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Pharmaceutical Sciences **Research Article……!!!**

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PREPARATION AND EVALUATION OF PROLONGED RELEASE DOSAGE FORM OF MULTIPLE EMULSIONS

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ABSTRACT

Multiple emulsions are primarily used for formulating sustained release dosage forms as the drug entrapped in the innermost layer has to pass through the other two phases before being released for absorption. The aim of this work was to prepare the stable W/O/W /multiple Emulsions and to investigate the usage of different ratio of surfactants of Span and Tween, to observe the influence of surfactant percentage on the preparation of multiple emulsions. Multiple W/O/W emulsion was prepared by using various concentrations of emulsifiers Span20 and Tween 80.Multiple emulsions are often stabilized using combination of hydrophilic and hydrophobic surfactants. The w/o/w multiple emulsion formulation containing 40% of span 20 and 3% tween80 showed best long term stability .The formulation No 10 showed the lowest creaming volume, while compared with other formulations in other batches.

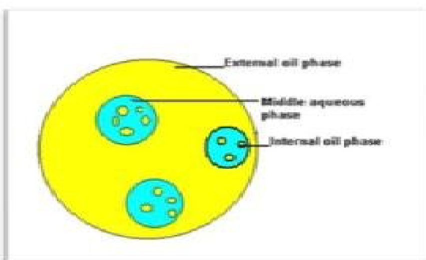
INTRODUCTION

A **dosage form** (**DF**) is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption. (1) Emulsions are biphasic systems consisting of two immiscible liquids, in which the dispersed phase is finely subdivided and uniformly dispersed as droplets throughout the other phase (the dispersion medium). The dispersed phase is also called as the internal phase and the dispersion medium as external phase or continuous phase. These immiscible liquids are made miscible by adding a third substance known as emulsifying agent. They stabilize the system by forming a thin film around the globules of the dispersed phase. (2)

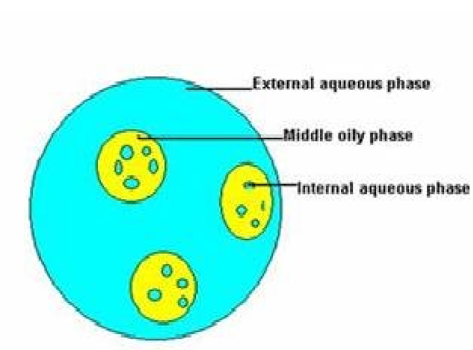
Types of emulsion

- Macro emulsion
- Micro emulsion
- Nano emulsion
- Multiple emulsion
- Pickering emulsion

Multiple emulsions: when primary emulsions (oil in water or water in oil) is dispersed in another liquid medium. (3) There two types of multiple emulsions:



1- Oil in water in oil (o/w/o) emulsion consists of very small droplets of oil dispersed in the water globules of water in oil emulsion.



2- Water in oil in water (w/o/w) emulsion consists of droplets of water dispersed in the oily phase of oil in water emulsion. (4)

Emulsification

Process by which emulsion are prepared, emulsion are thermodynamically unstable system because the contact between oil and water molecules is unfavorable and so they will always breakdown over time. Stabilizer is used to prepare emulsion that kinetically stable. Stabilizer can be classified according to their mode of operations either [5]

- Emulsifiers
- Texture modifiers

Each emulsifying agent has hydrophilic portion and lipophilic portion. Each agent is assigned HLB number indicating the substances polarity. Materials that are highly polar or hydrophilic have been assigned higher numbers than materials that are less polar and more lipophilic. [6]

The value ranges from 0-20

Low HLB………… soluble / dispersed in oil

High HLB………. Soluble / dispersed in water

Surfactant HLB number and application [7]

HLB range	Application
1.5-3	Antifoaming agents
4-6	W/O emulsion
7-9	Wetting agent
8-18	O/W emulsion
13-15	Detergents
15-18	Solubilizers

Reasons of formulation multiple emulsion

- The multiple structures of emulsion are act as the protection of the entrapped substances and the incorporation of several actives in the different compartments. [8]
- Multiple emulsions can be useful in many technologies, particularly in the pharmaceutical and in separation science.
- Their potential biopharmaceutical applications are unique as a consequence of the dispersal of one aqueous phase inside droplets of another. These include potential as vaccine adjuvant, drug delivery systems, and sorbent reservoirs in drug overdose treatments and for immobilization of enzymes.
- They can also be used for separation of hydrocarbons and in the removal of toxic materials from waste water.

