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THE CONTROL OF DRUG RELEASE FROM CONVENTIONAL MELT GRANULATION MATRICES

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ABSTRACT

Sustained release potassium chloride tablets were prepared using a melt granulation formulation in a Baker Perkins Granulator. Parts of the validation for this manufacturing process are highlighted in this paper including granulation end point temperature, incorporation of extragranular excipients, amount of wax in the formulation, granule cooling rate and scale of the operation. A number of other factors have been studied which are not included here although they are no less important. The release of potassium chloride from tablets was found to be dependent on the wax level and the amount of extragranular excipients ("wicking agent"). Within the controlled production process, any variation in granulation end point temperature and granule cooling rate should not have any significant effect.

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INTRODUCTION

The production of sustained release oral dosage forms has been achieved by a number of methods including; coated pellets, osmotic pumps and matrix devices. Matrix devices are relatively cheap and easy to manufacture. Most matrix formulations have first order release kinetics which are not ideal for a sustained release product depending of course on the type of drug and its absorption kinetics. However for potassium chloride, sustained release is required mainly to avoid gastric irritation and not to achieve constant blood levels so first order kinetics are satisfactory. The problem of gastric irritation and ulceration has been seen with potassium chloride formulations. Alsop et al have noted little difference between wax matrix and microencapsulated potassium chloride (1).

Melt granulation for rapid and sustained release has been used in Europe for a number of years. The process offers several advantages over alcoholic granulation, namely cost and safety. Solvents and the associated flame proof facilities, and solvent recovery equipment are not required. The heat required for the granulation process is generated by friction as the product is moved by the mixer blades. A heated jacket can also be used to supply the heat required but is relatively inefficient.

This development aims to validate a melt granulation process which has replaced an alcoholic granulation. The criterion for success is to produce a tablet of similar release profile by both routes of manufacture and determine the controlling factors. Consistency of quality allowing for production variations such as machine performance is an integral requirement. The quality of the product is determined by in-vitro tests on tablets which relate to the in-vivo performance.

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EXPERIMENTAL REVIEW

Formulation factors

It should be possible to change drug release by altering the wax content of the matrix or by the incorporation of extragranular or intragranular excipients which will aid the penetration of water into the matrix. These two factors should not change during production but their effects must be quantified if a robust or highly controlled manufacturing process is required.

Processing factors

These are perhaps more likely to vary during production since the process is operator controlled and machine performance may change. The factors we anticipate will control dissolution are granulation temperature, granule cooling rate and the scale of operation. The process should be so robust that, for example, a granulation temperature a few degreees high or low should still produce material of acceptable quality.

Granulate manufacture

The potassium chloride (ABM Chemicals, Stockport, Cheshire), Special Wax 4900 (H. Lux and Co. FRG) and other intragranular materials are mixed at high speed using the impeller and breaker. The heat produced by friction increases the temperature of the mix. When the desired temperature is reached the cooling water supply to the vessel jacket is applied. The mix is agitated using the impeller speed to prevent the granulate caking as it cools. It may be necessary to increase the agitation occasionally to prevent a build up of material on the bowl. When the mix has cooled extragranular excipients can be blended in. The granulate is discharged, screened to remove any oversize caked material (normally about 0.5%) and compressed. During processing, time, temperature, impeller current and

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breaker current are all monitored. A typical profile for a 60L machine is shown in Fig. 1 & 2. The resultant product is found to yield an Higuchi square root of time dissolution profile (Paddle method) shown in Fig. 3.

Machine details

The experiments reported here (except those relating to scale of processing) use a 60L Baker Perkins Granulator. This machine was chosen because of its ability to generate sufficient heat for granulation in a reasonably short time. (Fielder and Diosna mixers were unsuitable because of the long granulation time). The Baker Perkins Granulator is similar to many high speed mixer granulators in design having a large impeller blade in the base of the bowl and a side mounted breaker. Both blades have variable speed controls and current monitors. The temperature of the mix can be monitored by a built-in probe which passes through the jacket and vessel wall. This must be calibrated before use.

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Production variation due to granulation temperature changes

The results in Table 1 were obtained by manufacturing eight separate batches using a 60L Baker Perkins Granulator. For Special Wax 4900 the granulation is complete at about 89°C. Further increases in temperature produce only small decreases in dissolution rate. Any temperature above 89°C will produce a consistent but relatively slow dissolution. The slope of the dissolution temperature curve (Fig. 4) is very steep before this point, so small variations in the granulation temperature will produce a variable product.

It should be possible to have a lower granulation end point temperature by using a lower melting point wax i.e. for heat

