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MULTIPLE EMULSIONS AND ITS APPLICATIONS: A REVIEW

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ABSTRACT

Multiple emulsions square measure many-sided polydisperse systems wherever each oil in water and water in oil emulsion exists all at once that square measure stable by lipophillic and hydrophilic surfactants severally. Stability of multiple emulsions is completely dependent upon the ratio of these surfactants is used in the formulation. Among water-in-oil-in-water (w/o/w) and oil-in-water-in-oil (o/w/o) kind multiple emulsions; the previous has wider areas of application. Formulation, preparation methodology and in-vitro evaluation methods for multiple emulsions are reviewed. It has several of applications in controlled or sustained drug delivery, targeted drug delivery, taste masking, bioavailability enhancement, enzyme immobilization, etc. Multiple emulsions have conjointly been applicable as intermediate step within the microencapsulation method and square measure the systems of accelerating interest for the oral delivery of hydrophilic medicine, which are unstable in gastrointestinal tract like proteins and peptides. This review is focused on applications of multiple emulsions.

KEYWORDS

Multiple Emulsions, Surfactant and Stability of Emulsions.

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INTRODUCTION

Multiple emulsions area unit outlined as emulsions during which each forms of emulsions, i.e. water-in-oil (w/o) and oil-in-water (o/w) exist simultaneously[1]. They mix the properties of each w/o and o/w emulsions. These have been described as heterogeneous systems of one immiscible liquid dispersed in another in the form of droplets, which usually have diameters greater than 1 μm1. These two liquids forming a system are characterized by their low thermodynamic stability[2]. Multiple emulsions area unit terribly complicated systems

because the drops of dispersed particles themselves contain even smaller droplets, which normally consist of a liquid miscible and in most cases identical with the continuous phase[3]. Both hydrophilic and lipotropic emulsifiers area unit used for the formation of multiple emulsions. Multiple emulsions were determined to be promising in several fields, particularly in pharmaceutics and in separation science. Their potential biopharmaceutical applications[3] include their use as adjuvant vaccines[4], as prolonged drug delivery systems[5-8], as sorbent reservoirs in drug overdose treatments[9] and in mobilization of enzymes[10-11]. Multiple emulsions were conjointly investigated for cosmetics for his or her potential blessings of prolonged unleash of chemical agent, incorporation of incompatible materials and protection of active ingredients by dispersion in internal phase[12-14]. Also water-in-oil-in-water (W/O/W) multiple emulsions area unit emulsion systems wherever tiny water droplets area unit en-trapped among larger oil droplets that successively area unit distributed in a very continuous water section. Because of the presence of a reservoir phase inside droplets of another phase that can be used to prolong release of active ingredients[15]. Multiple W/O/W emulsions contain both W/O and O/W simple emulsions and require at least 2 emulsifiers to be present in the system when prepared using the 2-step method, one that features a low Hydrophile-Lipophile Balance (HLB) price to stabilize the first W/O emulsion and one that features a high HLB price to stabilize the secondary O/W emulsion. The low-HLB wetter is dominantly hydrophobic and is side to the oil section. The high HLB wetter is dominantly hydrophilic and is side to the outer continuous binary compound section. The concentration quantitative relation of those 2 surfactants is vital to get stable and high yields of W/O/W emulsions[16]. A unique property of W/O/W multiple emulsions com-pared to straightforward W/O emulsions is that the diffusion of water through the oil section as a result of unbalanced diffusion pressures between the inner and external aqueous phases. The oil layer acts as a membrane separating these 2 binary compound phases. Polar molecules dissolved in either the inner binary compound section or the external continuous binary compound section will have the oil layer by diffusion as a result of the concentration gradient. In the case of water this is driven by osmotic pressure. Molecules square measure usually transported via micelles of hydrophobic chemical agent gift within the oil section. Water diffusion causes swelling, bursting, or shrinkage of the internal aqueous droplets, affecting the stability of the multiple droplets as well as the release profiles of the active ingredients loaded in the inner dispersed aqueous phase[17]. Most cardiovascular events are attributed to high blood pressure. High blood pressure is quantitatively the largest single risk factor for premature death and disability due to its extremely high prevalence in industrialized countries. Hence, antihypertensive therapy considerably reduces the risk of developing cardiovascular complications that cause a high mortality rate in patients with hypertension[18-19]. Valsartan may be a new potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. Valsartan inhibits angiotensin II receptors, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow[20-21]. Valsartan is well tolerated after single and multiple dosing following single oral doses up to four hundred mg and when multiple dosing[22-24] with two hundred mg per day. The development of multiple emulsion indefinite quantity formulation of sure active ingredients is difficult. When formulating multiple emulsions indefinite quantity formulations, the objective is to provide an increased release of valsartan and increased oral bioavailability of valsartan in patient as compared to known solid oral dosage forms of valsartan. Development of multiple emulsions indefinite quantity formulation that have improved bioavailability to the far-famed oral indefinite quantity types of valsartan is difficult because of the multiplicity of challenges arising from pharmacokinetic aspects of oral drug delivery. Valsartan has associate degree oral bioavailability

