

In Situ Lyophilization of the Hydrophobic Drug Spironolactone to improve its dissolution



Amal Ali Elkordy, Ph.D
University of Sunderland
Sunderland Pharmacy School
Medicinal product team

Overview

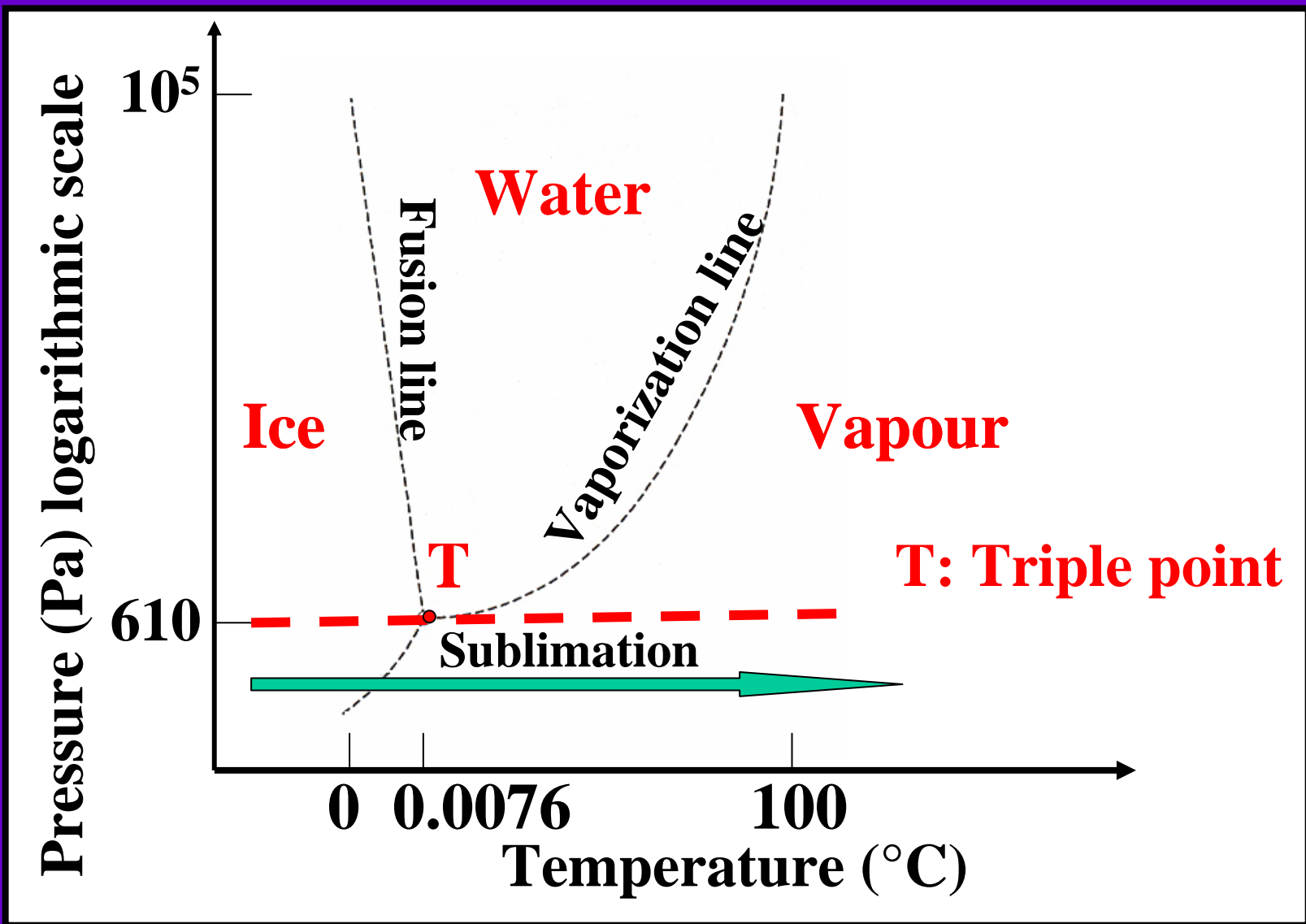
- ★ **What? Introduction**
- ★ **Why? Objective and Aims**
- ★ **How? Methods (preparations of lyophilizate in hard capsules and their characterization)**
- ★ **Results and Discussion**
- ★ **Conclusions**

What? Introduction

- ★ The formulation of hydrophobic drugs represents a challenge due to their poor aqueous dissolution and hence poor bioavailability
- ★ The oral route remains the preferred drug administration route due to its convenience and good patient compliance
- ★ The drug dissolution rate in the gastrointestinal fluid (GIF) is the rate limiting step for poorly water-soluble drugs, meaning that the drug should be dissolved in the GIF for clinical efficacy

