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REVIEW ARTICLE

MULTIPLE EMULSION : STRATAGIC AND TECHNOLOGY

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Abstract:

Multiple emulsion is the both emulsion which is W/O/W and O/W/O emulsions. Multiple emulsion are used to in the area of sustained release. Both hydrophilic and lipophilic emulsifiers are used for the formation of multiple emulsions. Multiple emulsion of the oil-in-water-in-oil (o/w/o) type is w/o emulsions in which the water globules themselves contain dispersed oil globules; conversely, water-in-oil-in-water (w/o/w) emulsions are those where the internal and external aqueous phases are separated by oil .Multiple emulsion or double emulsion consists of large and polydispersed droplets that are thermodynamically unstable with a strong tendency for coalescence, flocculation and creaming. The object of the review is the technology and the application of multiple emulsions.

Keywords: Multiple emulsion, o/w/o, w/o/w.

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Introduction:

Multiple emulsions are complex liquid description systems in which the droplets of the one dispersed liquid are further dispersed in another liquid. The inner dispersed globule/droplet in the multiple emulsions are separated from the outer liquid phase by a layer of another phase. There are mainly two types of multiple emulsions W/O/W and O/W/O emulsions.Although,w/o/w emulsions have many of the attributes of w/o emulsions, their lower viscosity, derived from water as the external phase, makes them easier to inject. Adjuvent effects have been reported to be improved compared to w/o emulsions or aqueous solution of antigen. Similar increase in the activity of the anticancer drug delivery using multiple emulsions has been observed. 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 type have been used to separate hydrocarbons where the aqueous phase serves as the membrane and a solvent as the external phase. The system w/o/w on the other hand can extract contaminents from waste water, which acts as the external phase[1]. Multiple emulsions are defined as emulsions in which both types of emulsions, i.e. water-in-oil (w/o) and oil-in-water (o/w) exist simultaneously. They combine the properties of both 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 1μm. These two liquids forming a system are characterized by their low thermodynamic stability. Multiple emulsions are very complex systems as the drops of dispersed phase themselves contain even smaller droplets, which normally consist of a liquid miscible and in most cases identical with the continuous phase.

Both hydrophilic and lipophilic emulsifiers are used for the formation of multiple emulsions. In other words multiple emulsions are complex liquid description systems in which the droplets of the one dispersed liquid are further dispersed in another liquid. The inner dispersed globule/droplet in the multiple emulsions is separated from the outer liquid phase by a layer of another phase. Multiple emulsions were determined to be promising in many fields, particularly in pharmaceutics and in separation science. Their potential biopharmaceutical applications include their use as adjuvant vaccines as prolonged drug delivery systems as sorbent reservoirs in drug overdose treatments and in mobilization of enzymes. Multiple emulsions were also investigated for cosmetics for their potential advantages of prolonged release of active agent, incorporation of incompatible materials and protection of active ingredients by dispersion in internal phase[2]. Multiple emulsions are vesicular and complex systems. They can be considered as emulsions of emulsions and have shown promise in cosmetic. Pharmaceutical and separation sciences .Corresponding author: Their potential pharmaceutical applications include uses such as taste masking, adjuvant vaccines, an immobilization of enzymes and sorbent reservoir of overdose treatments, and for enhancement of enteral or dermal absorption.

Multiple emulsions have been formulated as cosmetics, such as skin moisturizer. Prolonged release can also be obtained by means of multiple structures. These systems have some advantages, such as the protection of the entrapped substances and the incorporation of several actives in the different compartments. Despite their potential usefulness, applications of multiple emulsions have been limited because of thermodynamic instability and their complex structure[3]. Multiple emulsions, which are prepared from oil and water by the emulsification of an existing emulsion so as to provide two dispersed phases, are also of pharmaceutical interest. Multiple emulsion of the oil-in-water-in-oil (o/w/o) type is w/o emulsions in which the water globules themselves contain dispersed oil globules; conversely, water-in-oil-in-water (w/o/w) emulsions are those where the internal and external aqueous phases are separated by oil .Multiple emulsion

or double emulsion consists of large and polydispersed droplets that are thermodynamically unstable with a strong tendency for coalescence, flocculation and creaming.

