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Development of sulphamethoxazole-trimethoprim spheroidal granules: factors affecting drug release in vitro

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Summary

In the present study spheroidal granules of sulphamethoxazole (SMZ) and trimethoprim (TMP) were produced by the process of wet granulation of powders in a rotating pan with concomitant addition of a binder solution. Initially, preliminary trials were performed. In order to estimate the effect of binder, disintegrant and glidant on the dissolution rates of SMZ and TMP spheres a 2^3 factorial design was developed. After the correct formulation was obtained, SMZ and TMP spheres of pre-determined size fractions were encapsulated in a 5 : 1 weight ratio (400 mg SMZ and 80 mg TMP), and dissolution rates of active ingredients were examined against a commercially available product. Before encapsulation, TMP spheres were coated with Eudragit E 12.5% solution, in order to avoid interaction between SMZ and TMP molecules, which would probably produce a 1 : 1 molecular compound, as reported in the literature (Giordano et al., 1977).

Introduction

Spheroidal granules can be produced using the method of wet granulation of powders in a rotation pan, with concomitant addition of the binder solution. This method is considered to be one of the most valuable for the examination of granule growth mechanisms (Newit and Conway-Jones, 1958; Kristensen and Schaefer, 1987). The results published hitherto show that it is possible to examine the effect of the properties of starting materials and process variables on granule formation and growth as well as granule properties when this technique is applied.

Shape uniformity of the spheroidal granules, and the ability to control granule size and granule size distribution, by alteration of the process variables, are considered to be the most important advantages of this method (Capes and Danckwerts, 1965; Kapur and Fuerstenau, 1966). In addition, spheroidal granules present excellent flowability and uniform release profile of active ingredients, during dissolution in the gastro-intestinal tract.

The present study, in a first stage, examines the effects of binder, disintegrant and glidant on dissolution rates of sulphamethoxazole (SMZ) and trimethoprime (TMP) spheres, which were pro-

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duced by the previous method. For this reason, a 2^3 factorial design was established in order to evaluate the effect of the above factors on spheres physical properties and on dissolution profile of SMZ and TMP.

The results of the above preliminary study were used for the development of an appropriate formulation considering drug loading efficiency and dissolution rate.

Finally, SMZ and TMP spheres were encapsulated in a 5 : 1 weight ratio (400 mg SMZ and 80 mg TMP) and the dissolution profiles of active ingredients were examined against a commercially available product, according to USP XXI (Sixth Supplement) specifications.

Prior to encapsulation TMP spheres were coated with Eudragit E 12.5% solution, in order to avoid interaction between SMZ and TMP (Giordano et al., 1977).

Materials and Methods

Materials

Sulphamethoxazole (Wellcome Lot 27755), trimethoprime (Wellcome Lot 20273), talc USP.NF., Sugar USP.NF., calcium hydrogen phosphate USP.NF., polyvinylpirolidone (P.V.P. Gaf), sodium starch glycolate USP.NF. (Primogel Avebe), Eudragit E 12.5% (Rohm Pharma), acetonitrile, methanol (Prolabo HPLC grade) and hard gelatin capsules (No. 0, Capsugel) were employed. All other reagents were of analytical grade and were used without further purification.

Preparation of spheroidal granules

SMZ or TMP powders were placed in the coating pan. The speed and angle of rotation remained constant during the procedure (60 rpm, 45° respectively). Sodium starch glycolate, when used, was mixed with SMZ or TMP powders in a cubic mixer, and then the mixture was placed in the coating pan. The binder solution was added during the rotation, with the concomitant addition of talc. In order to improve the spherical shape of the granules the procedure was carried out for a further 15 min after the end of the liquid addition period. Thereafter, the spheres were dried at 30 °C for 24 h.

Factorial design

For the determination of the effects of binder disintegrant and glidant on sphere's physical properties and on dissolution rates of SMZ and TMP, a 2^3 factorial design was established (Bolton, 1984). The amounts of binder, disintegrant and glidant in each formulation, according to the factorial design, are listed in Table 1. The three factors were used at a low and a high level.

Encapsulation

The fraction between 60 μm and 1000 μm was used for filling the capsules. The SMZ and TMP spheres were mixed in a 5 : 1 weight ratio (after drug loading control), and the necessary quantity was encapsulated in hard gelatin capsules (No. 0).