of solely concerning twenty fifth with a good} vary of 25-40% in humans with large inter- and intra-subject variabilities. Valsartan additionally has hydrogen ion concentration dependent solubility whereby it ranges from terribly slightly soluble in a very acidic setting to soluble in a neutral setting of alimentary tract. The porousness of valsartan is low and additionally hydrogen ion concentration dependent wherever it decreases as environmental hydrogen ion concentration will increase from acidic to neutral hydrogen ion concentration values within the gastro enteric tract. As a result of these complex biopharmaceutical properties, development of a more releasable and bioavailable dosage form of valsartan with less inter and intrasubject variability is challenging. Accordingly multiple emulsions indefinite quantity formulation of valsartan that has increased unleash and bioavailability properties with less lay and intrasubject variability would be fascinating. Thus the aim of this study is to "formulate and appraise the multiple emulsion of valsartan"[25].

Method of Preparation

Multiple emulsions were prepared by two step emulsification process:

Preparation of primary emulsification

Primary emulsification: ten mil of H2O containing twenty five mg of drug was step by step side to fourteen mil of oil part containing primary wetting agent (Span40, Span60, and Span 80) and 25mg of drug with continuous stirring at 5000 rev for five minutes. It gives the primary emulsion.

Secondary emulsification[26-28]

Secondary emulsification: twenty mil of viscous primary emulsion was blended more with associate external binary compound part containing secondary wetting agent (Tween80) and fifty mg drug with continuous stirring at one thousand rev for 10 min. All the formulations were prepared by following the same procedure. Effect of primary wetting agent was discovered by evaluating many formulations.

Types of multiple emulsions

Oil in water in oil (o/w/o) emulsion-In O/W/O systems, an aqueous phase separates internal and external oil phases. In other words, O/W/O is a system in which water droplets may be surrounded in an oil phase, which in turn encloses one or more oil droplets.

Water in oil in water (w/o/w) emulsion-In W/O/W systems, an organic phase separates internal and external aqueous phases. In other words, W/O/W is a system in which an oil droplet may be surrounded by an aqueous phase, which in turn is encloses one or more water droplets. These systems area unit the foremost studied among the multiple emulsions

Advantages of Multiple Emulsions

1. They can mask the bitter taste and odour of drugs, thereby making them more palatable. E.g. Castor oil, Cod-liver oil, Chloroquine Phosphate etc.
2. They can be used to prolong the release of the drug thereby providing sustained release action.
3. Essential nutrients like carbohydrates, fats and vitamins will all be blended and may be administered to sick patients as sterile blood vessel emulsions
4. Emulsions provide protection to drugs which are susceptible to oxidation.

Limitations of multiple emulsions

The main problem associated with multiple emulsions is their thermodynamic instability and their complex structure, which has severely limited their usefulness in the many applications of multiple emulsions[29].

Preparation of Multiple Emulsions

Multiple emulsions can be prepared by the re-emulsification of a primary emulsion or they can be produced when an emulsion inverts from one type to another, for example W/O to O/W. The O/W emulsions have small size of internal dispersed phase therefore; it is not used in therapeutics[30].

Phase Inversion Technique or Single Step Technique

The increase in volume of dispersed phase may cause an increase in the phase volume ratio, which subsequently leads to the formation of multiple emulsions. The method involves the addition of associate degree liquid section containing the

deliquescent surfactant (Tween 80/Sodium Docedyl Sulphate) to associate degree oil section consisted of liquid paraffin and containing liophillic surfactant (Span 80).

A well outlined volume of oil section is placed in a very vessel of pin mixer. An solution of surfactant is then introduced in turn to the oil innovate the vessel at a rate of five ml/min, while the pin mixer rotates steadily at 88 rpm at room temperature. When volume fraction of the solution exceeds zero.7, the continuous oil phase is substituted by the aqueous phase containing a number of the vesicular globules among the simple oil droplets, leading to phase inversion and formation of W/O/W multiple emulsion[31].

Two-Step Emulsification

Multiple emulsions are usually formed by a two-step emulsification process using conventional rotor-stator or high pressure valve homogenizers. The primary W/O or O/W emulsion is prepared under high-shear conditions to obtain small inner droplets, while the secondary emulsification step is carried out with less shear to avoid rupture of the liquid membrane between the innermost and outer section. However, the second step usually ends up in extremely polydisperse outer drops (if homogenizing conditions square measure too mild) or in tiny encapsulation potency (if blend is simply too intensive)[31].

