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Calcium alginate matrices for oral multiple unit administration: II. Effect of process and formulation factors on matrix properties

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Summary

Small calcium alginate matrices were prepared by ionotropic gelation of droplets of an alginate solution containing dispersed theophylline, followed by air-drying of the gel beads. The effect of various production factors on the size, composition and drug release properties was investigated in two separate studies. A 2^3 factorial design and a 2^{5-1}_{V} fractional factorial design were applied. The size of the matrices was controlled mainly by the coaxial airstream applied during droplet production. However, the alginate concentration and the calcium concentration used for gelation also appeared to have a significant influence. The latter two factors, together with the amount of drug dispersed, determined the matrix drug content. The calcium concentration and the amount of drug affected matrix calcium content the most. The amount of drug also affected the moisture content. The calcium and alginate concentrations, the gelling time, the drug addition and the alginate G content affected the drug release rate in water. An increase in the level of all these factors caused a retardation in release. Several synergistic two-factor interactions were also observed.

Introduction

Gel beads of calcium alginate can be produced by adding droplets of a sodium alginate solution into a calcium chloride bath. The droplets instantaneously form gel spheres, entrapping material formerly dispersed in the alginate solution. The gelling properties are strongly dependent on the alginates' proportion of guluronic acid, G, and mannuronic acid, M, residues and block structure (Skjåk-Bræk et al., 1986; Smidsrød and Haug, 1968). The physical characteristics of calcium alginate gel beads are also influenced by the alginate concentration and molecular size, the calcium concentration and gelling time (Yotsuyanagi et al., 1987; Martinsen et al., 1989).

All these factors can also affect the properties of solid calcium alginate matrices, which are produced by drying the gel spheres. Both the calcium concentration (Badwan et al., 1985; Østberg and Graffner, 1992) and the alginate concentration (Salib et al., 1978; Badwan et al., 1985; Kim and Lee, 1992) appear to influence the release rate of

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model drugs from the matrices. The time for disintegration of the matrices in simulated intestinal fluid is reported to depend on the alginate viscosity grade, the calcium concentration and the gelling time (Bodmeier et al., 1989).

In a previous study (Østberg and Graffner, 1992), a small scale method was investigated for its ability to produce solid calcium alginate matrices containing the model drug theophylline. The aim of the present work is to evaluate the effect of some process and formulation factors by using experimental designs. Matrix size, composition and release rate in water are considered.

Materials and Methods

Materials

Sodium alginate isolated from *Laminaria hyperborea* stipe (Protanal LF 10/60) and blades (Protanal LF 10/40 RB) was a gift from Pronova Biopolymer A/S, Norway. The chemical compositions, determined by ^{1}H-NMR spectroscopy, and the intrinsic viscosities of the two grades are given in Table 1.

Theophylline monohydrate (Ph. Eur.) was purchased from Knoll AG, Germany. All other chemicals were of analytical grade. Deionized water was used throughout the study.

Methods

Characterization of the alginates

NMR spectroscopy ^{1}H-NMR spectra were recorded at 92°C using a Jeol FX-100 spectrometer (Jeol Ltd, Japan). The monomer compositions (F_G, F_M) and the diad frequencies (F_{GG}, F_{MM}, F_{GM} and F_{MG}) were determined as described by Grasdalen et al. (1979). The average length of the G-blocks ($\bar{N}_G$) was calculated from $\bar{N}_G = F_G/F_{MG}$.

Viscosity measurements 0.02–0.1 g/100 ml solutions of sodium alginate in 0.10 M NaCl were analyzed at 20.0°C in a Ubbelohde capillary viscometer (type no. 53101/0a; Schott-Geräte GmbH, Germany). The specific viscosity, η_{sp}, was determined according to Eqn 1:

$$\eta_{sp} = \frac{\nu_c - \nu_0}{\nu_0} \quad (1)$$

where ν_c and ν_0 are the kinematic viscosities of the alginate solutions and the solvent, respectively. The intrinsic viscosity, $[\eta]$, was determined by means of linear regression, according to the equation of Huggins (1942):

$$\eta_{sp}/C = [\eta] + k' \cdot [\eta]^2 \cdot C \quad (2)$$

where C is the polymer concentration and k' denotes the Huggins constant.