Coating of TMP spheres

Since the purpose of coating was simply for isolation, 20 g Eudragit E 12.5% solution was sprayed on 100 g of dried TMP spheres, during the rotation of the coating pan, as described in the

TABLE 1

Amounts of disintegrant, binder and glidant in each formulation of the factorial design (amount of active ingredient in each formulation: 100 g)

Factors	Factors at low and high levels							
Disintegrant	d (0 g)				D (4 g)			
Binder	b (20 g)		B (40 g)		b (20 g)		B (40 g)	
Glidant	g (20 g)	G (50 g)	g	G	g	G	g	G
Formulation	dbg	dbG	dBg	dBG	Dbg	DbG	DBg	DBG

manufacturer's application pamphlets (Rohm Pharma Technical info E-2/e).

Evaluation of the spheres

Granule size Granule size was determined by sieve analysis. The cumulative percent frequency oversize distribution was obtained, and the median diameter corresponding to the 50% cumulative granule weight was noted (Aulton, 1990).

Density The true density (ρ_g) of the spheres was determined on an air comparison pycnometer (Beckman, Model 930). The bulk density (ρ_b) and the tap density (ρ_t) were measured in a 50 ml graduated cylinder mounted on a mechanical taping device. An accurately weighed sample of spheres was carefully added to the cylinder with the aid of a funnel. The initial volume was noted and the sample was then tapped until a constant volume was reached. The change occurring in packing arrangment for the spheres subjected to the tapping procedure, are expressed as the compressibility index $= [(\rho_t - \rho_b)/\rho_t] \times 100$. The percentage of inter-sphere porosity was calculated as $e = [1 - (\rho_t/\rho_g)] \times 100\%$.

Angle of repose The angle of repose was obtained by the method of fixed funnel and free standing cone. The repose angle was the average of five readings (Aulton, 1990).

In vitro drug release

Release of SMZ and TMP from the spheres was determined using a standard USP (Method II) dissolution apparatus (Pharmatest-type PTW/SII Haiburg, Germany). The dissolution medium was 900 ml of 0.1 N HCl solution. The test conditions were: Temperature $37 \pm 0.1°$C, basket rotation speed 75 rpm (according to USP XXI, Sixth Supplement requirements). Aliquots were withdrawn at 5, 10, 15, 20, 30, 40, 50 and 60 min intervals. The samples were assayed with an HPLC method.

HPLC method

The HPLC system used was a Spectra Physics pump model 8800, equipped with a variable-wavelength detector, Spectra 100 (set at $\lambda_{max} = 230$ nm) which was connected with a Spectra Physics Chromjet integrator. Analytical samples were introduced into a C_{18} column through a Rheodyne 7125 injector with a 20 μl loop valve. The mobile phase consisted of acetonitrile : 0.1 M sodium acetate (30 : 70 v/v), adjusted to pH 6.00 by dropwise addition of glacial acetic acid. The flow rate was 1 ml/min.

Calibration curves show good linearity over the concentration range examined (2–24 μg/ml for SMZ and 0.4–4.8 μg/ml for TMP). Regression coefficients were 0.9998 for SMZ and 0.9993 for TMP.

Results and Discussion

Evaluation of physical properties

The physical properties, namely, median diameter $d_{(50)}$, density (true, bulk and tap), porosity (e%), compressibility index (%) and angle of re-

TABLE 2

Physical properties of spheres produced according to the factorial design

Formulation	Size $d_{(50)}$ (μm)	Density (g/ml)			Porosity (e%)	Compressib. index (%)	Angle of repose (°)
		True (ρ_g)	Bulk (ρ_b)	Tap (ρ_t)			
dbg	740	1.504	0.643	0.724	51.86	11.19	20.02
dBg	790	1.792	0.757	0.840	53.13	09.88	22.08
dbG	680	1.518	0.658	0.731	51.84	09.98	18.99
dBG	900	1.831	0.770	0.866	52.70	11.08	16.89
Dbg	610	1.324	0.522	0.609	54.00	14.28	23.99
DBg	380	1.459	0.620	0.701	51.95	11.55	25.79
DbG	510	1.394	0.592	0.684	50.93	13.45	19.99
DBG	490	1.500	0.603	0.683	54.47	11.70	17.28

pose of the spheres are listed in Table 2. The latter four properties correspond with the 600–1000 μm weight fraction, which was used for the filling of the capsules. The main and interaction effects of factors on the physical properties of spheres are listed in Table 3.

