

OPTIMIZATION AND SOLUBILIZATION STUDY OF NOVEL NANOEMULSION FORMULATION FOR 5-FLUOROURACIL BY APPLYING PSEUDOTERNARY PHASE DIAGRAM

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ABSTRACT

Objective: The aim of the present study was to formulate, optimize 5 fluorouracil nanoemulsions for targeting brain tumor.

Method: 5 Fluorouracil is an anticancer drug which has its effects on many types of tumor. The formulation was optimized for different components and the solubility study for the oil in surfactant & co-surfactant mix ratio was optimized using ternary phase diagram.

Result: The Smix ratio was optimized as 1:1 where the maximum concentration of the oil has solubilized and the nanoemulsion area was increased.

Conclusion: 5 Fluorouracil nanoemulsion for targeting brain tumor and the pseudo ternary phase diagram for the solubility studies and the components of different phases were optimized and achieved through this study.

Keywords: Nanoemulsion, 5-Fluorouracil, Pseudoternary phase diagram solubility, anti-cancer effect.

INTRODUCTION

Nanoemulsion [1] is also used for targeting diseases of the CNS such as migraine, tumor, Parkinson's diseases; Alzheimers diseases require delivery of drugs to CNS. Anticancer drugs are most commonly used to reduce cell division and cell propagation. There are plenty of drugs available for cancer treatment. 5-Fluorouracil is one among the anticancer drug which is a pyrimidine analog used in the treatment of cancer. It is well known as suicide inhibitor which works through irreversible inhibition of thymidylate synthetase. This drug is formulated in different formulations and also using different route of delivery of drug. The aim of the present study is to formulate and optimize 5 fluorouracil [1]. The droplet size of the nanoemulsion typically fall in the range of 20-30 nm and shows a narrow sized distribution. It consists of two phases, one is aqueous phase and the other is oil phase. The excipient to be used is selected using preformulation studies. The optimization of the oil, surfactant & water in the formulation is done by solubility study. The optimum concentration of the oil that could be solubilized with the surfactant mix is optimized using pseudo ternary phase diagram.

MATERIALS & METHOD

5-Fluorouracil (Spectrochem Pvt. Ltd., Mumbai), Castor Oil (S-d fine Chem, Mumbai), Tween 80 (S-d fine Chem, Mumbai), PEG 400 (S-d fine Chem, Mumbai), Methanol (Loba Chemic, Mumbai), Probe Sonicator (Sonic materials VCA 750), Bath Sonicator (PCI, Mumbai), Magnetic Stirrer (Remi Equipments, Mumbai), UV-Visible spectrophotometer (Shimadzu, UV1700, Japan)

Preformulation Studies

The preformulation study was mainly done to determine the physical, chemical and various pharmaceutical properties [2] of all the components (including drug) alone and also when combined together in the formulation. The main objective of the preformulation study was to produce a stable product with specified drug content (often 90-95%).

Solubility studies**Optimization of oil**

The optimization of oil [3] can be done by adding excess of drug in 2 ml of fixed oils like castor oil, olive oil, arachis oil and oleic acid separately in a 5 ml capacity stopper vials and mixed using vortex mixer. The samples were then centrifuged at 3000 rpm for 15 min. The supernatant was taken and then filtered. The concentration of 5-Fluorouracil in these oils were determined using UV-Spectrophotometer at 266nm.

Optimization of surfactant

The surfactant selection [4] was done by adding 4 ml of selected oil to 2.5 ml of surfactant solution (15% V/V surfactant in water) and mixed using vortex mixer. The mixing was performed until a clear solution obtained. In the similar way co-surfactant was also optimized.

Preparation of Pseudo Ternary Phase Diagram

On the basis of optimization [5] studies, Castor oil & Methanol were selected oil phase and Tween 80 and PEG were selected as surfactant & co-surfactant respectively. Distilled water was used as aqueous phase. The surfactant and co-surfactant were mixed at different mass ratios (1:0, 1:0.5, 1:1, and 1:2). These ratios were chosen in increasing concentration of co-surfactant with respect to surfactant for a detailed study of phase diagram. For each phase diagram, oil and Smix at specific ratios was mixed thoroughly at different mass ratios from 1:1 to 1:10 in different glass vials. Ten different combinations of oil and Smix were made so that maximum ratios were covered for the study.

The ternary phase diagram for oil, smix [6] and aqueous phase was developed using aqueous filtration method. To the oil and smix mixture aqueous phase is added slowly and titrated. Visual observations were made for emulsions. The physical state was marked on the pseudo ternary phase diagram with one axis

representing water, the second one representing oil phase and third representing a mixture of surfactant and co-surfactant at a fixed mass ratio.

RESULTS AND DISCUSSION

Solubility studies

Optimization of oil

Liphophilic drugs were preferably solubilized in o/w nanoemulsion where w/o system seems to be better choice for hydrophilic drugs. The volume of the formulation should be minimized as much as possible to deliver the therapeutic dose. Solubility of the drug in the oil phase was an important criterion for the selection of oils. The surfactant and co-surfactant is contributing to drug solubilization.