- Multiple emulsions according to the present invention can be formulated as cosmetics such as skin moisturizer and as household products such as wax polish.
- They have been used to immobilize insulin for depot injection and in foods. [9]

Advantage:

1. They can mask the bitter taste and odor of drugs, thereby making them more palatable. E.g. castor oil, cod-liver oil 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 can all be emulsified and can be administered to bed ridden patients as sterile intravenous emulsions.
4. Emulsions provide protection to drugs which are susceptible to oxidation or hydrolysis.
5. Intravenous emulsions of contrast media have been developed to assist in diagnosis.
6. Emulsions are used widely to formulate externally used products like lotions, creams, liniments,
7. Enhancement of enteric or dermal absorption. [10]

Limitation of formulation multiple emulsion

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. [11]

Drug Available as multiple emulsions

I. Pilocarpine hydrochloride [12]
II. acetyl dimethicone copolyol[13]
III. Prednisone [14]
IV. polygene antibiotic [15]
V. amphotericin B [16]
VI. sodium sailicylate [17]
VII. Vitamin C

Aim:

The aim of this work was to prepare the stable W/O/W /multiple Emulsion and to investigate the usage of different ratio of surfactants of Span and Tween, to observe the influence of surfactant percentage on the preparation of multiple emulsion

Objective:

To find the stability of multiple emulsions using different concentration of Span20 and Tween 80.

Plan

I. Formulation multiple emulsion with varies ratio of Span20 and Tween80

- Formulation of multiple emulsions with surfactant span20 (0.1%) and
  - Tween80 (o.1%)
  - Tween80 (3%)
  - Tween80 (10%)
- Formulation of multiple emulsions with span20 (10%) and
  - Tween80 (o.1%)
  - Tween80 (3%)
  - Tween80 (10%)
- Formulation of multiple emulsions with span20 (30%) and
  - Tween80 (0.1%)
  - Tween80 (3%)
  - Tween80 (10%)
- Formulation of multiple emulsions with span20 (40%) and
  - Tween80 (0.1%)
  - Tween80 (3%)
  - Tween80 (10%)
- Formulation of multiple emulsions with span20 (40%) and
  - Tween80 (o.1%)
  - Tween80 (3%)
  - Tween80 (10%)

II. Evaluation of multiple emulsion

- Measurement of Creaming Volume of multiple emulsions.
- Microscopic Observation of multiple emulsions.

MATERIALS

Chemicals:

- Span20, Tween80, Light mineral oil (Liquid paraffin),Gum Acacia, water

Apparatus:

- Mortar and pestle, Small Beaker, Magnetic mixer, Cylinder (10ml,100ml),Glass rod, Containers.

Equipment

- Olympus Microscopic
- Camera digital(Olympus)

METHODS

Preparation primary W/O emulsion [8]

Ingredients	For 100ml	For 20ml
Liquid paraffin	50 ml	10 ml
Gum Acacia	5g	1g
Water	Up to100 ml	Up to 20ml

Send: 20ml

Since the liquid paraffin is a mineral oil the ratio used for preparation is 3:2:1

1. Weigh 5g of gum and taken in dry motor.
2. Add 10ml of distilled water and triturate to get mucilage of gum.
3. Calculate amount of Span20 need in 0.1%, 10%, 30%, 40% solution.

Calculation Span20 Solution	
0.1% span20 : (0.1÷100)× 5=*0.005ml*	5ml of span20 solution = (0.005ml span20 + 4.995ml Liquid paraffin)
10% Span 20: (10÷*100)× 5=0.5ml*	5ml of span20 solution = (0.5ml span20 + 4.5 ml Liquid paraffin)
30% Span 20 :(30÷100)×5=1.5ml	5ml of span20 solution = (1.5ml span20 + 3.5ml Liquid paraffin)
40% Span 20 : (40÷100)×5=2ml	5ml of span20 solution = (2ml span20 + 3ml Liquid paraffin)

4. 5ml of 0.1% span83 solution is add to mixture.
5. 50 ml of oil add drop by drop with continuous one way trituration.
6. Stir the mixture with magnetic mixer for 15 minutes to produce primary emulsion.
7. Repeat steps 1-6 use Span83 of 10%, 30%, 40% percentage of solution, to form primary emulsion.

