Review Article **CODEN: AJPCFF** **ISSN: 2321 – 0915**

Asian Journal of Phytomedicine and Clinical Research

Journal home page: www.ajpcrjournal.com

A BRIEF STUDY ON: MULTIPLE EMULSIONS A REVIEW: A REVIEW

Navneet Kumar Verma*[1], Ankita Tripathi[1], Virendra Kumar Singh[2]

[1]*Faculty of Pharmacy, Kailash Institute of Pharmacy and Management, Gorakhpur, Uttar Pradesh, India.
[2]Faculty of Pharmacy, Sherwood College of Pharmacy Barabanki, Uttar Pradesh, India.

ABSTRACT

Multiple emulsions are the novel drug delivery in which different polydispersed systems where both oil in water and water in oil emulsion exists all together which are stabilized by hydrophilic and lipophillic surfactants respectively. Stability of multiple emulsions is completely dependent upon the ratio of these surfactants is used in the formulation. Along with water-in-oil-in-water (w/o/w) and oil-in-water-in-oil (o/w/o) type multiple emulsions; the former has wider range of application. Formulation, preparation methodology and *in-vitro* evaluation methods for multiple emulsions are reviewed. It has number of applications in controlled or sustained drug delivery, taste masking, bioavailability enhancement, targeted drug delivery, enzyme immobilization, etc. In the microencapsulation process Multiple emulsions have also role as intermediate step and are systems of enhancing interest for the buccal delivery of hydrophilic drugs, and these are unstable in GIT like proteins and peptides.

KEYWORDS

Multiple Emulsions, Surfactant and Stability of Emulsions.

Author for Correspondence:

Navneet Kumar Verma,
Faculty of Pharmacy,
Kailash Institute of Pharmacy and Management,
Gorakhpur, Uttar Pradesh, India.

Email: navneet_its04@rediffmail.com

INTRODUCTION

Multiple emulsions are the composition of simple emulsions in which water-in-oil (w/o) and oil-in-water (o/w) exist both types of emulsions simultaneously[1]. They have all the properties of both type of w/o and o/w emulsions. It has been defined 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 form a system are evaluated by their low thermodynamic stability[2]. Multiple emulsions are very multifarious systems

containing drops of dispersed phase even smaller droplets, which normally consist of a liquid miscible and in most cases identical with the continuous phase[3]. Lipophilic emulsifiers and hydrophilic emulsifiers are used for the preparation of multiple emulsions. Multiple emulsions are resolute to be promising in many fields, particularly in pharmaceutics and in separation science. Their potential biopharmaceutical applications 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 are also useful for cosmetic product preparation for their potential advantages of prolonged release of active agent, incorporation of incompatible materials and protection of active ingredients by dispersion in internal phase[12-14]. Water-in-oil-in-water multiple emulsions are systems where small water droplets are entrapped within larger oil droplets that in turn are dispersed in a continuous water phase. 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 it has a lower Hydrophile-Lipophile Balance (HLB) value to stabilize the primary W/O emulsion and one that has a high HLB value to stabilize the secondary O/W emulsion. The lower HLB surfactant is dominantly hydrophobic and it is added to the oil phase. The higher Hydrophile-Lipophile Balance (HLB) surfactant is dominantly hydrophilic and is added to the outer continuous aqueous phase. The concentration ratio of both surfactants is most important to find stable and high yields of W/O/W emulsions[16]. An exclusive property of W/O/W multiple emulsions compared to simple water in oil (W/O) emulsions is the diffusion of water through the oil phase because of unbalanced osmotic pressures between the internal and external aqueous phases. The oily layer acts as a membrane separator of these two aqueous phases. Polar molecules may be dissolved in the internal aqueous phase or the external continuous aqueous phase and it can cross through the oily layer by diffusion because of the concentration gradient. In case of water it is determined by osmotic pressure. Molecules are frequently elated via micelles of hydrophobic surfactant present in the oil phase. Water diffusion causes puffiness, stuffed 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. Hypertension is quantitatively the major 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 is a new molecule, which is highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. The mechanism of Valsartan is to inhibit 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 and after multiple dosing[22-24]. The formulation development of multiple emulsion dosage for certain active ingredients is too much challenging. When prepared a multiple emulsions dosage formulation, 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 dosage formulation that have improved bioavailability to the known buccal dosage forms of valsartan is challenging due to the multiple challenges arising from pharmacokinetic aspects of buccal drug delivery. Valsartan has an oral bioavailability is about 25% with a wide range of 25-40% in humans with large inter and intra subject variabilities. Solubility of Valsartan is pH dependent, it very

slightly soluble in an acidic medium and soluble in a neutral medium of gastrointestinal tract. The permeability of valsartan is lower and it is also pH dependent where it decreases as medium pH increases from acidic to neutral pH range in the gastro intestinal 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. Due to multiple emulsions dosage formulation release kinetics and bioavailability properties enhanced with less inter and intrasubject variability would be desirable[25].

