(1.65)
5′	600	167	2.67	37	0.64	44.6	61.8
		(1.8)	(0.01)	(3)	(0.08)	(3.04)	(3.01)
6′	600	166	2.24	40	1.58	70.9	76.5
		(1.6)	(0.01)	(2)	(0.27)	(1.57)	(1.95)
7′	490	167	2.36	47	15.43	37.6	88.6
		(2.0)	(0.02)	(3)	(0.46)	(1.51)	(0.98)
8′	380	167	2.77	45	6.57	86.3	90.4
		(1.8)	(0.01)	(4)	(0.18)	(7.19)	(3.73)

[a]Standard deviations given in parentheses (n = 6 for dissolution; n = 10 for others).

Effect of Intra- and Extragranular MCC on Granule and Tablet Dissolution

As indicated earlier, intragranular MCC prolongs tablet disintegration time for the very soluble drug METOP, but shows little effect on the slightly soluble drug HCTZ. The initial tablet dissolution rate (Q_{10}), on the other hand, decreases significantly when the granulation mode of MCC is changed from extra to intra. Figure 6 displays the dissolution profile for metoprolol granules and tablets containing either extra- or intragranular MCC (runs 4′ and 5′) and similarly for HCTZ

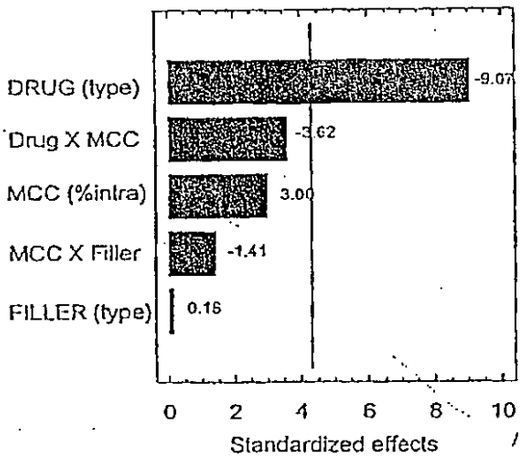

Figure 3. Standardized Pareto chart for tablet disintegration: 2^3 factorial design.

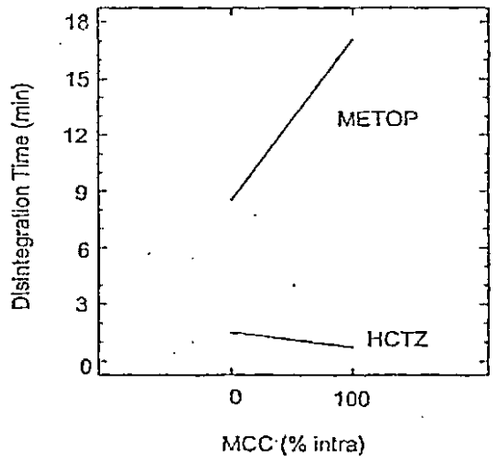

Figure 4. Interaction plot for tablet disintegration: 2^3 factorial design.

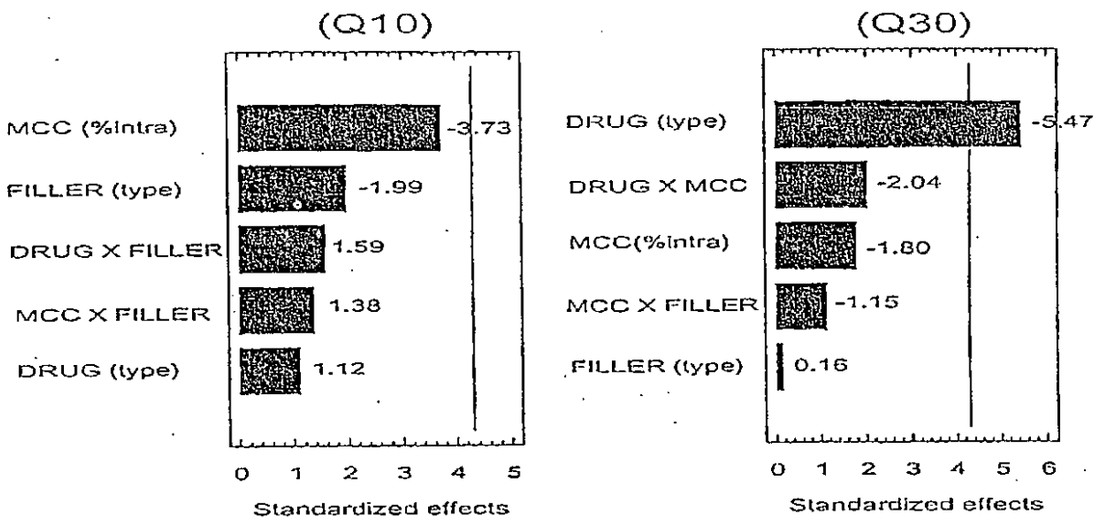

Figure 5. Standardized Pareto chart for percent drug release in 10 (Q_{10}) and 30 min (Q_{30}): 2^3 factorial design.