Preparation of multiple emulsions

a. Calculate the amount of Tween 80 need in 0.1 % , 3% ,5 % solution

Calculation Tween80 Solution	
3% Tween80 : (3÷100)× 5=*0.15ml*	5ml Tween80 of solution = (0.15ml Tween80 + 4.85ml distilled water)
5% Tween80: (5÷*100)× 5=0.25ml*	5ml Tween80 of solution = (0.25ml Tween80 + 4.75ml distilled water)
10% : Tween80 (10÷100)×5=0.5ml	5ml Tween80 of solution = (0.5ml Tween80 + 4.5ml distilled water)

b. Add 5ml of primary emulsion to equal amount of Tween80 solution.
c. Stir the mixture with magnetic mixer for 5 minutes.

Evaluation

1) Measurement creaming Volume

The volume of the creamed phase and the remaining W/O/W multiple emulsion were recorded. The creaming volume was defined in this study as the relative difference in volume of the multiple emulsions and the volume of the creamed phase. The expression used for calculation of the creaming volume is as follows**:**

$$\mathbf{V_{cream} = ((V_{multiple\ emulsion} - V_{creamed\ phase}) \div V_{multiple\ emulsion}) \times 100\%}$$

2) Microscopic Observation

An Olympus BH-2 polarized light microscope equipped with a 3CCD Olympus camera and a computer was used to take photomicrographs. Glass microslides (3 x 1 in.) and cover slips (No. 11/2) were used to prepare microscopic samples throughout the experiments. The W/O/W emulsion samples were then placed on a micro slide with care to minimize possible destruction of emulsion structures by shear stress. The samples were covered with a cover slip and. Light intensity was kept at a minimum to reduce sample heating. Multiple emulsion structure was observed under 4X, 10X, 40X.

Result:

Creaming Volume:

Multiple Emulsion containing .1% of Span20 and 10% of Tween 80

$$V_{cream} = ((V_{multiple\ emulsion} - V_{creamed\ phase}) \div V_{multiple\ emulsion}) \times 100\%$$
$$V_{cream} = ((10\ ml - 3ml) \div 10ml)) \times 100\% = 70\%$$

Table 1: Formulation Composition of w/o/w Emulsion Formulations containing Various Concentrations of Span 20 and Tween 80

Batch NO	I			II			III			IV		
Formulation (Batch NO)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Span20 %	**0.1**	**0.1**	**0.1**	**10**	**10**	**10**	**30**	**30**	**30**	**40**	**40**	**40**
Tween 80 %	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**
Creaming volume %	**72**	**70**	**81**	**78**	**74**	**86**	**88**	**82**	**80**	**68**	**74**	**70**