Method of Preparation

There are two step emulsification process for the preparation of Multiple emulsions are involved:

Preparation of primary emulsification

Primary emulsification: 25 mg of drug is mixed with 10 ml of distilled water, gradually added to 14 ml of oil phase containing primary emulsifier (Span40, Span60, and Span 80) and 25mg of drug with continuous stirring at 5000 rpm for 5 minutes. It gives the primary emulsion.

Secondary emulsification[26-28]

Secondary emulsification: 20 ml of viscous primary emulsion was emulsified further with an external aqueous phase containing secondary emulsifier (Tween80) and 50 mg drug with continuous stirring at 1000 rpm for 10 min. All the formulations are prepared by the same method of preparation. Effect of primary emulsifier was observed by characterizing several formulations.

Types of multiple emulsions

a) 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.
b) 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 are the majority considered with the multiple emulsions.

Advantages of Multiple Emulsions

a) 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.
b) They can be used to prolong the release of the drug thereby providing sustained release action.
c) Essential nutritional substances like carbohydrates, fats, protiens and vitamins can all be emulsified and can be administered to bedridden patients as sterile intravenous emulsions
d) 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

When an increase in the volume of dispersed phase has been developed, it may cause an increase in the phase volume ratio, which subsequently leads to the formation of multiple emulsions. The method involves the addition of an aqueous phase containing the hydrophilic emulsifier (Tween 80/Sodium Docedyl Sulphate) to an oil phase consisted of liquid paraffin and containing liophillic emulsifier (Span 80).

When a well-defined volume of oil phase is placed in a vessel of pin mixer, then an aqueous solution of

emulsifier is introduced sequentially to the oil phase in the vessel at a rate of 5 ml/min, while the pin mixer rotates steadily at 88 rpm at room temperature. When volume fraction of the aqueous solution exceeds 0.7, 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 outermost phase. However, the second step often results in highly polydisperse outer drops (if homogenizing conditions are too mild) or in small encapsulation efficiency (if homogenization is 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 aPorous 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:

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

Breakdown Pathways

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

a) Coalescence of multiple oil drops, single or multiple.
b) Expulsion of Single Internal Droplets.
c) Expulsion of More than one Internal Droplet.
d) Coalescence of Internal Droplets before being expelled.
e) Shrinkage of Internal Droplets due to diffusion.

Methods to Stabilize Multiple Emulsions

The followings are some of the attempt or studies made to restore or strengthen the stability of multiple emulsions:

a) Liquid crystal stabilized multiple emulsions.
b) Stabilization in presence of electrolytes.
c) Stabilization by forming polymeric film.
d) Stabilization by interfacial complexation between non-ionic surfactant and macromolecules.
e) Stericstabilization.
f) 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 first order kinetics and obeyed Fick's law of diffusion.

Micellar transport

Inverse micelles consisting of nonpolar part of surfactant lying outside and polar part inside encapsulate hydrophilic drug in core and permeate through the oil membrane because of the outer lipophillic nature. Inverse micelle can encapsulate both ionized and unionized drugs. Recently, the release of tetradecane from a tetradecane/water/hexadecane multiple emulsions was investigated using the differential scanning calorimetry technique. Micellar diffusion rather than molecular diffusion was considered to be the preponderant mechanism for mass transfer.

Thinning of the oil membrane

Due to osmotic pressure difference, the oil membrane became thin, so the water and drug easily diffused. This pressure difference also provides force for the transverse of molecule.

Rupture of oil phase

According to this mechanism, when rupturing of oil membrane takes place then both aqueous phases unite and thus drug is released easily.

Facilitated diffusion (Carrier mediated transport)

An special molecule (carrier) involves in this mechanism which combines with the drug and makes it compatible to permeate through the oil membrane. These molecules can be incorporated in oil membrane or internal aqueous phase.