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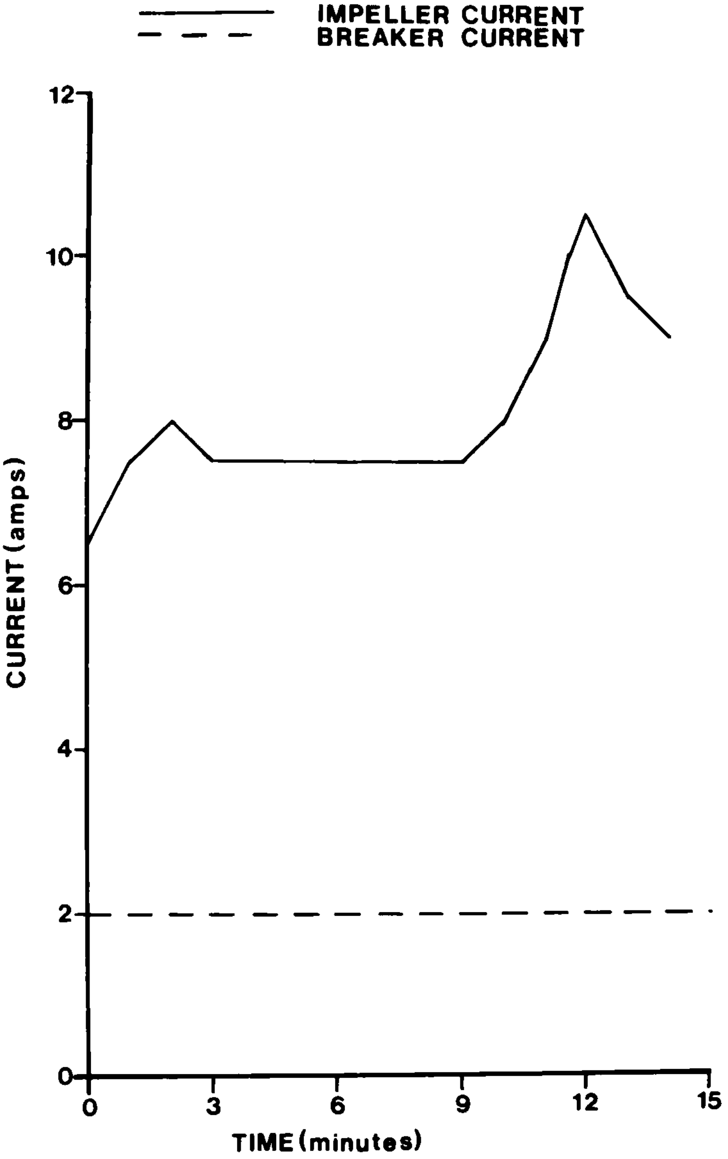

FIGURE 1

Impeller and breaker current demand during granulation

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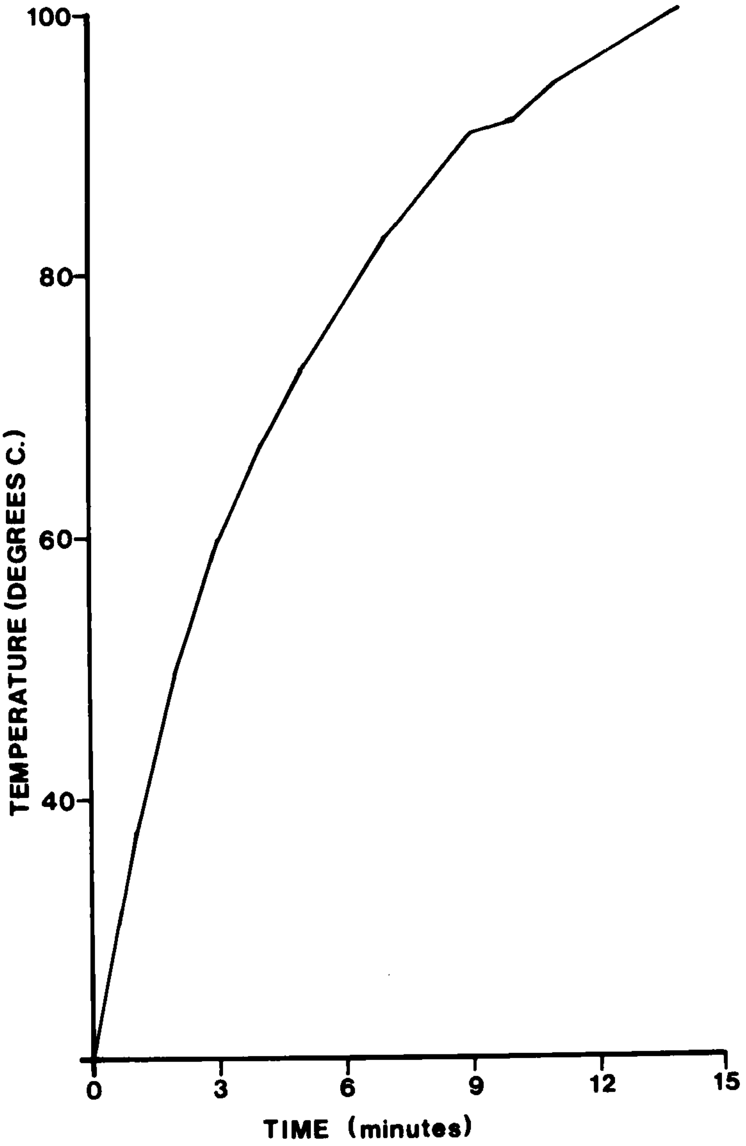

