DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(6), 1001-1022 (1987)

# 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.

## 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.

## 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 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.

## 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

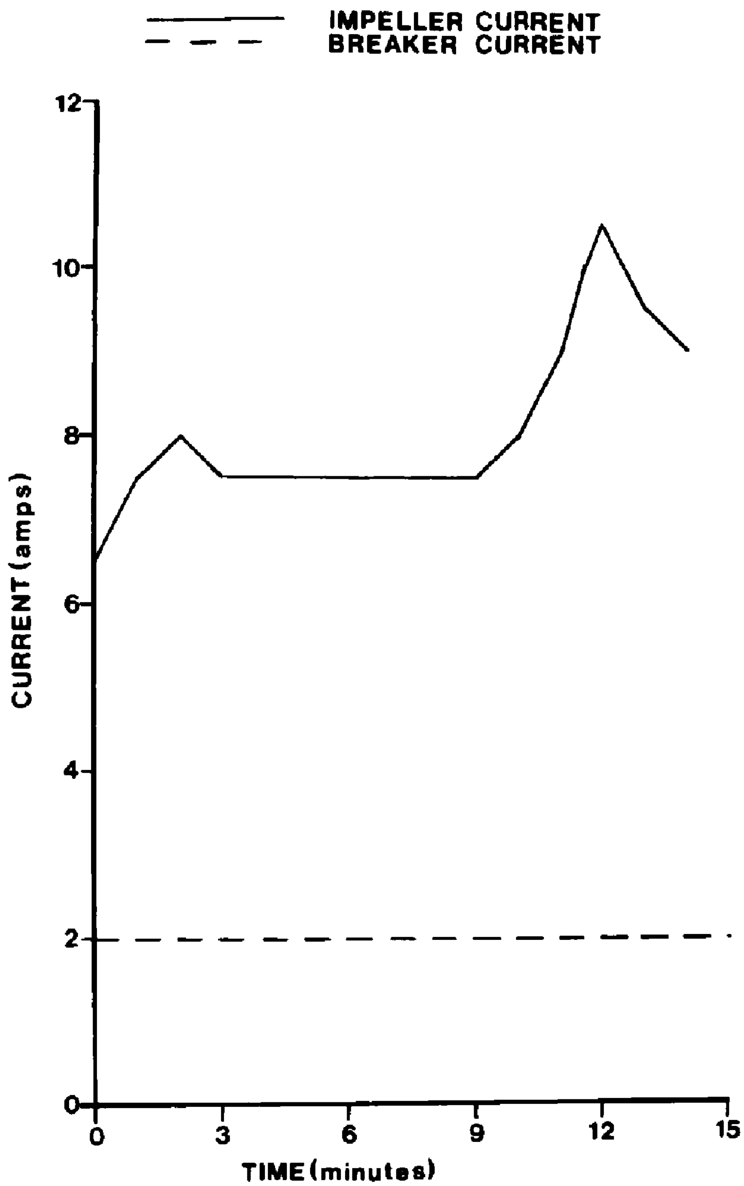


FIGURE 1

Impeller and breaker current demand during granulation

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