The most common multiple emulsions are of w/o/w but in some specific applications o/w/o emulsions can also be prepared. Many potential applications for multiple emulsions are aimed for slow and sustained release of active matter from an internal reservoir into the continuous phase (mostly water). Multiple emulsions can serve also as an internal reservoir to entrap matter from the outer diluted continuous phase into the inner confined space. In other applications, multiple emulsions are reservoirs for improved dissolution or solubilization of insoluble materials. The active matter will dissolve in part in the inner phase, in part at the internal and occasionally at the external interface. Protection of sensitive and active molecules from oxidation in the external phase can also be observed. Multiple emulsions system has been previously used to enhance the stability of ascorbic acid[4].

The basic rational for the use of w/o/w and o/w/o type multiple emulsion as a means of prolonged delivery of drugs is that the drug contained in the innermost phase is forced to partition itself through several phases prior to release at the absorption site.Thus the partition and diffusion coefficient of the drug and the strength of the middle membrane phase, which is a multimolecular layer of oil, water, and emulsifier molecules at both the interfaces of multiple emulsion system, controls the drug release from these systems.

PREPARATION AND YIELD OF MULTIPLE EMULSIONS

A two-step procedure developed by matsumoto et al., is the most common method for the preparation of multiple emulsions. For preparing a w/o/w emulsion, a simple w/o emulsion is first prepared by gradual addition of internal aqueous phase to oil phase (containing a suitable lipophilic emulsifier) with continuous stirring which is then added to the external aqueous phase (containing a suitable hydrophilic emulsifier) with continuous stirring. Suitable modifications, like a pre-emulsification step, can be made in this process to achieve proper emulsification.[5] Similarly for preparing o/w/o emulsion, an o/w emulsion is prepared first which is then emulsified with external oil phase.