Production of calcium alginate matrices

Calcium alginate gel beads were prepared analogously to the main method described earlier, using the same equipment (Østberg and Graffner, 1992). The suspension of theophylline monohydrate in 250 g sodium alginate solution was forced out of a cylindrical container through 10 cannulae, and the droplet size was controlled by applying a coaxial airstream over the cannulae. After gelation in 500 ml calcium chloride solu-

TABLE 1

Compositional characteristics and viscosity data for the alginates used

Alginate	Monad frequencies		Diad frequencies			Average length of G-blocks	Intrinsic viscosity
	F_G	F_M	F_{GG}	F_{MM}	$F_{GM} = F_{MG}$ [a]	$\bar{N}_G$	(100 ml/g)
LF 10/60	0.68	0.32	0.56	0.20	0.12	5.7	6.70
LF 10/40 RB	0.51	0.49	0.34	0.32	0.17	3.0	6.68

[a] Valid for long chains where the contribution from end-groups can be neglected.

TABLE 2

Levels of the factors studied in the 2^3 factorial design

Factor	Level	
	−1	+1
A: alginate concentration (%)	1.5	2.25
B: suspension flow rate (ml/min)	28	48
C: coaxial airstream (l/min)	2.2	7.2

tion, saturated with drug, the beads were washed and dried at room temperature.

Experimental designs The effects of the alginate concentration, suspension flow rate and rate of the coaxial airstream on matrix size were studied in a conventional 2^3 factorial design (Montgomery, 1991). The transformed levels of the investigated factors are depicted in Table 2. 3.0 g of theophylline monohydrate was dispersed in the alginate (LF 10/40 RB) solution. The suspension droplets were gelled in 0.10 M calcium chloride for 30 min. All the experiments were performed in duplicate to allow estimation of the experimental error.

The effects of the calcium concentration, gelling time, alginate concentration, amount of drug dispersed and alginate type on matrix size, matrix composition and drug release were studied in a 2_V^{5-1} fractional factorial design (Montgomery, 1991) (Tables 3 and 4). The drug suspension was dripped into the calcium chloride solution at a flow rate of approx. 30 ml/min, while the total coaxial airstream was kept at 7.2 l/min. In order to estimate the experimental error, five replicates of an experiment with one factor (alginate type) at the −1 level and the other factors at the 0 level were performed.

The experiments were performed in a randomized order in both factorial designs. The responses are given as mean values where replicate measurements were run on each batch. The estimated effects of increasing the factors from a low to a high level were tested for significance by analysis of variance.

Characterization of the matrices

Particle size The size distribution of the matrices was determined using an Image Analysis System (IBAS 2000; Kontron Bildanalyse GmbH, Germany). The solid matrices were spread on a dull, illuminated glass plate and images were recorded with a video camera equipped with a macro lens.

TABLE 3

Matrix of the 2_V^{5-1} design, defining relation $I = ABCDE$

Treatment	Factor				
	A	B	C	D	E
e	−	−	−	−	+
a	+	−	−	−	−
b	−	+	−	−	−
abe	+	+	−	−	+
c	−	−	+	−	−
ace	+	−	+	−	+
bce	−	+	+	−	+
abc	+	+	+	−	−
d	−	−	−	+	−
ade	+	−	−	+	+
bde	−	+	−	+	+
abd	+	+	−	+	−
cde	−	−	+	+	+
acd	+	−	+	+	−
bcd	−	+	+	+	−
abcde	+	+	+	+	+

The maximum diameter (d_{max}) of about 1000 matrices from each batch was measured. The mean d_{max} ($\bar{d}_{max}$) was used as a response parameter in the factorial designs. This parameter was regarded as rather insensitive to variations in matrix roundness and orientation. The solid matrices were mostly rounded with a flattened shape. When spread on a plane surface the matrices

TABLE 4

Levels of the factors studied in the 2_V^{5-1} fractional factorial design

Factor	Level		
	−1	0	+1
A: calcium concentration (M)	0.03	0.065	0.10
B: gelling time (min)	15	30	45
C: alginate concentration (% w/w)	1.5	2.0	2.5
D: amount of drug dispersed (g)	1.5	3.25	5.0
E: alginate type (low G/high G)	LF 10/40 RB		LF 10/60

tended to become oriented with the flattened face upwards.

Content of drug, moisture and calcium The amount of drug, moisture and calcium in the matrices was determined as described earlier (Østberg and Graffner, 1992). Two replicates were performed for the calcium determinations, while the others were made in triplicate. The matrix drug content was given as wt% theophylline monohydrate. Drug crystal water was not included in the matrix moisture content.

Release rate The release rate of theophylline in water was determined as described earlier (Østberg and Graffner, 1992). Three replicates were performed on each batch. The times for 50% ($t_{50\%}$) and 80% ($t_{80\%}$) of the drug to be released were used as response parameters.