FIGURE 2

Temperature increase during granulation

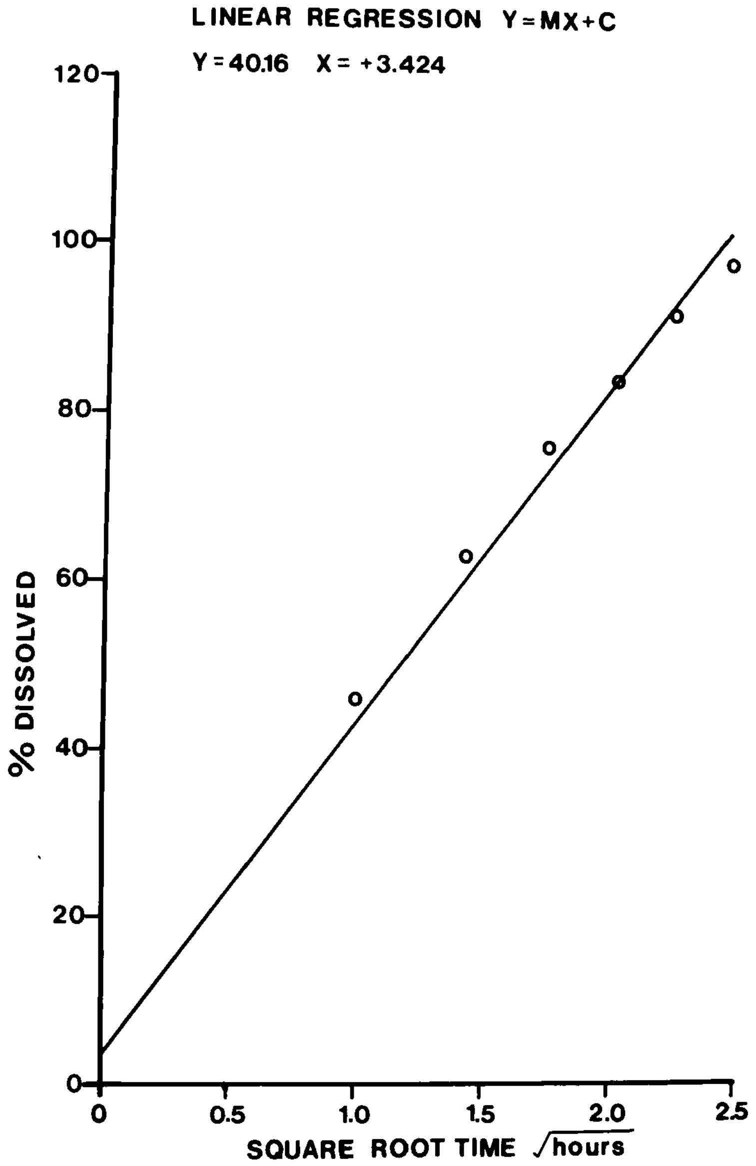

FIGURE 3

Dissolution versus square root of time for tablets produced from a 60L granulation

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TABLE 1 - Processing Parameters for Granulations at Different Temperatures

Batch no.	Granulation temperature (°C)	Granulation time (minutes)	Cooling time (minutes)	Granules Mass Median Diameter (μ)
1	70	9.25	38	81
2	80	11.0	48	111
3	89	9.0	50	143
4	90	13.67	64	119
5	92	11.0	50	116
6	95	12.0	47	114
7	100	15.5	95	119
8	110	15.75	110	137

TABLE 2 - Dissolution Results for Granulations in Table 1

Batch Number	Dissolution % hr. 1	2	3	4	5	6
1	80	100	-	-	-	-
2	71	92	100	-	-	-
3	47	65	77	87	93	102
4	47	65	77	85	92	98
5	45	63	77	84	90	99
6	44	62	75	84	89	96
7	42	57	69	77	84	92
8	42	58	71	81	86	93

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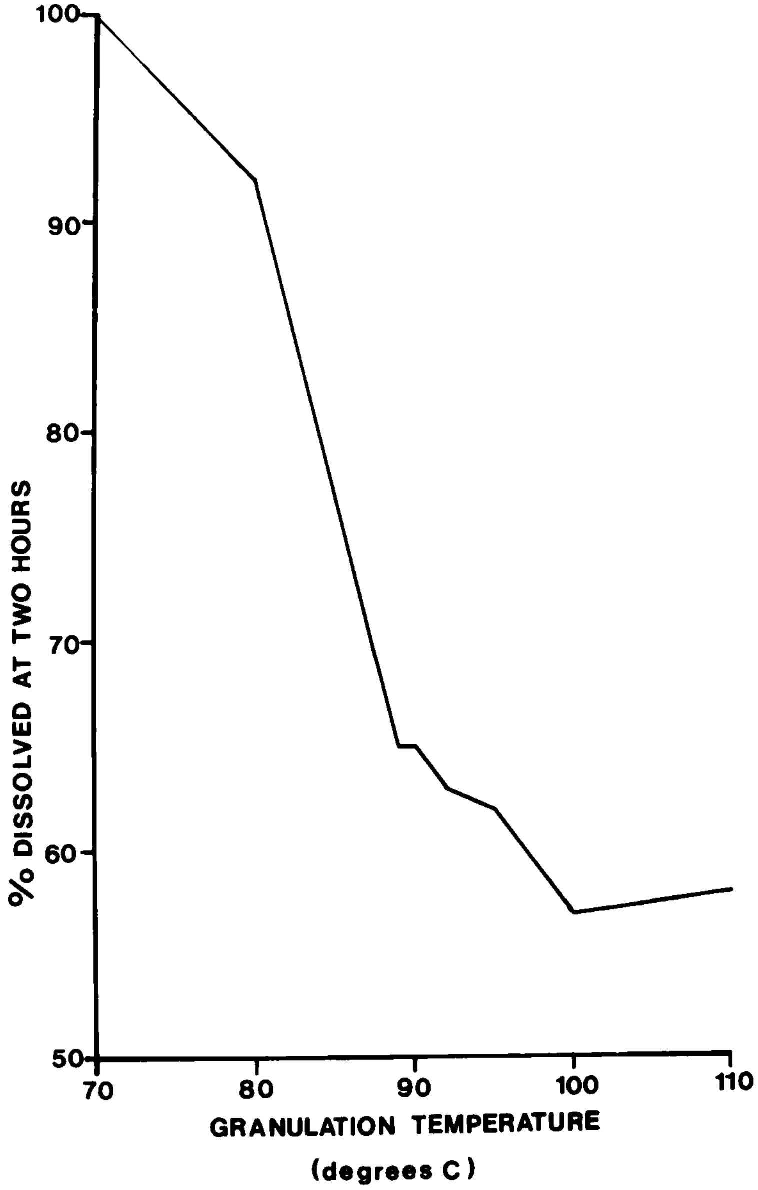