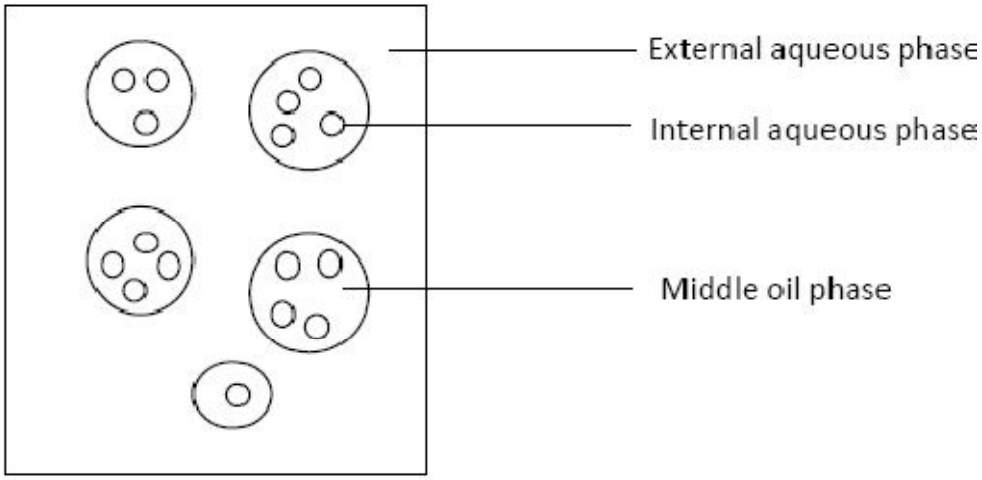

Fig no.1: w/o/w Multiple Emulsion

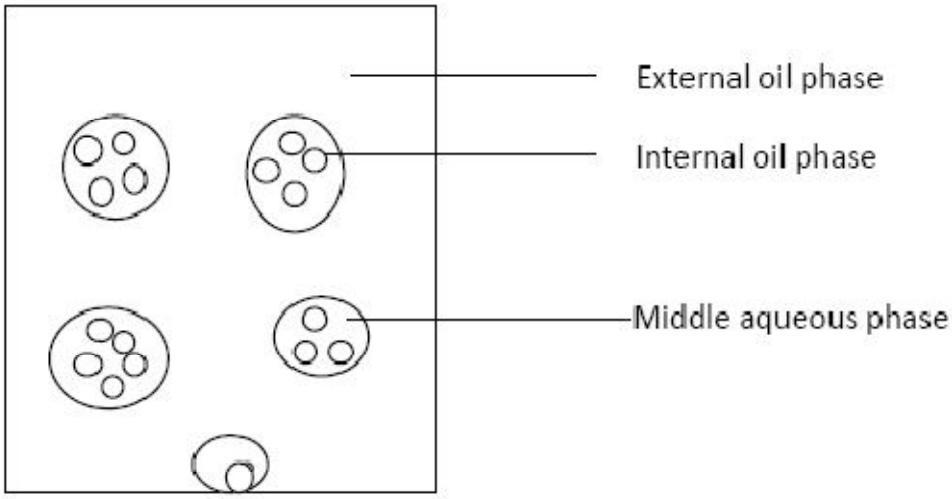

Fig no.2: o/w/o Multiple Emulsion

Sphere-in-oil-water emulsions are specialized forms of multiple emulsions where microspheres containing the drug form the innermost phase. Such emulsions are made by emulsifying (preformed) microspheres with an oil phase to produce a sphere-in-oil emulsion which is again emulsified with an external aqueous to produce s/o/w emulsion.[6] Partial phase solubilization inversion technology is another technique for one step production of stable w/o/w emulsion[7]. This process is based on controlled salting out of the hydrophilic emulsifier during the multiple droplet formation. This process is reported to assure a droplet multiplicity of more than 85%.

Yield (or entrapement efficiency) can be expressed in two ways; first is the percentage of multiple droplets relative to simple droplets and second as the fraction of internal aqueous phase entrapped as multiple droplets. Primary phase volume ratio, Secondary phase volume ratio and additives affect the yield of multiple emulsions.

Yield of a w/o/w emulsion decrease with an increase in the primary phase volume ratio but Matsumoto et al.[8], found no significant effect of internal of phase volume on yield. Collings has suggested the optimal aqueous phase volume to be 25-50 percent of the oil phase. Primary phase volume ratio also has an effect on particle size and viscosity of the w/o/w emulsion and it was observed that the entrapment efficiency increased from 81.2% to 99.3% with change in phase ratio from 1:1:2 to 1:4:5. Increase in primary volume of inner aqueous phase increases the cumulative drug release from w/o/w emulsions. Second emulsification step is critical as excess of shearing can cause rupture of multiple droplets leading to an emulsion with marked simple o/w character and decreased yield. Davis and walker[9] found that yield of w/o/w emulsions decrease in a zero order manner as a function of increasing second emulsification time. An increase in secondary emulsification time reduced particle size and increase amount of drug in external aqueous phase thus decreasing the yield. Increase in second sonication time might retard the phase separation but increase the release rate from these systems and droplet size decreased with increase in second emulsification time. Davis and walker reported yield to be relatively independent of the secondary phase volume ratio. In contrast matsumoto et al., found that the yield of liquid paraffin based emulsion system increases from 55% to 90% when secondary phase volume ratio was increased from 0.1 to 0.5.

Yield/stability of a w/o/w multiple emulsion increases upon addition of various agents viz. Surfactant and sorbitol, sodium chloride, dextrose, bovine serum albumin, glucose to the internal aqueous phase of w/o/w emulsions[10]. This in yield in case of surfactant was found to be due to a increase in the interfacial tension between the internal aqueous phase and oil phase of the w/o/w emulsion. This decrease in interfacial tension leads to formation of smectic type liquid crystals upon addition of hydrophilic surfactant to the internal aqueous phase. Osmotic additives (sodium chloride, bovine serum albumin and dextrose) when added to the internal aqueous phase cause the transfer of water from external aqueous phase to internal aqueous phase leading to improvement in formation percentage and stability due to increase in the viscosity of the

emulsion[11]. Increase in the concentration of glucose or sodium chloride in aqueous inner phase increases the percentage of solute entrapped in the inner aqueous phase and viscosity of the emulsion and later delayed the separation of aqueous phase and release of the solute[12].

FORMULATION OF MULTIPLE EMULSIONS

The oils used to prepare multiple emulsions include liquid paraffin, vegetable oils such as sesame oil, olive oil, arachis oil, isopropyl myristicate and others. Mixtures of oils can also be used to minimize the differences in specific gravity between the oil and aqueous phase of emulsion and to vary the viscosity of the oil phase in order to control the movement of solute across the oil membrane. In case of o/w/o emulsion system, the two oil phases can be same or different. A novel o/w/o emulsion containing castor oil as the internal oil phase and a fluorocarbon as the external oil phase has been has been described for pulmonary delivery of the drug[13].

