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PREPARATION AND EVALUATION OF DICLOFENAC SODIUM MULTIPLE EMULSION

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ABSTRACT

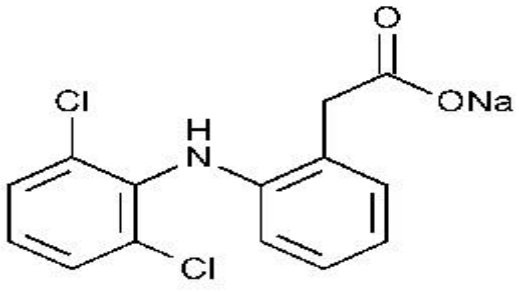
Drug delivery system represents one of the most rapidly advancing areas of pharmaceutical science and technology. DDSs such as multiple emulsion, micro/nano solid lipid and polymer particles can entrap drugs or biomolecules onto their interior structures and / or absorb drugs or biomolecules onto their interior surfaces. It is used for antitumour theropy, AIDS therapy and radiotherapy in the delivery of proteins, antibiotics, virastatics and vaccines as drug carries pass to the blood brain barrier. Water in oil in water emulsion had been used as drug delivery system. The three major methods to prepare multiple emulsions as Homogenisation, Micro channel emulsification and Membrane emulsification. It is used to many industrial products including food, cosmetics, pharmaceuticals etc.

KEY WORDS: Drug delivery system, Diclofenac Sodium, Multiple Emulsion.

INTRODUCTION

Diclofenac is a non-steroidal anti-inflammatory drug (NSAIDS) taken or applied to reduce inflammation and as an analgesic reducing pain in certain conditions. It is used to treat mild to moderate pain or signs and symptoms of osteoarthritis or rheumatoid arthritis [1].

Chemical name of Diclofenac sodium:*2-[(2,6-*dichlorophenyl)amino]benzene acetic acid monosodium salt



The targeting drug delivery and controlled drug release properties of DDSs are closely related to their size and size distribution. However, the preparation of these DDSs with controlled size and size distribution is still a challenge. the conventional technique for manufacturing multiple emulsion and micro/nano particles include high pressure homogenization [2], ultrasonication method [3], rotor/stator systems (such as stirred vessels, colloid mills and toothed disc dispersing machines), solvent evaporation, solvent diffusion, coacervation, spray drying and direct polymerization. None of these techniques can give a good control over the size and size distribution. The technique is attractive for the better control of emulsion droplet size and size distribution, the mildness of the process, the low energy consumption, and easy to industrial scale production.

Emulsion

Emulsions are disperse system of two immiscible or poorly miscible liquid phases. It can be classified as the following:

1. oil in water (O/W)emulsions
2. water in oil (W/O)emulsions
3. water in oil in water (W/O/W)emulsions
4. oil in water in oil (O/W/O)emulsions

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Multiple Emulsions

Multiple emulsion are a type of polydisperse, system where both oil in water and water in oil emulsion exist simultaneously. Multiple emulsion have been proposed to have numerous uses including their use as prolonged drug delivery system [4]. Emulsions are thermodynamically unfavourable system that tends to break down over time due to a variety of physiochemical mechanisms, including gravitational separation, flocculation, coalescence and Ostwald ripening. Water in oil in water emulsions have high potential for applications in the field of pharmaceutical cosmetics, food and chemical industries. W/O/W emulsion had been used as drug delivery system. Preparation of monodiperse multiple emulsion is important in drug delivery system to improve their stability and to facilitate control of their properties. By using membrane emulsification w/o/w emulsion used as a vehicle for the delivery of cancer treatment drugs [5].

Preparation of emulsions:

The three methods to prepare multiple emulsions is as follows:

1. Homogenisation
2. Micro channel emulsification
3. Membrane emulsification

The membrane emulsification has great potential to produce monodisperse emulsions.

1. Homogenisation

Usually micron-sized emulsion are made from a premix emulsion, which is produced by mixing gently, followed by homogenization to further reduce the droplet size. In general, homogenisation is an intense process. It introduces a large amount of energy into the smaller ones.