granules and tablets (runs 2′ and 8′). With metoprolol, the granule dissolution rates are the same with and without intragranular MCC. However, there is large difference in tablet dissolution at 10 min, but little difference at 30 min. Obviously the fast initial tablet dissolution for metoprolol is attributed to the fast tablet disintegration, which is promoted by extragranular MCC. With HCTZ, the granule dissolution is much faster without the intragranular MCC, and similarly for tablet dissolution through the entire 30 min. In addition, the disintegrating action of extragranular MCC appears to compensate for the effect of tablet compression on dissolution. On the other hand, intragranular MCC retards tablet and granule dissolution throughout the 30 min. These results, including both metoprolol and HCTZ, are consistent with our observations during the disintegration and dissolution tests on both metoprolol and HCTZ tablets, and their granulations. During the dissolution testing on

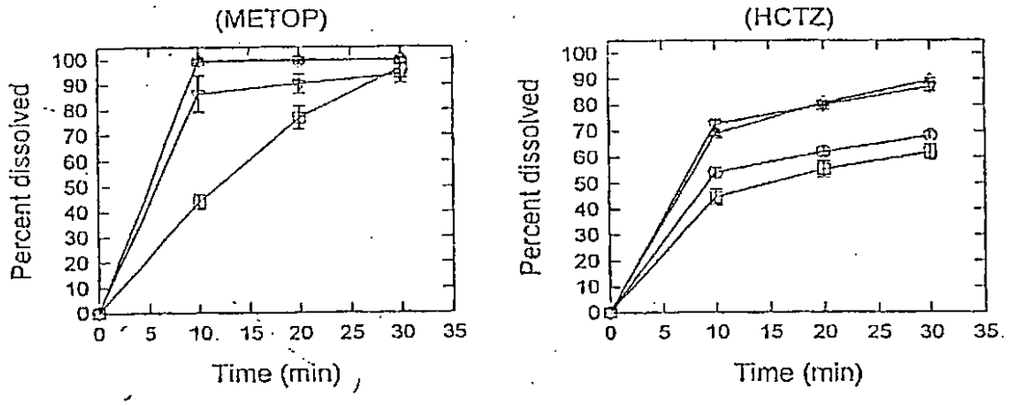

Figure 6. Effect of granulation mode of MCC on drug dissolution (Δ, granules and ∇, tablets with extragranular MCC; ○, granules and □, tablets with intragranular MCC).

granulations, we observed that the metoprolol granules with or without intragranular MCC dissolve very rapidly. However, the HCTZ granules disintegrate or dissolve much more slowly, especially those with intragranular MCC. Based on our observations and the results from the disintegration and dissolution tests, it is suggested that extragranular MCC promotes initial tablet dissolution by different mechanisms depending on the solubility of drug. For a very soluble drug, the shorter tablet disintegration time induced by the extragranular MCC plays a major role in promoting tablet dissolution, while the fast dissolution of HCTZ granules with extragranular MCC (without MCC inside the granules) results in the fast drug release from the tablets.

Effect of Granulating Fluid Level on Drug Dissolution

Figure 7 shows the effect of granulating fluid level on the dissolution rate of tablets containing intragranular MCC. For both drugs, the tablet dissolution was slower when the amount of granulating fluid was increased. These results are in accordance with the data reported by Chowhan and Amaro (6). The effect of granulating fluid level on drug dissolution from granules with MCC is shown in Fig. 8. An increase in the amount of granulating fluid resulted in slower dissolution of HCTZ granules but did not affect the dissolution of metoprolol granules. This could be the reason for slower tablet dissolution over a 30-min period for HCTZ, but only over 10 to 20 min for metoprolol tablets. The more water used in wet granulation, the denser were the granules obtained after drying. Furthermore, more drug particles may be embedded into the MCC matrix during wet granulation, which subsequently retards drug dissolution from the granules. These findings are similar to the effect of changing the granulation mode of MCC (the level of intragranular MCC) on tablet dissolution.

Compactibility of the Formulations and Its Correlation with Tablet Dissolution

The tablet disintegration and dissolution results presented earlier are based on tablets with similar hardness. The compression force used in the Plackett–Burman design experiment ranged from 380 to 980 kg. The standardized Pareto chart for the compression force (Fig. 9) indicates that the granulation mode of MCC affects the compression force used most significantly, followed by drug type, impeller speed, and filler type. The larger the portion of MCC used in wet granulation, the higher the compression force needed to achieve the same tablet hardness. The change in compactibility of MCC after wet granulation is attributed to the hard granules formed; therefore, a higher compression force is needed to cause the granule deformation and fracture necessary to form a hard tablet (14). The higher the impeller speed used for wet massing, the greater the compression force required to target the same tablet hardness. This is due to the greater energy exerted on the wet mass under the high agitation, and to the harder granules formed after drying. As a result, a greater compression force would be necessary for the deformation and fracture of the granules.