Selection of oil phase can affect various emulsion parameters like yield, release profile, particle size and emulsion stability. The mineral oils give much higher yield than the vegetable oils. In a study, phase volume ratios giving rise to 50% yield were found to be 0.35, 0.29, 0.11, 0.22, and 0.15 for emulsions based on light liquid paraffin, squalane, maize oil and arachis oil, respectively. The release of drug from multiple emulsions is affected by the nature of the oil phase due to difference in partition coefficient of different oil phases for the drug[14]. W/o/w emulsions prepared with high viscosity oils tend to have larger particle sizes. A positive correlation between that the interfacial tension at the oil water interface and the internal droplet size has been proposed. Viscous oils produce w/o/w emulsions which are more stable in terms of percentage breakdown.

The two aqueous phases of w/o/w emulsions can be simple aqueous solutions of drugs, buffered solutions, aqueous suspensions of the drug, gelled aqueous phases and aqueous phase containing viscosity enhancers. Release rate can be modified by changing the ph of the two aqueous phases. Increase in pH difference between two aqueous phases destabilizes the w/o/w emulsions.

Surfactants are used to reduce the interfacial tension at o/w or w/o interface. For formulation of multiple emulsions, at least two stabilizing surfactant are needed. For w/o/w emulsion a lipophilic surfactant is used as primary emulsifier and a hydrophilic surfactant is used as

secondary emulsifier while in case of o/w/o emulsion hydrophilic surfactant is required for first emulsification and lipophilic surfactant is required for secondary emulsification. The optimum surfactant needed to emulsify given oil can be determined by use of hydrophile lipophile balance (HLB) system. However HLB system does not take into account the effects of surfactant concentration on stability. Florence and Whitehill suggested the optimal HLB value of the primary surfactant to be in the range 2-7 and that of secondary surfactant to be in the range of 6-16 for a w/o/w emulsion .Surfactant blends can be used to achieve optimal HLB. Combination of surfactants produces more stable emulsions[15].

Concentration of surfactant also affects the emulsion yield. The use of very low or very high concentration of surfactant is not advocated because very low concentration may not be able to stabilize the emulsions while use of very high concentration may cause toxicity. Matsumoto et al. suggested that concentration of lipophilic surfactant (span80) required for 90% and more yield was more than 30% w/w of the oil phase but high concentration of hydrophilic surfactant in external aqueous phase of w/o/w emulsion decreased the yield. Also, an excess of lipophilic surfactant can cause the inversion of w/o/w emulsion to simple o/w emulsion[16]. For preparation of w/o/w emulsions, Jager-Lezer et al,. calculated the minimal lipophilic surfactant concentration needed to saturate the primary w/o interface by taking into account the primary emulsion composition, molecular mass of lipophilic surfactant, average diameter of the internal aqueous droplets and the molecular area occupied by lipophilic surfactant on the saturated primary interface (determined by interfacial measurements). It was assumed that the oil phase formed a lipophilic surfactant reservoir when surfactant concentration in it was more than the above calculated value. Thus by these calculations optimal surfactant concentration can be found.

Excess of hydrophilic surfactant destabilizes the w/o/e emulsion by solubilization of lipophilic surfactant and thereby reducing its concentration at the primary w/o interface. Attempts have been made to correlate interfacial film strength with stability of w/o emulsion and w/o/w emulsions[17]. Excess of hydrophilic surfactant reduces the interfacial film strength at the primary w/o interface by co-adsorption at primary interface or by solubilization of lipophilic emulsifier in aqueous phase or by both mechanisms. The nature of hydrophilic surfactant also affects the structure of multiple droplets[16]. Jager-Lezer et al,. showed that swelling capacity of multiple w/o droplets increases with an increase in lipophilic surfactant concentration. These workers have

proposed that swelling causes appearance of voids in the hydrophilic surfactant membrane. When an excess of lipophilic surfactant is present in the oil phase, it moves to the o/w interface and fills up the voids created, by droplet swelling, in the hydrophilic surfactant membranes. Thus the swelling capacity of multiple droplets increases and bursting and subsequent release of markers is decreased or delayed. High swelling capacity also leads to stable multiple emulsions. Geiger et al, [18]. Used a novel micropipette aspiration method to evaluate elastic shear modulus of multiple globules and confirmed the predominant role of lipophilic surfactant during the swelling phase.

