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Formulation and Evaluation of Multiple Emulation of Diclofenac Sodium

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Abstract: ***Multiple emulsion is novel approach of drug delivery system for enhancement of bioavailability and pharmacological activity. It is important to prevent the problem of oral drug delivery system and they are stabilized by using of combination of hydrophilic and lipophilic surfactant. The specific ratio of surfactant concentration is responsible for maintaining the stability of multiple emulsions, the importance of this study was to prepare multiple emulsion of Diclofenac sodium by using two step emulsification process, by using the non-ionic surfactant units. In multiple emulsion, the stability of multiple emulsion was evaluated, percent entrapment efficiency as well as in vitro studies are conducted. The objective of this study was to prepare multiple emulsion of Valsartan by two step emulsification using different nonionic surfactants, Tweens & Spans, and evaluate for stability,percentage drug entrapment, in vitro drug release.***

I. INTRODUCTION

An emulsion can be defined ascolloid consisting of two or more non-homogenous typeof liquids wherein one of the liquid contains the dispersion of the different form of liquids. Emulsions are the mixtures of two or more type of liquids where, one is such as droplets, of tiny or even ultramicroscopic size, which are distributed throughout each other. These are usually formed from the component of liquids either in natural form or, more often, using mechanisms such as the agitation, which is provided that these fluids mixed have no kind of mutual solubility.Emulsions are said to be stabilized by some agents forming films at the surface of droplets or those which impart to them a kind of mechanical stability. The stable emulsions are destroyed by destroying or by deactivating the emulsifying agent—for example by the addition of appropriate third party substances or even by the process of freezing or by heating. Emulsions basically consist of a dispersion of two liquids that are immiscible with each other. One of the liquids act as the dispersion medium and the other will act as the dispersed phase. In simple words, emulsions are colloids in which both the dispersed phase and dispersion medium are liquids. Oil and the mixtures of water are the emulsions when are shaken together. Multiple emulsions are complex polydispersed systems where both oil in water and water in oil emulsion exists simultaneously which are stabilized bylipophillic and hydrophilic surfactants respectively. The ratio of these surfactants is important in achieving stable multiple emulsions. Among water- in-oil-in-water (w/o/w) and oil-in- water-in-oil (o/w/o) type multiple emulsions, the former has wider areas of application and hence are studied ingreat detail. Formulation, preparation techniques and in vitro characterizationmethods for multiple emulsions are reviewed. Various factors affecting the stability of multiple emulsions and the stabilization approaches with specific reference to w/o/w type multiple emulsions are discussed in detail. Favorable drug release mechanisms and/or rate along with in vivo fate of multiple emulsions make them a versatile carrier. It finds wide range of applications in controlled or sustained drug delivery, targeted delivery, taste masking, bioavailability enhancement, enzyme immobilization, etc. Multiple emulsionshave also been employed as intermediate step in the microencapsulationprocess and are the systems of increasing interest for the oral delivery of hydrophilic drugs, which are unstable in gastrointestinal tract like proteins and peptides. With the advancement in techniques for preparation, stabilization and rheological characterization of multiple emulsions, it will be able to provide a novel carrier system for drugs, cosmetics and pharmaceutical agents.In this review, emphasis is laid down on formulation, stabilization techniquesand potential applications of multiple emulsion system.

II. MATERIAL AND METHOD

A. Diclofenac Sodium

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). Thismedicine works by reducing substances in the body that cause pain and inflammation. Diclofenac is used to treat mild to moderate pain, or signs and symptoms of osteoarthritis or rheumatoid arthritis. Voltaren is also indicated for the treatment of ankylosing spondylitis. The Cataflam brand of this medicine is also used to treat menstrual cramps. Diclofenac powder (Cambia) is used to treat a migraine headache attack. Cambia will only treat a headache that has already begun. It will not prevent headaches or reduce thenumber of attacks.

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B. Paraffin Oil

Paraffin, also known as liquid paraffin, paraffin oil or kerosene, is a combustible hydrocarbon liquid that's burned as a fuel. Paraffin fuel refers to a mixture of different types of hydrocarbons with the chemical formula CnH2n+2; specifically paraffins are a group of alkanes.