The tablets made with a fixed compression force (700 kg) in the factorial design had various hardness. Figure

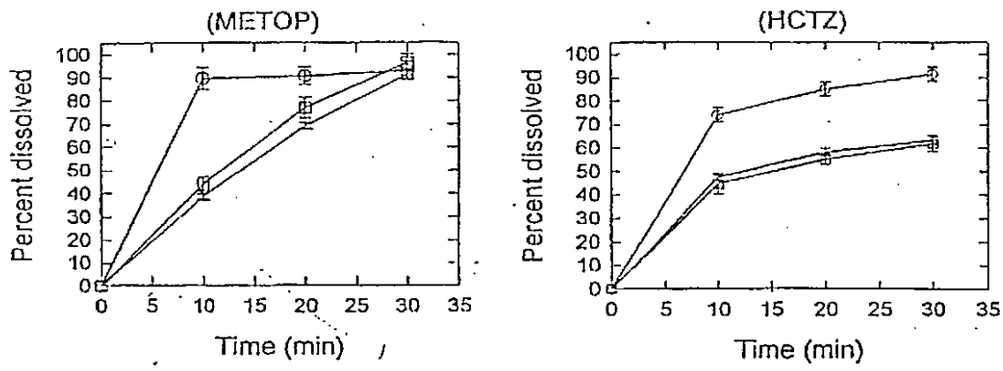

Figure 7. Effect of granulating fluid level on tablet dissolution (METOP: ○, 7%, □, 10%, △, 13% on run 2'; HCTZ: ○, 20%, –△,25%, □, 30% on run 5').

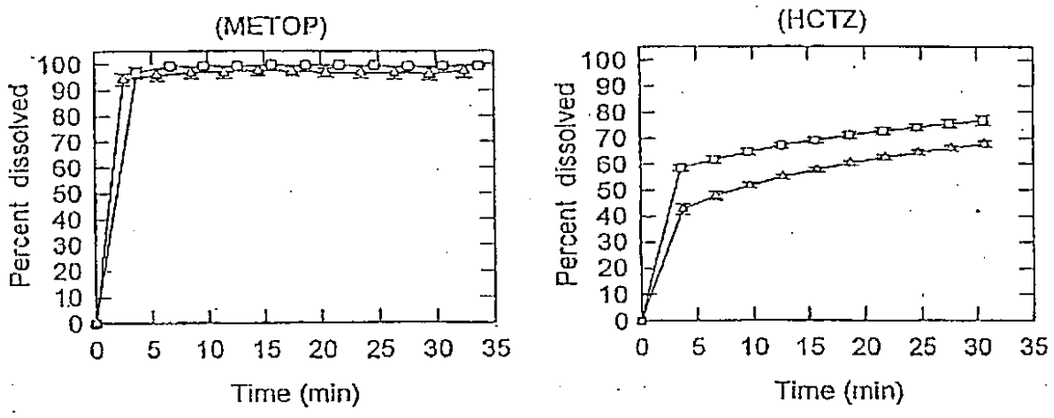

Figure 8. Effect of granulating fluid level on granule dissolution (METOP: □, 7% and Δ,13%; HCTZ: □, 20% and Δ, 30%).

10 demonstrates results similar to those found for tablets with the same hardness. The formulations with intragranular MCC were less compactible than the ones with extragranular MCC.

The dissolution data obtained by keeping compression force constant in this design were also analyzed statistically. Figure 11 indicates that the results are similar to those obtained from tablets of same the hardness (Fig. 5). It appears that fixing compression force has more of an effect than fixing tablet hardness on dissolution (Q_{10} and Q_{30} values), as seen with the variation in the granulation mode of MCC.

CONCLUSIONS

The role of intra- and extragranular microcrystalline cellulose on tablet dissolution was studied through the

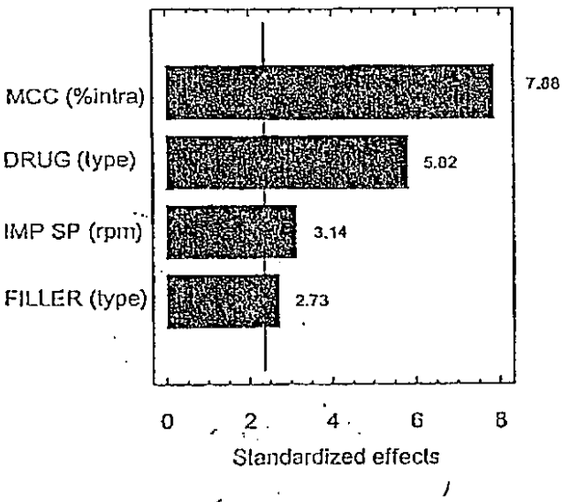

Figure 9. Standardized Pareto chart for compression forces used to achieve same tablet hardness in Plackett-Burman design.

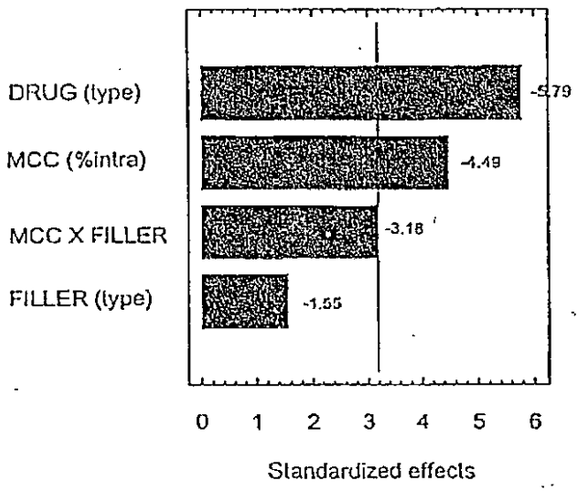

Figure 10. Standardized Pareto chart for tablet hardness (2^3 factorial design).