Magdassi et al, [19]. Reported that yield and stability of w/o/w emulsions was dependent upon the type of emulsifier and it's HLB. It was found that most stable w/o/w emulsions were formed when there was a chemical similarity between the oil phase and the hydrophobic part of the emulsifier and as well as between the pair of emulsifier. The most commonly used lipophilic and hydrophilic emulsifiers are Spans and Tweens respectively. These are nonionic type of emulsifiers, having a wide range of HLB, available commercially. Ionic emulsifiers are not used because they can react with the ionic drugs moreover, the yield of w/o/w emulsions is better with ionic drugs. Moreover, the yield of w/o/w emulsions is better with nonionic type off emulsifiers than the ionic type.

STABILITY OF MULTIPLE EMULSIONS

Some of the breakdown pathway that may occur in a multiple emulsion are coalescence of multiple droplets with each other, coalescence of internal droplets, expulsion of internal droplets, and shrinkage of internal droplets due to diffusion of water through the oil phase. The causes for instability of multiple emulsions are migration of emulsifier, osmotic instability and creaming.

Migration of lipophilic emulsifier to the external aqueous phase can occur leading to the depletion of lipophilic emulsifier in the oil phase and rupture of oil layer with consequent loss of the internal aqueous droplets. Emulsifier migration leads to decrease in effective HLB of the second emulsifier proportional to the concentration of primary emulsifier in the oil phase. The shift of the optimal HLB at various emulsifier concentration is due to the existence of free primary emulsifier in the in the oil phase of the primary emulsion. A linear correlation between

the optimal HLB, the concentration of the second emulgant and the reciprocal of concentration of primary emulsion was observed. At a fixed concentration of primary emulsifier, the HLB shift is inversely proportional to the concentration of secondary emulsifier. This relationship is helpful in predicting optimal HLB if the two emulsifier concentration and the required HLB of the oil are known. Inversion of w/o/w emulsion to a simple o/w emulsion can occur if the HLB of the total emulsifier (i.e., the migrated lipophilic emulsifier and the hydrophilic one) approaches the HLB of the oil or if the droplet size becomes too small to hold internal aqueous droplets due to increasing secondary emulsifier concentration[20].

Collings reported rapid breakdown of w/o/w emulsions at the site of injection and no prolonged effect of the formation was obtained. It was due to the fact that the osmotic pressure in the external environment (body fluids) was greater than that in the internal aqueous phase of the emulsion. This leads to the movement of water from the internal aqueous phase to the external aqueous phase through the oil layer with consequent shrinkage of the internal aqueous droplets and rupture of the oil layer. If the osmotic pressure in the internal aqueous phase is higher than that of the external aqueous phase, water may pass from the external phase to the internal aqueous phase leading to swelling of internal aqueous droplets which eventually burst releasing the solutes. Since the viscosity of w/o/w emulsion depends on continuous phase viscosity, movement of water across the oil phases due to osmotic effects the viscosity of the system[21].

A w/o/w emulsion, upon keeping, may show phase separation due to density difference between the oil phase and the aqueous phase or due to large size of multiple emulsion drops. Decreasing the density difference between aqueous and oil phase, increasing the concentration of secondary surfactant or increasing the viscosity of external aqueous phase, can reduce creaming.

METHODS TO STABILISE MULTILE EMULSIONS

Interfacial complexation improves the stability of w/o/w emulsions by reducing coalescence of internal aqueous droplets. Interfacial complexations refer to a physical interaction between a nonionic lipophilic surfactant (present in the oil phase) and some macromolecule (eg. Bovine serum albumin, gelatin) present in the internal aqueous phase of the w/o/w emulsion. This interfacial complex is formed at the primary w/o interface and occurs in form of a complex membrane and develops over a period of time. Release of solute from such system is slow.