Paraffins are key components of petroleum and natural gas. Those with fewer than 5 carbon atoms per molecule tend to be gases at room temperature, whereas those with between 5 and 15 carbon atoms are usually fluid in form. Straight-chain varieties with over 15 carbon atoms per molecule are solid at room temperature. Paraffin is less hazardous than gasoline and boils at 150-275oC. It can be extracted fromcoal, wood and oil shale, but is mostly acquired from the distillation of petroleum.

C. Span 80

Polysorbate 80 is a nonionic surfactant and emulsifier often used in pharmaceuticals, foods, and cosmetics. This synthetic compound is a viscous, water-soluble yellow liquid.

D. Tween 20

Polysorbate 20 (common commercial brand names include Kolliphor PS 20,[2] Scattics, Alkest TW 20, Tween 20, and Kotilen-20) is a polysorbate-type nonionic surfactant formed by the ethoxylation of sorbitan monolaurate. Its stability and relative nontoxicity allows it to be used as a detergent and emulsifier in a number of domestic, scientific, andpharmacological applications. As the name implies the ethoxylation process leaves the molecule with 20 repeat units of polyethylene glycol; in practice these are distributed.

III. METHOD AND PREPARATION OF MULTIPLE EMULSION

Multiple emulsion is prepared by two step emulsification process

1) *Primary Emulsification:* 20ml of distilled water containing 28mg of drug was graduallyadded to 40ml of oil phase (Paraffin oil) containing primary emulsifier (Span 80 (con. 10%) and 56mg of drug with continuous stirring at 5000r/min for 15min. (Using Mechanical Stirrer and High Pressure Homogenizer (HPH) having continuous stirring). (Total Quantity of Primary emulsion is 60ml)
2) *Secondary Emulsification:* 60ml previously prepared viscous primary emulsion was emulsified further with an external aqueous phase (water (40ml)) containing secondary emulsifier (Tween 20 (con. 10%)) and 140mg drug with continuous stirring at 5000r/min for 30min. (Using Mechanical Stirrer and High Pressure Homogenizer (HPH)having continuous stirring). After continuous stirring to form homogenous or uniform W/O/W type of Multiple Emulsion (Total quantity of Multiple Emulsion is 100ml).

IV. EVALUATION PARAMETER OF MULTIPLE EMULSION

A. Melting Point Method

The melting point of Diclofenac sodium is determined by Conventional and DigitalMethod and melting point of Diclofenac sodium is reported in Table 1.

B. Log P Value

Log P Value is determined by Partition Coefficient Phenomenon and Log P Value ofDiclofenac sodium is reported in Table 1.

C. Solubility Studies

The solubility of Diclofenac sodium in given solution. (Water, pH 1.2 acidic buffer, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer) is reported in Table 2 and concentration of drug soluble in different solution is shown in Figure

1) CalibrationCurve of Diclofenac in Water

The calibration curve of Diclofenac sodium is determined by using U.V. Spectroscopic method. In which the absorbance of Diclofenac sodium in differentconcentration (0, 2, 4, 6, 8, 10, and 12) is reported in Table 3. And the calibrationcurve is shown in Figure

2) Evaluation of Multiple Emulsion

Entrapment Efficiency

The % entrapment efficiency is important for determination % content of activeingredient. The percentage entrapment efficiency (% ee) was determined by taking freshly prepared W/O/W Multiple Emulsions and immediately centrifuged at 4000rpmfor 10min.

Then 1ml of the aqueous phase (the lower layer) was precisely withdrawn through 2ml hypodermic syringe and diluted properly with phosphate buffer 6.8. The solution was filtered through a millipore filter (0.22mm in pore size) and drug contentwas analysed on UV spectrophotometer at 275nm. The Encapsulation Efficiency was determined by following equation:

% EE = (Total drug incorporated – Free Drug) / Total drug * 100

The Entrapment Efficiency of Multiple Emulsion is reported in Table 7.