What? Introduction

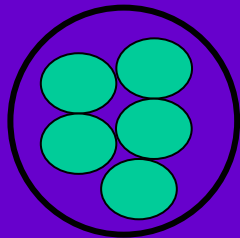
- ★ **Solid dispersion of a drug in a water-soluble carrier is an effective technique to enhance the drug dissolution**
- ★ **Obstacles of solid dispersion technology in pharmaceutical formulations are:**
 - **a large amount of a carrier is required**
 - **scale-up of the process**
- ★ **Lyophilization or freeze drying: Removal of water or solvent by:**
 - **sublimation**



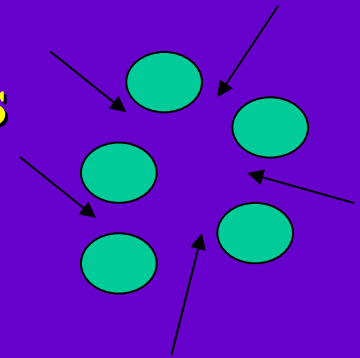
Equilibrium pressure-temperature diagram for water

Suggested models

Fluid can penetrate



Modification of surface properties



Poorly water soluble drugs,
the available surface area
is small

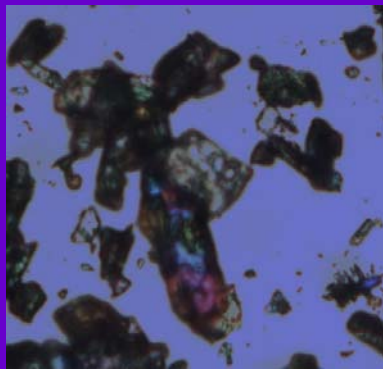
Decreased aggregation,
the available surface area
is large

Why? Objective and Aims

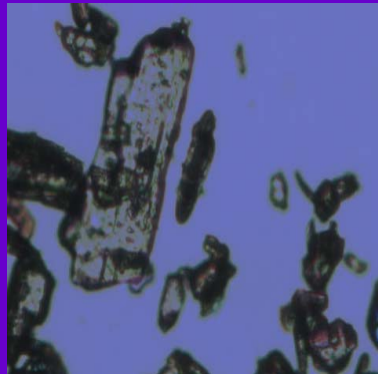
- ★ Evaluation of dissolution enhancement of spironolactone (a model hydrophobic drug) via *in situ* lyophilization
- ★ Aims:
 - To prepare spironolactone solid dispersion formulations in hard gelatin capsules using lyophilization
 - To study the effects of excipients, citric acid, mannitol and sodium dodecyl sulfate (SDS) on dissolution behaviors and conformational integrity of the drug