Formation of a polymetic gel in the internal or external aqueous phase of w/o/w emulsion renders good stability of these systems[22]. Gelling agent can be added to the two aqueous phases or the gel may be formed by in situ polymerization. Using gamma-radiation to affect crosslinking between molecules of gelling agent present in either of aqueous phase. Gelling affords stability by blocking the coalescence of multiple droplets (by gelling of external aqueous phase) and by blocking coalescence of internal aqueous droplets (by gelling of internal aqueous phase). A viscosity enhancer (like hydroxypropylmethylcellulose, poly vinyl pyrrolidone, acacia, and gelatin) can be added to the two aqueous phases of a w/o/w system to prevent creaming and coalescence of multiple droplets[23].

Various studies suggested the use of hypertonic inner aqueous phase to reduce (or delay) the separation of aqueous phase from w/o/w emulsions. Kawashima et al,[24]. Reportsed that entrapement percentage of solute in the internal aqueous phase is increased with in concentration of solute (glucose or sodium chloride) in the internal aqueous phase of w/o/w emulsions. Such emulsions had delayed separation of aqueous phase and lesse decrease in percentage entrapement upon storage. Mechanism of stabilization is the thickening of oil membrane. Such emulsions have high viscosity and consequently delayed flocculation and phase separation. Judicious use of osmotic additives in the internal or external aqueous phase, as demanded by the system, can be done to overcome osmotic instability. Adjustment of osmotic imbalance by addition of osmotic agents to the external aqueous phase also leads to retarded release of drug from the w/o/w emulsions[25]. Adjusting the density difference between the oil phase and the aqueous phase can reduce creaming They added lipodal ultra fluid to isopropyl myristate in order to obtain a mixture, which has density equal to that of water.

DRUG RELEASE FROM MULTIPLE EMULSIONS

Diffusion of solute through the oil layer seems to be the most obvious mechanism for transport of unionized lipid soluble drugs. Diffusion of unionized drug 5-fluouracil entrapped inner aqueous phase of w/o/w emulsion across oil phase or through localized thin oil lamellae is the primary transport mechanism. This is supported by the fact that a w/o/w emulsion of 5-fluorouracil, after release of drug by diffusion. Liquid membrane systems used for treatment of drug overdosage are based on diffusion controlled transport of drug from the external to internal

aqueous phase through the oil layer[26]. Drug transport in vitro has been found to follow first order kinetics, Ficks law being obeyed.

Mechanism involving transport of ionized materials through the oil layer has been proposed. One is carriage of water in mixed inverse micelles of hydrophobic and hydrophilic surfactant and second mechanism involvs diffusion of water across very thin lamellae of surfactant formed where the oil layer is very thin. Garti et al[27], also proposed micellar transport for water permeability. Ionized materials can thus permeate the oil layer along with the diffusion water. A third possible mechanism involves carrier mediated transport. Additives were also found to be successful carrier for the transportation of glucose. Also solubilization of small amount of internal phase in the intermediate membrane phase may account for transport of very small of materials.

Recently many authors have reported that release of water soluble drugs from w/o/w emulsions occurs by a swelling breakdown behavious. When a w/o/w emulsion is placed in hypertonic media (hypertonic with respect to the internal aqueous phase of the w/o/w emulsion) water moves from the external to the internal aqueous phase due to osmosis. The oil membrane acts as a semipermeable membrane. The internal aqueous droplets (and consequently the multiple droplets) swell and eventually burst thus releasing these solutes.

Brodin and Frank[28] studied the in vitro release of naltroxone and thymol from o/w/o emulsions and found that a biphasic drug release patterns was observed. A rapid alpha (a) phase followed by a slower beta (b) phase was observed with naltroxone release. However, a lower drug concentration, only b phase was observed. This biphasic pattern is probably due to initial fast release originating from drug leaked due to initial fast release originating from drug leaked in the outermost phase during the preparation of emulsion followed by slower release of drug from the innermost phase of the system.

Florence and Whitechill[29] have suggested release of unionized material from w/o/w multiple emulsion follows first order kinetics. Magdassi and Garti have proposed a kinetic model for release of electrolytes from w/o/w emulsions by considering the internal aqueous phase to be analogous to a dispersed solid in the oil membrane. This system is similar to a polymetic matrix containing the drug in dispersed form. Higuchi has given release kinetics from a polymeric

matrix. The model assumed that drug is dissolved from the surface layer of the matrix; when first layer gets exhausted of the drug, drug release from second layer starts .For a matrix of slab geometry, the release fraction is dependent linearly on the square root of time and reciprocal of initial drug concentration. The model for release of dispersed dug from a spherical matrix was to be suitable for the release of electrolyte from multiple emulsions[30].