Scanning electron microscopy (SEM) Morphological examination of the matrix surfaces was carried out using SEM as described in a previous study (Østberg and Graffner, 1992).

Results

The characteristics of the matrices produced in the two separate factorial designs are listed in Tables 5 and 6. The mean effects of increasing the investigated factors from a low to a high level are shown in Tables 7 and 8.

Matrix size and shape

Air-drying of the gel beads gave small, rounded matrices with a flattened appearance on two sides.

TABLE 5

Mean size of the matrices produced in the 2^3 factorial design

Treatment	$\bar{d}_{max}$ (mm)	
	Parallel 1	Parallel 2
(1)	1.41	1.38
a	1.40	1.36
b	1.52	1.24
ab	1.34	1.43
c	1.15	1.04
ac	0.96	1.05
bc	1.17	1.13
abc	1.16	1.31
MS_{error}	0.0083	

The degree of flattening was dependent on the amount of drug dispersed in the alginate solution and on the calcium concentration. At the high levels of these factors, matrices of a more spherical, less flattened shape were produced.

The size of the matrices was mainly controlled by the flow rate of the coaxial airstream passed over the cannulae during droplet production and by the calcium concentration used for gelation. The mean effect of increasing the airflow from 2.2 to 7.2 l/min was a decrease in the average maximal diameter, $\bar{d}_{max}$, of 0.26 mm. A decrease of 0.14 mm was observed when the calcium concentration was increased from 0.03 to 0.10 M. The latter result is possibly due to the more extensive gel bead shrinkage observed during gelation in a more concentrated $CaCl_2$ solution (Martinsen et al., 1989; Østberg and Graffner, 1992). An increase in alginate concentration from 1.5 to 2.25% (w/w) did not affect the matrix size when investigated in the 2^3 design. However, when the alginate concentration was increased from 1.5 to 2.5% in the 2_V^{5-1} design, a significant increase of 0.14 mm in $\bar{d}_{max}$ was observed. The more viscous suspension possibly gives larger droplets under the given flow conditions, resulting in a higher $\bar{d}_{max}$ of the dried product. Gel beads of a higher alginate concentration may also shrink less during air-drying than those of a lower concentration.

Drug content

The matrix content of theophylline monohydrate was mainly dependent on the alginate concentration and drug content of the suspension used for gel bead production. A significant negative interaction between the two factors indicated, however, that the effect of adding 5 g drug instead of 1.5 g was smaller when the alginate concentration was at the high level.

The matrix drug content was lowered when the suspension droplets were gelled in the more concentrated calcium chloride solution. This was consistent with observations made in our pilot study, where an increase in calcium concentration was shown to reduce drug encapsulation efficiency (Østberg and Graffner, 1992). The lower encapsulation efficiency was explained by the

TABLE 6

Measured responses in the 2_V^{5-1} design and the five replicates of an experiment with the factors A–D at 0 level and factor E at the −1 level (parallel 1–5)

Treatment	Response					
	$\bar{d}_{max}$ (mm)	Drug content (%)	Calcium content (%)	Moisture content (%)	$t_{50\%}$ (min)	$t_{80\%}$ (min)
e	1.12	23.2	5.6	11.1	12	37
a	0.92	19.7	7.1	9.7	11	82
b	1.01	21.3	6.3	7.6	7	28
abe	0.94	19.7	7.5	8.0	13	67
c	1.29	18.7	5.1	10.3	4	10
ace	1.07	16.2	7.1	9.7	18	248
bce	1.24	17.0	5.8	9.9	11	29
abc	1.09	14.5	6.9	8.5	20	116
d	1.10	55.5	3.8	2.8	18	51
ade	1.10	50.0	5.0	3.2	46	213
bde	1.15	52.7	4.1	3.4	42	170
abd	0.99	50.8	4.4	4.0	35	137
cde	1.25	42.8	3.9	5.3	13	25
acd	1.13	40.6	5.1	4.6	36	160
bcd	1.28	42.6	4.3	3.7	11	24
abcde	1.11	39.6	5.0	5.3	90	456
Parallel 1	1.03	34.0	5.6	5.2	23	103
Parallel 2	1.03	33.6	5.6	5.3	21	91
Parallel 3	1.00	33.6	5.6	5.8	22	94
Parallel 4	1.07	33.9	5.6	5.9	25	111
Parallel 5	1.07	32.4	5.5	8.9	27	123
MS_{error}	0.0009	0.41	0.002	2.34	5.80	169.8

higher degree of gel bead shrinkage in more concentrated calcium chloride. Bead shrinkage can be observed as a loss of water from the beads to the gelling solution. The lost water is saturated with drug which originally dissolved in the suspension medium.