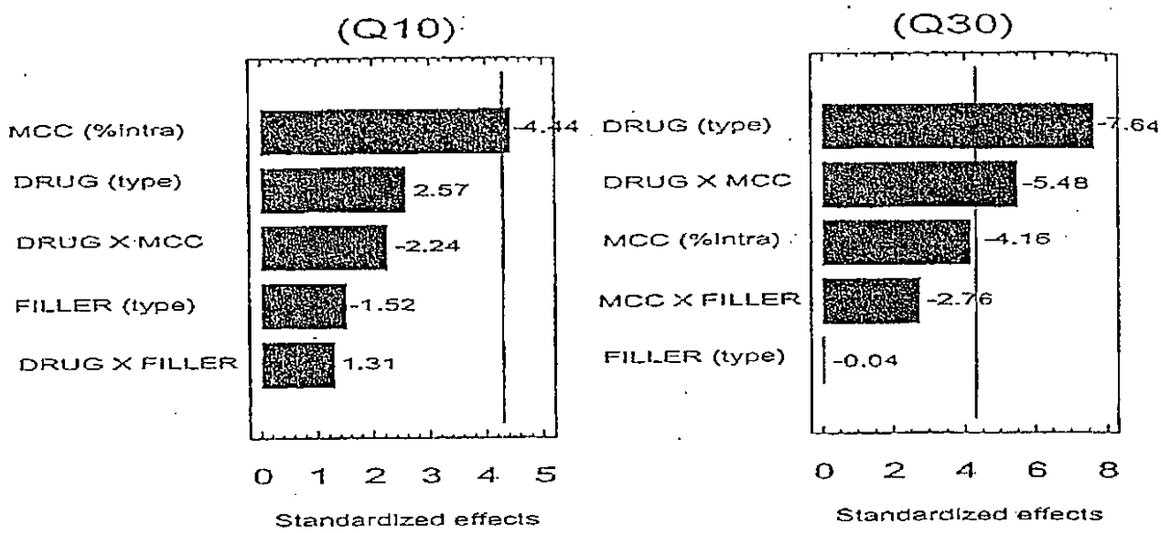

Figure 11. Standardized Pareto chart for dissolution Q_{10} and Q_{30} (2^3 factorial design, fixed compression force).

use of statistical experimental design techniques and conventional testing. The influence of other formualtion and processing variables was also investigated. The granulation mode of MCC is very critical to the compactibility and initial dissolution rates of tablets. Although intragranular MCC can assist in the granulation process by enhancing end point control, it has negative impact on tablet dissolution, especially for the system containing a slightly soluble drug. For a formulation containing intragranular MCC, the influence of granulating fluid level on tablet dissolution is also a potential concern. On the contrary, the inclusion of MCC extragranularly tends to have the reverse effect in that dissolution rates and compactibility increase. Changes in the type of filler from lactose to dicalcium phosphate, the type of disintegrant from sodium starch glycolate to croscarmellose sodium, and the impeller speed did not appear to affect tablet dissolution. Formulations with intragranular MCC are less compactible than those with extragranular MCC. However, it appears that the compression force used for tableting and the resulting tablet hardness in the study have a minor effect on tablet dissolution. Optimizing the distribution of MCC between and within granules may make it possible to optimize dissolution and compactibility without changing overall tablet composition. The significance of these findings for drug bioavailability is debatable but should be tested.

ACKNOWLEDGMENTS

This work was partially supported by UMAB/FDA Collaborative Agreement RFP 223-91-3401. Financial support from FMC Corporation and the gift of hydrochlorothiazide from Merck & Co. are greatfully acknowledged.

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European Journal of Pharmaceutical Sciences, 5 (1997) 63–69

EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES

Improvement of dissolution of poorly soluble drugs by solid deposition on a super disintegrant. II. The choice of super disintegrants and effect of granulation

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Received 6 February 1996; accepted 22 July 1996

Abstract

It is demonstrated that the dissolution from capsules and tablets of poorly soluble, hydrophobic drugs can be strongly improved by solid deposition of the drug upon hydrophilic, strongly swelling carriers like the super disintegrants sodium starch glycolate and croscarmellose sodium. As an effect of its lower swelling power, the super disintegrant crospovidone is far less effective than the other super disintegrants. Wet granulation of poorly soluble drugs with high concentrations of sodium starch glycolate resulted likewise in a strongly improved drug release and bioavailability from capsules and tablets. It was found, however, that granules containing a too high concentration of the super disintegrant slow down the drug release from tablets. This effect is caused by the formation of a viscous barrier of the super disintegrant in the granules during the dissolution process.

Keywords: Solid deposition; Granules; Dissolution rate; Super disintegrants; Swelling

1. Introduction

For poorly soluble, orally administered drugs, the rate of adsorption is often controlled by the rate of dissolution of the drug in the gastro-intestinal tract. Although theoretically the dissolution rate can be enhanced by increasing the surface area of the drug by micronization, in practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tableted (Aguiar et al., 1967; Finholt and Solvang, 1968; Lin et al., 1968). This phenomenon was attributed to the agglomeration tendency of micronized, poorly soluble, hydrophobic drugs, which effect results in a decreased effective surface for dissolution.