It is interesting to note that the presence (4 g) of Primogel (formulations Dbg, DBg, DbG and DBG) dramatically decreased the median diameter ($d_{(50)}$). As shown in Table 3, an increase in Primogel concentration from a low to high level resulted in a decrease of 280 μm in median diameter. This could be attributed to the water-absorbing nature of sodium starch glycolate (Avebe product information, Ref. no. 05.13.32.103F). Because of this property of Primogel, local overwetting is avoided and consequently granule size is reduced.

Besides the above-mentioned effect, Primogel has a negative influence on the spherical shape of spheres. As shown in Table 3, the increase in Primogel from a low to high level resulted in a decrease in true density, an increase in porosity and an increase in the compressibility index. The above findings, in combination with the smaller size of the spheres, when Primogel was incorporated, indicate a decrease in flowability of the spheres. This is also confirmed by the increase in repose angle. The decrease in flowability and the increase in porosity imply a less spherical shape of the granules when Primogel is present. The increase in porosity indicates that the surface of the spheres became more irregular, and also that an increase in the volume of the surface connected pores occurred.

The increase in binder from a low to high level resulted in an increase in sphere size and a decrease in compressibility index, indicating better flowability, which was also confirmed by the decrease in the repose angle.

The increase in glidant from a low to high level had a pronounced effect on the increase in flowability indicated by the increase in size and decrease in compressibility index and, particularly, the decrease in angle of repose ($-4.683°$, Table 3). This was attributed to the glidant and anti-adherent properties of talc, and an improvement in the spherical shape of Re granules (decrease in porosity of -0.250%, Table 3).

It is interesting to note that, although the main effect of disintegrant and binder was to increase granule porosity, the interaction effect of those two factors was a decrease in both porosity and angle of repose (Table 3), indicating that the interaction of the two factors resulted in an improvement of the spherical shape of the granules despite the fact that Primogel alone had the opposite effect.

Dissolution test

The dissolution test results are depicted in Figs 1 and 2. In formulations where sodium starch glycolate was not incorporated (Table 1, F: dbg, dBg, dbG, dBG), according to the factorial design,

TABLE 3

Main and interaction effects of factors on the physical properties of spheres

Factors	Effect on size	Effect on true density	Effect on porosity	Effect on compressibility index	Effect on repose angle
Disintegrant	−280	−0.968	0.390	2.2125	2.268
Binder	5.00	0.2105	0.905	−1.1725	−0.238
Glidant	15.0	0.0410	−0.250	−0.1725	−4.683
Interaction of factors	Effect on size	Effect on true dens.	Effect on porosity	Effect on compr. index	Effect on repose angle
D, B	−130	−0.30	−0.160	−1.0675	−0.87
D, G	−10	0.015	−0.025	−0.1675	−1.57
D, G	95	−0.001	1.295	0.8475	−2.17

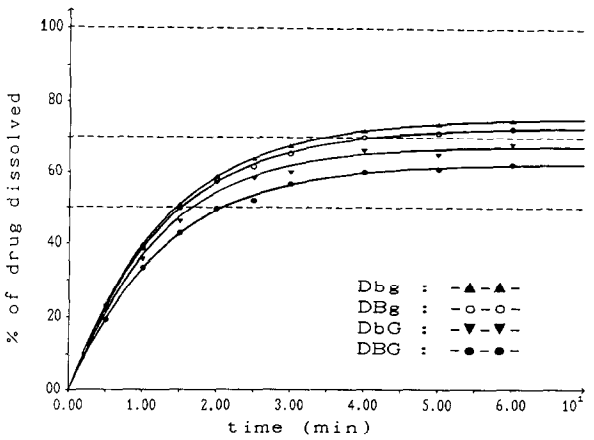

Fig. 1. Dissolution profile of SMZ from spheroidal granules produced according to formulations Dbg, DBg, DbG, DBG, [Dbg (▲———▲), DBg (○———○), DbG (▼———▼), DBG (●———●)].

$T_{50\%}$ was not obtained, after 60 min of testing. For this reason, $T_{25\%}$ was used for the analysis of the results.

