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Microemulsion Drug Delivery Systems for Radiopharmacy Studies

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ABSTRACT

Microemulsions have been used increasingly for last year's because of ideal properties like favorable drug delivery, ease of preparation and physical stability. They have been improved the solubility and efficacy of the drug and reduce the side effects. Use of radiolabeled microemulsions plays an alternative role in drug delivery systems by investigating the formation, stability and application of microemulsions in radiopharmacy. Gama scintigraphic method is well recognized for developing and detecting the biodistribution of newly developed drugs or formulation. This review will focus on how radionuclides are able to play role with characterization studies of microemulsion drug delivery systems.

Keywords: microemulsion, technetium-99m, radiolabeling, drug delivery system

INTRODUCTION

The definition of microemulsion was stated by Professor, Jack H. Shulman at Columbia University in 1959. [1] The concept of microemulsion has shown changes over time and accepted that of a system of water, oil and amphiphile which is a isotropic and thermodynamically stable liquid solution. Surfactant is localized at a particular boundary between the aqueous and oily phase in the microemulsion. [2]

Depending on the proportion between constituents, in the two extremes the microstructure of the microemulsions range from dispersed in the oil phase with a very small water droplets (w/o microemulsion) to dispersed oil droplets in the water phase (o/w microemulsion). The microstructure of the mixture changes continuously from a spherical to cylindrical tubular and interdependent the oil and water phases are separated by a very thin layer of surfactant molecules that defined as bicontinues microemulsion. [3] Microemulsions consist of oil, water, surfactant and cosurfactant. They are isotropic and thermodynamically stable systems. The droplet size of microemulsions is usually in the range of 10-100 nm. These homogeneous systems are low viscose fluids and are prepared over a wide range of surfactant concentration and oil to water ratio. [4-6] In w/o microemulsion, water droplets are dispersed in the continuous oil phase while o/w microemulsion is composed when oil droplets are dispersed in the continuous aqueous phase. When equel amounts of water and oil bicontinuous microemulsion is occured. In all three types of microemulsions, the interface is stabilized by a suitable combination of surfactants and/or co-surfactants. The flexibility of the surfactant film is a significant factor. A flexible film of surfactant will allow the presence of various structures such as droplet size, aggregates and bicontinuous structures, and therefore it increasing the range of microemulsion formation. A very tough surfactant film will not allow presence of bicontinuous structures in this case will prevent the range of microemulsion formation. The internal structure of a microemulsion is very important for the diffusivity of the phases, moreover these respective phases is important for drug diffusion. Researchers have been trying to understand the complex phase behaviour and the various microstructures encountered in the microemulsion systems. [7]

The characterizations of microemulsions are evaluated using ternary phase diagrams. Ternary phase diagrams are triangular. These edges are the components of a microemulsion that oil, water and surfactant/co-surfactant.

The favorable drug delivery, solvent properties, ease of preparations and the physical stability of these oil-water-surfactant mixtures, makes microemulsions very promising vehicles for future formulations. In pharmaceutical

fields, microemulsions interest is increasing and so they are implemented in various administration routes. The aim of this review is to demonstrate the recent literature with respect to use of microemulsions for drug delivery and to investigate the formation, stability and application of microemulsions in radiopharmacy.

Affecting Factors for Microemulsion Drug Delivery System

Microemulsion systems in drug delivery systems that allow for sustained or controlled release have appeared as a new tool for transdermal, topical, oral, nasal, intravenous, ocular, parenteral and other administration routes of drugs. Furthermore microemulsion is a drug delivery system that is used to increasing specific targeting and therapeutic activity and reducing toxic effects of drugs. [8] Due to the lipids increase the absorption of oral drugs, oil-in-water (o/w) microemulsions are promising as drug delivery systems [9, 10]. Also, o/w microemulsions protect the advantages of traditional colloidal systems that improving physical stability, protection of drug molecules from degradation in the body, controlled drug release, specific targeting, biocompatibility. [11-14] Microemulsions have very low surface tension and small droplet size therefore they have high absorption and permeation. [4]

Advantages of microemulsion as delivery system: Thermodynamically stable, increasing the solubility of the drug, enhances the percutaneous uptake of the drug, improve the efficacy of the drug by allowing the dose reduction and side effect minimization, prevention of hydrolysis and oxidation of the drug.