2. Micro channel emulsification

Emulsion droplets with diameters of 0.1-10 micrometer have diverse applications, including foods, cosmetics, pharmaceuticals, monodisperse emulsions with very narrow size distribution can improve stability against droplet coalescence, enabling us to more easily clarify many important emulsion properties.

Microchannel technology allows fabrication of monodisperse emulsions with an average droplet diameter ranging from 10 to 100µm. The principle is reminiscent of membrane emulsification. The disperse phase is forced into the continuous phase through microchannel manufactured via photolithography [6].

There are two types of micro channel:

1. Grooved Micro Channel
2. Straight Micro Channel

Grooved microchannel, which consists of a microfluidic channel array with a slit-like terrace on a silicon chip and generally enables the production of single micrometer-sized droplets with a relatively low through put capacity.

Straight microchannel, which is an array of channel vertically manufactured on a silicon chip. generally producing, mono disperse droplets with average droplet diameter lower than 30µm and considerable through put capacity, which has been scalded upto several tons of millimetres per hour [7].

3. Membrane emulsification

Membrane emulsification consists of forcing the dispersed phase to permeate into the continuous phase through a membrane having a uniform pore size distribution. The dispersed phase is pressed perpendicular to the membrane while the continuous phase is flowing tangential to the membrane [8]. Membrane emulsification is also depends on many parameters such as membrane properties, fluxes and formulations. Hydrophilic membrane should be used to produce an oil-in-water emulsions [9].

MATERIALS

Material	**Manufacturer / Supplier**
Diclofenac	
Propylene Glycol	Madras-pharmaceuticals,
Liquid Paraffin	Chennai
Arachis Oil	
Tween 80	Alzer, Tanjore
Span 80	
Equipment	**Manufacturer / Supplier**
U.V.Spectrophotometer	Shimedzu, Japan
Magnetic stirrer	Electro lab, India
Electronic weighing balance	
Sonicator	Biocon Ltd, Bangalore

Experimentation: Characterization studies

Flow Property Study: (Angle of repose)

Funnel Method

Weighed quantity of the drug was passed through a funnel kept at a height of 2cm from the surface. The powder was passed, till it formed a heap that touch the tip of the funnel. The radius (r) was measured and angle of repose was calculated using the following formula:

$$\theta = \tan^{-1}[h/r]$$

Where, $\theta = Angle\ of\ repose$

h = Height of heap from surface

r = Radius of heap.

Particle Size Determination

Sieve Analysis

Principle

The pharmaceutical powders are polydispersed in nature. Particle size is an important parameter in performulation study. It is expressed in micrometers the particles of pharmaceutical powder may range from extremely coarse about 100nm in diameter to extremely

fine. The approaching colloidal dimension of 1m or less. In order, the characterize particle size of the given powder the USP uses the description terms very coarse moderately coarse fine powder which are related to the preparation of powder that are capable of passing through the openings of standardized sieves of varying dimensions in a specified time period under shaking generally using a mechanical sieve shaker.

Procedure

All the sieves are arranged in a manner such that sieve with layer mesh is placed on the top and the sieve with smaller mesh number are placed at the bottom. 100gm of drug are weighed and placed on the top of the arranged sieve system and the sieves are shaken mechanically for 20 minutes. The percentage of powder weight retained is calculated. The arithmetic median is calculated by adding up the value of the weight of the powder retained.

$$\text{Percentage retained} = \frac{\textit{Weight of powder retained}}{\textit{Total weight of powder}} \times 100$$

Particle size distribution

Determination of Bulk density, Hausner's ratio, True density

Weighed quantity of powder was taken in a graduated measuring cylinder upto the 70ml markings and was tapped in density tests 500 taps / 750 taps / 1250 taps, fill the level of powder in measuring cylinder remains same after tapping. The final volume made was then observed and bulk density, tapped density, hausner's ratio and compressibility index were calculated.

Formula:

$$\text{Bulk Density} = \frac{\textit{Weight of the powder}}{\textit{Bulk volume}}$$

$$\text{True Density} = \frac{\textit{Weight of the powder}}{\textit{True volume}}$$

$$\text{Hausner's Ratio} = \frac{\textit{True density}}{\textit{Bulk density}}$$

$$\text{Compresibility index} = [1- v/v_0] \times 100$$

Morphology Study of Diclofenac

Description: white to slightly yellowish crystalline powder, slightly hygroscopic.