The main and interaction effects of the three factors on $T_{25\%}$ are listed in Table 4. The presence of Primogel resulted in a decrease of 30.75 min in $T_{25\%}$. The increase in binder from a low to high level resulted in a corresponding increase of 4.25 min in $T_{25\%}$. Accordingly, increase in glidant from

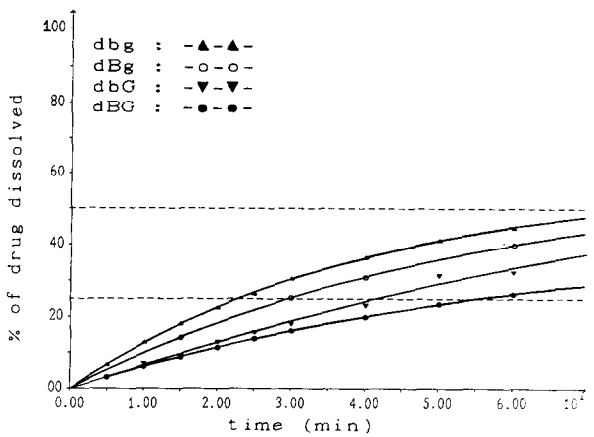

Fig. 2. Dissolution profile of SMZ from spheroidal granules produced according to formulations dbg, dBg, dbG, dBG. [dbg (▲———▲), dBg (○———○), dbG (▼———▼), dBG (●———●)].

TABLE 4

Main and interaction effects of factors on $T_{25\%}$

Factors	Effect of factors on $T_{25\%}$
Disintegrant	−30.75
Binder	4.25
Glidant	12.75
Interaction of factors	Interaction effects on $T_{25\%}$
D, B	−3.25
D, G	−9.75
B, G	1.25

a low to high level resulted in an increase of 12.75 min in $T_{25\%}$ (Table 4).

The results of dissolution tests clearly indicate that primogel had a pronounced effect on the dissolution rate of active ingredients (Figs 1 and 2), compared to the effect of glidant and binder.

Although talc had a pronounced effect on the increase of T_{25}% (because of its hydrophobic nature), its addition appeared to be quite necessary, since the anti-adherent properties prevent sticking between the particles of the powder and the wall of the pan (both SMZ and TMP powders were cohesive), and also promotes the flow of the spherical beads, during rotation.

Taking the above into consideration, efforts were focused on improving dissolution rates and increasing drug loading efficiency.

In the second stage of study, an attempt was made to decrease the amount of talc which was utilized during the procedure, to the minimum necessary levels (Table 5). In formulation 1 of Table 5, it was found that, although the presence of calcium hydrogen phosphate increased dissolution rate to acceptable levels (Fig. 3), further examination was abandoned since drug loading was not sufficient for the encapsulation of SMZ beads.

In formulation 2, the addition of PVP (2.5% w/v solution in ethanol) resulted in an increase in drug loading, but SMZ beads became harder and consequently, the dissolution rate was decreased (Fig. 3).

Finally, in formulations 3–5 (Table 5) the amounts of talc and binder solution (sugar 37.5% in distilled water) were progressively reduced to

TABLE 5

Formulations used in the second part of the study

Ingredients (g)	Formulation					
	1	2	3	4	5	6
SMZ	100	100	100	100	100	–
TMP	–	–	–	–	–	100
Primogel	–	–	4	4	4	4
Talc	20	8	30	10	8	7
$CaHPO_4 \cdot 2H_2O$	80	35	–	–	–	–
PVP (2.5%)	–	1.5	–	–	–	–
Sugar	34	17	46.5	41.25	34	30
H_2O	56	28	77.5	68.8	56	48
Drug loading	44%	60.30%	55%	57.74%	65.40%	68.06%

the minimum necessary levels. As a result spheronization processing time was increased to 30 min after the end of the liquid addition period. The dissolution profiles of formulations 3 and 4 are shown in Fig. 3 and for formulation 5 in Fig. 4. Moreover formulation 5 exhibits the highest drug loading capacity and also the dissolution rate complies with USP XXI (Sixth Supplement) specifications.