Disadvantages of microemulsion as delivery system: In many cases high concentration of surfactant and co-surfactants which required formulating a stable microemulsion can be caused cytotoxicity. [4, 15-18]

The affecting factors for microemulsion drug delivery systems are described below:

Property of Surfactant: Surfactant contains lipophilic and hydrophilic groups. Hydrophilic single chain surfactants such as cetylethyl ammonium bromide dissociate completely in dilute solution and have a tendency to form o/w microemulsion. When the surfactant is in presence of salt or when high concentration of surfactant is used, degree of dissociation of polar groups becomes lesser and resulting system may be w/o type. Chosen surfactant must have lower interfacial tension to a very small value to aid dispersion, provide a flexible film that can readily deform round small droplets and be of appropriate Hydrophilic and lipophilic balance (HLB) character to provide the correct curvature at the interfacial region for the desired microemulsion type. It is generally accepted that low HLB value surfactants are favored for the formulation of w/o microemulsion, whereas surfactants with high HLB value (>12) are preferred for the formation of o/w microemulsion. Surfactants with HLB value greater than 20 often require the presence of cosurfactants to reduce their effective HLB to a value within the range required for microemulsion formation. [4]

Property of Oil Phase: Oil phase also influence curvature by its ability to penetrate & swell the tail group region of the surfactant monolayer, swelling of tail results into an increased negative curvature to w/o microemulsion. [19-21]

Packing Ratio: HLB of surfactant determines the type of microemulsion through its influence on packing and film curvature. The analysis of film curvature for surfactant association`s leading to the formation of microemulsion. [22]

Temperature: Temperature is extremely important in determining the effective head group size of nonionic surfactants. At low temperature, they are hydrophilic and form normal o/w system. At higher temperature, they are lipophilic and form w/o systems. At an intermediate temperature, microemulsion coexists with excess water and oil phases and forms bicontinuous structure. [23]

Property of Cosurfactant: Single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form. [24-27] The presence of cosurfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition. [28-31] If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidizing groups (e.g. unsaturated bonds). Short to medium chain length alcohols (C3-C8) are commonly added as cosurfactants which further reduce the interfacial tension and increase the fluidity of the interface.

Characterization of Microemulsion Drug Delivery System

Microemulsions are the nano-structured vehicles which prominently affect the performance of drug delivery system; hence its characterization needs to be completely assessed. Microemulsion drug delivery system should be characterized by using ternary components, ternary phase diagram, phase behavior, selection of specific microemulsion region from phase diagram, identification and characterization of microemulsion region selected for formulation development, dispersed phase droplet size and its distribution and rheological behavior. [32] Apart from

these characteristics, the developed microemulsion formulation needs to be characterized for physical properties such as pH, surface tension and specific gravity. [33-35]

pH, viscosity, refractive index, conductivity, particle size, polydispersity index, zeta potential and phase inversion temperature and osmolality of the water phase were evaluated by Okur et al. for characterization of developed formulations (Table 1). [36] The results of characterization parameters of microemulsion formulations, the formulation with the high oil content, small particle size and low viscosity was selected as optimum. [37]

Table 1: Characterization of the microemulsion formulations

Parameters	Microemulsion I	Microemulsion II	Microemulsion III	Microemulsion IV
pH	3.787 ± 0.015	3.797±0.015	4.073±0.012	4.693±0.030
Viscosity (cP)	17.793±0.047	11.356 ± 0.015	19.71±0.043	11.223±0.025
Droplet size (nm)	1.538±0.111	6.239±0.338	1.023±0.074	2.902±0.044
Polydispersity index	0.224±0.088	0.306±0.053	0.288±0.042	0.493±0.161
Zeta potansial (mV)	0.113±0.015	-0.0472±0.028	0.660±0.0250	0.199±0.021

A cone-plate viscometer (Model LVDV-II, Brookfield Engineering Laboratories, Middleboro, MA, USA) was used to determine the viscosity of the microemulsions by Rhee et al. A photo correlation spectroscope equipped with laser light scattering (Zetasizer 3000HSA, Malvern Instruments, Malvern, UK) was used to measure the droplet sizes in the microemulsions. The droplet size of the microemulsions was found 13.2 nm to 38.0 nm. The polydispersity index was found 0.30 to 0.47. All measurements below 0.5 were indicated narrow deviation from the average size. The viscosity of the microemulsions ranged from 7.08 to 13.07 × 10^3 cps at 37°C. Rhee and friends' results demonstrated that the combinations in the formulation had a predominant effect on the physicochemical properties of the microemulsions. All the drug-loaded microemulsions remained clear during the in vitro experimental period and at room temperature for more than one year. [21]

