CRYSTALLIZATION OF ULTRAFINE (NANO AND MICRO) PARTICLES OF ACTIVE PHARMACEUTICAL INGREDIENTS (API) USING LIQUID ANTISOLVENT TECHNIQUE

Research Experience for Teachers (RET)program Summer 2007
New Jersey Institute of Technology

INSTRUCTIONAL MODULE

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MODULE TOPIC: Crystallization of ultrafine (nano and micro) particles of active Pharmaceutical ingredients (API) using liquid Antisolvent Technique.

SUBJECT AREA(S): **Chemistry:** Solution mixing and crystallization
Physics: Crystallization, solubility and graphing techniques.
Engineering: Determination of optimum concentration for Crystallization and effect of surfactants.

LEARNING OBJECTIVE: The students will be able to:

- Explain antisolvent and precipitation
- Discuss the techniques of crystallization
- Prepare fine particles of some drugs (Asprine and Ibuprofen) using liquid antisolvent precipitation.
- Determine the amount of antisolvent required to precipitate nanoparticles for different concentration API.
- Plot and interpret graphs to show the variation of antisovents with API concentration.

Engineering Aspect
The engineering aspect here involves optimizing the precipitation technique by determining the optimum amount of antisolvent and surfactants needed for crystallization.

MATERIALS:
Aspirin 20 grams

Ibuprofen 20 grams
Acetone 2 liters
Teen 80 100 ml
PEG 10 grams
Distilled water
Sonicator
measuring cylinder100ml
Beakers 250ml, 500ml, I liter
Graduated pipettes

APPROXIMATE TIME REQUIRED:5 class periods of 40 minutes duration each.

BACK GROUND INFORMATION:

When an organic compound been made, it needs to be purified, particularly, if it is a pharmaceutical chemical. This is because the purity standards for many products are so stringent that small amounts of other compounds have to be removed. In the laboratory, this is often done by crystallization. The general method is to find a solvent that dissolves the product more readily at high temperature than at low temperature, make a hot solution, and allow crystallizing on cooling. The solvent it self has also to be removed or it behaves as an impurity. It must not leave behind any residue. Study of the principle factors which control crystallization is important

During the past few years, it has been observed that advances in the preparation of nano particles, can significantly contribute to the development of new drug delivery routes[1,2]. Uniform and narrow particle size distribution is essential for developing uniform dosage form. In order to be able to commercially exploit the enormous potential of nano medicine, it is necessary to develop efficient technologies for the manufacture of contaminant free material at an industrial scale

Anew technology called liquid anti solvent method has gained important advancement in this field by the formation of nanoparticles of different compounds. This technique involves dissolving the water insoluble compound in suitable organic solvent, followed by a fast decrease of its solvent power by the addition of a liquid antisolvent, usually water or an aqueous solution. This results in a very high super saturation of the solute, extremely rapid phase change and subsequent formation of ultra fine solid particles. This was the main focus of our research in Dr Dave's lab at the New Jersey Institute of Technology during the RET summer program.

This method has the following advantages over other conventional methods of manufacture
1. It does not require high pressure or costly instruments
2. Involves a single step operation
3. Very narrow size distribution of particles with controlled morphology
4. Improved oral bioavailability of poorly absorbed drugs.

Class Room Activity Description

1.Students will be given a 40 munite lesson on this topic, based on the outcome of our research.

2.Students in group discuss the various crystallization methods and advantages of liquid antisolvent method

Laboratory Activity

Make solutions of Aspirin and Ibuprofen in acetone (various strengths as instructed) and find the amount of anti solvent needed to precipitate the given amount of drug substance according to the following procedure.

Experimental Procedure:

Take the required weight of the sample using an electronic balance

Dissolve the sample in10 ml of acetone:

By adding 1) surfactant Tween80 or PEG if needed

2) Sonicate the sample untill the powder dissolves

Add required amount of anti solvent (water) drop by drop using a graduated pipette

Stop the addition when the precipitate first appears.

Find the volume of water used by subtracting the final volume- initial volume .

Lab. Activity Number 1

Find the volume of anti solvent needed to precipitate the given amount of Aspirin

Experiment No.	Weight of Aspirin In grams	Concentration of Aspirin in g/mL	Volume of Water mL
1	0.200		
2	0.150		
3	0.100		
4	0.050		
5	0.030		
6	0.025		
7	0.20		
8	0.10		

Lab. Activity Number 2

Find the volume of anti solvent needed to precipitate the given amount of Ibuprofen

Experiment No.	Weight of Ibuprofen in grams	Concentration of Ibuprofen g/mL	Volume of Water mL
1	0.200		
2	0.150		
3	0.100		
4	0.050		
5	0.030		
6	0.025		
7	0.020		
8	0.010		

Home Work Activity:

Plot graph of concentration of drug substance verses amount of antisolvent needed for precipitation of aspirin and Ibuprofen

Assessment of learning outcomes:

1. What is the optimum concentration of the API's in acetone?
2. What happens if you add more solvent to the solution after the precipitates are formed?
3. Compare anti solvent method with other crystal growth techniques.
4. Draw the crystal geometry of different crystal systems (Refer to your class textbook).

References

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1. B. Y. Shekunov, P. Chettopadhay, J. Seitzinger and R. Huft “Nanoparticles of water-insoluble drugs prepared by supercritical fluid extraction of emulsions” J. of Pharmaceutical Research, **22,** 196-204 (2006).

2 R. H. Muller, Proceed. Int'l Symposium Control Rel Bioact Matter, Controlled Release Society, Inc 25 (1998)