The solubility of 5-Flourouracil in different oils were shown in table 1. The solubility of drug is found to be highest in castor oil as compared to other oils. The castor oil was selected as the oil phase for the development of nanoemulsion formulation.

Table 1:

Solubility of 5-Flouroracil in various oil

S.No	Name of Oil	Solubility%
1	Castor Oil	91.6%
2	Olive Oil	32.8%
3	Oleic Oil	14%
4	Arachis Oil	64.2%

Optimization of surfactants

It is important to determine the surfactant concentration in the formulation. O/W nanoemulsion dosage forms [7] for oral or parental use based on nonionic surfactants are likely to offer in vivo stability. Another important criterion is the selection of cosurfactant to lower the necessary interfacial energy to form the nanoemulsion, consequently improving the solubility. In the present study Tween 20, Tween 60, Tween 80, Span 80 was chosen for screening. Tween 20 with Span 80 was selected as the surfactant and cosurfactant due to its high miscibility with oil phase.

Preparation of Pseudoternary Phase Diagram

Pseudoternary phase diagram were constructed separately for each Smix ratio [8], so that O/W nanoemulsion region could be identified and optimized. The relationship between the phase behaviour of the surfactant mixture and other components is captured using phase diagram. In fig2 the surfactant mix ratio was 1:0.5 where the nanoemulsion area has been narrow when the surfactant ratio is high. In fig3 the surfactant and cosurfactant were mixed in same ratio 1:1 where the maximum concentration of oil 84 % has been solubilized and the nanoemulsion area increased. It may be due to further reduction of the interfacial tension, increasing the fluidity of the interface, thereby increasing the entropy of the system. In fig4 the ratio was 1:2 where the cosurfactant increased and the nanoemulsion area has been decreased which states that high amount of cosurfactant mixture may not have the effect on interfacial tension. Hence, using a constructed phase diagram, the optimum ratios of the components for nanoemulsion which would remain stable and prevent drug precipitation over infinite dilution was selected as 84µl.

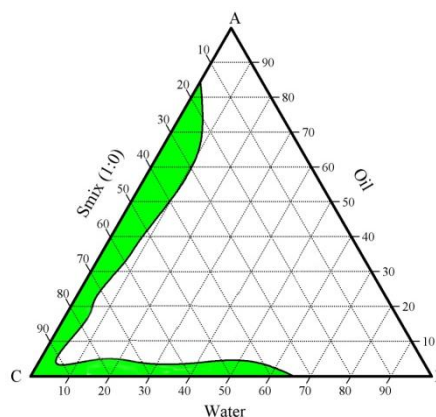


Fig.1: Construction of Pseudo ternary phase diagram with Smix ratio 1:0

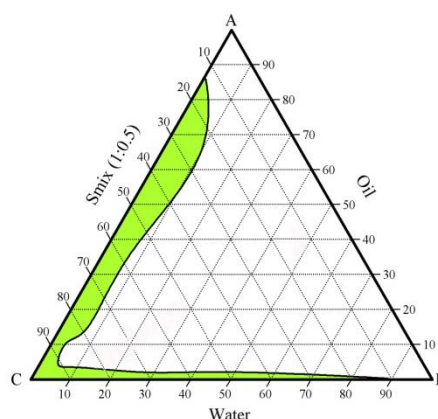


Fig.2: Construction of Pseudo ternary phase diagram with Smix ratio 1:0.5

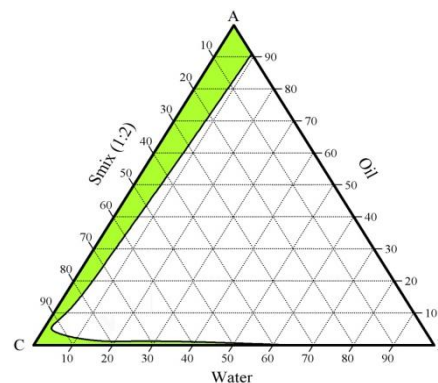


Fig.3: Construction of Pseudo ternary phase diagram with Smix ratio 1:1

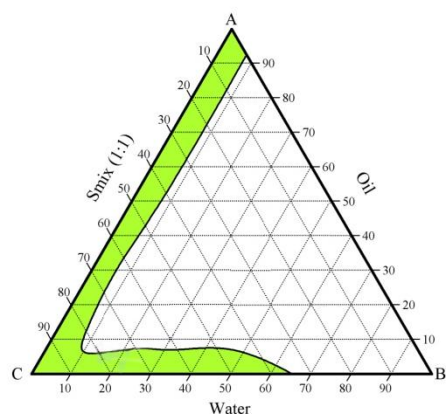


Fig. 4: Construction of Pseudo ternary phase diagram with Smix ratio 1:2

CONCLUSION

Pseudo ternary phase diagram for the solubility studies was constructed and the components of different phases were optimized for further formulation of 5 fluorouracil into nanoemulsion for targeting brain tumor.

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