Solubility: freely soluble in methanol, ethanol, sparingly soluble in water, glacial acetic acid. Partially insoluble in ether, toluene and chloroform.

I.R.

Procedure

By pressed pellet technique in which solid samples are mixed with potassium bromide compressed into a thin transparent pellet using a hydraulic press and is used for analysis. Alternatively, the sample can be mixed with Nujol (mineral oil) and a film of liquid (Nujol Mull) is applied on a liquid sample cell.

Differential Scanning Colorimetry (DSC)

Principle

DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample & reference is measured as a function of temperature. Both the sample & reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature program for a DSC analysis is designed. Such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well defined heat capacity over the range temperature to be scanned.

Preparation of phosphate buffer

Place 50ml of 0.2M potassium dihydrogen phosphate in a 200ml volumetric flask and specified volume of 0.2M NaOH and add water to volume.

Preparation of Multiple Emulsion with Phosphate Buffer at pH 7.4

F1: Aqueous Drug Suspension

To 50 mg of diclafenac drug add 10 ml of solvent like propylene glycol and 1% tween 80. Stirr it at 600Rpm for 5 minutes and then dilute to 50ml with phosphate buffer of pH 7.4 continue stirring at 600 Rpm for 15minutes using mechanical stirrer.

F2: W/O Simple Emulsion

To 30ml above suspension add 20ml of liquid paraffin containing15% w/v span 80. Stirr it at 300 Rpm for 5 minutes using mechanical stirrer.

F3: O/W Simple Emulsion

To 30ml above suspension [F2] add 20ml of [F1] stir it at 3000 Rpm for 5 minutes using mechanical stirrer.

F4: W/O/W Multiple Emulsion: (F1+F2+F3)

Aqueous drug suspension 30 ml was taken then 20ml liquid paraffin containing 15% W/V span80 was added and stirred well using a mechanical stirrer. And to the above 30ml suspension 20ml of w/o emulsion was added and stirred at 3000rpm for 5minutes to make w/o/w multiple emulsion.

Preparation of Multiple Emulsion with Phasephate Buffer at pH 7

F1: Aqueous drug suspension

To 50mg of diclofenac drug add 10ms of solvents like propylene glycol and 0.1% tween 80. Stir it at 600 Rpm for 5 minutes. Then dilute to 50ml with phosphate buffer of Ph 7. Continue stirring at 60Rrpm for 15 minutes using a mechanica stirrerl.

F2: W/O Simple Emulsion

To 30ml of above suspension add 20ml of arachis oil containing 25% W/W span 80. Stirr at 3000Rrpm for 5 minutes using a mechanical stirrer.

F3: O/W Simple Emulsion

To the 30 ml of above suspension [F2] and add 20ml of [F1]. Stir at 3000 Rpm for 5 minutes. Using a mechanical stirrer.

F4: W/O/W Multiple Emulsion: (F1+F2+F3)

Aqueous drug suspension 30ml was taken then 20ml of arachis oil containing 25% W/W span 80 was added and stirred well using a mechanical stirrer. And to the above 30ml suspension 20ml W/O emulsion was added and stirred at 3000 rpm for 5minutes to make W/O/W multiple emulsion.

RESULTS AND DISCUSSION

Preformulation studies

Angle of repose

$$\theta = \tan^{-1}[h/r]$$

Where,

$\theta = Angle\ of\ repose$

h = Height of heap from surface

r =Radius of heap

Angle of repose =35.375

From the of repose value it is clear that the property of drug is found to be passable and should be improved (Table 1).

Sieve Analysis

$$\text{Average particle size} = \frac{TOtal\ percentage\ weight\ retained}{Total\ weight\ of\ powder\ retained}$$

= 1.341µm

The particle size of the given granules was determined by frequency distribution analysis using sieve technology.

Average particle size of the powder was found to be 1.341 µm.

The maximum percentage of weight retained was found to be 95.6% on the sieve no 85.