TMP beads were prepared according to formulation 5 (formulation 6 of Table 5) and their dissolution profile is also shown in Fig. 4. Prior to encapsulation, TMP spheres were coated with Eudragit E 12.5% solution in order to avoid interaction between SMZ and TMP, which would probably produce a 1 : 1 molecular compound between SMZ and TMP molecules (Bettinetti et al., 1981; Bettinetti and Giordano, 1988). The coating had no significant effect on the dissolution profile of TMP spheres.

The reproducibility of the manufacturing procedure was evaluated with the production of two more batches, in terms of the coefficient of variation. It was found that all three batches had almost the same drug loading capacity (SD ±0.78; CV, 1.18% for SMZ; SD, ±0.98; CV, 1.42% for

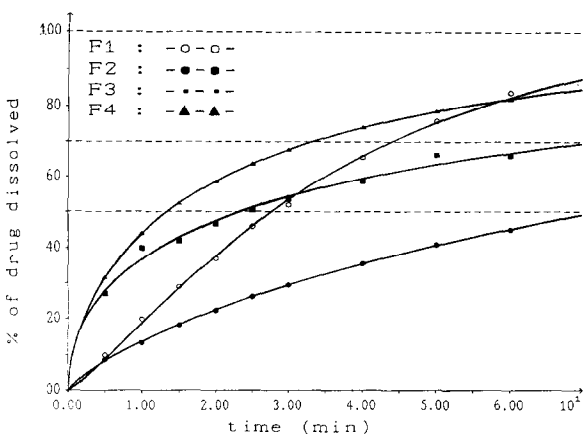

Fig. 3. Dissolution profile of SMZ from spheroidal granules produced according to formulations 1–4 of Table 5. [F1: (○———○), F2 (●———●), F3 (■———■), F4 (▲———▲)].

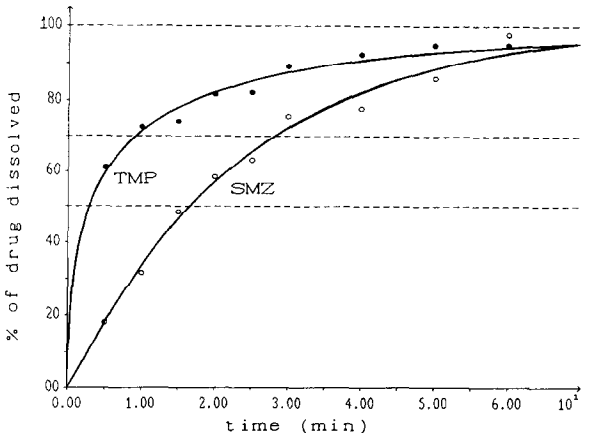

Fig. 4. Dissolution profiles of SMZ and TMP from spheroidal granules produced according to formulation 5 of Table 5. [SMZ (○———○), TMP (●———●)].

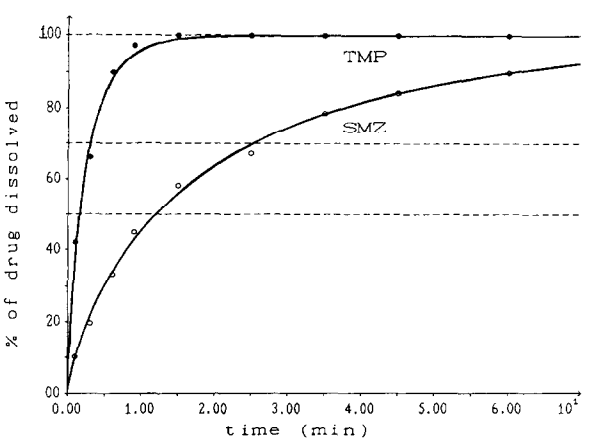

Fig. 5. Dissolution profile of SMZ and TMP from a commercially available product [SMZ (○———○), TMP (●———●)].

TMP). The CV was not more than 2% for the three batches studied.

The dissolution profiles of SMZ and TMP obtained from a commercially available product are shown in Fig. 5.

Conclusions

The above method of wet granulation is an important technique for producing spherical granules of pre-determined physical properties, shape and size, by alteration of the process variables.

Sodium starch glycolate is a useful excipient not only in improving dissolution rate of active ingredients, in the produced spheres, but also in controlling granule size and granule-size distribution.

The option of TMP sphere coating is very useful in overcoming any possible interactions between TMP and SMZ.

Factorial design is a useful method in order to determine the effect of several granulating factors on the properties of the final product.

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