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COMMUNICATION

A NOVEL METHOD FOR THE GRANULATION AND COATING OF PHARMACOLOGICALLY ACTIVE SUBSTANCES.

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INTRODUCTION

In the pharmaceutical industry granulation and coating of various materials is resorted to for a multitude of reasons. Some of the reasons may be technical such as the wish to improve the tractability of powdery and cohesive raw materials, to enhance the stability of a product, or to make possible the manufacture of a direct compressible material. Other purposes may be medical where in particular modified-release formulations are of interest from the point of view of efficacy, side-effects or patient compliance, where frequency of dosage and taste play important roles.

CURRENT METHODS

Traditionally,the granulation and coating of powders, crystals, and pellets have been effected by the use of water or organic solvents. Those methods imply the utilization of a drying process to evaporate the solvents employed. This in turn, tends to make the pellets porous, bulky, and in some cases fragile.

Over time, methods have been developed substituting molten substances for organic solvents or water and in the literature a number of papers are found describing granulation and/or coating with such processes. The most commonly found processes are based on **batchwise mixing**. In a heated mixer the powder is heated so as to reach a temperature that is close to the melting point of the molten granulation substance. When the preset temperature has been reached the molten material is added under intense stirring. The temperature is then slowly lowered, the mixture being continuously stirred in order to build granules. **(Ref.1)**

A further method has been described where the powder to be granulated is mixed with a fine meltable binding agent in a fluid bed. By raising the temperature of the fluid bed to a point slightly above the melting point of the binder granulation can be achieved.

For coating purposes Dr Sparks has developed a spray disc process **(Ref 2).**

The features that are common to most methods are their inability to handle other than heat stable materials and their batchwise operation, facts that severely limit their industrial use.

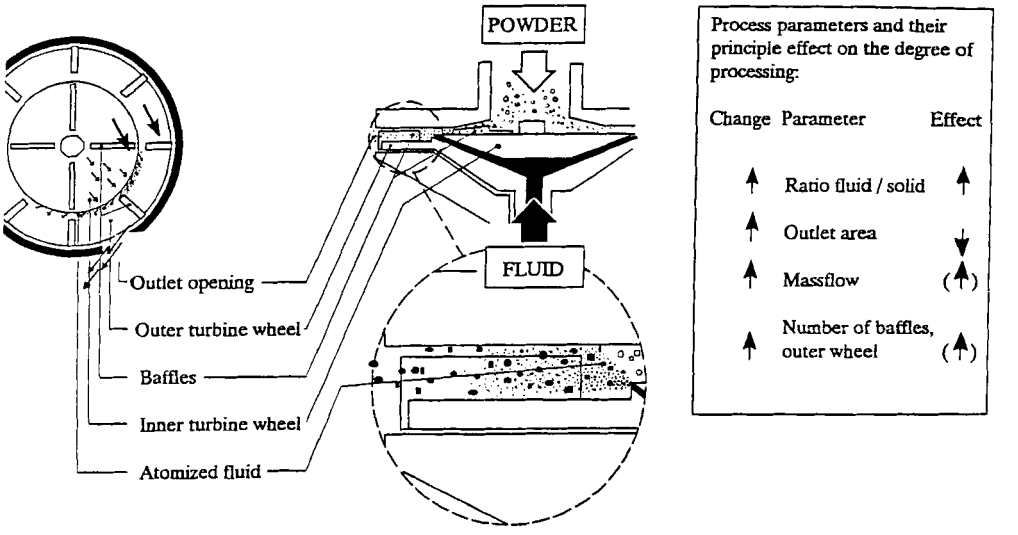

Figure 1: Technical description and outline of main process parameters

THE NOVEL CMT METHOD

In 1984 work was started in the laboratories of Lejus Medical AB of Mölndal, Sweden, with the express purpose of developing a process exhibiting none of the draw-backs of the currently available melt granulation and coating technologies. After a considerable amount of experiments and engineering work we finally arrived at a design that met the criteria set. The process is named the **'Continuous Multi-Purpose Melt Technology', 'CMT'.**