Preparation of solid dispersions

★ Melting method



Drug

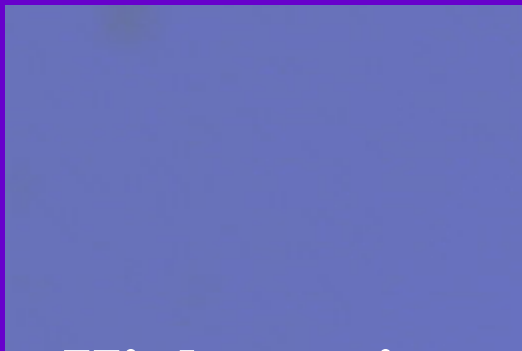


Carrier

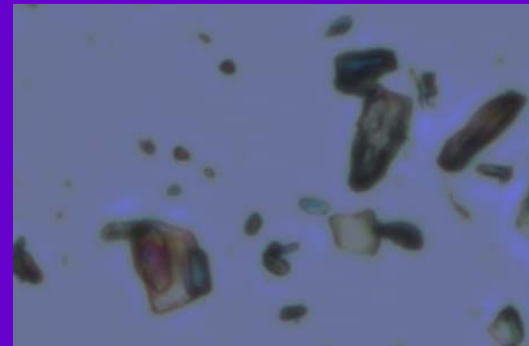


Molten product

Grounded or filled into capsules



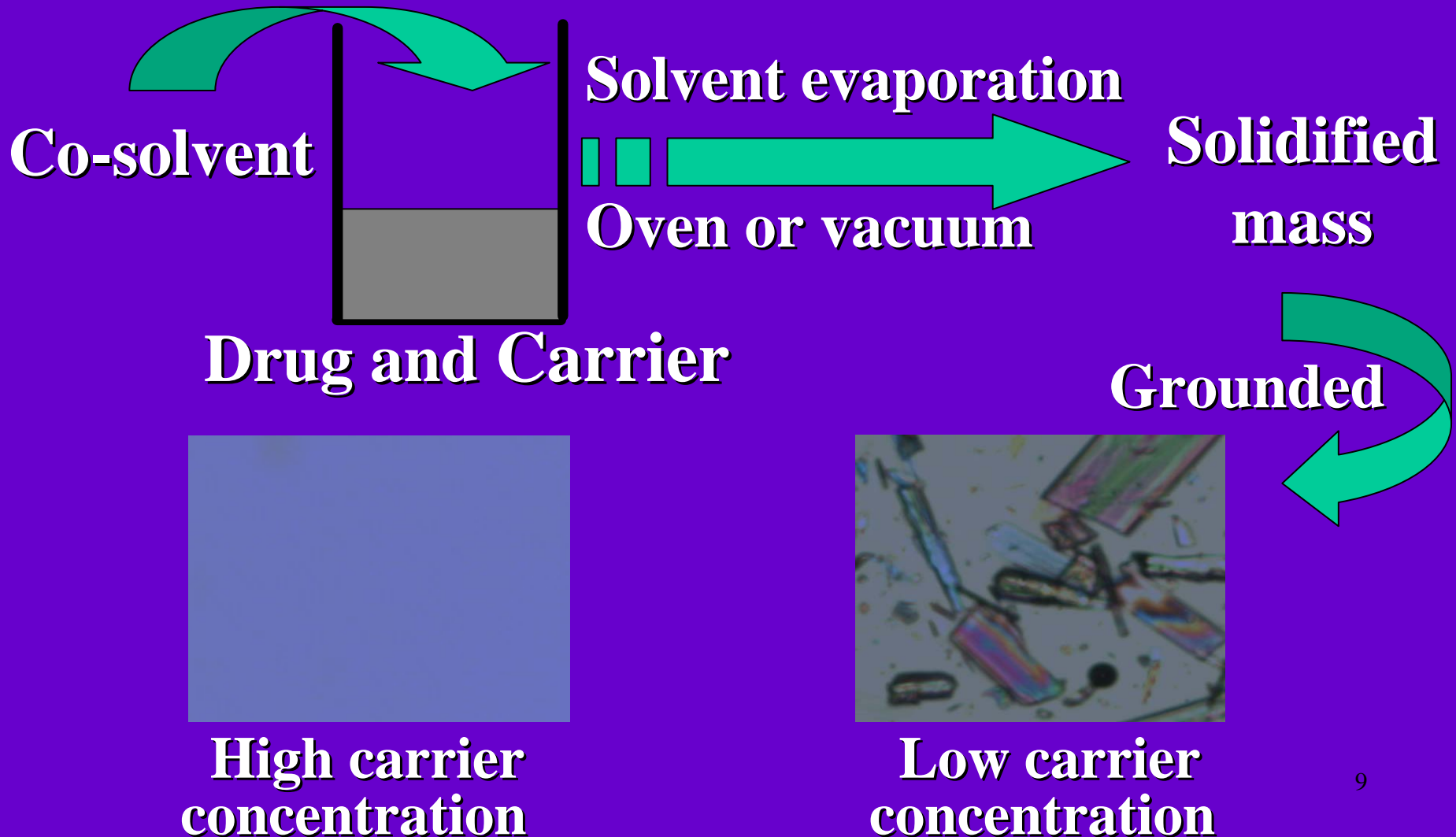
High carrier concentration



Low carrier concentration

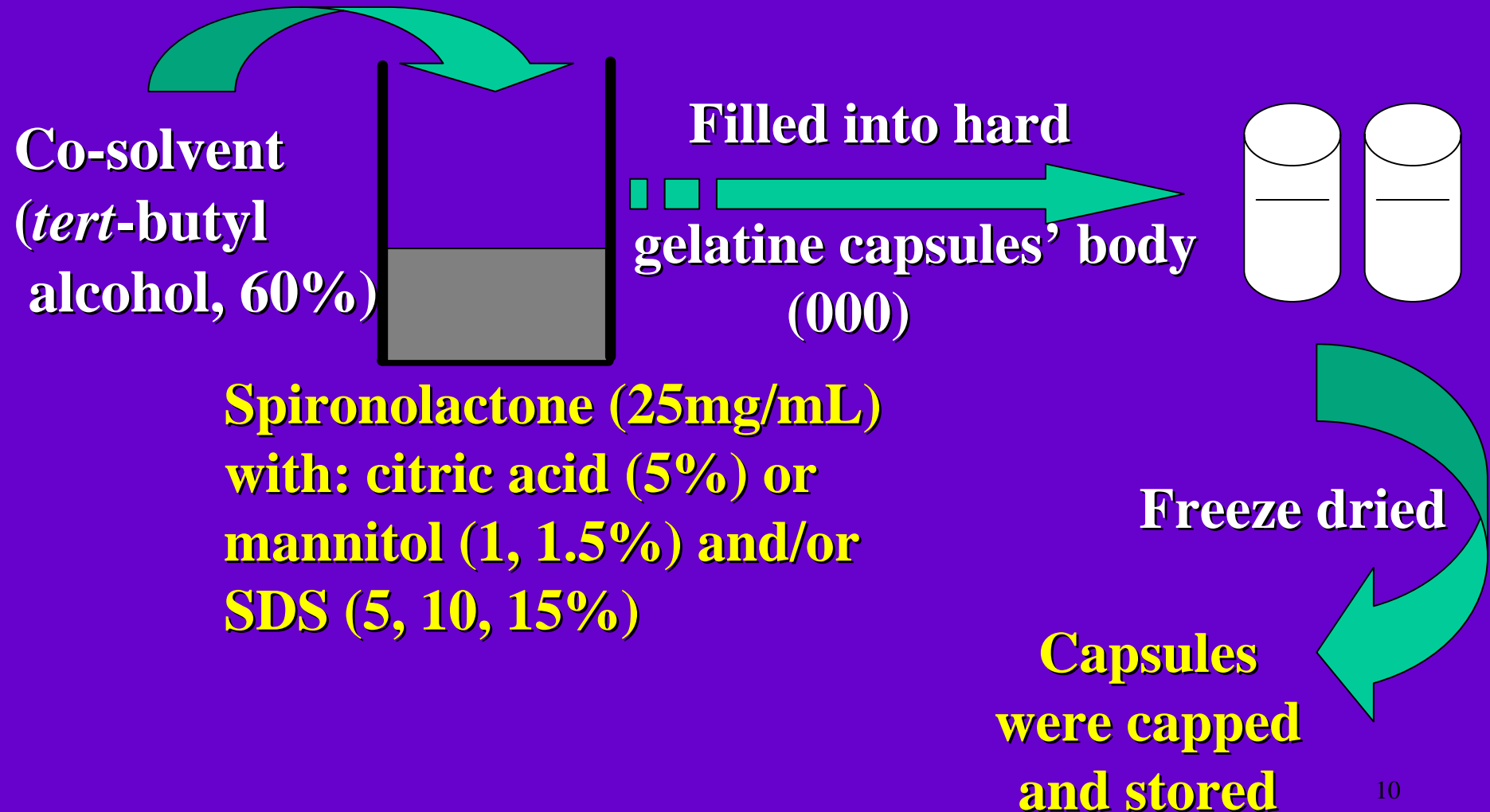
Preparation of solid dispersions

★ Solvent method



How? Methods

★ Preparation of lyophilized capsule formulations



How? Methods

★ Characterization of lyophilized products

➤ Dissolution testing

Capsules tested at 37°C and 50rpm paddle speed. The dissolution media was 1000mL of 0.1N HCl.

➤ Differential scanning calorimetry (DSC)

Solid samples, sealed in aluminium DSC pans and loaded in sample cells under nitrogen, were scanned from 20-270°C at 10°C/min.

➤ Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectra were collected for lyophilisate samples of various formulations using KBr discs. ¹¹