TABLE 7

Mean effects on mean matrix diameter of increasing the factors of the 2^3 factorial design from a low to a high level

Factor/interaction	Effect on $\bar{d}_{max}$ (mm)
A: alginate concentration	0.00
B: suspension flow rate	0.07
C: coaxial airstream	−0.26 [a]
Interaction AB	0.05
Interaction AC	0.00
Interaction BC	0.07
Interaction ABC	0.04

[a] Significant, $\alpha = 0.01$.

Calcium content

The calcium content of the matrices was influenced by all the factors investigated in the 2_V^{5-1} design. The factors either gave significant main effects, participated in significant two-factor interactions or both. The calcium concentration used for gelation and the amount of drug in the suspension had the greatest effect. An increase in the calcium concentration from 0.03 to 0.10 M gave matrices with a higher calcium content. Dispersion of 5 g drug instead of 1.5 g had the opposite effect. The increase in gelling time and alginate G content resulted in the binding of slightly more calcium to the gel beads.

The five replicates from one experiment, performed to estimate the experimental error of the

TABLE 8

Mean effects on matrix properties of increasing the factors in the 2_V^{5-1} design from a low to a high level

Factor/interaction	Effects on					
	$\bar{d}_{max}$ (mm)	Drug content (%)	Calcium content (%)	Moisture content (%)	$t_{50\%}$ (min)	$t_{80\%}$ (min)
A: calcium concentration	−0.14 [a]	−2.8 [a]	1.15 [a]	−0.1	19 [a]	138 [a]
B: gelling time	−0.02	−1.1	0.20 [a]	−0.8	9 [a]	25
C: alginate concentration	0.14 [a]	−7.6 [a]	−0.08	0.9	2	35 [a]
D: amount of drug dispersed	0.05	28.0 [a]	−1.98 [a]	−5.3 [a]	24 [a]	77 [a]
E: alginate type (low G/high G)	0.02	−0.3	0.13 [a]	0.6	13 [a]	80 [a]
Interaction AB	0.00	0.6	−0.33 [a]	0.4	3	−7
Interaction AC	−0.03	0.3	0.10	−0.1	12 [a]	85 [a]
Interaction AD	0.02	−0.3	−0.30 [a]	0.6	12 [a]	36 [a]
Interaction AE	0.00	0.3	0.15 [a]	−0.7	3	43 [a]
Interaction BC	0.02	0.1	0.00	0.2	6 [a]	20
Interaction BD	0.01	0.3	−0.20 [a]	0.9	7 [a]	59 [a]
Interaction BE	0.00	0.3	0.00	0.1	8 [a]	25
Interaction CD	−0.03	−3.2 [a]	0.33 [a]	0.4	0	−12
Interaction CE	−0.05	0.1	−0.03	0.2	2	32 [a]
Interaction DE	0.01	0.8	−0.03	−0.1	10 [a]	43 [a]

[a] Significant, $\alpha = 0.01$.

2_V^{5-1} design, produced matrix batches of extremely reproducible calcium content. The value of the error mean square for this response was very low and even minute effects and interactions thus appeared significant.

Moisture content

The increase in level of drug addition also reduced the amount of moisture retained in the matrices.

Release rate

Different drug release rates were obtained from the different matrix formulations. The time taken for 50% ($t_{50\%}$) and 80% ($t_{80\%}$) drug dissolution in water ranged from 4 to 90 min and from 10 to 456 min, respectively. Three of the formulations (treatments cde, bcd and c in the 2_V^{5-1} design) swelled visibly in the dissolution medium. The other remained as small, dense particles which gradually became more transparent as the incorporated drug particles dissolved. None of the matrix compositions disintegrated.

All the factors investigated in the 2_V^{5-1} design had a significant effect on either $t_{50\%}$ or $t_{80\%}$ or on both. An increase to the higher levels of calcium concentration, gelling time, alginate concentration, amount of drug dispersed and alginate G content caused a slower drug release rate. The first and the last two factors had the greatest estimated effect on $t_{50\%}$ and $t_{80\%}$. Several synergistic two-factor interactions were also observed, the most important one being between the calcium-and the alginate concentration.

Discussion

Choice of experimental designs

The effects of a total of seven process and formulation factors were investigated in two separate factorial designs. Variables considered likely to interact were studied in the same design. The two process factors coaxial airstream and suspension flow rate were only expected to affect the size of the matrices. It was also considered un-

likely that they would interact with any factors other than the alginate concentration. Hence, the effect of these three factors on matrix $\bar{d}_{max}$ were investigated in a 2^3 factorial design.