The CMT process is a **continuous** method, in principle working as follows: In a vessel a solid or viscous material is heated until reaching an acceptable viscosity. The ensuing fluid is then pumped into a specially designed mixer where in a narrow chamber a turbine wheel revolves at a high velocity. The speed and pressure of the rotating disc instantly cause the fluid to disintegrate into a fine mist **(FIGURE 1)** enveloping the solid particles that are simultaneously fed into the turbine chamber through a separate inlet as desagglomerated primary particles. The parameters of influence to the degree of processing, as well as the direction of their effect, are outlined in the description of the process . **(FIGURE 1)** The ability to create an optimal contact surface is one of the key features of the CMT-method. After a residence time of a fraction of a second in the turbine chamber the processed material is discharged from the mixer as a granulated or coated product, depending on the setting of the relevant equipment parameters. **(FIGURE 2).**
The product is then cooled. Since neither water nor organic solvents are used no drying or venting off of solvents residues is needed. **(Ref. 3)**

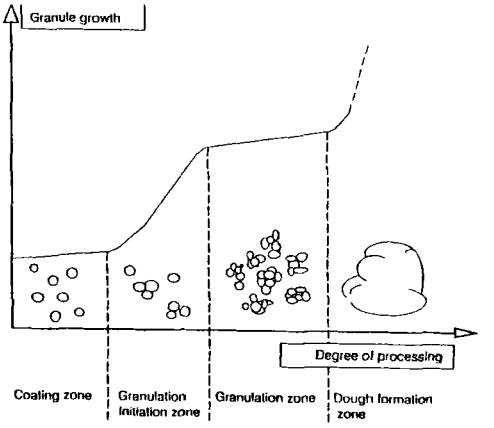

Figure 2: CMT-Processing

THE CMT METHOD IN THE PHARMACEUTICAL INDUSTRY

The 'CMT' process was first developed to meet certain needs of the pharmaceutical industry. The primary objective of the development work was to find a method that would lend itself to the continuous granulation or coating of substances to which traditional methods have failed or are not ideally suited. During the development work the following applications were found to be of the greatest interest:

- **Granulation of heat sensitive material**
- **Manufacturing of direct compressible (DC) masses**
- **Taste-masking**
- **Granulation of water-soluble fibres or other substances where unwanted reactions between solvent and substance occur.**
- **Production of granules for controlled release matrix tablets**
- **Production of controlled release multi-unit dosage formulations (MUDF ®) as tablets or capsules through matrix formation or coating of granules.**

EXAMPLES OF APPLICATIONS

Heat sensitive materials.

It has been shown that consumption of certain bacteria have a very beneficial effect on the disturbed gastro-intestinal microflora. One such bacterium is the Lactobacillus Acidophilus which is common in cultured milk products. Lejus was given the task to develop a tablet formulation of L. Acidophilus, each tablet containing a very large number of live bacteria. Traditional granulation methods that were at first applied were rapidly shown to be unsuitable, a very large portion of the bacteria being killed during the process as shown in **Figure 3:**

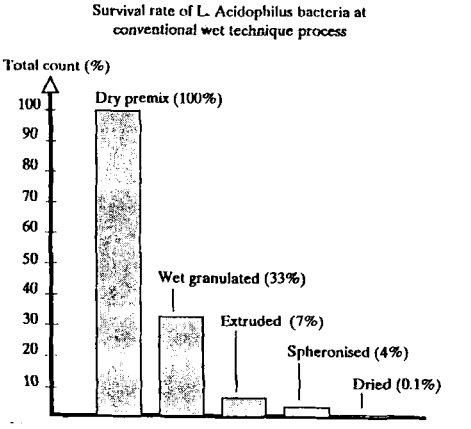

Figure 3:

The 'CMT' method was then tried. In spite of the fact that the temperature of the molten substance, employed as granulation fluid, reaches more than 100 centigrade it was shown to be possible to granulate the freeze-dried bacteria at a very high survival rate. A long series of experiments confirmed the first findings and led on to tabletting trials, the aim being to establish a tablet formulation that would safeguard the passage of a sufficient number of live

bacteria through the stomach. In vitro tests of the acid tolerance clearly demonstrate the well-functioning protection given the bacterial powder by this formulation. This should be seen in contrast to the results given for some other products tested (FIGURE 4).
The work was highly successful and the final product could be introduced in Sweden in 1988 under the name of DOCIDUS®. (Ref. 4)

Direct compressible ibuprofen.