Bulk density

$$\text{Bulk density} = \frac{Weight\ of\ granules\ (gm)}{Initial\ volume\ of\ granules}$$

= 0.33 gm/ml

$$\text{True density} = \frac{Weight\ of\ granules\ (gm)}{Final\ volume\ of\ granules}$$

= 0.512 gm/ml

Compressibility index

$$C.I = [1\text{-}v/v_0] \times 100$$

V= volume after tapping

V0 = volume before tapping

$$C.I = (1\text{-}0.065) \times 100$$

$$= 0.35 \times 100$$

= 35%

Hausner's ratio

After 500 tapings

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

=0.65

From this value it is observed that drug have the free flowing property (Table 4).

Dissolution Studies:

Drug Release Formula:

$$\frac{Sample\ absorbance}{Standard\ absorbance} \times Standard\ dilution \times sample\ dilution \times \frac{1}{label\ claim} \times 100$$

Table 1. Preformulation Studies

S.No	Angle of repose [θ]	Flow property
1	<25°	Excellent
2	25-30°	Good
3	30-40°	Passable
4	>40°	Poor

Table 2. Sieve Analysis

S.No	Sieve no	Weight of powder retained (gms)	Percentage weight retained
1	8	0	0%
2	10	3.48	4.7%
3	25	3.24	4.33%
4	44	3.14	4.18%

5	60	3.14	4.18%
6	85	6.1	8.24%
		Total: 73.92gms	**99.29**%

Table 3. Standard Compressibility index

Compressibility index	Flow property
<15%	Good
15-25%	Passable
>25%	Poor

Table 4. Hausner's ratio

Hausner's ratio	Flow property
<12	Free flowing
1.2-1.6	Cohesive powder

Table 5. Comparative Drug Release from difference Phosphate buffer medium pH 7 and 7.4

S.No	Time	Percent drug release	
		7	**7.4**
1	15	33.8	36.33
2	30	49.9	50.6
3	60	71.10	**80.6**

Best drug release (80.6%) was found at pH 7.4 after 60 minutes.