The effect of changing the calcium concentration, gelling time, alginate concentration, amount of drug dispersed and alginate G content on $\bar{d}_{max}$, matrix composition and drug release were subsequently studied in a 2_V^{5-1} reduced factorial design.

$I = ABCDE$ was used as the defining relation for the design, giving a design of resolution V (Whitwell and Morbey, 1961; Montgomery, 1991). The main effects and the two-factor interactions are thus only confounded with the four-factor and three-factor interactions, respectively. Interactions between three factors or more were assumed to be negligible. Consequently, all the main effects and two-factor interactions could be estimated.

Choice of the factor levels

Since the study was intended only to screen for the most important production variables, each factor was studied at two levels. The responses were thus assumed to be approximately linear over the factor levels chosen. The levels of the quantitative factors in the experiments performed to estimate the error mean square of the 2_V^{5-1} design were selected in the central region. The variance was supposed to be constant over the entire experimental area.

The levels of the factors studied in the 2^3 design had to be chosen within a comparatively small experimental area due to limitations in the production equipment. To achieve reproducible droplet formation at the given alginate concentrations, the flow rate of the suspension and of the coaxial airstream could only be varied within restricted limits. In the 2_V^{5-1} design these two factors were kept constant and it was possible to set the upper level of the alginate concentration slightly higher.

The gel beads were allowed a maximal 45 min stay in the calcium chloride solution to keep the time for manufacture at a reasonable level. Other studies have shown that a reduction in the gel bead volume (Yotsuyanagi et al., 1987; Martinsen et al., 1989) can continue for a longer time period. However, maximum mechanical strength of the wet gel beads is reported to be reached within 1 h (Martinsen et al., 1989).

Our earlier pilot study (Østberg and Graffner, 1992) indicated an increase in drug release rate from the matrices when the calcium concentration used for gelation was increased from 0.05 to 0.20 M. As the retardation of drug release was our objective, the lower and upper levels of calcium concentration in the present study were set at 0.03 and 0.10 M, respectively.

The levels for the amount of drug dispersed in the alginate solution were set rather low. This was carried out to give a relatively high coat to core ratio in all the formulations as it was intuitively expected that this might lead to better retardation of drug release.

Matrix composition

The drug, calcium and water content of the calcium alginate matrices were influenced by several formulation factors. When the weight percent of one component is changed due to variations in production conditions, the relative content of the other components is affected in turn. Hence, an increase in drug addition results in a higher matrix drug content, but also displaces calcium and moisture in the matrix on a weight percent basis.

Drug release

An increase to the high level of all the factors investigated in the 2_V^{5-1} design caused a decrease in the release rate of theophylline from the matrices. Many of the factors showed synergistic interactions and the highest $t_{50\%}$ and $t_{80\%}$ values were achieved when all the production factors were kept at their upper level (treatment abcde).

An increase in the calcium concentration of the gelling solution from 0.03 to 0.10 M resulted in retardation of drug release from the matrices. Our exploratory study (Østberg and Graffner, 1992) suggested the opposite when the calcium concentration was increased from 0.05 to 0.20 M. A direct comparison between the two experimental series is not possible due to variations in other production conditions. However, the results might