Due to the necessity of adding a fairly large proportion of non-active ingredients to the active principle in order to achieve acceptable tablet formulations, many tablet products are very large sized often creating swallowing problems for many patients. One such example is **ibuprofen**. Studies of the physico-chemical properties of ibuprofen made us believe that with the 'CMT'

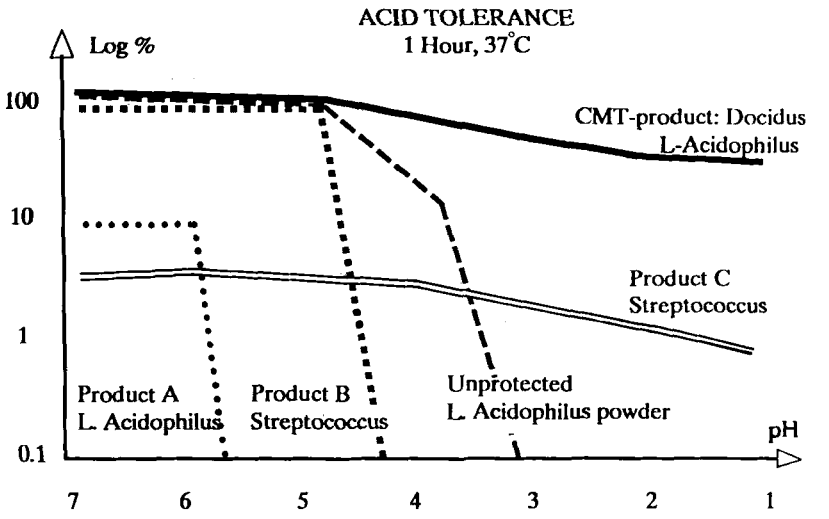

Figure 4: In vitro studies of acid tolerance of live bacteria

Direct compressible antacid.

An Al-free chewable antacid tablet was developed in our laboratories according to the CMT-process. The objectives beside from having the required acid binding capacity and being well accepted and tolerated, was to formulate a chewable tablet of outstanding palatability regarding both texture and taste. All of these objectives were reached togethter with excellent direct compressible properties.

process, ibuprofen could be granulated with a melt of itself. If this could be shown to be true, it would be possible to manufacture tablets containing more than **90 per cent.** active substance, the result being smaller tablets. Our experiments substantiated our ideas, also concerning the tabletting properties of the granules. Compression trials showed that a formulation containing **92.5 % Ibuprofen, 5.0 % Avicel, 2.0 % AcDiSol, and 0.5 % Magnesium Stearate** yielded a tablet mass of well functioning technical properties, and in vitro studies in phosphate buffer pH 7.2 showed a **T50%** of **4 min.** according to USP XXI. A bioavailabilty study has also been undertaken proving the tablet in vivo **(Figure 5, Ref. 5)**

Summary of Pharmacokinetic Data from Comp. G and Nuprin

Mean Concentration of Ibuprofen in plasma (ug/ml)

Formulation	Pre-dose	20 m.	40 m.	1 h	1.5h	2 h	3 h	4 h	6 h	8 h	Cmax ug/ml	Tmax (h)	TE (h)	AUC ug.h./ml
Comp. G*	0	1.9 (1.9)	8.1 (4.3)	11.9 (4.9)	13.7 (4.8)	14.8 (3.9)	13.0 (3.1)	11.3 (2.0)	5.3 (0.9)	2.9 (0.7)	15.9 (2.9)	2.3 (0.9)	2.09 (0.51)	78.1 (10.7)
Nuprin (ref)	0	8.0 (8.3)	15.5 (7.1)	17.1 (6.5)	16.4 (5.0)	17.1 (4.7)	13.5 (3.0)	8.6 (2.0)	3.9 (1.0)	2.1 (0.7)	22.4 (3.4)	1.4 (0.9)	1.87 0.33	79.1 (8.1)

Cmax - peak plasma concentration; Tmax - time of peak plasma concentration;

AUC(0-∞) - area under the plasma concentration - time curve;

TE - elimination rate half time.

*) Manufactured by the CMT-process.

Figure 5: Bioavailability studie of Ibuprofen.

Direct compressible Xylitol.

A further example of the use of the 'CMT' for the production of direct compressible materials is DC xylitol, intended for use as a base for chewable tablets. DC xylitol exhibits excellent technical properties such as hardness, low friability etc. **(Ref. 6)**

Taste masking.

In order to formulate substances of disagreeable taste, it can sometimes be unavoidable to in a first process step cover or embed the substance prior to making the final formulation. This can be valid for formulations as chewable tablets and suspensions. Acetaminophen (APAP, paracetamol) is one such substance. At Lejus we have run a short series of trials whereby APAP crystals, 30 - 70 mesh, have been coated with a taste masking substance for the production of chewable tablets. The initial results are very encouraging and the experiments will be continued. Also the general project testing the 'CMT' method as a means of masking foul taste will continue **(FIGURE 6)**.