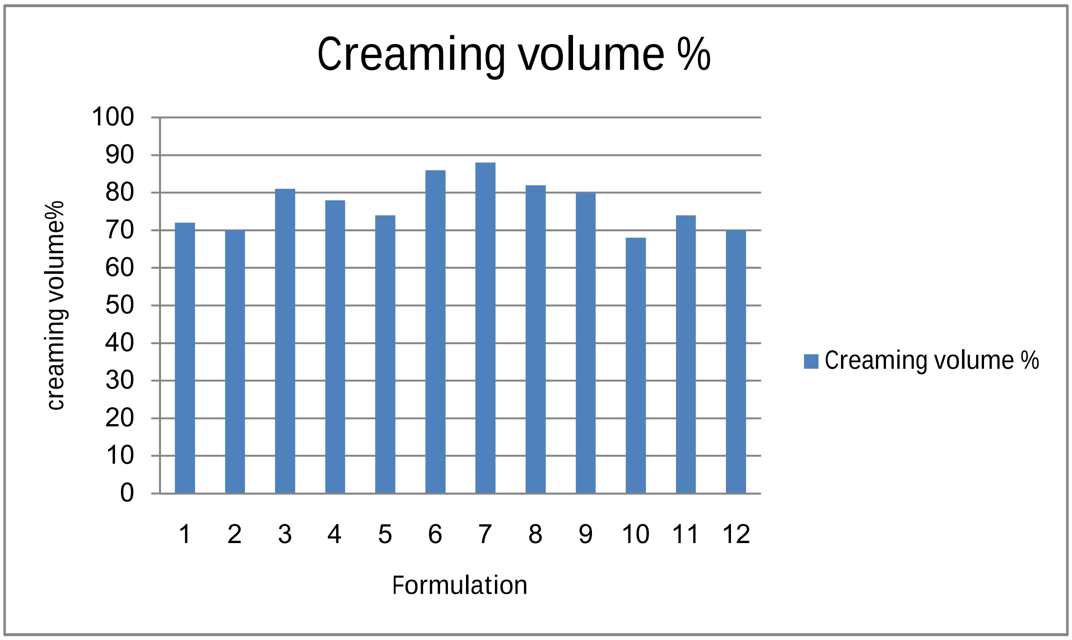
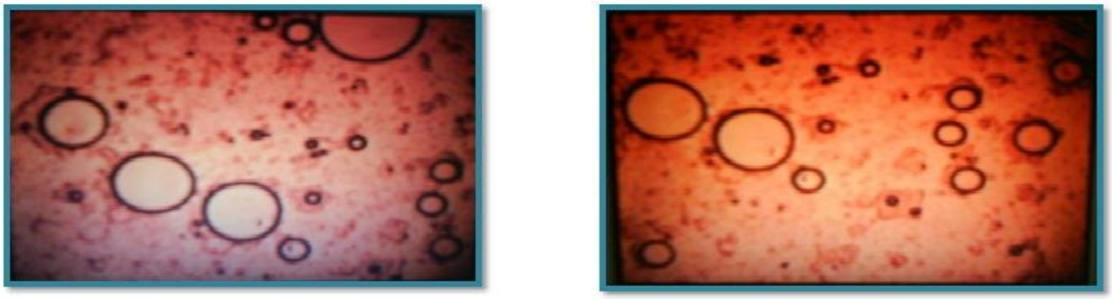


Figure 1: Creaming volume of formulation W/O/W Emulsion containing various concentration of Span20 and Tween80



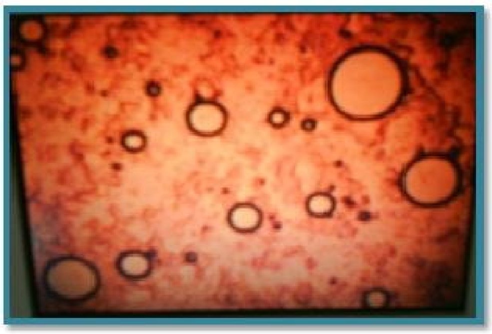
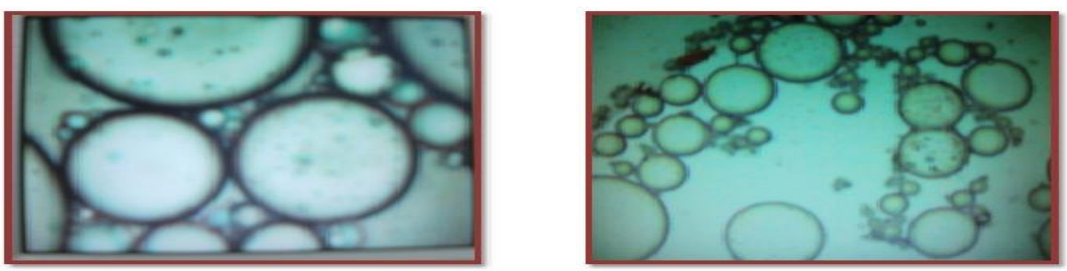


Figure 2: Photomicrographs of freshly prepared primary W/O emulsion containing A) 0.1% of Span20, B) 10 % of Span20, C) 30% of Span20

Batch I : formulation (1,2,3)