Radiolabeling Studies

The behavior of microemulsions can also be obtained by radioactive studies by incorporating a gamma ray emitting radionuclide into the dosage form. [38] The role of gamma scintigraphic methods is well recognized for developing and detecting the biodistribution of newly developed drugs or formulation. [39] Although radiolabeled formulations are widely used in gamma scintigraphy studies (biodistribution, gastric transit time, etc), their usage in in vitro release studies is a very innovative approach for drug delivery. The benefit of using radiolabeled drugs in release studies is that the radioactivity can simply be noticed and measured using liquid scintillation detector. [40] The selection of the radioisotope, radiochemical purity and stability, and the specific activity are main factors. These factors can have a result on the metabolic, chemical, and radiochemical stability of drug, metabolite finding, and the recovery of radioactivity. [41] During the last 20 years, important improvements have been achieved in drug development using radiopharmaceuticals as tracers [42]. Selection of an appropriate radionuclide for scintigraphic experiments could be determined by regarding issues such as half-life, cost and availability. The ideal photon energy for radionuclides is between 100-200 KeV. Half-life should impact the length of time that can do experimental studies with radiolabeled formulations. ^{99m}Tc is one of the most popular radionuclide in gamma scintigraphy studies with its good photon energy and suitable half-life. Furthermore, it could be easily obtained with transportable generators. [43, 44]

In the development of drugs, radionuclides are applied as signal sources since they can be incorporated into the formulation without any change of their characteristics. The main benefit of using radiolabeled compounds in drug development is to be sensitive and detectable for minimal amounts. The development of powerful radiotracers requires careful consideration in the selection of the radionuclide. [45]

Radiolabeling Studies for Microemulsion Drug Delivery Studies

Many radiolabeling studies were carried out with microemulsion drug delivery systems. In this part, the example of radiolabeled microemulsions would be given.

Ustundag Okur et al. loaded radiolabeled drug (^{99m}Tc-Aprotinin) into microemulsion formulation for evaluated to in vitro release studies. [46] Aprotinin (APT) release from ^{99m}Tc-APT loaded microemulsions was evaluated with two different methods to find out best in vitro release method, vertical diffusion cells and dialysis bag methods were used to compare the release rates of ^{99m}Tc-APT loaded microemulsion (M-APT) and ^{99m}Tc-APT solution (SOL-APT). [36] Firstly, vertical diffusion cells were used to determine the in vitro release behavior of aprotinin and the release performance of aprotinin from M1-APT and M2-APT formulations showed a slower and continuous release for 6h compared to SOL-APT ($P>0.05$). Secondly, the in vitro release behavior of ^{99m}Tc-APT from microemulsions (M1-APT and M2-APT) and APT solution was evaluated with dialysis bag method and the release rate of ^{99m}Tc-

APT from SOL-APT was higher than APT incorporated microemulsion formulations and in vitro release of APT from M1-APT and M2-APT was found by Ustundag Okur et al. Microemulsions have several advantages over microemulsion formulations when applied parenterally since they have fine particles and they are cleared more slowly than the rough particle emulsions resulting to have an extended staying time in the body. Controlled release could be advantageous for parenteral formulation because it offers an advantage of decreasing the frequency of injection. Intravenous formulations with prolonged activity have medical and economic importance and the physicians are concerned with keeping therapeutic concentrations over long time and decreasing the number of applications. In addition; when considering economically, only well-educated person can apply intravenous administration, and if frequency of application is decreased, the cost of treatment is reduced and time is protected. [47]

Doxycycline Hyclate (DOX) was radiolabeled by Ilem Ozdemir et al. for asses the permeability of microemulsion and solution with radioactive studies. [48] DOX is an antibacterial drug which is member of the second tetracycline group and the absorption of DOX is reduced about 20% in the presence of skimmed milk. Therefore new drug delivery system can be advisable for DOX to reduce the food and drug interaction and improve the bioavailability. Permeability of DOX from ^{99m}Tc-DOX solution (^{99m}Tc-DOX-S) and ^{99m}Tc-DOX loaded microemulsion (^{99m}Tc-DOX-M) was investigated with in vitro cell culture studies by using human colonic adenocarcinoma cell line (Caco-2). The radioactivity of ^{99m}Tc-DOX-M for the apical to basolateral direction (P_{app} (A→B)) and basolateral to apical direction (P_{app} (B→A)) were found higher than ^{99m}Tc-DOX-S. Based on the in vitro cell culture studies the authors suggest this dosage form as a promising alternative for oral drug delivery of DOX.