Nyström and Westerberg (1986) and Westerberg et al. (1986) demonstrated that ordered mixtures where micronized drug particles are fairly evenly distributed on relatively large hydrophilic carrier particles can prevent reagglomeration and increase the drug dissolution rate as an effect of the large effective surface for dissolution. A prerequisite for fast dissolution from an ordered mixture seemed to be that the carrier particles dissolve rapidly, delivering a fine particulate suspension of drug particles.

In the first part of this series, it was shown that the dissolution from capsules and tablets of poorly soluble and hydrophobic drugs can be strongly improved by solid deposition of the drug upon the surface of the hydrophilic and strongly swelling super disintegrant sodium starch glycolate (Te Wierik et al., 1992). The improvement of the dissolution rate was found to be better than from systems with a hydrophilic soluble carrier like lactose or with a carrier with limited swelling properties, such as potato starch.

In the present study, the effect of two other super disintegrants, croscarmellose sodium and cros-

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0928-0987/97/$32.00
PII S0928-0987(96)00256-4

povidone on the dissolution profiles of the hydrophobic, poorly soluble drug nifedipine was investigated. As super disintegrants, unlike other carriers, have poor flow properties due to their rather small particle size, the flowability of physical blends of drugs and super disintegrants may be a problem in capsule filling or tableting. For this reason also the effect of wet granulation of the hydrophobic, poorly soluble drugs, methylprednisolone and phenylbutazone, with sodium starch glycolate on their dissolution rate from capsules and tablets was studied.

2. Experimental procedures

2.1. Chemicals

The filler binders used were α-lactose monohydrate 100 Mesh (mean particle size 81.6 μm) from DMV (Veghel, The Netherlands), microcrystalline cellulose (Avicel PH 101 and Avicel PH 102, mean particle size of the latter 100 μm) from FMC Europe SA (Brussels, Belgium) and dicalcium phosphate dihydrate (Emcompress, mean particle size 100 μm) from Edward Mendell (Carmel, NY, USA). The super disintegrants used were sodium starch glycolate (Primojel, mean particle size 34 μm), croscarmellose sodium (Primellose, mean particle size 26 μm), both from Avebe (Veendam, The Netherlands) and crospovidone (Plasdone XL, mean particle size 10 μm) from GAF Corp. (Frechen, Germany). The active substances used were nifedipine (mean particle size 3.0 μm) kindly donated by Bayer (Leverkusen, Germany), methylprednisolone (mean particle size 2.5 μm) from Upjohn (Kalamazoo, MI, USA), and phenylbutazone (mean particle size 4.5 μm) from BUFA (Castricum, The Netherlands). All mean particle sizes were measured by air permeametry. The aqueous solubilities of nifedipine, methylprednisolone and phenylbutazone at room temperature are 50 mg/l, 80 mg/l and 700 mg/l, respectively.

2.2. Preparation of capsules and tablets from physical blends

For the nifedipine capsules, 20% nifedipine and 80% excipient were mixed for 15 min in a Turbula mixer (model 2P, W.A. Bachofen, Basle, Switzerland) at a rotation speed of 90 revs./min. Then, 50 mg of the blend was filled in capsules nr 1. The composition of the physical mixes for nifedipine tablets is listed in Table 1. Drug and excipients, except magnesium stearate were mixed in the Turbula mixer for 15 min. After addition of magnesium stearate, the mixing procedure was continued for 5 min.

2.3. Preparation of capsules and tablets from granules

Granules of drug (methylprednisolone or phenylbutazone) only and drug with different percentages sodium starch glycolate were prepared by wet granulation. First, the drug was dispersed in a small, home-made planetary mixer with a quantity of water being half of the weight of the drug, which resulted in a thick paste. The sodium starch glycolate was added and dispersed with the paste until a rough mass was formed. Water was added until the weight was 25% of the weight of sodium starch glycolate. For granules with drug only, the drug was mixed with water until a rough mass was formed. The wet mass was screened through a 1 mm sieve, dried 1–2 h at 50°C in a ventilated tray drier and screened again through a 850 μm sieve. Capsules were prepared by filling a quantity of granules, containing 40 mg methylprednisolone or 60 mg phenylbutazone in capsules nr. 1 or 0. Tablets with a diameter of 9 mm were prepared by compressing on a hydraulic press

Table 1
Composition of the nifedipine tablets in mg per tablet

	A	B	C	D	E	F
Nifedipine	10	10	10	10	10	10
Microcryst. cellulose (type 101)	42.5	42.5	42.5	—	—	—
α-Lactose monohydrate	109	109	115.8	—	—	—
Sodium starch glycolate	6.8	—	—	158.3	—	—
Croscarmellose sodium	—	6.8	—	—	158.3	—
Crospovidone	—	—	—	—	—	158.3
Magnesium stearate	1.7	1.7	1.7	1.7	1.7	1.7

(ESH, Brierley Hill, UK), at a compaction load of 15 kN with both a compression and decompression rate of 1.5 kN/s. The die was prelubricated with magnesium stearate before each compression.

2.4. Dissolution rate measurements

The dissolution profiles were measured, for the tablets according to the USP XXIII paddle method at 100 revs./min, and for the capsules as described by Proost (1987) at 100 revs./min. Methylprednisolone was analysed in water, nifedipine and phenylbutazone were analysed in phosphate buffer (pH 7.5; USP XXIII). Nifedipine solutions were protected from light. The drug concentrations were measured spectrophotometrically using an Ultraspec 4052 TDS apparatus (Pharmacia Biotech Benelux, Roosendaal, The Netherlands). All experiments were carried out six times.

