OPTIMIZATION OF PARTICLES SIZE FOR LUNG SPECIFIC DRUG DELIVERY BY WAY OF MICROSPHERES

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OBJECTIVES:

- Introduction
- Therapy
- Solution
- Formula
- Preparation
- Evaluation
- Conclusion
- References

INTRODUCTION:

- Lung cancers are among the most harmful cancers and are increasingly hazardous to human.
- World Health Organization 1.37 million deaths are accounted worldwide.
- Saudi Arabia, every year 12,000 new cancer cases are been recorded.
- Lung cancer ranked 3rd in male population and 12th among the female population.[1]

THERAPY:

- Surgery, Radiotherapy, and Chemotherapy[2]
- However, most anticancer drugs are potentially toxic and often ineffective, leading to systemic toxicities.
- Methotrexate is an antitumour drug and has been proven efficiency in many types of cancer.
- Still, these drugs affect not only cancer cells but also normal cells leading to side effects!

SOLUTION:

- Hence, it is very important to invite new therapeutic protocol to treat lung cancer.
- Microsphere can be effective by administered into body intravenously will distribute itself in difference organs.
- Depending on the size of the particles and particles between 5 – 15 um are normally entrapped in the capillary network of lungs[4].

- An attempt has been made to developing microspheres of **Methotrexate**(Mxt) using carbopol as a polymer to over come its main side effects.

FORMULA:

Carbopol (0.25 g),
Methotrexate(0.25 g)
100 ml water

→ Solution

↓

Spray

↓

7 µm spray nozzle

↓

Dried fine particles was collected

EXPERIMENTAL DESIGN METHODOLOGY

- **Optimization of particle size - 20 runs**

Stat-Ease software (Design-Expert V.8.0.7.1)

- The three independent variables selected were
  - Polymer concentration (A).
  - Inlet temperature (B)
  - Feed flow rate (C)

PREPARATION: SPRAY DRYING TECHNIQUE:

BUCHI: Nano Spray Drier B-90

EVALUATION OF FINE POWDER (MICROSPHERES):

- Drug content
- Percentage yield
- Surface morphology
- Particle size analysis
- In vitro release studies

DRUG CONTENT

- Content = $\left(\frac{Estimated\ drug\ content}{Total\ amount\ of\ drug\ added}\right) X\ 100$

- UV-1601 spectrophotometer, Shimadzu, Tokyo, Japan
- Methotrexate content analyzed at 262 nm

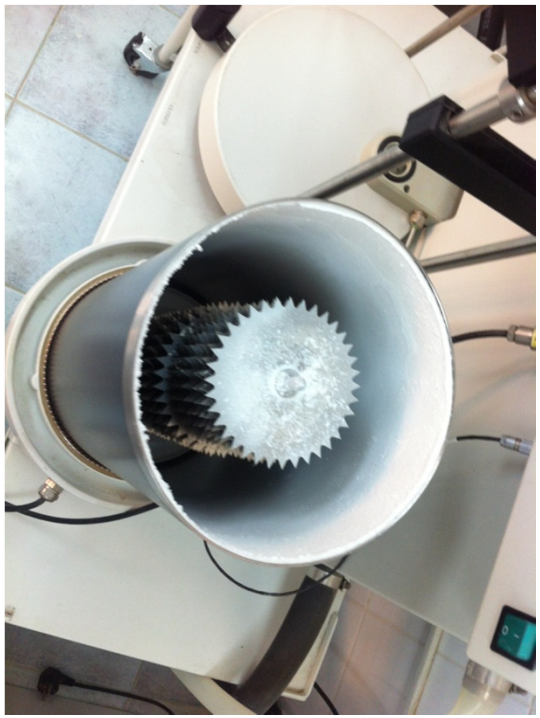
77%±0.3%

PERCENTAGE YIELD:

- $\%\text{Yield} = \left(\frac{Microspheres\ recovered}{Total\ amount\ of\ drug{+}polymer\ added}\right) X\ 100$