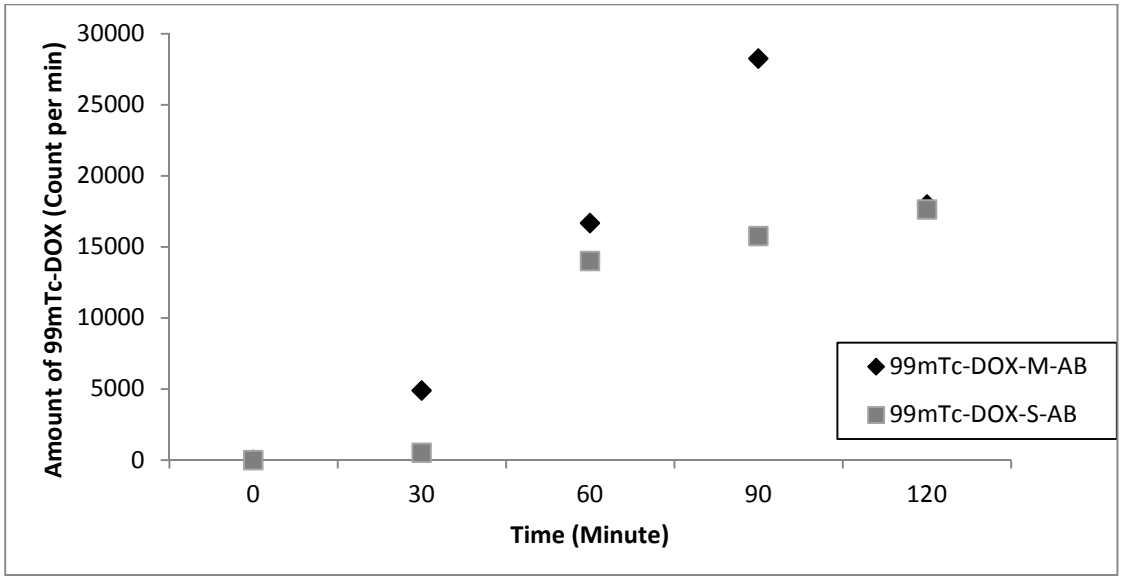

Fig. 1: The permeability amount of ^{99m}Tc-DOX from apical to basolateral direction for microemulsion and solution form [48]

To evaluate the biodistribution of APT solution (SA) and APT-loaded microemulsion (MA) in rats with acute pancreatitis, APT was radiolabeled with ^{99m}Tc by Karasulu et al. [49] Gamma scintigraphy and biodistribution studies were performed with radiolabeled formulation. According to the gamma scintigraphy studies, ^{99m}Tc-APT-loaded microemulsion and ^{99m}Tc-APT solution have different in vivo behavior in the body. While ^{99m}Tc-APT solution had higher uptake in kidney, ^{99m}Tc-APT loaded microemulsion had higher uptake in the spleen and liver. In mild pancreatitis, ^{99m}Tc-APT loaded microemulsion was slowly distributed in speed compared to ^{99m}Tc-APT solution. According to the published paper, gamma scintigraphy studies were indicated that ^{99m}Tc-APT solution show two times higher uptake than ^{99m}Tc-APT loaded microemulsion in kidneys. [49, 50]

Risedronate sodium (RSD) was radiolabeled with ^{99m}Tc by Ilem-Ozdemir et al. to investigate the permeability of RSD solution and SMEDDS by using human colonic adenoma carcinoma cell line (Caco-2 cell). [51] Permeability studies were performed from apical to basolateral (A→B) and basolateral to apical (B→A) directions. ^{99m}Tc-RSD included formulations were applied to the cells and and the permeability of drug was evaluated by detecting the samples radioactivity. The results of in vitro permeability results indicate that a significant enhancement of permeability for ^{99m}Tc-RSD SMEDDS formulations in Caco-2 cells compared with the ^{99m}Tc-RSD solution in apical to basolateral and basolateral to apical directions.

In a study, Elitez et al. radiolabeled alendronate sodium (ALD) containing microemulsion and evaluated its permeability using Caco-2 cells. [52, 53] Permeability studies were performed from apical to basolateral and basolateral to apical directions. The cells were incubated with radioactive samples during 120 min. Permeability results showed that ^{99m}Tc-ALD microemulsion was more permeated from apical to basolateral when compared to basolateral to apical directions and ^{99m}Tc-ALD solution.

CONCLUSION

Information about behavior of microemulsions can be obtained with radioactive studies by incorporated a radionuclides into the dosage form. The role of gamma scintigraphic methods is well recognized for developing new drugs and detecting the biodistribution of medicines. Radionuclides also use to assess the permeability of microemulsion with in vitro cell culture studies.

Obtained from the studies based on the results; microemulsions enhance the solubilization capacity and dissolution efficiency of poorly soluble drugs and drug solubilization capacity and dissolution efficiency are reliant on the microstructure of the microemulsions. Solubilized drugs may influence the boundaries of structural regions and the transition point between different microemulsion microstructures.

Microemulsions have been shown to be able to control drug delivery, increase drug solubility, increase bioavailability and reduce side effects.

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