Membrane Emulsification Technique

1. In this, a W/O emulsion is extruded into an external aqueous phase with a constant pressure through a Porous Glass Membrane, which should have controlled and homogenous pores.
2. The particle size of the resulting emulsion can be controlled with proper selection of porous glass membrane.
3. The relation between membrane pore size and particle size of W/O/W emulsion exhibits good correlation as described by the following equation: $Y = 5.03\ X + 0.19$ Where, X is the pore size, Y is particle size of the multiple emulsions[30].

Stability of Multiple Emulsions

Multiple Emulsion stability is a phenomenon, which depends upon the equilibrium between water, oil and surfactant. Unfortunately multiple emulsions are thermodynamically unstable. The possible indications of instability include:

1. Leakage of the contents from the inner aqueous phase.
2. Expulsion of internal droplets in external phase.
3. Constriction or distension of the internal droplets due to osmotic gradient across the oil membrane.
4. Flocculation of internal aqueous phase and multiple emulsion droplets.
5. Disruption of oil layer on the surface of internal droplets.
6. Phase separation[31].

Breakdown Pathways

Some of the breakdown pathways that may be involved in W/O/W emulsion destabilization are:

- Coalescence of multiple oil drops, single or multiple.
- Expulsion of Single Internal Droplets.
- Expulsion of More than one Internal Droplet.
- Coalescence of Internal Droplets before being expelled.
- Shrinkage of Internal Droplets due to diffusion.

Methods to Stabilize Multiple Emulsions

The followings area unit a number of the try or studies created to revive or strengthen the steadiness of multiple emulsions:

- Liquid crystal stabilized multiple emulsions.
- Stabilization in presence of electrolytes.
- Stabilization by forming polymeric film.
- Stabilization by interfacial complexation between non-ionic surfactant and macromolecules.
- Stericstabilization.
- Phase-inversion stabilization of W/O/W emulsion[32].

Mechanism of drug release from multiple emulsions

In multiple emulsions, the drug is released from internal to external phase through the oily layer by different mechanism. The release rates are affected by the various factors such as droplet size, pH, phase volume and viscosity etc. The various Mechanisms are:

Diffusion mechanism

This is most common transport mechanism where unionized hydrophobic drug diffuses through the oil layer in the stable multiple emulsions. Drug transport has been found to follow initial order dynamics and obeyed Fick's law of diffusion.

Micellar transport

Inverse micelles consisting of nonionic half of} wetter lying outside and polar part within encapsulate hydrophilic drug in core and permeate through the oil membrane attributable to the outer lipophillic nature. Inverse micelle can encapsulate both ionized and unionized drugs. Recently, the discharge of tetradecane from a tetradecane/water/hexadecane multiple emulsions was investigated mistreatment the differential scanning measuring technique. Micellar diffusion instead of molecular diffusion was thought of to be the paramount mechanism for mass transfer.

Thinning of the oil membrane

Due to pressure level distinction, the oil membrane became skinny, therefore the water and drug simply subtle. This pressure distinction additionally provides force for the crosswise of molecule.

Rupture of oil phase

According to this mechanism rupturing of oil membrane will unite each liquid phases and so drug may be discharged simply.

Facilitated diffusion (Carrier mediated transport)

This mechanism involves a special molecule (carrier) which mixes with the drug and makes it compatible to permeate through the oil membrane. These carriers can be incorporated in internal aqueous phase or oil membrane.

Photo-osmotic transport

The mechanism of this transport process is not very clear. Transport of the drug through the oil membrane takes place with the help of the light.

Solubilization of internal phase in the oil membrane

It is a conspicuous transport mechanism. In this solubilization of minute amounts of the internal phase in the membrane phase results in the transport of very small quantities of materials[32].

Applications of Multiple Emulsions

The most promising use of multiple emulsions is in the area of sustained release, drug formulation since the oil layer between the two aqueous phases can behave like a membrane controlling solute release. Liquid membrane emulsions of the o/w/o sort are accustomed separate hydrocarbons wherever the liquid part is the membrane and a solvent because the external part. The system w/o/w on the other hand can extract contaminants from waste water, which acts as the external phase[33].

Controlled and Sustained Drug Delivery

The basic potential of ME's in clinical therapeutics is in the prolonged and controlled release of drugs. In both systems drug contained in innermost phase partitions through several phases prior to release at the site of absorption and the rate of release is governed by its ability to diffuse through various phases and cross interfacial barriers[31].