Results and Discussion

★ Macroscopic examination of lyophilized products

SDS → White and fluffy mass that collapsed within the hard capsules

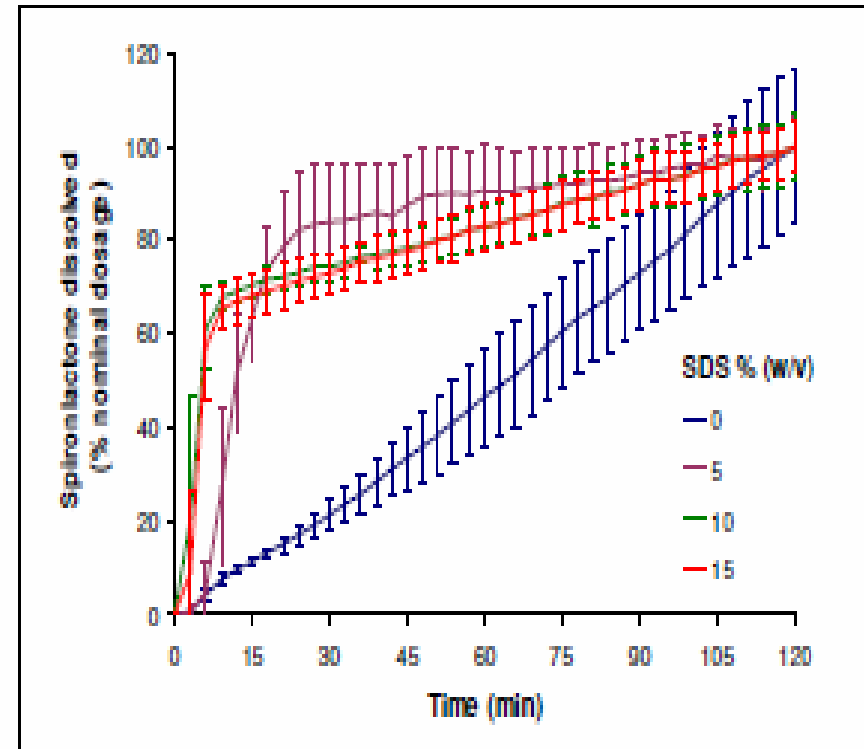
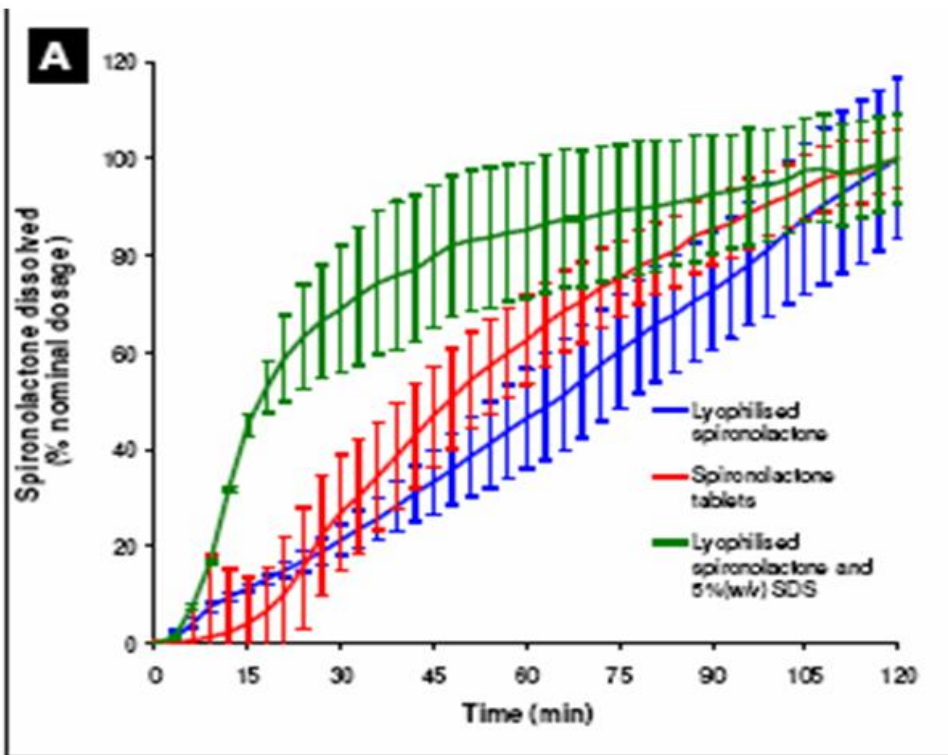
Mannitol → Improved the structure of lyophilizate