Results and discussion

3.1. Dissolution rate of nifedipine from capsules and tablets with different excipients as carrier

Fig. 1a shows the dissolution profiles of nifedipine from capsules containing physical mixtures of drug with 80 percent of different fillers or super disintegrants. As expected, all release profiles start with a delay of about 2 min, corresponding with the time required to dissolve the capsule wall. The figure shows a slow drug release for capsules containing insoluble fillers such as dicalcium phosphate dihydrate and microcrystalline cellulose (type 102). Just as could be expected from previous work (Westerberg et al., 1986; Te Wierik et al., 1992), a faster release was found from capsules containing the more soluble filler α-lactose monohydrate as a carrier. For capsule formulations with super disintegrants, a fast dissolution rate and a high total amount of drug release was found for both sodium starch glycolate and croscarmellose sodium. The dissolution rate of nifedipine from capsules with crospovidone was low, however, as compared with the other super disintegrants, and even slightly lower than found for capsules containing α-lactose monohydrate.

Fig. 1b illustrates the dissolution profiles of nifedipine from tablets compressed from different

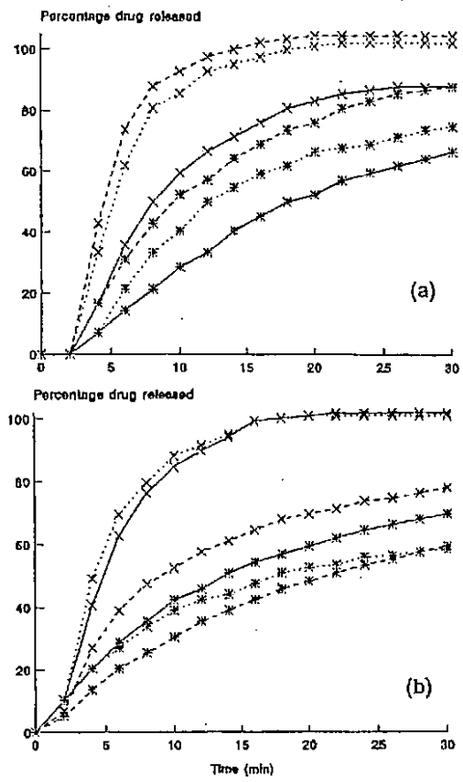

Fig. 1. (a) Release of nifedipine from capsules containing a physical mixture of 10 mg drug with 40 mg (—*—) dicalcium phosphate dihydrate, (..*..) microcrystalline cellulose, (–*–) crospovidone, (—X—) α-lactose monohydrate, (..X..) sodium starch glycolate, and (–X–) croscarmellose sodium, respectively. (b) Release of nifedipine from tablets containing 10 mg nifedipine. Key: (—*—) formulation A, (..*..) formulation B, (–*–) formulation C, (—X—) formulation D, (..X..) formulation E, (–X–) formulation F. The composition of the formulations is presented in Table 1.

drug/excipient blends. The composition of the tablets is given in Table 1. Formulations A and B are commonly used formulations for direct compaction, containing microcrystalline cellulose and α-lactose monohydrate 100 mesh as filler-binders and 4% sodium starch glycolate or croscarmellose sodium as a disintegrant (Van Kamp et al., 1987). Formulation C contains no disintegrant. Formulations D, E and F are physical mixtures of 6% drug and 93% super disintegrant. All formulations contained 1.0% magnesium stearate as a lubricant. Table 2 lists both crushing strength and disintegration time of the tablets. The disintegration time of all the tablets

Table 2
Crushing strength and disintegration time of the nifedipine tablets

Formulation	Crushing strength (N)	Disintegration time (s)
A	47±15	7±2
B	34±6	4±1
C	57±8	18±1
D	16±4	44±4
E	25±6	103±4
F	>300	48±1

during the dissolution test was less than 2 min. Fig. 1b shows that the release of nifidepine from commonly used directly compressible tablet formulations (A, B and C) is slow and incomplete, in spite of the fast tablet disintegration. The fast disintegration of the tablets without disintegrant can be attributed to the synergistic effect of α-lactose monohydrate and microcrystalline cellulose with respect to the disintegration process (Lerk et al., 1974; Van Kamp et al., 1987). The addition of 4% of a super disintegrant enhances disintegration to some extent, but has only a small effect on the rate and extent of nifedipine release (Fig. 1b). The figure shows, however, that an almost complete and fast drug release was obtained for the formulations D and E, containing nifedipine and a high concentration of sodium starch glycolate and croscarmellose sodium, respectively. Just as found for the capsules, a high concentration of the super disintegrant crospovidone (formulation F) was far less effective as compared with the other disintegrants. Both from the capsules (Fig. 1a) and from tablets (Fig. 1b) different formulations showed a very low standard deviation being less than 3% drug released.