FIGURE 4

Granulation temperature versus percent dissolved at two hours from tablets

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labile drugs. Special Wax 4900 melts at ~100°C but the granulation takes place when the bulk temperature is less than this.

Table 1 also shows there is a relationship between the required granulation temperature and the time to reach it, although it is more variable than expected. The granule size produced seems to be unrelated to the granulation temperatures above 80°C.

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Product Variation due to Changes in Wax Level

Variation in wax level can be used to change the dissolution of drug from tablets. There is a general increase in dissolution rate as wax level falls although the lowest level of wax still produces a significant slowing of dissolution (Fig. 5). A change in formulation of ± 10 mg of wax produces a small change in dissolution. In production there should be little variation in dissolution due to varying wax level.

Product variation during scale up

The product has been made at three different scales using Baker Perkins 10L, 60L and 600L granulators. The mean process details are given in Table 5.

A few points are worthy of note. A relatively small batch size is used in the 60L machine because problems have been found with overloading on the main impeller and breaker circuits early in the process. The batch size was reduced to produce an acceptable current requirement throughout the process. The current demand seems to follow a pattern for the 10L and 60L machines through the granulation cycle (Fig. 1) although the absolute values are different. The 600L machine behaves differently in that this pattern may or may not be observed and

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TABLE 3 - Process Parameters for Granulations containing Different Levels of Wax

Batch No.	Wax Level (mg/tablet)	Granulation Temperature (°C)	Granulation Time minutes	Cooling Time minutes	Granule Mass Median Diameter µm
1	100	98	12.42	75	124
2	90	96	14.5	58	117
3	80	98	15	49	121
4	70	98	14	41	112
5	60	98	12.5	75	128
6	50	98	15	-	70

TABLE 4 - Dissolution Results from Granulations containing Different Levels of Wax from Table 3

Batch No.	Wax Level (mg/tablet)	Dissolution % hr. 1	2	3	4	5	6
1	100	31	52	64	74	81	88
2	90	42	58	70	79	88	93
3	80	44	60	72	80	87	94
4	70	47	65	77	86	93	100
5	60	47	65	78	87	95	102
6	50	51	70	82	90	97	101

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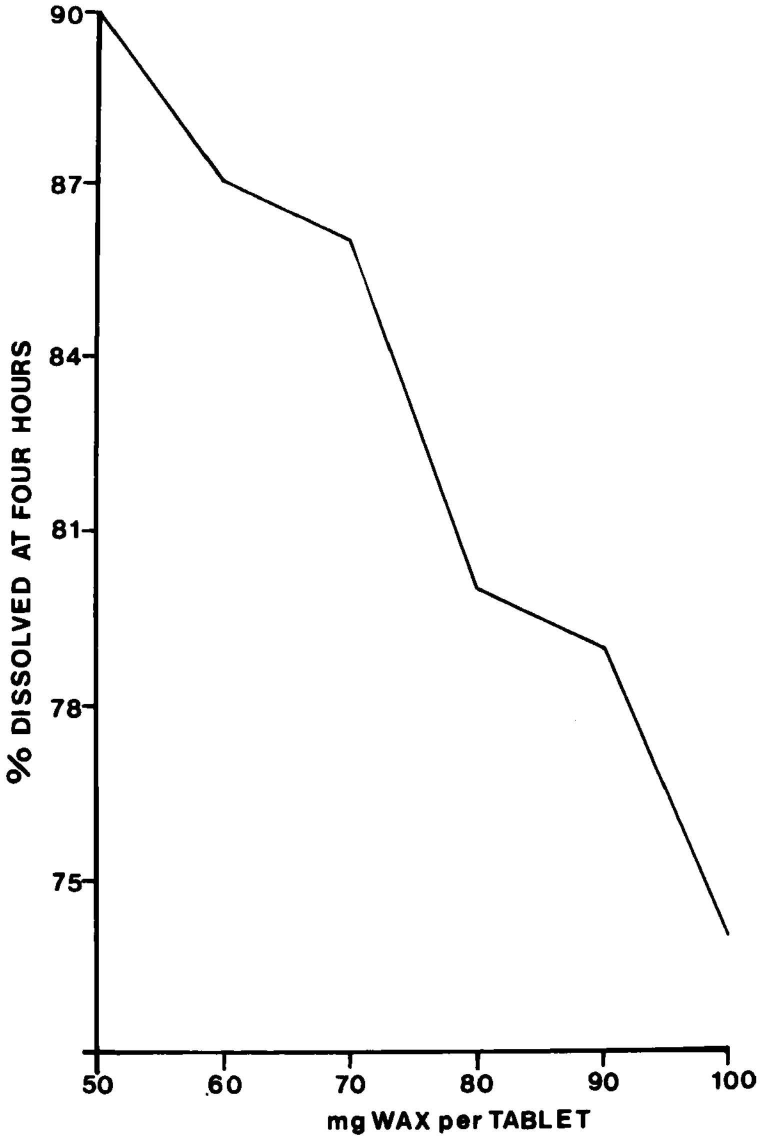