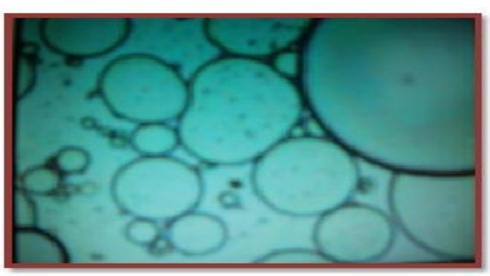
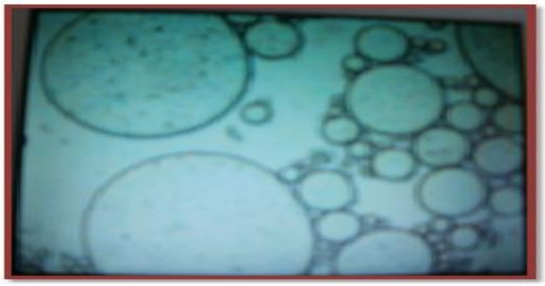
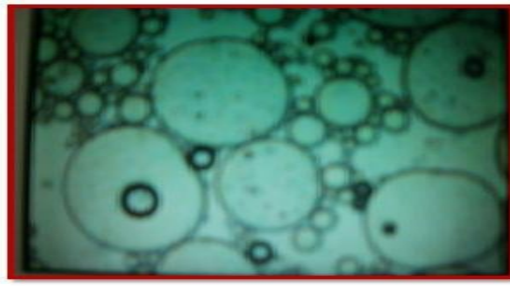


Figure 3: Photomicrographs of freshly prepared W/O/W emulsion containing 0.1% Span20 and various amount of Tween80. 1) 3% of Tween80, 2) 5%of Tween80, 3) 10%of Tween80.

Batch II : formulation (4,5,6)





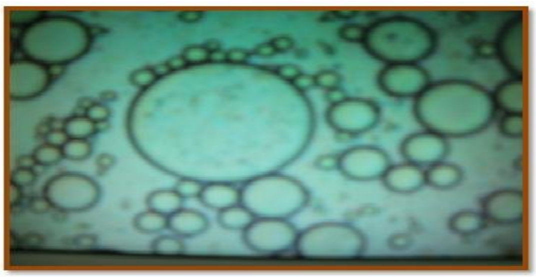
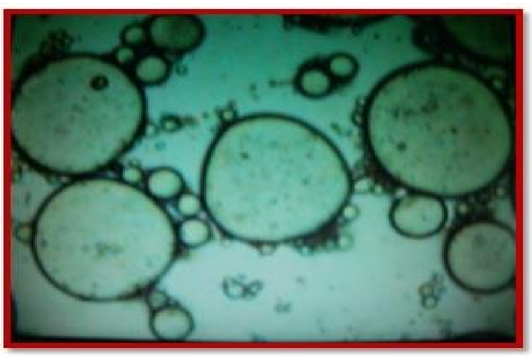
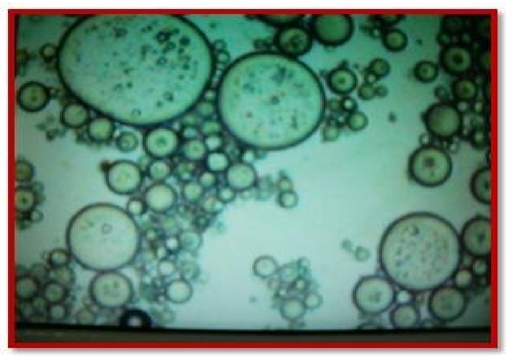


Figure 4: Photomicrographs of freshly prepared W/O/W emulsion containing 1% Span20 and various amount of Tween80. 4) 3% of Tween80, 5) 5% of Tween80, 6) 10%of Tween80.