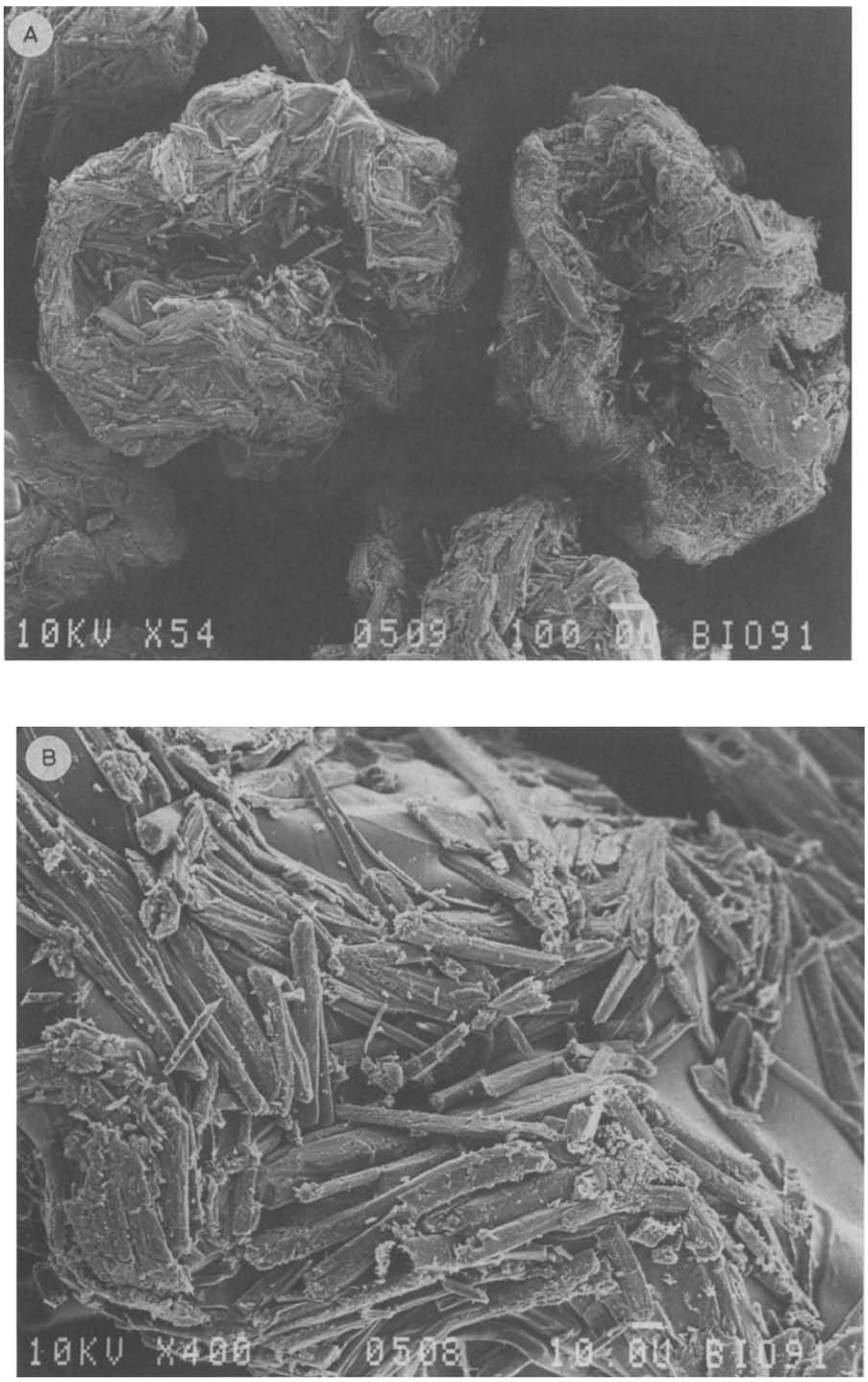

Fig. 1. SEM pictures of matrix formulations produced in the 2_V^{5-1} design: (a,b) treatment combination c, containing 18.7% drug; (c,d) treatment combination abcde, containing 39.6% drug.