The strong improvement of the dissolution rate of the poorly soluble and hydrophobic drug nifedipine by high percentages of sodium starch glycolate and croscarmellose sodium, respectively, can be explained by deagglomeration of the micronized drug by the disintegrant particles and solid deposition upon the surface of strongly swelling super disintegrants which act as a carrier, just as was found in Part I of this series (Te Wierik et al., 1992). The results presented agree with a previously reported paper (Giunchedi et al., 1990) concerning the improvement of the carbamazepine release by croscarmellose sodium. As an effect of swelling of the super disintegrant, the 'wetted' surface of the carrier increases, which promotes wettability and dispersibility of the particulate system. Fig. 1a and b show, however, that the choice of the super disintegrant has a paramount effect on their efffectivity as a dissolution enhancer. The disintegration efficiency of the super disintegrant crospovidone is based on capillary action rather than on swelling properties (Van Kamp et al., 1986). The swelling properties of the super disintegrants and the fillers used are listed in Table 3 (Bolhuis et al., 1982). The table shows that the swelling properties of crospovidone are poor as compared with those of sodium starch glycolate and croscarmellose sodium, respectively. This effect is caused by the absence of cationogenic groups in the crospovidone molecule. When used as a carrier, the increase in 'wetted' surface area by crospovidone apparently will be insufficient to improve the drug release to a large extent.

3.2. Effect of granulation on the dissolution rate of methylprednisolone and phenylbutazone, respectively, from capsules and tablets with sodium starch glycolate as carrier

Fig. 2a shows the release of methylprednisolone from capsules filled with drug/sodium starch glycolate granules. Granulation of methylprednisolone without sodium starch glycolate resulted in a strongly decreased dissolution rate and availability, which can be explained from the decreased effective surface area for dissolution. The addition of sodium starch glycolate strongly improved dissolution rate and availability of methylprednisolone from the capsules. Comparison of the drug profiles with the drug profiles from capsules with physical mixes in Part I of this series shows that wet granulation of the methylprednisolone with sodium glycolate as a method to improve the flow properties, had almost the same effect on drug release as dry blending with the super disintegrant. Capsules containing 80% sodium starch

Table 3
Swelling of disintegrant particles in water of 20±0.5°C (taken from Bolhuis et al., 1982)

Disintegrant	Volume increase ($cm^3 \cdot cm^{-3}$)	
	Unlubricated	Lubricated
Sodium starch glycolate	30	30
Croscarmellose sodium	11	11
Crospovidone	1.2	1.3
Microcrystalline cellulose	0.4	0.4

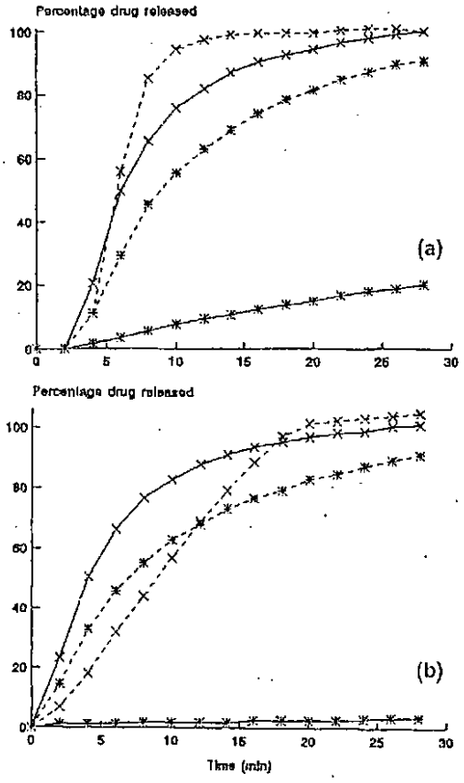

Fig. 2. (a) Release of methylprednisolone from capsules containing 40 mg drug as granulate with different concentrations sodium starch glycolate. Key: (—*—) 0%, (–*–) 20%, (—X—) 35% and (–X–) 80% sodium starch glycolate. (b) Release of methylprednisolone from tablets containing 40 mg drug as granulate with different concentrations sodium starch glycolate. Key: see Fig. 2a.

glycolate gave the highest methylprednisolone release, both for physical mixes (Te Wierik et al., 1992) and for granules (Fig. 2a).

Fig. 2b presents the dissolution profiles of methylprednisolone from tablets prepared from drug/sodium starch glycolate granules. The figure shows that the presence of sodium starch glycolate in the granules resulted in a strong increase in drug release as compared with tablets prepared from methylprednisolone granules only. It should be noted, however, that the fastest release rates were found for tablets prepared from granules containing 35% sodium starch glycolate. Higher concentrations of the super disintegrant in the granules resulted in a complete, but retarded drug release, as can be seen for tablets, prepared from granules with 80% sodium starch glycolate. This is in contrast to methylprednisolone tablets prepared from physical mixes (Te Wierik et al., 1992) and to the capsules filled with the granules (Fig. 2a). In both cases the drug dissolution rate steadily increased with the sodium starch glycolate concentration.