Enhancing Oral Bioavailability or Oral Absorption

The various drugs have been incorporated in Multiple Emulsions for the enhancement of the increase of Oral bioavailability from the stomach. For eg: Heparin, Insulin, Griseofulvin etc. The Griseofulvin's oral absorption was increased by forming W/O/W emulsion and which may lead to the enhancement of therapeutic effect of the drug[31].

Multiple emulsions in cancer therapy

Most anticancer drugs are used as emulsions because they are water-soluble. In the kind of Associate in Nursing emulsion it's potential to regulate unleash rates of medication and suppress robust aspect effects of the drug. However, one emulsion cannot be used since W/O emulsions

typically have such a high consistence that infusion of emulsions to arteries/capillaries via catheters is tough. Also O/W emulsions don't seem to be Associate in Nursing choice as a result of they are doing not encapsulate the drug. But W/O/W emulsion systems are suitable drug carriers because of the encapsulation of the drug in the internal water phase and the low viscosity due to the external water phase. For the application of W/O/W emulsions as drug delivery systems it is important to prepare a very stable W/O/W emulsion in which countless submicron water droplets are encapsulated. Higashi and coworkers prepared such a new drug delivery system for treating hepatocellular carcinoma (HCC) using W/O/W emulsions prepared with iodinated poppy-seed oil (IPSO) and water soluble epirubicin. The emulsion accumulates in the small vessels in the tumor when injected to the liver via the hepatic artery[32].

Multiple emulsions in herbal drugs

Apart from its targeted sustained unleash, manufacturing the flavoring drug into emulsion will strengthen the soundness of the hydrolyzed materials, improve the perviousness of medicine to the skin and mucous, and reduce the drugs' stimulus to tissues. So far, some kinds of herbal drugs, such as camptothecin, Bruceajavanica oil, coixenolide oil and zedoary oil have been made into emulsion[32].

Vaccine/vaccine adjuvant

The use of w/o/w multiple emulsion as a replacement variety of adjuvant for matter was 1st rumored by musician. These emulsions elicited better immune response than antigen alone. Rishendra and Jaiswal developed a multiple emulsion immunizing agent against Pasteurella multocida infection in oxen. This immunizing agent contributed each body substance in addition as cell-mediated immune responses in protection against the infection. It was concluded that this multiple emulsion based vaccine can be successfully used in the effective control of haemorrhagic septicaemia[32].

Oxygen substitute

A multiple emulsion of binary compound O carrying material in oil in outer binary compound part is appropriate for provision of O for O transfer processes. Hemoglobin multiple emulsion in physiologically compatible oil in associate degree outer compound saline is provided in sufficiently little drop size to produce O flow through blood vessels to desired body tissues or organs thereby providing a blood substitute. A process is provided wherein hemoglobin, a fragile material, is formulated into high hemoglobin content water-in-oil-in-water multiple emulsions while maintaining high yields and high oxygen exchange activity[32].

Taste masking

Bitter taste of Multiple emulsions of chloroquine, an antimalarial agent has been successfully prepared mask taste and had been found to the efficiently. Taste masking of antipsychotic agent, an antipsychotic drug has also been reported by multiple emulsions[32].

Multiple Emulsions in Diabetes

The S/O/W emulsion for oral administration of insulin has been developed by Toorisaka *et al.* Surfactant coated internal secretion was distributed within the oil by ultrasonication, this dispersion was mixed with the outer water part with a homogenizer and at last, the S/O/W emulsion therefore obtained was studied for their hypoglycemic properties[32].

Multiple Emulsions in Food

The ME's can also be used in Food industry. Susceptible food materials and flavors can be encapsulated in W/O/W emulsions. Sensory tests have indicated that there is a delayed release of flavor in double emulsions[34].

Drug over dosage treatment

ME's can be utilized for the over-dosage treatment by utilizing the difference in pH. For Example:- barbiturates. In these emulsions, the inner binary compound part of emulsion has the fundamental buffer and once emulsion is taken orally, acidic pH of the abdomen acts as associate degree external binary compound part. In the acidic part street drug remains in the main in unionized kind that transfers through oil membrane into inner binary compound part and gets ionized. Ionized drug has less affinity to cross the oil membrane thereby obtaining entrapped. Thus, entrapping excess drug in multiple emulsions cures over dosage[32].

CONCLUSION

The Multiple Emulsion is one of the advanced drug delivery systems for the improvement of the various characteristics of the drugs like bioavailability, taste, release rate etc. The advances include various novel formulations for the betterment of the drug administration and improvement in the palatability of the drug by incorporating them into the various formulations. The Multiple Emulsion is the complex polydispersed system containing an emulsion incorporated in another emulsion, which can be used in many applications like taste masking, sustained release, delivering the unstable drug and prevention of the drug from the environment etc.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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