FIGURE 5

Wax level versus percent dissolved at four hours from tablet

TABLE 5 - Process Parameters of Three Baker Perkins Granulators

	10L	60L	600L
Batch size (kg)	4.5	23	330
Granulation time (minutes)	50	14	30
Cooling time (minutes)	15	40	70
Granule size	134	110	120
Batch size as % w/v capacity	45	38	55

we are not attempting to identify the causes for this. This pattern does not seem to have an effect on dissolution.

The cooling time increases with batch size due to the relative decrease in surface area of the cooling jacket per unit mass of granulate.

The granulate produced from each scale seems similar in size distribution and flow properties, and the dissolution of tablets from the 60L and 600L appears similar on compression using the same equipment (Table 6).

Cooling rate variation

This experiment is designed to illustrate the dissolution variation of the cooling water temperature changed between the processing of each batch. Table 7 and Fig. 6 show that the dissolution rate will only change in extreme circumstances. The cooling water at standard set temperatures 26°C and 46°C produce

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TABLE 6 - Typical Dissolution Profiles of Tablets

Scale	Dissolution % at Hour					
	1	2	3	4	5	6
10L	30	42	52	60	65	72
60L	47	64	77	85	93	99
600L	36	55	64	75	83	90

TABLE 7 - Dissolution of Tablets from Material Cooled in Different Ways

Cooling Method	Dissolution % hr.					
	1	2	3	4	5	6
In situ	34	48	59	68	74	81
Glatt	39	54	65	75	82	96
Oven	43	58	70	80	87	93
46°C Cooling Water	33	47	58	67	74	80
26°C Cooling Water	34	48	58	69	76	83
The granules are left	49	67	81	90	95	102
to cool to 60°C before	47	66	77	87	93	98
the water supply is	48	65	78	87	92	97
turned on	48	66	77	87	95	

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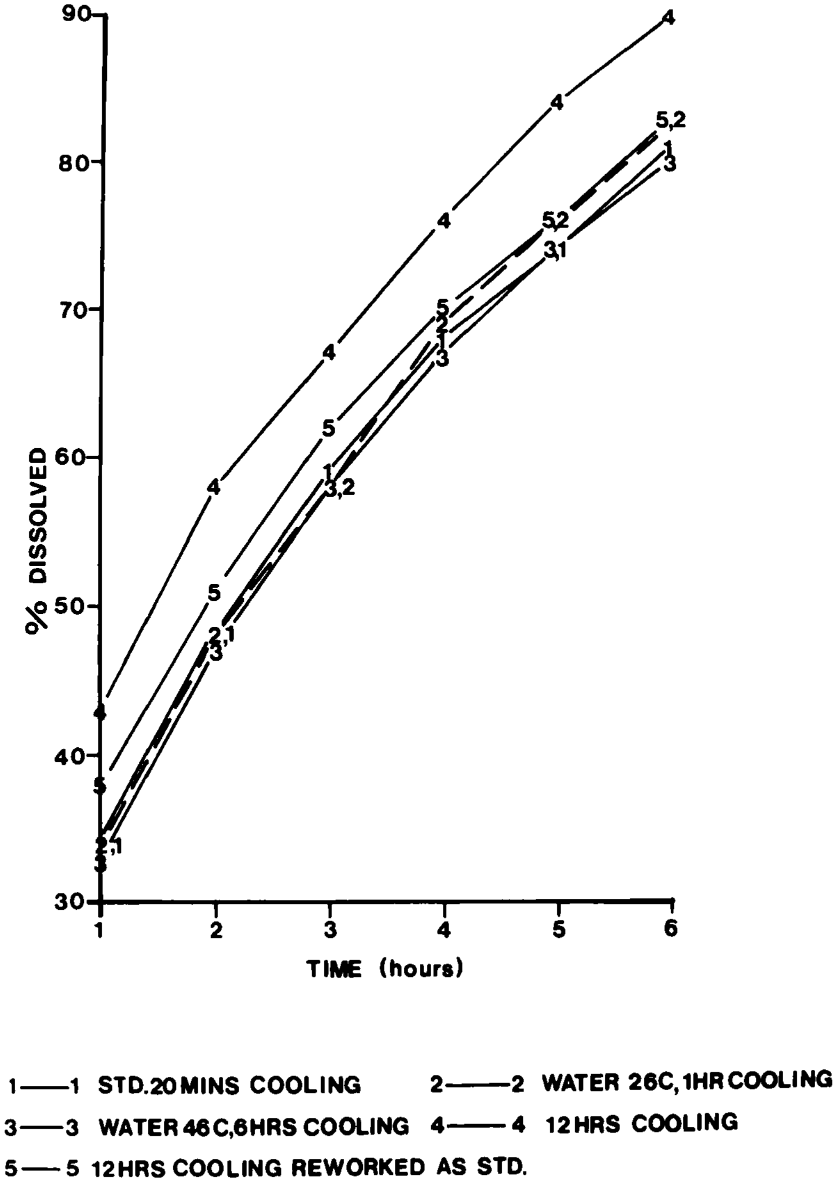