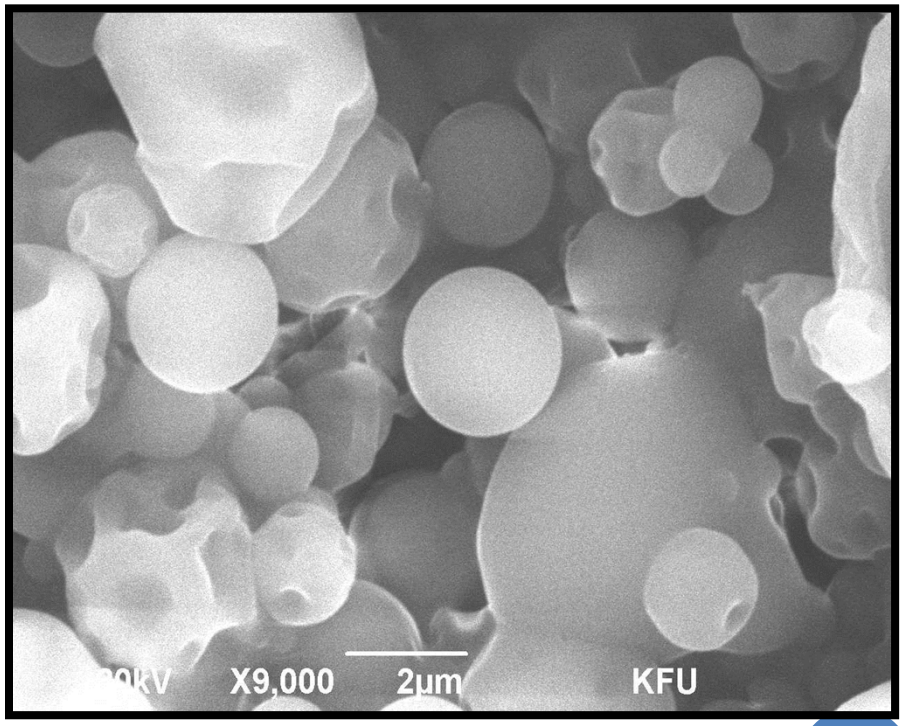
89%±0.4%

The low product yield is due to the powder sticking on the dryer *chamber* wall *during* drying



SURFACE MORPHOLOGY:

- Scanning Electron Microscope.
- (Jeol Analytical Scanning Microscope, JSM-6390LA, Tokyo, Japan)
- Methotrexate microspheres obtained was surprisingly were shriveled (due to surface folding).

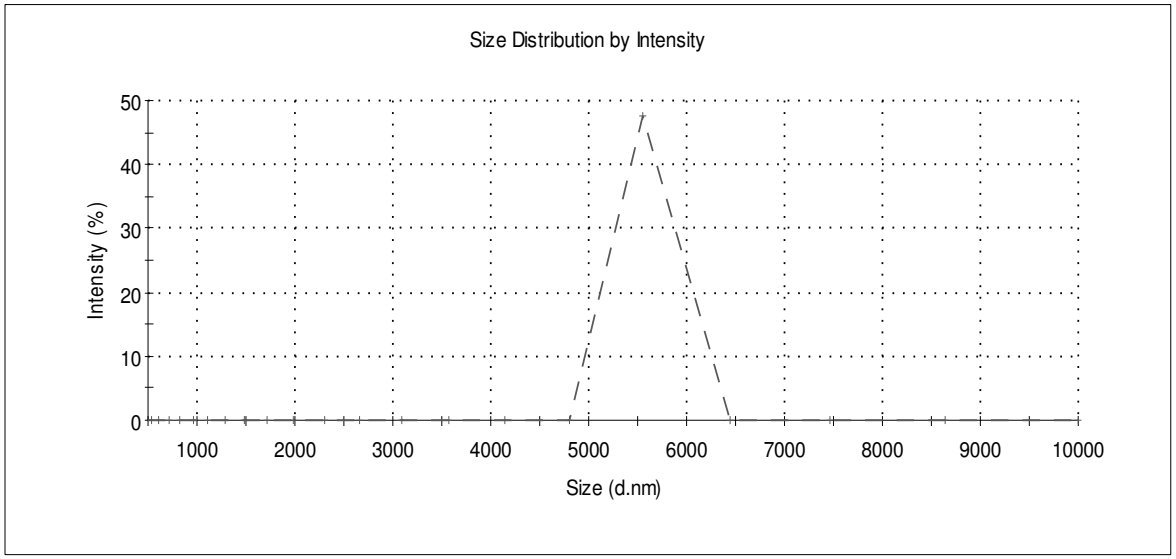


- Powder lost its moisture very rapidly during the drying process in the drying chamber
- due lack of a plasticizer.
- Microspheres were intended to stay for longer time, plasticizer was not added in our formulation due to chances of irritation in the target site, lung.

PARTICLE SIZE ANALYSIS:

- Nano Series Nano-ZS, Malvern Instruments Inc, Westborough, MA.