Globule size or Particle Size

The particle size globules of Multiple Emulsion is reported in Table 7, the peak of sizedistribution report is shown in Figure 5. (By using Zeta Analyser Apparatus)

The standard range of globule size is between 0.25 to 25 µm

In Vitro Release Studies: The in vitro release of multiple emulsion, in which the standard calibration curve of Diclofenac in phosphate pH 6.8 is reported in Table 5 and shown in Figure 6. The in vitro release of Diclofenac sodium Multiple emulsion is reported in Table 6 and shown in Figure 7. The in vitro release study is reported.

V. RESULT AND DISCUSSION

The Objective of present work is to formulation and evaluation of multipleemulation of diclofenac sodium. The globule size of the emulsion is according to standard size and appearance of emulsion is good. This emulsion is useful aches and pains, as well as problems with joints, muscles and bones. These include: rheumatoid arthritis and osteoarthritis sprains and strains in muscles and ligaments, back pain toothache, migraine, gout , ankylosing spondylitis.

Table 1: Melting point and Log P Value

Sr. NO.	Parameters	Results	Std.
1.	Melting point (°c)	282- 285°c	284-286
2.	log p value	4.51	4.52

Table 2: Solubility Studies of Pure Drug in Different Solvent

Sr. No.	Medium	Concentration of drug Soluble (mg
1	Water	1.34
2	pH 1.2 Acidic Buffer	2.96
3	pH 6.8 Phosphate Buffer	3.68
4	pH 7.4 Phosphate Buffer	5.22

Result	Class of drug	BCS Class II

Table 3: Calibration Curve of Diclofenac sodium in Water

Concentration	Absorbance
0	0
2	0.085
4	0.160
6	0.237
8	0.296
10	0.384
12	0.480

Table 4: Standard Calibration Curve of Diclofenac in Phosphate pH 6.8

Concentration	Absorbance
0	0
2	0.223
4	0.375
6	0.579
8	0.763
10	0.935

Table 5: The TLC of Drug, Drug and Excipient before Stability Chamber and After Stability Chamber

Sr. No.	Samples (Pure From of Drug material) (Drug + Excipient Mixture)	Retention factor of drug Before the Stability Chamber	Retention factor of drug After the Stability Chamber
1	Pure Drug Diclofenac sodium	0.77	0.81
2	Diclofenac + Paraffin oil	0.80	0.84
3	Diclofenac + Span 80	0.74	0.78
4	Diclofenac + Tween 20	0.72	0.75

Table 6: In vitro Drug Release of Multiple Emulsion

Time		Conc		Conc	Conc	Conc	Conc		
(min.)		µg/ml		µg/ml	mg/ml	mg/5ml	mg/900ml		
0	0	0	0	0	0	0	0	0	0
15	0.081	0.71	10	7.21	0.0070	0.036	6.49	6.48	32.48
30	0.083	0.73	10	7.43	0.0073	0.037	6.69	6.70	33.63
45	0.085	0.75	10	7.65	0.0075	0.038	6.88	6.91	34.61
60	0.087	0.77	10	7.86	0.0077	0.039	7.079	7.10	35.58
75	0.120	1.13	10	11.42	0.010	0.057	10.28	10.31	51.59
90	0.144	1.40	10	14.00	0.013	0.070	12.60	12.65	63.32
105	0.160	1.56	10	15.73	0.014	0.078	14.15	14.21	71.14
120	0.188	1.86	10	18.75	0.017	0.093	16.87	16.94	84.93