CHARACTERIZATION OF MULTIPLE EMULSIONS

Rheology of multiple emulsions: Stability assessment can be made by suitable rheologic measurements. Viscosity changes over time show the volume fraction instability of the dispersed globules and therefore multiple emulsion instability. Elucidation of drug release kinetics can be done by using rheological analysis. Viscosity measurements in combination with conductivity measurements, can give information about release mechanism from w/o/w emulsions. In one such study w/o/w emulsions with sodium lactate in the internal aqueous phase were prepared and diluted with various concentrations of glucose solutions. The diluted emulsions were subjected to rheological and conductometric analysis. Emulsions diluted with glucose solution of certain concentration, showed no variation in apparent viscosity (suggesting stability of multiple droplets) but showed an increase in conductivity value, revealing release of electrolyte. Thus it was proposed that release was due to diffusion of electrolyte through oil membrane and notdue to rupture of oil film. When the w/o/w emulsion was diluted with distilled water, the rheogram showed an increase in apparent viscosity followed by a decrease. This was attributed to initial movement of water from external to internal aqueous phase, leading to swelling of multiple droplets, followed by their rupture.

Rheological behavior of w/o/w emulsions was studied by Kawashima et al, [31] using cone and plate viscometer. A negative thixotropic behavior was observed at low shear rates. This negative thixotropic behaviour becomes more pronounced and the apparent viscosity increased upon increasing thee shear rate, prolonging the shear time, or repeating the shear. Further shearing caused a rapid increase in the shear stress of emulsion and induced phase inversion. This phase inverted emulsion was of w/o type and in a semisolid state. This type of rheological behaviour was attributed to the increase in the volume fraction of the oil droplets by entrapment of water molecules and by coalescence of the oil droplets upon shearing.

Aging conditions can be generated in the multiple emulsions by subjecting them to excessive shearing. Such studies can be used to determine the effect of aging upon stability of multiple systems. In addition to stability determination, rheological measurements have cast light on the phenomenon of permeation of solutes and water through oil membrane of w/o/w emulsions. In an interesting study Tomita and coworkers[32], studied the viscosity changes in w/o/w emulsion upon dilution with various solutions. It was seen that solutions of urea and potassium thiocyanate increased the viscosity while glucose, calcium chloride, and potassium chloride decreased the viscosity. Based on this observation they suggested that solutes which produced a greater increase in viscosity contributed to a smaller degree to the osmotic pressure of the outer phase i.e., the solutes could more or less permeate to oil layer. The permeability sequence was according to the following order, urea>potassium thiocyanate>potassium chloride>glucose>calcium chloride. This sequence of permeability was found to be in good accordance with the permeability coefficient values. Such studies suggest that water and solutes can permeate the oil membrane of the w/o/w emulsions leading to change in vesicle volume, thereby causing change in emulsion viscosity. Such studies also raise question on validity of the dialysis based methods of yield determination as they are based on the assumption that the solutes detected in a dialysis media originate only from leakage during the preparation procedure of w/o/w emulsions and during dialysis. However if the solute can permeate the oil layer, these is no way to distinguish between the solute diffused (permeated) from the internal aqueous phase and solute leaked out due to destruction.

Compared to w/o/w systems very limited work has been done on rheology of o/w/o system. The o/w/o multiple emulsions are highly non-Newtonian. The degree of shear thining in multiple emulsions increases with increase in volume fraction of primary o/w emulsion in o/w/o emulsion. However an increase in viscosity with aging is only marginal in case of o/w/o emulsions[33].