Citric acid → Collapsed lyophilizate

This was confirmed by characterization methods

Results and Discussion

★ Dissolution testing

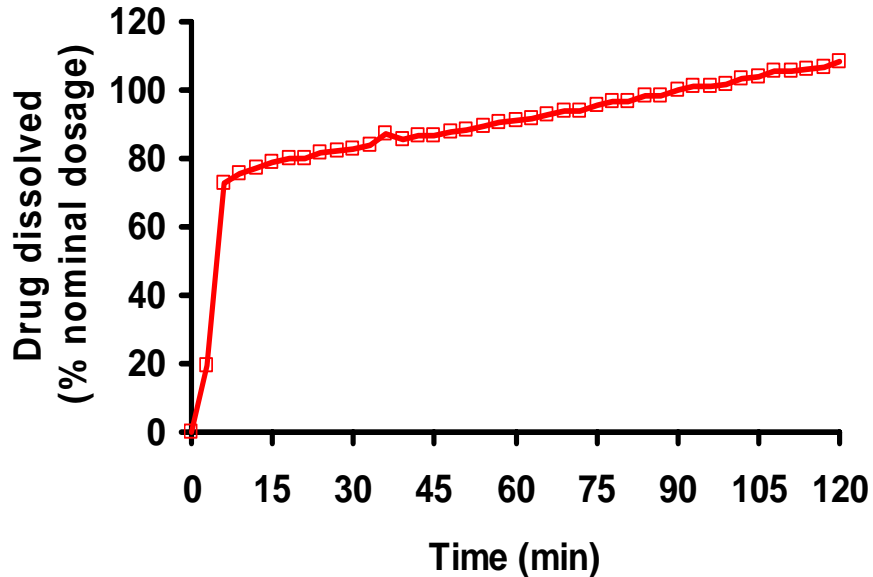


Lyophilized drug compared to control

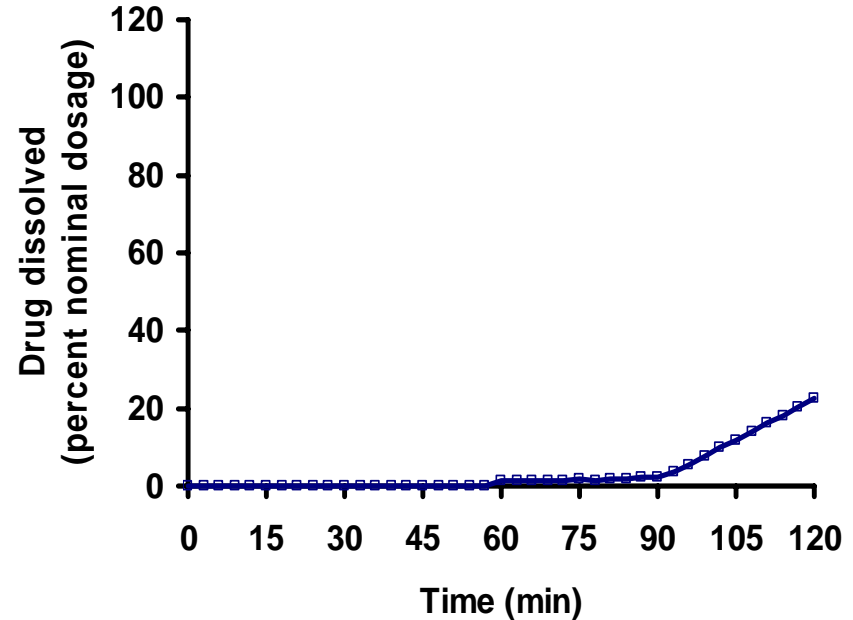
Lyophilized drug, different % of SDS

Results and Discussion

★ Dissolution testing



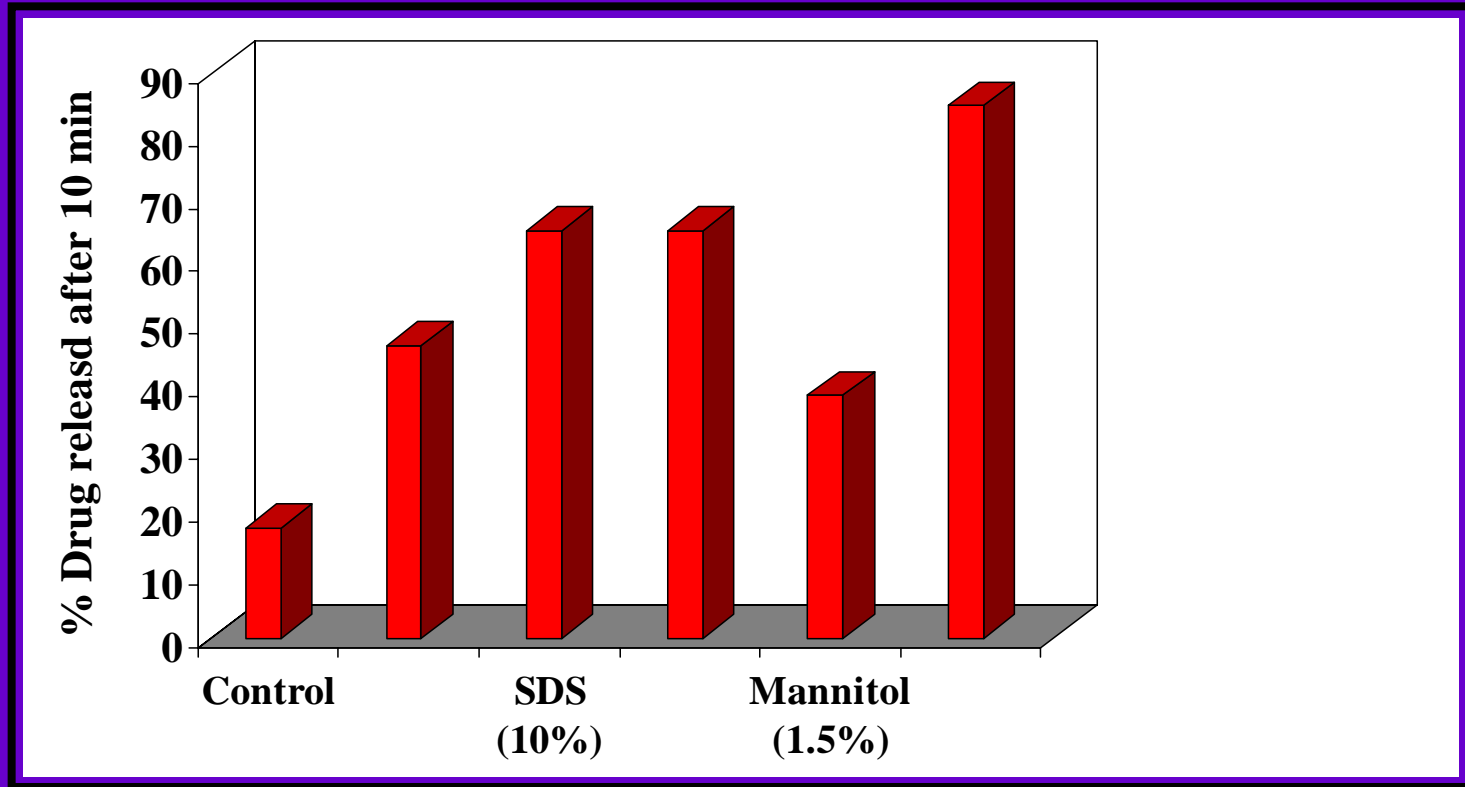
**Lyophilized drug,
10% SDS, 1%
mannitol**