Fig. 3a presents the dissolution profiles of phenylbutazone from capsules filled with granules containing different drug/sodium starch glycolate ratios. Comparison with capsules filled with physical mixtures in Part I of this series shows that 10% sodium starch glycolate improves the dissolution rate and availability much more for the capsules containing granules (Te Wierik et al., 1992). The drug

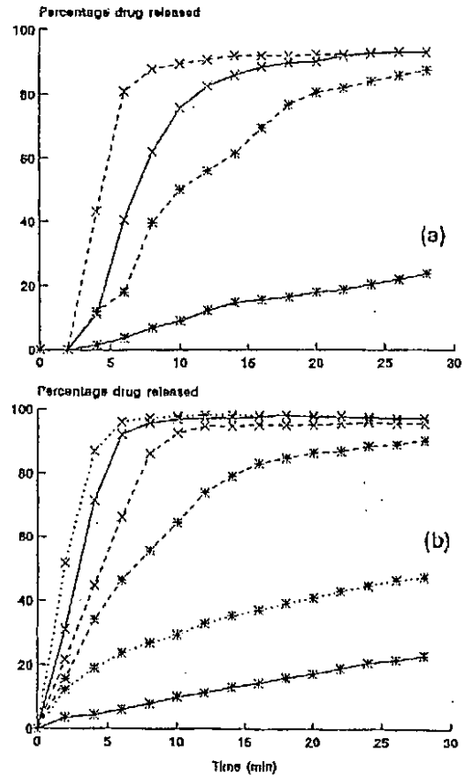

Fig. 3. (a) Release of phenylbutazone from capsules containing 60 mg drug as granulate with different concentrations sodium starch glycolate. Key: (—*—) 0%, (–*–) 10%, (—X—) 20% and (–X–) 40% sodium starch glycolate. (b) Release of phenylbutazone from tablets containing 60 mg drug as granulate with different concentrations sodium starch glycolate. Key: (—*—) 0%, (...*...) 5%, (–*–) 10%, (—X—) 20%, (...X...) 30% and (–X–) 40% sodium starch glycolate.

release from granules containing 20% sodium starch glycolate is almost complete after 30 min, whereas for capsules filled with physical mixtures, the availability never exceeded 80% (Te Wierik et al., 1992). A concentration of 40% sodium starch glycolate resulted in a faster dissolution rate and also an availability of almost 100%. The addition of more than 40% of the super disintegrant resulted in similar dissolution profiles as found for granules containing 40% sodium starch glycolate. These profiles are not taken up in the figure because they overlap the profiles of the capsules with 40% sodium starch glycolate.

The dissolution profiles of phenylbutazone from tablets, compressed from granules (Fig. 3b) differ from the previously found profiles of tablets compressed from physical mixtures (Te Wierik et al., 1992). Although 10% sodium starch glycolate gave comparable results, tablets compressed from granules with 20% sodium starch glycolate show a faster dissolution rate and a higher availability than tablets compressed from the physical blend (Te Wierik et al., 1992). Using granules with 30% sodium starch glycolate increased the dissolution rate furthermore, but granules with 40% or more carrier gave a complete but retarded drug release. The latter agrees with the results as obtained for tablets with methylprednisolone/sodium starch glycolate granules (Fig. 2b). As found earlier for the experiments with the physical mixtures (Fig. 1) the tablets and capsules containing granulates (Figs. 2 and 3) showed extremely low values for the standard deviations being not higher than 3%.

Figs. 2 and 3 show that the improvement of the dissolution rate and availability of poorly soluble, hydrophobic drugs by means of solid deposition on sodium starch glycolate can be obtained both by mixing the drug with the super disintegrant (Te Wierik et al., 1992) and by wet granulation of drug and super disintegrant. Granulation may be of benefit when the flow properties of the physical mix are too bad for proper capsule or tablet machine filling. There are, however, some differences between the physical mixing method and the granulation method. For the granules, high drug dissolution profiles can often be obtained with lower sodium starch glycolate concentrations as compared with the physical mixes. This effect may be caused by a fixation of the micronized hydrophobic drug particles upon the hydrophylic sodium starch glycolate carrier particles during the granulation process. This leads to a better drug distribution over the carrier particles than in a physical mix. The advantage of the granulation method is most pronounced for phenylbutazone with a mean particle size of 4.5 μm, where the adhesion forces of the drug to the carrier particles in a physical mix are assumed to be much lower than those of methylprednisolone particles (mean particle size 2.5 μm) to carrier particles. A second difference between the physical mixing method and the granulation method is that the drug dissolution rate from tablets slows down when the sodium starch glycolate concentration is too high. This effect, which is shown for methylprednisolone in Fig. 2b and for phenylbutazone tablets in Fig. 3b, may be caused by the formation of a viscous gel layer by sodium starch glycolate, which forms a barrier for drug diffusion from the tablet to the dissolution medium. For capsules filled with granules, this effect was not seen, because each individual granule forms a gel layer, being too small to be effective in retarding drug release.

In conclusion, it is demonstrated that the dissolution from capsules and tablets of the poorly soluble and hydrophobic drug nifedipine can be strongly improved by solid deposition of the drug upon hydrophylic, strongly swelling carriers like the super disintegrants sodium starch glycolate and croscarmellose sodium. For tablets prepared from physical mixes of drug and a high concentration super disintegrant, the drug dissolution rate and availability were much better than from tablets, prepared according to a commonly used directly compressible formulation. As an effect of its low swelling power, crospovidone is far less effective than the other super disintegrants.

Wet granulation of methylprednisolone or phenylbutazone with high concentrations sodium starch glycolate resulted likewise in a strongly improved drug release and bioavailability from capsules and tablets, respectively. However, granules containing a too high concentration sodium starch glycolate slow down the drug release from tablets, as an effect of the formation of a viscous barrier of the super disintegrant in the granules during the dissolution process.

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