Batch III : formulation (10,11,12)





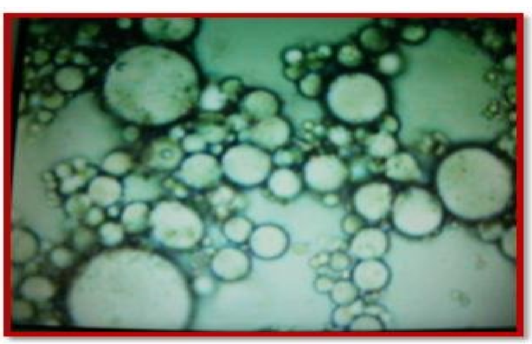


Figure 5: Photomicrographs of freshly prepared W/O/W emulsion containing 40% Span20 and various amount of Tween80. 10) 3% of Tween80, 11) 5%of Tween80, 12) 10%of Tween80.

Batch IV : formulation (7,8,9)

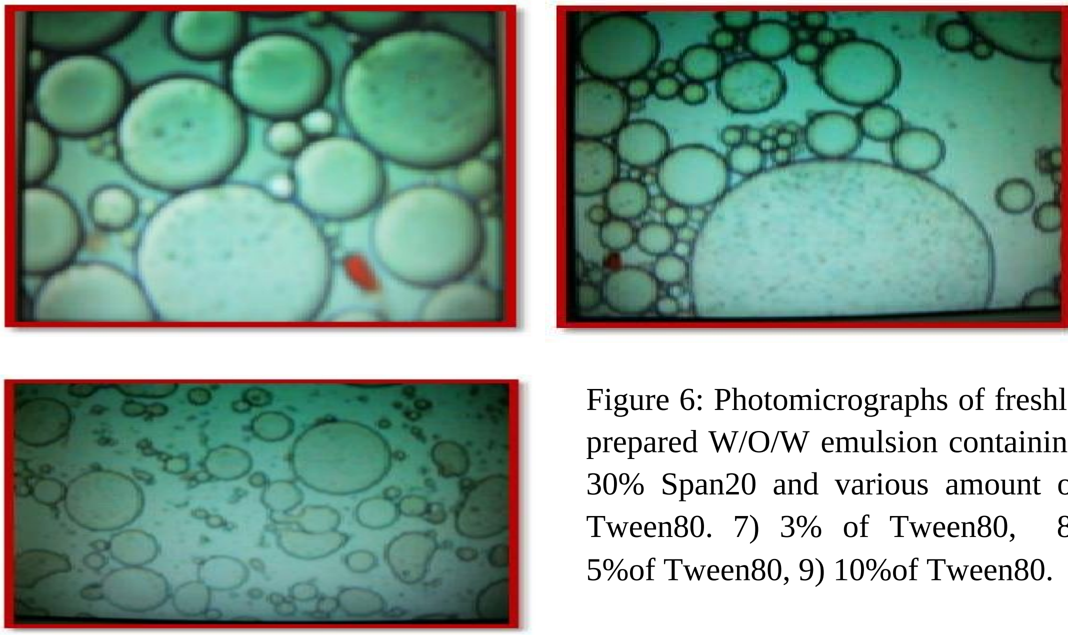


Figure 6: Photomicrographs of freshly prepared W/O/W emulsion containing 30% Span20 and various amount of Tween80. 7) 3% of Tween80, 8) 5%of Tween80, 9) 10%of Tween80.

DISCUSSION

Preparation of multiple emulsions

Multiple W/O/W emulsion was prepared by using various concentrations of emulsifiers Span20 and Tween 80.Multiple emulsions are often stabilized using combination of hydrophilic and hydrophobic surfactants. The ratio of these surfactants is important to achieving stable multiple emulsions. One of the surfactants that has low hydrophilic lipophilic balance (HLB) value to stabilize the primary W/O emulsion which is Span20. In addition of Tween 80 has high HLB value to stabilize the secondary O/W emulsions.[(37)] In other hand all the other ingredients and procedures that were used in preparation were stable. All preparations with different construction of Span 20 and Tween 80 were yield multiple emulsions with different droplet size. There are 2 interfaces in a W/O/W multiple emulsions. The primary interface, lying between the inner aqueous phase and the oil phase, contains the low-HLB surfactant. In contrast, both the high- and the low-HLB surfactants are present at the secondary interface (between the multiple droplets and the outer continuous aqueous phase). To maintain a sufficient amount of the hydrophobic surfactant in the oil phase in order to prevent the oil layer

Tween 80 belongs to a class of food additives also known as Polysorbates. Span 20 or Sorbitan monooleate is a Sorbitan Ester widely used in food products and oral pharmaceuticals. The acceptable daily intake (ADI) of both Tween 80 and Span 20 per the WHO is set at 25 mg per kilogram of body weight, which means an adult weighing 70 kilo can consume 1,750 mg of Tween 80 daily on a long term chronic basis without toxic.

