STUDIES ON MICROENCAPSULATION OF LOWDOSE DRUGS

by

A. K. Madan

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for the degree of

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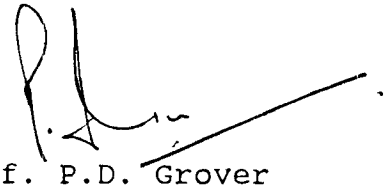
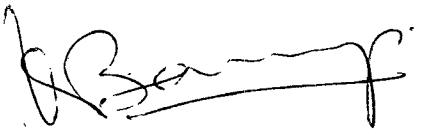
CERTIFICATE

This is to certify that the thesis entitled,**"STUDIES ON MICROENCAPSULATION OF LOWDOSE DRUGS"** being submitted by **Mr. A.K. Madan** to the Indian Institute of Technology, Delhi, for the award of the degree of **"Doctor of Philosophy"** is a record of bonafide research work carried out under our guidance and supervision and has fulfilled the requirements for the submission, which, to our knowledge, has reached the requisite standard.

The results obtained in this thesis have not been submitted in part or in full to any other University or Institute for the award of any degree.



Prof. P.D. Grover
(Supervisor)



Dr. K.K. Baveja
(Supervisor)

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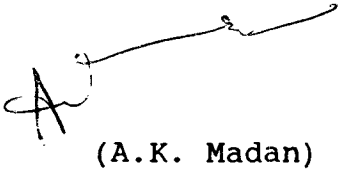

(A.K. Madan)

Since various adducts, containing different guest components but based on same host lattice normally belong to same space group and possess almost similar unit cell dimensions, therefore, adduction was employed for development of suitable isomorphic systems for microencapsulation of a drug.

Vitamin A palmitate was selected as a model drug candidate and urea and bile acids as adductors. Urea normally forms adducts with long straight-chain compounds. *Vitamin A palmitate which does not form adduct with urea under any known conditions was successfully included in urea in the presence of rapidly adductible endocyte to yield coadduct or coinclusion compound.* Formation of coinclusion compound was confirmed by *differential scanning calorimetery* (DSC), X-ray-diffraction and infra-red *spectroscopy.*

Minimum amount of rapidly adductible endocytes required per unit weight of drug for coinclusion with urea was experimentally determined by a modified method based on temperature rise. Studies revealed a gradual decrease in heat of decomposition (owing to transformation from hexagonal to tetragonal form), heat of fusion and decomposition temperature with corresponding increase in endocytic fraction of vitamin A palmitate in urea based coinclusion compounds. This phenomenon is attributable to distortion of crystalline lattice by vitamin A palmitate -

ABSTRACT

Novel microcapsules have been conceptualised in present investigations so as to overcome most of the disadvantages of conventional microcapsules for containment applications of lowdose drugs. Appropriate simple and inexpensive techniques have also been developed for preparation of these microcapsules.

Proposed technique envisages cocrystallization of a drug and an isomorphic carrier from a common solvent to yield cocrystals which are subsequently employed as seeds in a supersaturated solution of the same carrier in a liquid which is a nonsolvent for the drug. Carrier is allowed to crystallise onto the surface of cocrystal seeds leading to formation of microcapsules which are subsequently separated from mother liquor and dried.

Aforementioned technique can only be accomplished if an appropriate *isomorphic* carrier is available for a particular drug. *Survey of crystallographic data from literature revealed difficulties in obtaining suitable isomorphic carrier for numerous drugs owing to existence of 230 space groups and wide variation in unit cell dimensions.* Therefore, in order to increase *versatility* of the technique, alternate means such as *interstitial solid solution* and *adduction* were explored for developing suitable *isomorphic systems* for *microencapsulation of lowdose drugs.*

a highly substituted endocyte. Experimental data was also subjected to regression analysis and correlations with average error ranging from 2.06% to 11.7% were obtained.

Various urea based inclusion/coinclusion compounds containing vitamin A palmitate and fatty acids were prepared. These compounds were subjected to infra-red spectroscopy, *elemental analysis*, *polycrystalline X-ray diffraction and DSC*. Urea which normally exists in *tetragonal* structure (space group $P\bar{4}2_1m$) transforms to *hexagonal* structure (space group $P6_1$ 22) upon adduction. Since this change is accompanied by *alteration in interatomic bonds*, therefore, *infra-red* spectroscopical analysis provided valuable information for confirming formation of coinclusion/inclusion compounds. *Polycrystalline X-ray diffraction* data of various inclusion/coinclusion compounds not only confirmed *hexagonal* structure but also revealed *isomorphism* between these inclusion/coinclusion compounds.

Microcapsules of vitamin A palmitate were prepared by the proposed technique by employing fine crystals of urea-vitamin A palmitate-palmitic acid coinclusion compound (UVPP) as seeds in supersaturated solution of urea-palmitic acid inclusion compound (UPA) to yield microcapsules comprising of UVPP as core coated with UPA. Other urea based microcapsules of vitamin A palmitate were similarly prepared.

Like urea, *deoxycholic acid* and other *bile acids* were also investigated on similar lines. Adducts of vitamin A palmitate and fatty acids with bile acids were prepared and subjected to evaluation for polycrystalline X-ray diffraction, DSC and elemental analysis. After establishing *isomorphism*, fine crystals of deoxycholic acid-vitamin A palmitate adduct were *microencapsulated* by deoxycholic acid-stearic acid adduct by the proposed technique.

All the microencapsulated products were evaluated by *transmission electron microscopy* (TEM). *Transparent coatings were clearly visible onto the surface of darker core containing vitamin A palmitate as one of the components, thus confirming successful accomplishment of preparation of novel microcapsules by the proposed technique.*

Various microencapsulated products and core materials were also analysed by *scanning electron microscopy* for surface characteristics.

Accelerated stability studies revealed adducts to be more stable than the drug alone while microencapsulated vitamin A palmitate based on urea as well as deoxycholic acid exhibited many times more stability than the corresponding adducts constituting the core material.

Various microencapsulated products as well as corresponding core materials were analysed for content uniformity. Core materials exhibited excellent content uniformity owing to homogeneity of the coinclusion compounds whereas microencapsulated products showed some deviation. This may be attributable to somewhat uneven coating of microcapsules as revealed by TEM. However process optimization can easily overcome this problem.

Multicomponent polymeric coating in impermeable conventional microcapsules can easily be replaced by crystalline coating consisting of only one or two components in novel microcapsules leading to reduced material cost and decreased possibility of incompatibility between various components. Since coating in proposed microcapsules is actually an extension of core lattice, therefore, problems associated with poor adhesion between core and coating are easily overcome.

Investigations reveal that these microcapsules can serve as viable inexpensive alternative to conventional microcapsules for containment applications for lowdose drugs. Since vitamin A palmitate was employed only as a model drug, therefore, further studies are necessary to exploit the vast potential of this technique for numerous other drugs for multiplicity of applications of diverse nature.

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