Photo-osmotic transport

The mechanism of the transport process is not very certain. The 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. For the separation of hydrocarbons, Liquid membrane emulsions of the o/w/o type have been used 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 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

Due to better water solubility most anticancer drugs are used as emulsions. An emulsion has capability to control release rates of medicine and suppress strong side effects of the drug. However, a single emulsion cannot be used since W/O emulsions generally have such a high viscosity that infusion of emulsions to arteries/capillaries via catheters is difficult. O/W emulsions do not encapsulate the drug so it is not an option. But W/O/W emulsion systems are good drug carriers because of the encapsulation of the drug in the internal water phase and the low viscosity due to the external water phase. W/O/W emulsions as drug delivery systems have the more applications so it is important to prepare a very stable W/O/W emulsion in which

countless submicron water droplets are encapsulated. Such a new drug delivery system for treating hepatocellular carcinoma (HCC) prepared by Higashi and coworkers, 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 and controlled drug release, producing the herbal drug into emulsion will also strengthen the stability of the hydrolyzed materials, improve the penetrability of drugs 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

Herbert first reported the use of w/o/w multiple emulsion as a new form of adjuvant for antigen. These emulsions elicited better immune response than antigen alone. A multiple emulsion vaccine against Pasteurella multocida infection in cattle was first developed by Rishendra and Jaiswal. The vaccine contributed both cell-mediated immune responses as well as humoral 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 aqueous oxygen transportation material in oil in outer aqueous phase is suitable for provision of oxygen for oxygen transfer processes. Multiple emulsion of Hemoglobin in physiologically compatible oil in an outer aqueous saline solution is provided in sufficiently small droplet size to provide oxygen 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 chlorpromazine, 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 insulin was dispersed in the oil by ultrasonication, and this dispersion was mixed with the outer water phase with a homogenizer and finally, the S/O/W emulsion thus 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[32].

Drug over dosage treatment

ME's can be utilized for the over-dosage treatment by utilizing the difference in pH. For Example:- barbiturates. In the inner aqueous phase of emulsion has the alkaline buffer and when emulsion is taken orally, acidic pH of the stomach acts as an external aqueous phase. In the acidic medium barbiturate remains mainly in unionized form which transfers through oil membrane into inner aqueous phase and gets ionized. Ionized drug has lower affinity to pass the oil membrane thereby getting 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.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Faculty of Pharmacy, Kailash Institute of Pharmacy and Management, Gorakhpur, Uttar Pradesh, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Akhtar N, Yazan Y. Formulation And Characterization of ACosmetic Multiple Emulsion system Conta ining Macadamia Nut Oil And Two Antiaging Agents, *Turkish J. Pharm. Sci,* 2(3), 2005, 173-185.
2. Jim, J David G R, Diane J B. Multiple Emulsion Stability: Pressure Balance and Interfacial Film Strength, *J. Coll. Interf. Sci,* 250(2), 2002, 444-450.
3. Sinha V R, Kumar A. Multiple Emulsions: An Overview of Formulation, Characterization, Stability and Applications, *Indian J. Pharm. Sci,* 64(3), 2002, 191-199.
4. Lynda M S, Wayne H R. "Protein Delivery Physical Systems", *Amazon.com,* 1997, 208.
5. Kochi H O, Nakano M. Basic Studies on Formulation, Method of Preparation and Characterization of Water-in-Oil-in-Water Type Multiple Emulsions Containing Vancomycin, *Chem. Pharm. Bull,* 44(1), 1996, 180-186.
6. Omotosho J A, Florence A T, Whateley T L. Absorption and lymphatic uptake of 5-fluorouracil in the rat following oral administration of w/o/w multiple emulsions, *Int. J. Pharm,* 61(1-2), 1990, 51-56.
7. Nisisako T. Microstructured Devices for Preparing Controlled Multiple Emulsions, *Chem. Engin. Tech,* 31(8), 2008, 1091-1098.
8. Asuman B, Ongun M S. "Multiple Emulsions", *John Wiley and Sons, Inc, eu: Wiley.com,* 2008, 293-306.
9. Bhushan P S, Shrinivas C K, Shamim A M. *Cosm and Toil,* 82, 2008, 57.
10. Françoise N, Gilberte M. "Pharmaceutical Emulsions and Suspensions", *Amazon.com,* 1st Edition, 2000, 222.
11. Masahiro G, Masaki M, Noriho K, Fumiyuki N. *Biotec. Tech,* 9, 2004, 81.
12. Eugenia M C, Gallarate M, Sapino S, Ugazio E. Morel S J. W/O/W Multiple Emulsions for Dermatological and Cosmetic Use, Obtained with Ethylene Oxide Free Emulsifiers, *Disp. Sci. Tech,* 26(2), 2005, 183-192.
13. Semenzato A, Dall A C, Boscarini G M, Ongaro A, Bettro A. Chemico-physical and functional properties of inorganic sunscreens in cosmetic products, *Int. J. Cosm. Sci,* 16(6), 1994, 247-255.
14. Dhams G H, Tagawa M. Proceedings of the 19th IFSCC Congress: *Sydney,* 1996, 79.
15. Matsumoto S, Kita Y, Yonezawa D. "An attempt at preparing water-in-oil-in-water multiple phase emulsions", *J Colloid Interface Sci,* 57(2), 1976, 353-361.
16. Opawale F O, Burgess D J. "Influence of interfacial rheological properties of mixed emulsifier films on the stability of water-in-oilin-water emulsions", *J Pharm Pharmacol,* 50(9), 1998, 965-973.
17. Davis S S. "Physicochemical criteria for semisolid dosage forms. In: Grimm W, ed.