FIGURE 6

Percent dissolved at four hours from tablet

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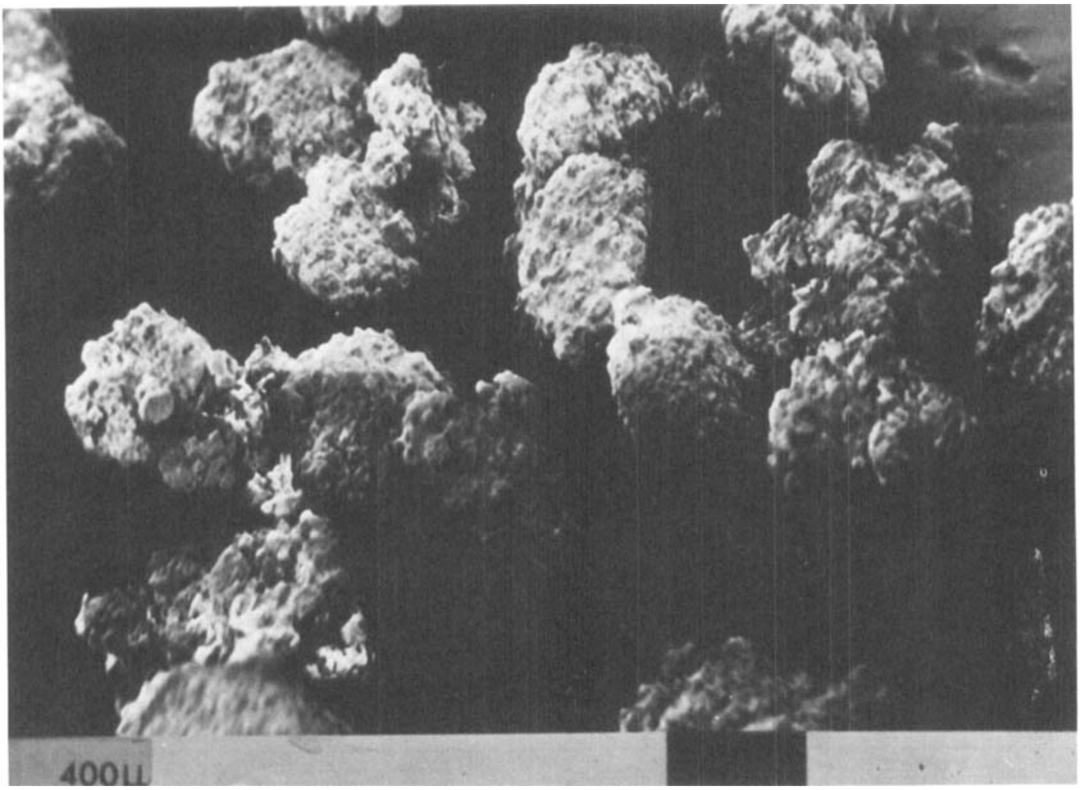

FIGURE 7

Scanning electron micrograph of potassium chloride granules cooled in a fluid bed dryer (355-500 μm fraction)

little change in dissolution of the final product. However if the cooling water is not applied until the mix reaches 60°C as in line 4 of the graph the dissolution is significantly more rapid. This batch was subsequently reworked as standard and the dissolution fell to a level between standard and rapid dissolution. Care should be taken with the granule cooling as it relates significantly to consistency of quality. The unusual result (Table 7) is the dissolution from granulate cooled in the Glatt fluid bed dryer. This method produces different granule shapes compared to the material cooled in situ (ref. Fig. 7 & 8).