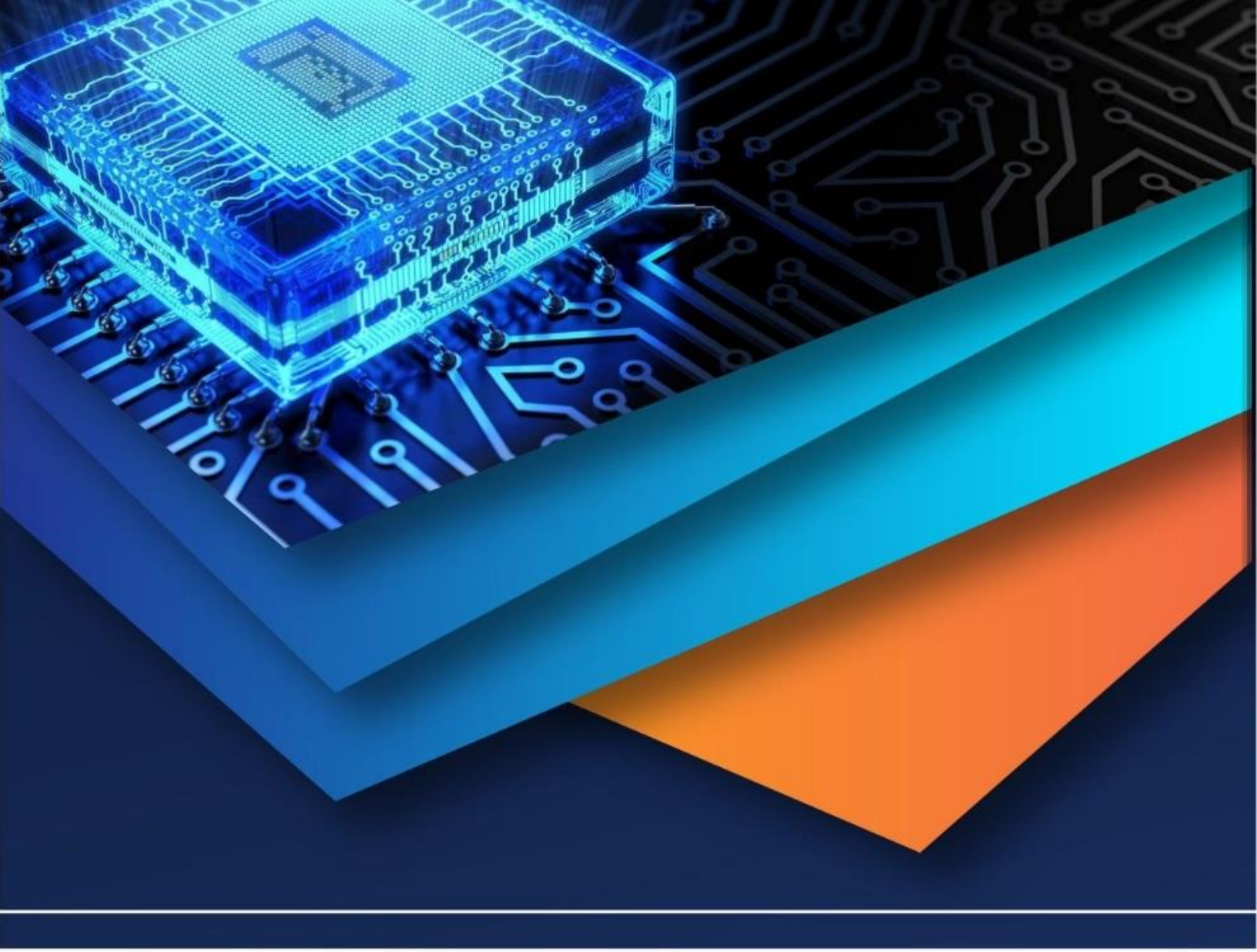
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VI. SUMMARY AND CONCLUSION

Multiple Emulsion is prepared by two step emulsification method in which first step under formation of pre-emulsion (W/O) and second step under treatment of aqueous water phase emulsified with previously prepared W/O emulsion to form W/O/W type of multiple emulsion. Using different W/O emulsions for the second emulsification step the finest W/O emulsion lead to W/O/W emulsions with the highest encapsulation rate. To prevent a production-induced reduction of encapsulation rate the inner water droplets have to be much smaller than the oil droplets in the Multiple Emulsion. Diclofenac sodium is in the inner water phase of a multiple Emulsion. Due to the same reason Diclofenac sodium is unsuitable as marker substance, if the inner W/O emulsion.

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