Per cent released in phosphate buffer, pH 6.5

(In vitro release USP XXI, App 2, 100 rpm, 37°C)

Time (min)	Uncoated crystals	Reference*	CMT- coated crystals
2	56	4	5
4	79	8	6
6	90	11	11
8	96	13	13
10	98	16	16

*)Crystals coated with ethyl cellulose by coacervation technique

Figure 6: In vitro studies of APAP

Granulation of water-soluble fibres.

Water-soluble fibres such as guar gum have been demonstrated to lower elevated cholesterol and blood glucose levels. The most attractive and safe way of ingesting guar gum is as a flavoured drink. Because of the very large water-binding capacity of guar gum, (30-40 times its own weight) it is however necessary to granulate the gum so as to slow down the absorption of water and hence the gelation process.

Existing granulated products are agglomerated with a solution based on organic solvents and a binder. The organic solvent is necessary to prevent gelation at agglomeration. In the 'CMT' process we have found a way of granulating guar gum flour with molten xylitol without the aid of organic solvents, and at the same time adding a desired flavour to the product. In this way we have been able to develop a well-tasting guar presentation totally free from solvent residues and of well controlled dispersibility and viscosity increasing properties. **(Ref. 7)**

Granulation of wet filter cake

For substances that exhibit a suitable melting point and that do not degrade when molten, the 'CMT' process opens up the possibility of utilizing the wet filter cake as the granulation medium. The wet filter cake is transferred to a heated vessel to melt, the remaining solvents being extracted simultaneously.

The ensuing fluid will then be used for the granulation of the powder portion of the substance fed into the granulator. After sieving, granules of too small a size can be granulated anew. In this manner free-flowing granules holding 100 per cent. of substance can be manufactured using the damp non-dusting filter cake. **(Ref. 5)** **(FIGURE 7)**

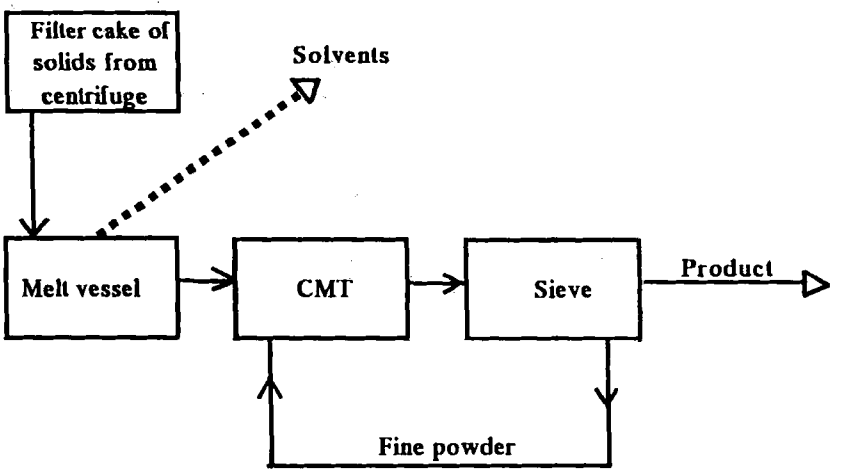

Figure 7: Granulation of wet filter cake

DISCUSSION

As can be seen from the above description of the method, the 'CMT' process opens up a wide avenue of potential applications. From the **technical** point of view, the most interesting area of use would seem to be the facilitation of the handling of various substances that in their common presentations are cohesive and thus are not adapted to today's automated pharmaceutical production.

If **environmental** considerations are given special emphasis, then the capacity of the 'CMT' process to eliminate dusting and its non-dependence of solvents should be highlighted. Of particular interest seems to be the use of the damp filter cake as the granulation medium to achieve a granulate of 100 per cent. substance. Concerning the **medical** aspects, the use of the 'CMT' process for the convenient manufacture of controlled-release drug presentations would seem to be highly interesting.

Patient compliance to a given prescription is of great importance and it is not uncommon that patients refrain from taking their drug because of its bad taste. Therefore, taste-masking with the aid of the 'CMT' process should be considered an attractive opening from medical and marketing points of view.

Last but not least important is the possibilty of producing medicinal products to competive prices which **económical** advantages the 'CMT' truly offers.

CONCLUSION

The 'CMT' process is a valuable combination of hardware and know-how making it a highly versatile production method with a wide variety of applications within the pharmaceutical industry.

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