Yield/entrapement efficiency determination

Yield of a w/o/w multiple emulsion can be defined in terms of number and volume percentage of simple and multiple droplets, and in terms of efficiency of entrapment of an marker molecule in the internal aqueous phase of w/o/w system. Thus the methods for yield analysis can be divided in two groups. First is size analysis technique in which particle size distribution of the system is

analysed by a suitable method such as microscopy or coulter counter. The relative proportion of simple and multiple droplets is found[34]. Second is internal phase tracer technique which is based on establishing the entrapement efficiency of a marker in the internal aqueous phase of the w/o/w system. The two groups of methods cannot be compared directly as they measure different parameters altogether. The size analysis technique measures merely the physical presence of multiple droplets and not the entrapement efficiency. Thus it is possible that a system may be having good yield in terms of observed multiple droplets but with little marker entrapped in the internal aqueous phase. In contrast, the tracer technique measures only the difference in concentration of marker in the internal and external aqueous phase. It is very much possible to have maximal theoretical marker present in external aqueous phase (i.e., apparent zero yield) and yet many multiple droplets present in the system.

Freshly prepared emulsion placed in a dialysis bag are dialyzed against a suitable volume of dialysis media for a suitable period of time and the quantity of marker migrated to the dialysis media is analyzed and the yield/entrapment efficiency of emulsion is calculated by a suitable equation. These methods assume that the marker detected in the dialysis media originates only due to leakage during the preparation of emulsion. Migration of marker through the oil phase, during the dialysis process, is taken as negligible. In some methods, the external aqueous phase is separated from the w/o/w emulsion by a suitable technique (centrifugation). The concentration of marker present in the external aqueous phase is analyzed and yield is calculated. Conductivity measurements of w/o/w emulsions, diluted with water, could give the concentration of (ionic) marker in the diluted external aqueous phase and thus the yield can be calculated[35].

Particle size analysis of multiple emulsions:

Methods like optical microscopy and coulter counter can be used for size analysis of the dispersed oil phase. Some of oil droplets contain small aqueous droplets and this results in biomodal size distribution. The size characteristics of the two types of emulsion particles and their change with time can be resolved using a graphical inflection method. Size analysis of internal aqueous droplets is relatively difficult and tedious by optical microscopy; although used by various authors. Moreover small simple drops may pass below the layer of simple droplets to give a false impression of multiple droplets. Reflection of light from the surface of oil droplets

and Brownian movement of droplets are other problems. Size analysis of the internal aqueous droplets can be done easily by sophisticated particle dispersion analyzer.

A freeze etching method[36] using the electron microscope has been used successfully for size analysis of internal aqueous droplets. But it is an expensive and time consuming method, based on semipermeable nature of thin oil membranes; the emulsion was exposed to the osmotic gradient provided by electrolyte in the external aqueous phase. Droplet shrinkage resulted from movement of water from internal aqueous phase to external aqueous phase. The rate of shrinkage, related to surface area and the volume of internal aqueous phase was measured by coulter counter. But it was not able to distinguish between a simple and multiple droplets. Granulometric analysis, using particle size analysers, can be used to obtain parameters like volume/surface diameter.

APPLICATONS OF MULTIPLE EMULSIONS

The rationale behind use of multiple emulsions as prolonged and controlled drug delivery systems is that the drug present in the innermost phase has to cross several phases before it is available for absorption from the system. W/o/w emulsions for parenteral delivery are more convenient to handle, use, and inject due to lower viscosity of these systems. Many authors have studied the use of multiple emulsions for oral, parenteral and topical and ophthalmic, prolonged release of various drugs. Multiple emulsions have been found to be useful in enhancing lymphatic accumulation of anticancer drug[37]. Enhanced lymphatic accumulation of these drugs leads to better anticancer activity. Various workers have proposed the use of w/o/w multiple emulsions in treatment of drug overdosage. Frankenfeld et al.[38], reported in vitro removal of salicylates and barbiturates by w/o/w emulsion and observed that the emulsion was capable of rapid uptake of drug in vitro.

Liquid membranes have been used for various separation purposes like separating hydrocarbons and treatment of waste water. The liquid membranes are similar to multiple emulsions except that no secondary surfactant is used in these systems. Use of multiple emulsions for taste masking of bitter drugs has been described by some authors. W/o/w emulsions have been successfully used as carrier of insulin and bioavailability of insulin from these systems was much improved. The cause of improved bioavailability from multiple emulsion system is that the drug

contained in the innermost phase is protected from the enzymes present in the GIT. Nowadays multiple emulsion technique is utilized extensively for formulation of microspheres. Multiple emulsions have been utilized for many other users like as immunological adjuvants and carriers of vaccines, for immobilization of enzymes, as cosmetic formulations, and as food products[39].

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