On the other hand, to avoid any potential toxicity associated with surfactants, a minimal concentration of the hydrophobic surfactant is desired in multiple emulsion preparations used pharmaceutically. Therefore, the optimal concentration of hydrophobic surfactant needs to be determined during formulation development. [(40).]

Evaluation Stability of multiple emulsions

- Using creaming volume
- Using microscopic Observation

1. Creaming volume

An emulsion is said to cream when the oil rises to the surface, but remains in the form of globules, which may be redistributed throughout the dispersion medium by shaking. An oil of low viscosity tends to cream more readily than one of high viscosity. Increasing the viscosity of the medium decreases the tendency to cream. Creaming is a reversible phenomenon which can be corrected by mild shaking. The factors affecting creaming are best described by strokeâ, s law [(41)]

V= 2r2 (d1-d2) g/9Î·

- Where V= rate of creaming
- r=radius of globules
- d1= density of dispersed phase
- d2= density of dispersion medium
- g= gravitational constant
- Î· = viscosity of the dispersion medium

The following approaches can be used for decreasing Creaming

Reduction of globule size: According to stroke’s law, rate of creaming is directly proportional to the size of globules. Bigger is the size of the globules, more will be the creaming. Therefore in order to minimize creaming, globule size should be reduced by homogenization.

Increasing the viscosity of the continuous phase:

Rate of creaming is inversely proportional to the viscosity of the continuous phase i.e. more the viscosity of the continuous phase; less will the problem of creaming. Therefore to avoid creaming in emulsions, the viscosity of the continuous phase should be increased by adding suitable viscosity enhancers like gum acacia, tragacanth.

The composition of W/O/W emulsion formulations and creaming value given in Table1. Creaming, resulting from table1and figure1 were showing that formulation #10 which containing 40% of Span20 and 3%of Tween80 has less creaming volume. “These emulsions were more stable, as evidenced by lower creaming volumes .Stability increased with an increase in Span 20 concentration” [35]. The stability of multiple W/O/W emulsion formulations containing varying amounts of Tween 80 and a constant concentration of Span 20 was evaluated (table1). It was observed that the stability of the formulations decreased as creaming Volume increase with increasing concentration Tween 80.

The formulation variable is the ratio of span20 and Tween 80 in this study. All other variable is kept constant.

- Speed of stirring
- Time of stirring
- Direction of stirring

2. Microscopic Observation

Photomicrographs was showing different structure between primary emulsion and Multiple emulsion which containing various concatenations of span20 and tween 80.*(figure 2, 3, 4, 5, 6). The inner phase of primary emulsion consists of liquid paraffin with emulsifier span20 solution and outer phase is water (figure2). While multiple emulsion consist of (Tween80 solution) in outer continuous phase and inner phase was primary W/O emulsion.

Photomicrograph of primary emulsion (figure2) showed dispersed phase globules (non continuous) dispersed in phase. The inner phase is showed off-white color is non continuous, while outer phase is red color which is continuous medium.
Photomicrograph of multiple Emulsion showed that three phase of water in oil in water. From Photomicrograph(Batch I,II,III,IV) the brown color globules indicate as inner phase , the off white color globule indict is middle phase, outer phase is show brown color globule.

CONCLUSION

The W/O/W multiple emulsion formulation containing 40% of span 20 and 3% tween80 (Batch IV: formation 10) showed best long term stability.

The Batch IV: formulation NO 10 showed the lowest creaming volume, while compared with other formulations in other batches (I, II, III).

As the Span 20 concentration was further increased, the size of the inner droplets remained relatively unchanged, but the size of multiple droplets decreased considerably (figure 3, 4, 5, 6).The reduced droplet size is believed to provide an enhanced kinetic stability to coalescence in addition to lowered interfacial tension and increased interfacial film strength as a result of increased surfactant concentration.

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