Average particle size of 6.8 µm

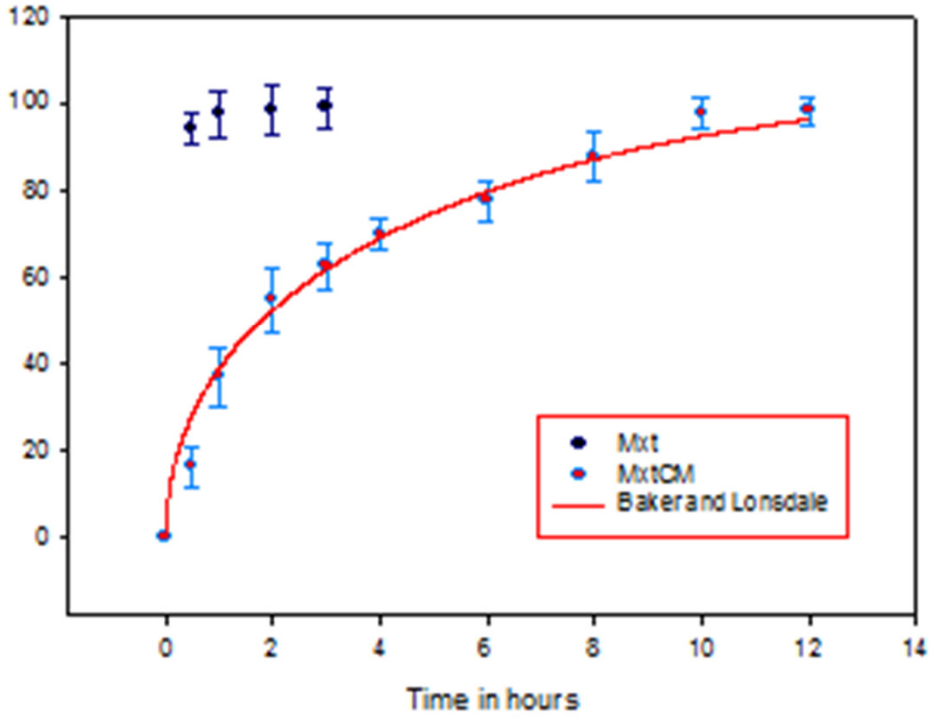


Microspheres with the particle size range of 5–15µm have a prominent lung-targeting.

IN VITRO RELEASE STUDIES:

- Mxt carbopol microspheres were placed in a dialysis bag and dialyzed against 500 mL of phosphate saline buffer (PBS), pH 7.4 at 37+1~ ^{o}C. Samples were withdrawn and sink conditions were maintained.
- Time interval: 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, and 12 h).

- 37% methotrexate in MxtCM first hour released.
- Mxt adsorbed on or merged close to the external surface of th microspheres.



In clinical practice this would lead to 'burst effect', which enables the formulation to show fast therapeutic effect to the patients.

- However, the methotrexate released from carbopol microspheres in 12 h was 98.2% %.
- In comparison with MxtCM, the methotrexate injection releases methotrexate very fast 94.2% in 30 min.
- The results directed that MxtCM had sustanined release efficiency.

RELEASE KINETICS:

- Results obtained from in vitro release studies fitted to various kinetic models.
- (i.e., Higuchi, Korsmeyer's Peppas, Hixon and Crowell, first-order, Baker and Lonsdale) to prove the mechanism of drug release.
- The best fit with $R^2 = 0.9807$ was seen in Baker and Lonsdale model resulting to polymer swelling and drug diffusion kinetic mechanism.

STABILITY STUDIES:

- Microspheres were placed into a bottle and stored for 12 months at 3-5^{0}C, 15-25^{0}C, and 37^{0}C, respectively. The surface morphology and methotrexate content were examined periodically.

- During storage at 3-5^{0}C or room temperature (15-25^{0}C) for 12 months surface morphology and drug content of methotrexate had no notable changes.
- However, at 37^{0}C and RH 75% the characteristic of liquification was observed.

CONCLUSION:

- The findings of the work can also be applied for developing effective blue-print for targeted organ specific drug delivery.
- Decrease the side effects.
- Decrease the dose and frequency of drug administration.
- It is gives sustained release.
- Avoid first pass metabolism.
- as intracellular therapy with other drugs, by a slight modification in the techniques employed in the preparation of microspheres.

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Questions!?

THANK YOU…