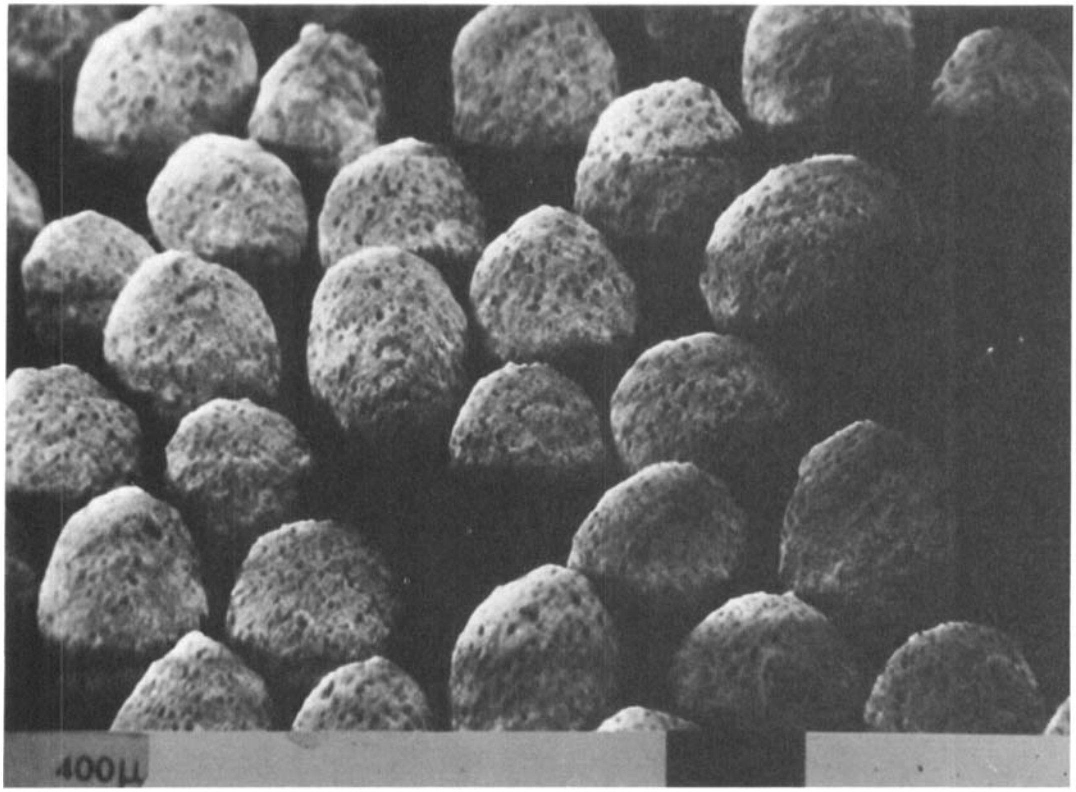

FIGURE 8

Scanning electron micrograph of potassium chloride granules cooled "in situ" (355-500μm fraction)

The constant mixing required for in situ cooling to prevent the granulate caking "moulds" the granulate into quite regular spheres. The "shock" cooling of the granulate in the Glatt moulds the granules to a lesser extent as it cools very rapidly. Cooling the granulate in a fluid bed dryer takes approximately ten minutes (90° - ~ 30°). In situ cooling takes ~ 40 minutes (60L scale) and delaying the time before cooling water is put into the jacket lengthens the process time to 3 hours. Oven cooling the hot granulate involved placing the granulate in an

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oven at the granulation temperature. The oven was turned off and allowed to cool. The material produced also had a more rapid dissolution compared to the fluid bed and in situ cooled material.

The use of extragranular wicking agents to increase product dissolution

Extragranular excipients can be added to the matrix formulation to aid the dissolution. Colloidal silica (Wacker Chemicals) has been used although the effect is variable depending on the matrix formulation and mixing conditions. Figs. 9 and 10 show a typical series of dissolution profiles, for various colloidal silica levels. The results (Table 8) indicate that up to 15 mg colloidal silica per tablet can produce a significant increase in dissolution. Further additions of colloidal silica have a lesser effect. Surprisingly the level of colloidal silica produce more dramatic changes in dissolution than changes in wax level. Prolonged mixing can produce a reduction in dissolution rate of the final product. The production process needs to take this into account. Care must be taken with weighing and mixing.

DISCUSSION

The melt granulation of potassium chloride produces a consistent product on the 10L and 60L scales which the quoted results refer to. The factors which can change the release profile are the level of colloidal silica wax, granulation end point temperature, cooling rate and scale level of operation. However the level of the excipients should be fixed in the production process and errors will only occur if materials are not added or incorrectly weighed. The colloidal silica level is perhaps the most significant as this can produce the largest

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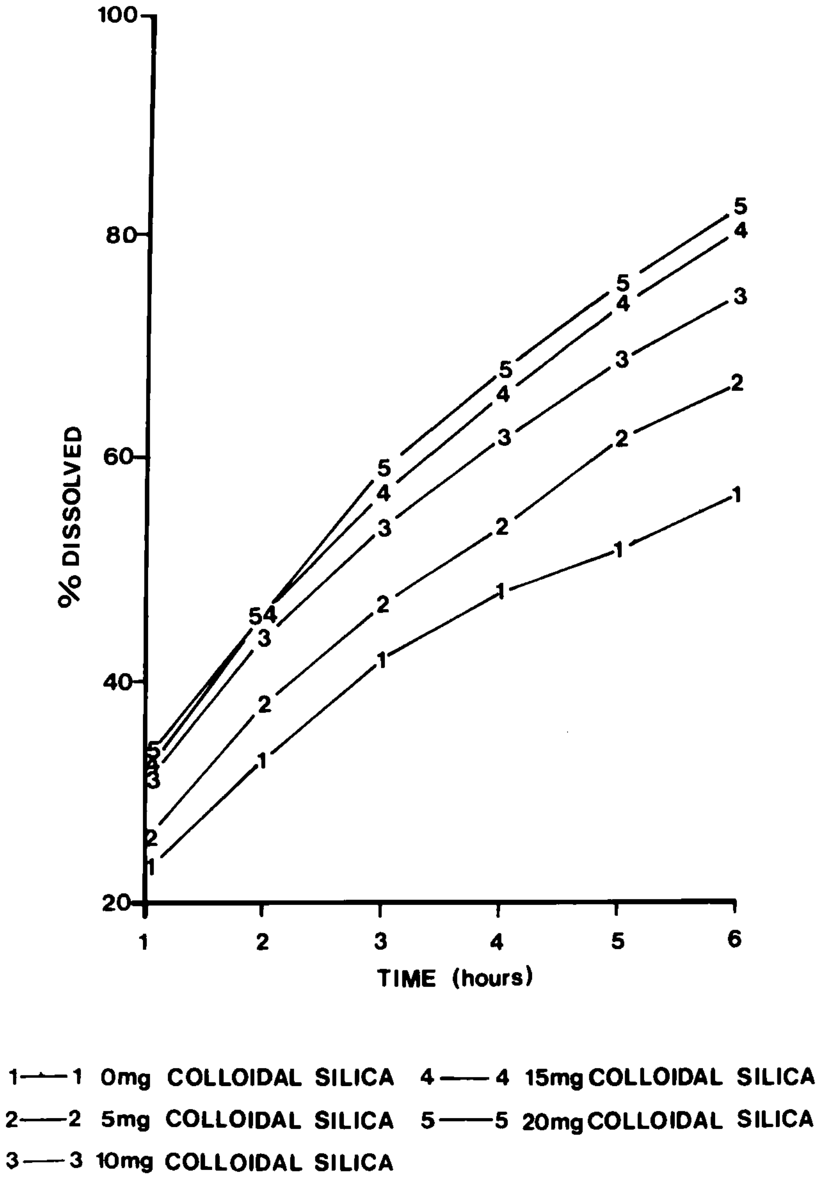