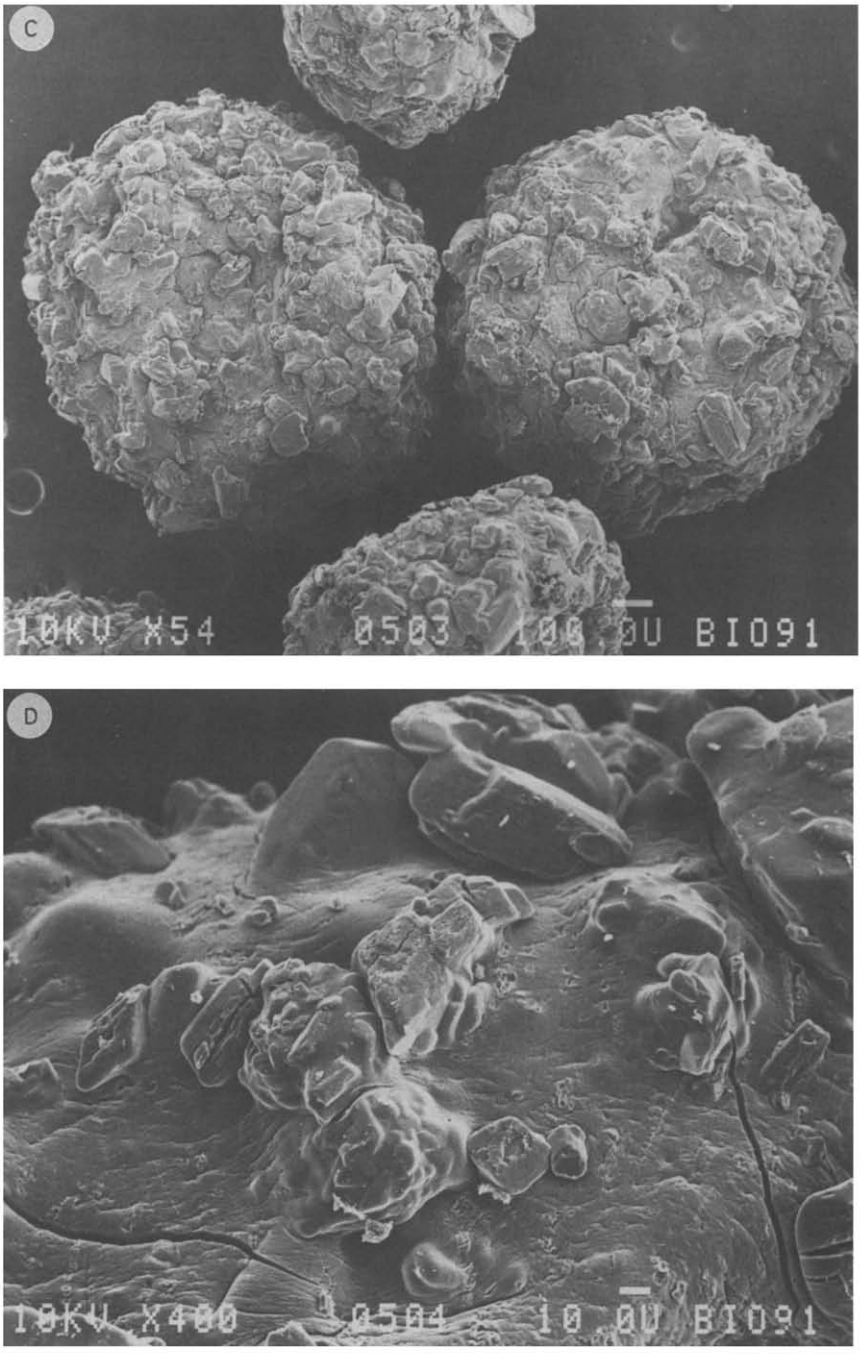

Fig. 1 (continued).

indicate a non-linear relationship between the calcium concentration and the responses $t_{50\%}$ and $t_{80\%}$ obtained in the investigated experimental area. Further investigations on the effect of the calcium concentration on drug release rate should therefore be performed using more than two fac-

tor levels. In a similar study with encapsulated sulfamethoxazole, the rate of drug release in 0.1 M HCl was shown to decrease when increased calcium concentrations were used for gel bead production (Badwan et al., 1985).

Scanning electron microscopy (SEM) was applied to visualize the surface structure of the different matrix formulations. More drug crystals appeared on the surface of those matrices which were low in drug content (Fig. 1). Where the drug content was greater, the drug crystals seemed to be more extensively covered by the alginate. Hence, drug encapsulation appeared to be improved when the matrices were produced from a more concentrated drug suspension. This might partly explain the greater retardation of drug release from matrices of higher drug content.

Alginate monomer composition

The suspension droplets form gel beads in the calcium chloride bath due to the binding of calcium ions to the alginate and formation of interchain bridges mainly between the G-blocks of the polymer chains (Grant et al., 1973; Smidsrød, 1974). Two alginates which differ in G content and length of G-blocks, but which have a similar viscosity grade (Table 1), were chosen as levels for the qualitative factor alginate type in the 2_V^{5-1} design.

Alginates rich in G residues, with long G-blocks, have been reported to shrink less during gelation and to provide wet gel beads with greater mechanical strength and higher porosity than alginates containing more M residues (Martinsen et al., 1989). Proteins have been shown to diffuse more readily from gel beads made of a high G alginate (Martinsen et al., 1992). High G alginates also have a stronger tendency to build inhomogeneous gels with a greater polymer density near the gel surface (Skjåk-Bræk et al., 1989).

The reported variations in the properties of wet gel beads are difficult to relate to the dried product. The higher porosity reported for high G alginate gel beads, for example, was not reflected in a higher drug release rate from the solid matrices. In contrast, matrices made from alginate of 68% G content gave a slower drug release than matrices consisting of an alginate with 51% G content.

Dried beads made of high G alginate are reported to swell only slightly in water due to the build-up of a stronger gel network during production (Smidsrød and Skjåk-Bræk, 1990). Only a few of the investigated formulations swelled visibly in the release medium. Nevertheless, a possible difference in re-uptake of water might contribute to variations in drug release from matrices made of different alginate types.