**Lyophilized drug,
5% citric acid**

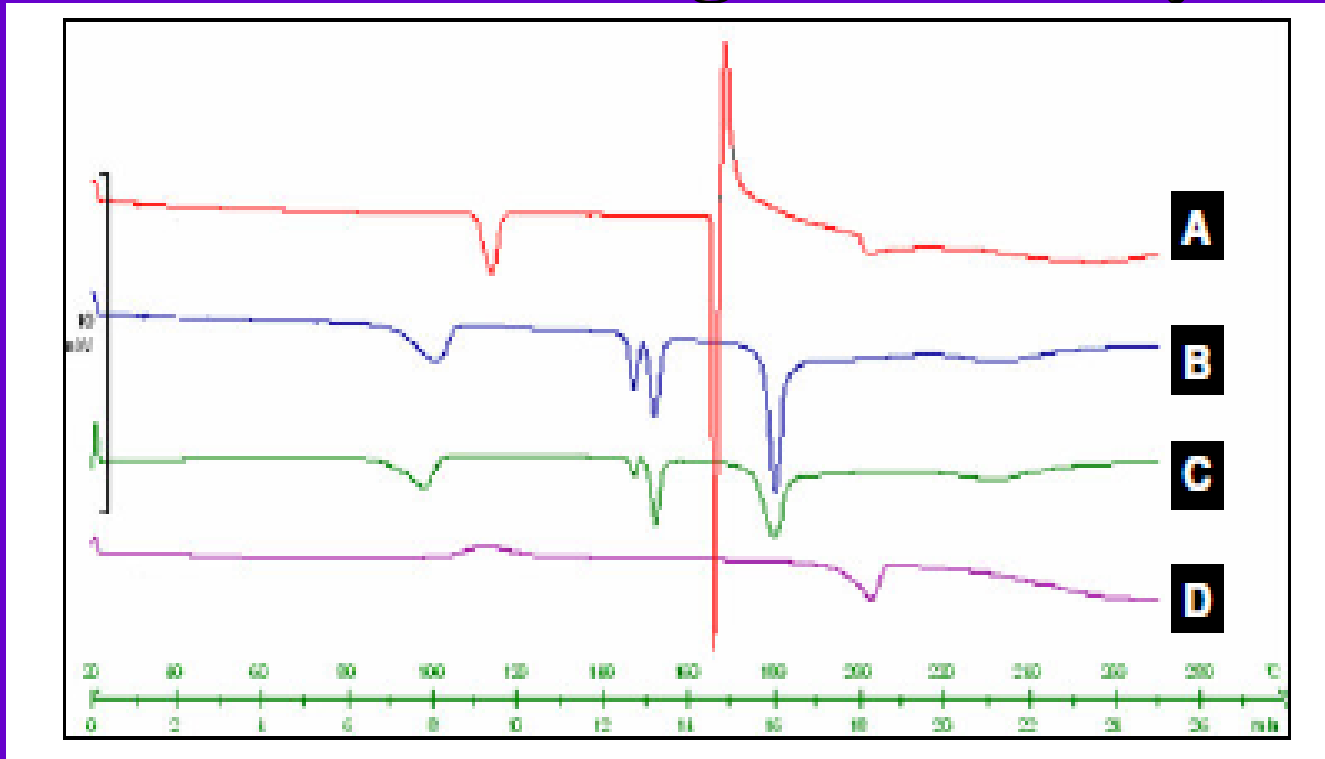
Results and Discussion

★ Dissolution testing



Results and Discussion

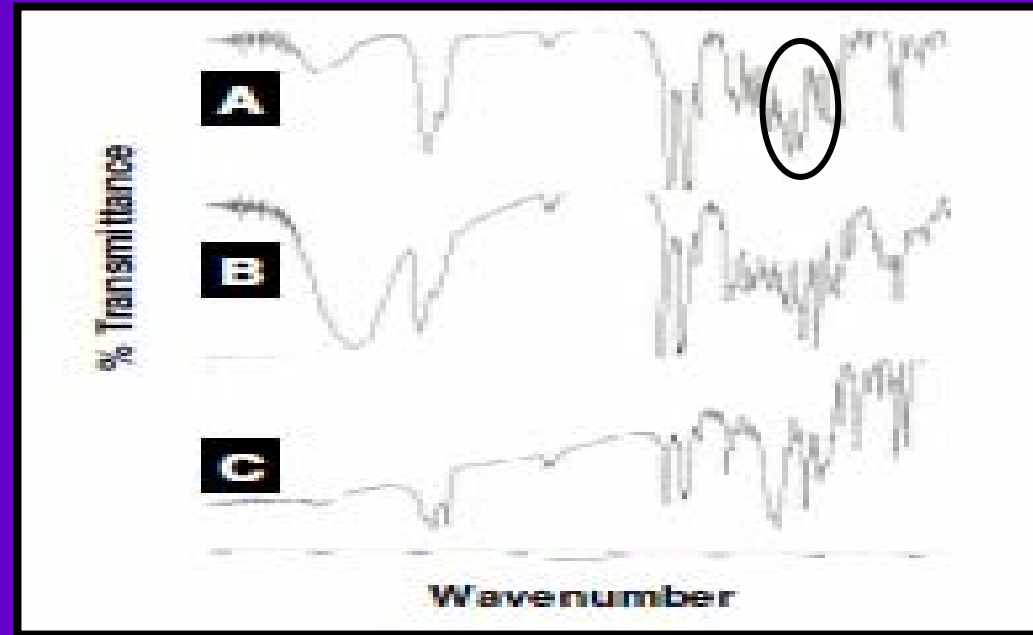
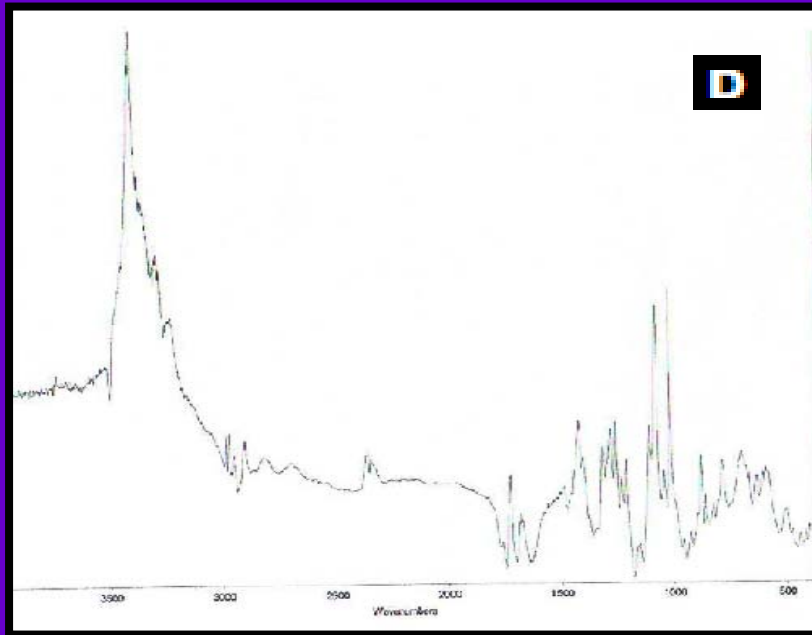
★ Differential scanning calorimetry (DSC)



DSC thermograms of (A) spironolactone + 5% SDS, (B) spironolactone + 1%(w/v) mannitol + 5% SDS, (C) spironolactone + 1%(w/v) mannitol + 10% SDS, (D) spironolactone alone.

Results and Discussion

★ Fourier Transform Infrared Spectroscopy (FT-IR)



FT-IR spectra of (A) spironolactone, (B) spironolactone + 1% (w/v) mannitol, (C) spironolactone + 10% SDS, (D) spironolactone + citric acid.

Advantages and disadvantages of freeze drying

★ Advantages :

- Drying at very low temperatures
- Freeze dried solid occupies as much volume as original solution
- Enhances solubility and stability
- No contact with air (no oxidation)

★ Disadvantages:

- Products are very hygroscopic
- Control the particle size of the solid is difficult

Pharmaceutical applications of freeze drying

- ★ Used for drying of heat sensitive products for example: antibiotics, blood products and vaccines
- ★ Development of solid protein pharmaceuticals (for long term storage)
- ★ Lyophilised nasal inserts
- ★ Drying of micro- and nano- particles

Examples for formulations containing lyophilized drugs

★ Prostavasin®

- Prostaglandin E1/ α -cyclodextrin complex
- Storage as lyophilisate
- Aqueous solubility increased

★ Sporanox®

- Itraconazole/ β -cyclodextrin complex
- IV administration

Conclusions

★ **LYOPHILIZATION: WHY NOT USED FOR PREPARATION OF SOLID DISPERSIONS BY *IN SITU* LYOPHILIZATION USING HARD CAPSULES TO ENHANCE THE DISSOLUTION OF POORLY WATER SOLUBLE DRUGS**

Conclusions

★ *In Situ* lyophilization of spironolactone with mannitol and SDS show promise for dissolution enhancement of hydrophobic drugs

Acknowledgements



Dr. Alex Mullen

Dr. Lee Ann Hodges

THE END

THANK YOU FOR YOUR

ATTENTION