FIGURE 9

Percent dissolved versus time for tablets made from granules containing various levels of colloidal silica

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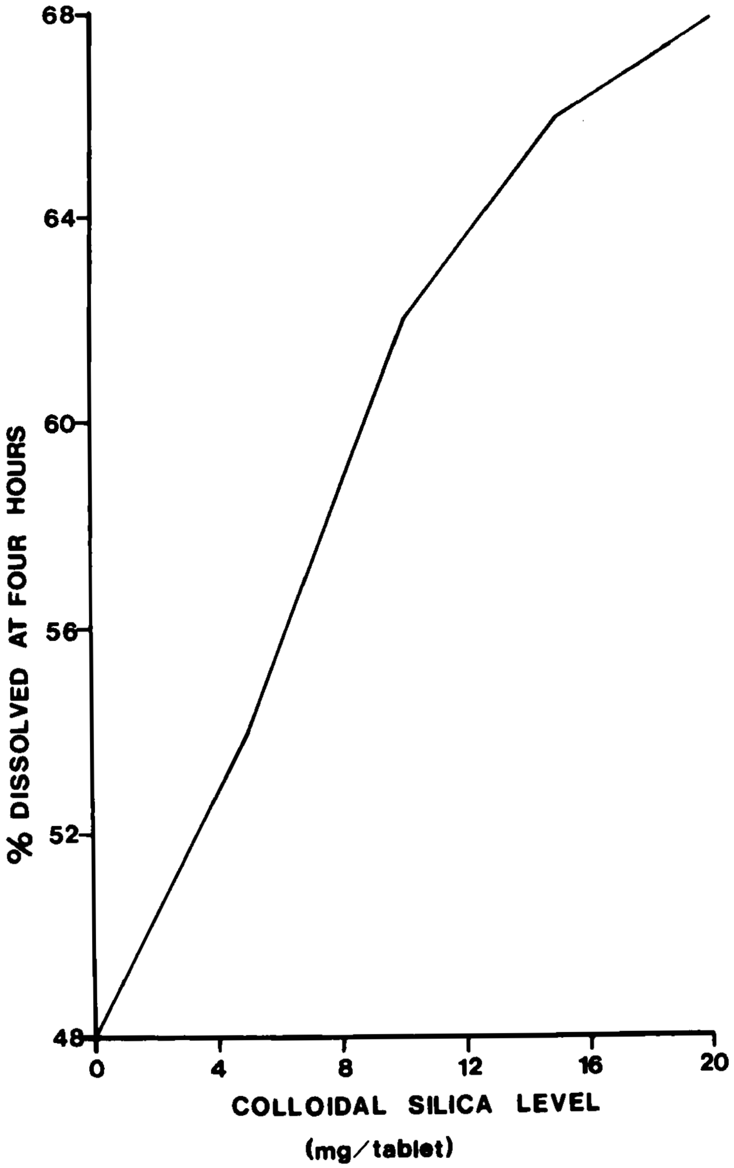

FIGURE 10

Colloidal silica level versus percent dissolved at four hours

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TABLE 8 - Dissolution of Tablets Containing Different Amounts of Colloidal Silica

Batch No.	Colloidal Silica mg/tablet	% Dissolved					
		1	2	3	4	5	6
1	0	23	33	42	48	52	57
2	5	26	38	47	54	62	67
3	10	31	44	54	62	69	75
4	15	33	46	57	66	74	81
5	20	32	46	59	68	76	83

dissolution changes per unit weight of the excipients. Care should be taken to blend this material optimally, a step requiring separate validation.

The process has been controlled using an end point temperature of 90°-95°C, clearly remote from the steep portion of the temperature versus dissolution profile. Slight variations should not therefore produce undesirable changes in dissolution. The cooling conditions clearly have some effect but, providing cooling water is applied immediately, little variation will be seen. In setting meaningful, performance related acceptance criteria for this process, it has also been possible to identify some procedural or formulation related aspects which have proven to be non-critical. Although being controlled within reasonable practical limits of manufacture, such points need not be closely monitored for compliance with the performance related parameters in subsequent full scale validation trials.

CONCLUSION

A number of granulation parameters which affect the dissolution of potassium chloride from tablets have been quantified. The most noteworthy are the levels of colloidal silica and wax. Strict control of these parameters in the manufacturing guide should lead to a reproducible product whose dissolution quality will be highly predictable despite the vagaries of the melt granulation process.

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