Conclusions

The process and formulation factors are of utmost importance for the size, composition and release properties of solid calcium alginate matrices containing theophylline.

The size of the matrices is mainly determined by a coaxial airstream that regulates the size of the suspension droplets gelled in the calcium chloride bath. In addition, a decrease in particle size is mediated by lower alginate concentrations or higher calcium concentrations.

The amount of drug suspended in the alginate solution and the alginate concentration are the main factors controlling the drug content of the matrices. An increase in the calcium concentration used for gelation reduces the drug content of the matrices. The moisture content is only dependent on the amount of drug added during production. When more drug is dispersed, the relative amount of both polymer and polymer bound moisture in the matrices is reduced. The addition of drug and the calcium concentration have the greatest effect on matrix calcium content.

The release of theophylline monohydrate from the matrices is influenced by the conditions used for gelation, the type and concentration of alginate and the amount of drug dispersed. A relatively good retardation of drug release in water can be achieved when the matrices are produced from an alginate of high G content and the calcium concentration, the gelling time, the alginate concentration and the drug addition are kept at high levels.

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References

Badwan, A.A., Abumalooh, A., Sallam, E., Abukalaf, A. and Jawan, O., A sustained release drug delivery system using calcium alginate beads. *Drug Dev. Ind. Pharm.*, 11 (1985) 239–256.

Bodmeier, R., Chen, H. and Paeratakul, O., A novel approach to the oral delivery of micro- or nanoparticles. *Pharm. Res.*, 6 (1989) 413–417.

Grant, G.T., Morris, E.R., Rees, D.A., Smith, P.J.C. and Thom, D., Biological interactions between polysaccharides and divalent cations: The egg-box model. *FEBS Lett.*, 32 (1973) 195–198.

Grasdalen, H., Larsen, B. and Smidsrød O., A P.M.R. study of the composition and sequence of uronate residues in alginates. *Carbohydr. Res.*, 68 (1979) 23–31.

Huggins, M.L., The viscosity of dilute solutions of long-chain molecules. IV. Dependence on concentration. *J. Am. Chem. Soc.*, 64 (1942) 2716–2718.

Kim, C.-K. and Lee, E.-J., The controlled release of blue dextran from alginate beads. *Int. J. Pharm.*, 79 (1992) 11–19.

Martinsen, A., Skjåk-Bræk, G. and Smidsrød, O., Alginate as immobilization material: I. Correlation between chemical and physical properties of alginate gel beads. *Biotechnol. Bioeng.*, 33 (1989) 79–89.

Martinsen, A., Storrø, I. and Skjåk-Bræk, G., Alginate as immobilization material: III. Diffusional properties. *Biotechnol. Bioeng.*, 39 (1992) 186–194.

Montgomery, D.C., *Design and Analysis of Experiments*, 3rd Edn, Wiley, Singapore, 1991.

Østberg, T. and Graffner, C., Calcium alginate matrices for oral multiple unit administration: I. Pilot investigations of production method. *Acta Pharm. Nord.*, 4 (1992) 201–208.

Salib, N.N., El-Menshawy, M.A. and Ismail, A.A., Utilization of sodium alginate in drug microencapsulation. *Pharm. Ind.*, 40 (1978) 1230–1234.

Skjåk-Bræk, G., Grasdalen, H. and Smidsrød, O., Inhomogeneous polysaccharide ionic gels. *Carbohydr. Polym.*, 10 (1989) 31–54.

Skjåk-Bræk, G., Smidsrød, O. and Larsen B., Tailoring of alginates by enzymatic modification in vitro. *Int. J. Biol. Macromol.*, 8 (1986) 330–336.

Smidsrød, O., Molecular basis for some physical properties of alginates in the gel state. *Faraday Disc. Chem. Soc.*, 57 (1974) 263–274.

Smidsrød, O. and Haug A., Dependence upon uronic acid composition of some ion-exchange properties of alginates. *Acta Chem. Scand.*, 22 (1968) 1989–1997.

Smidsrød, O. and Skjåk-Bræk, G., Alginate as immobilization material. *TIBTECH*, 8 (1990) 71–78.

Whitwell, J.C. and Morbey, G.K., Reduced designs of resolution five. *Technometrics*, 3 (1961) 459–477.

Yotsuyanagi, T., Ohkubo, T., Ohhashi, T. and Ikeda, K., Calcium-induced gelation of alginic acid and pH-sensitive reswelling of dried gels. *Chem. Pharm. Bull.*, 35 (1987) 1555–1563.