Stability Testing of drug Products", *Stuttgart, Germany, Wissenschaftliche Verlagesellschaft,* 1987, 161-175.

18. McVeigh G E, Flack J, Grimm R. "Goals of antihypertensive therapy", *Drugs,* 49(2), 1995, 161-175.
19. Li H, Wang Y, Jiang Y, Tang Y, Wang J, Zhao L, Gu J. "A liquid chromatography/tandem mass spectrometry method for the simultaneous quantification of valsartan and hydrochlorothiazide in human plasma", *J Chromatogr B,* 852(1-2), 2007, 436-442,
20. Markham A, Goa K L. "Valsartan: a review of its pharmacology and therapeutic use in essential hypertension", *Drugs,* 54(2), 1997, 299-311.
21. Flesch G, Lloyd P, Müller P H. "Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man", *Eur J Clin Pharmacol,* 52(2), 1997, 115-120.
22. Criscione L, Gasparo M, Buhlmayer P, Whitebread S, Ramjoune H P, Wood J. "Pharmacological profile of valsartan; a potent, orally active, nonpeptide antagonist of the angiotensin II AT1-receptor subtype", *Br J Pharmacol,* 110(2), 1993, 761-771.
23. Flesch G, Muller P H, Degen P, Lloyd P, Dieterle W. "Repeated dose pharmacokinetics of valsartan, a new angiotensin-II antagonist, in healthy subjects", *Eur J Drug Metab Pharmacokinet,* 18(3), 1993, 256-260.
24. Schmidt E K, Antonin K H, Flesch G, Racine Poon A. "An interaction study with cimetidine and the new angiotensin II antagonist valsartan", *Eur J Clin Pharmacol,* 53(6), 1998, 451-458.
25. Joshi *et al*. "United States patent application publication, US", 2010/0035949 A1, 2010, 1-8.
26. Florence A T and Whitehill D. "The formulation and stability of multiple emulsions", *Int J Pharm,* 11(4), 1982, 277-308.
27. Raynal S, Grossiord J L, Seiller M, Clausse D A. "Topical W/O/W multiple emulsion containing several active substances: formulation, characterization and study of release", *J Control Rel,* 26(2), 1993, 129-140.
28. Hideki O and Masahiro N. Preparation and evaluation of W/O/W type emulsions containing vancomycin", *Adv Drug Rev,* 45(1), 2000, 5-26.
29. Mullaicharam A R, Qasmi M A A. "Preparation and Evaluation of Prolonged Emulsions", *Int. J. Instit. Pharma and Life Sci,* 2(1), 2012, 44-57.
30. Nimberkar T P, Wanjari B E, Sanghi D K, Gaikwad N J. "Formulation and Evaluation of Sustained Release Multiple Emulsion of Hydroxprogesterone", *Int. J. Pharm. and Pharm. Sci,* 4(1), 2012, 76-80.
31. Vyas S P, Khar R K. "Targeted and Controlled Drug Delivery- Novel Carrier Systems", *CBS Publishers and Distributors,* 1st Edition, 2002, 303-330.
32. Lachman L, Lieberman H A. "The Theory and Practice of Industrial Pharmacy", *CBS Publishers and Distributors,* 4th Edition, 2009, 502-532.
33. Kumar Rajesh, Kumar Murugesan, Mahadevan Nanjaian. "Multiple Emulsions: A Review", *Int. J. Recent Adv. Pharm. Research,* 2(1), 2012, 9-19.

Please cite this article in press as: Navneet Kumar Verma *et al.* A brief study on: multiple emulsions a review: a review, *Asian Journal of Phytomedicine and Clinical Research,* 6(4), 2019, 133-139.