Table 6. Standard Curve for drug in pH: 7

Concentration	Absorbance
10	0.980
20	0.901
30	0.911
40	0.930
50	0.954

Table 7. Standard Curve for drug in pH: 7.4

Concentration	Absorbance
10	0.810
20	0.931
30	0.942
40	0.961
50	0.982

Table 8. Sample pH: 7

Time	Absorbance
15 min	0.272
30 min	0.402
60 min	0.572

Table 9. Sample pH: 7.4

Time	Absorbance
15 min	0.302
30 min	0.421
60 min	0.670

Fig. 1. DSC of Simple Emulsion

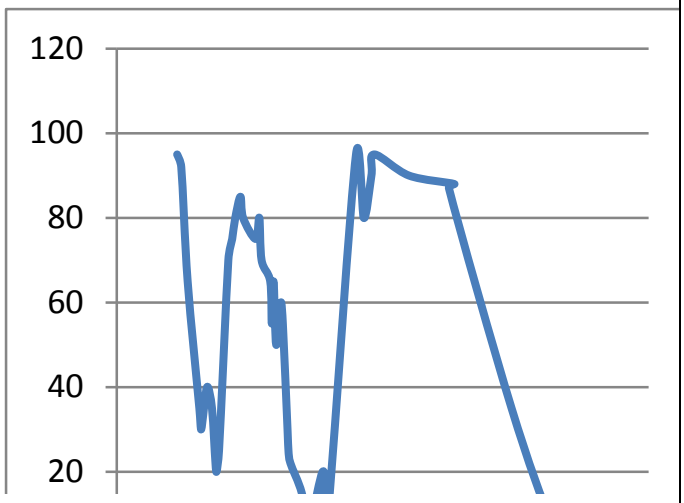


Fig. 2. DSC of Multiple Emulsion

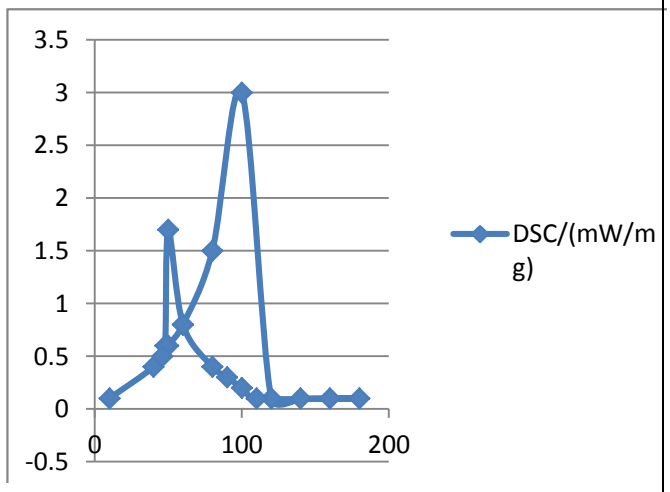


Fig. 3. Standard Curve for pH:7

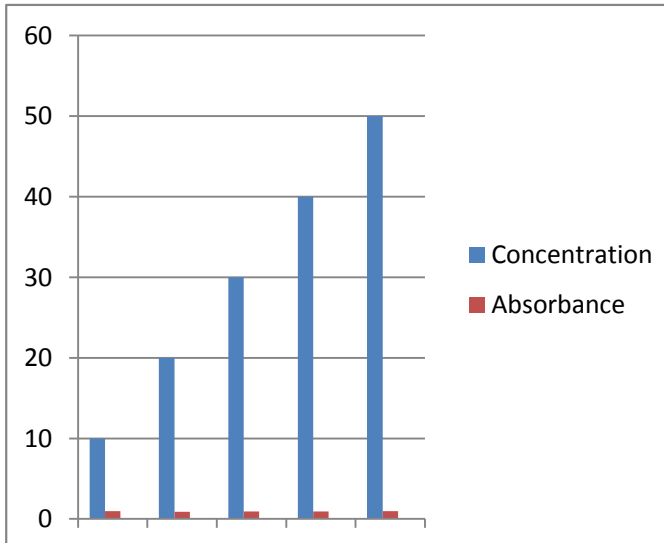


Fig. 4. Standard Curve for pH7.4

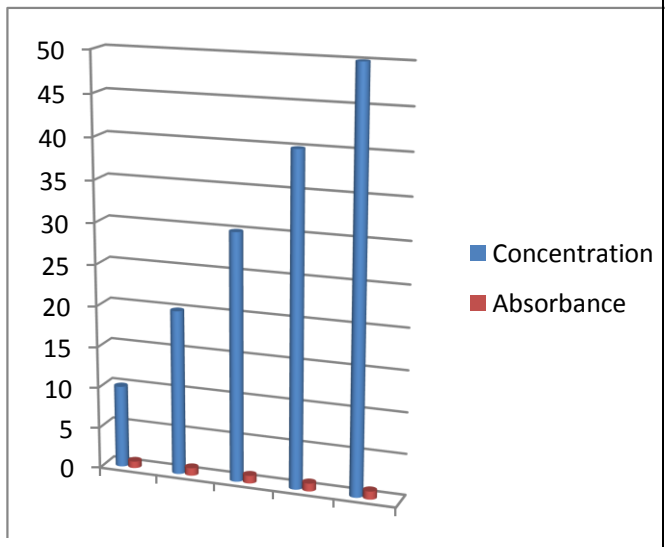


Fig. 5. Sample pH: 7

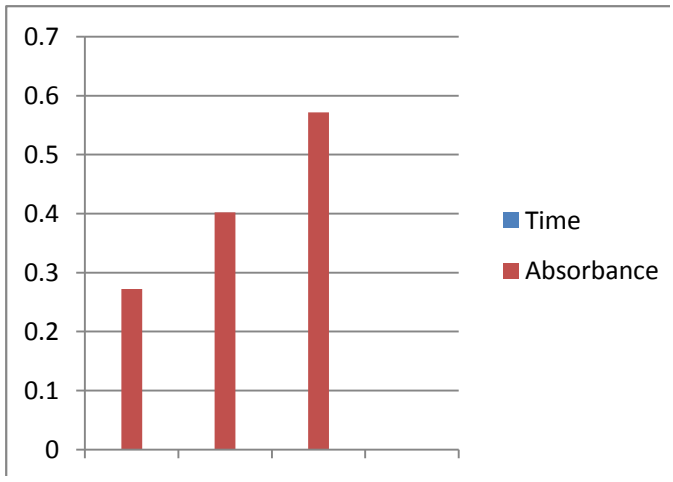
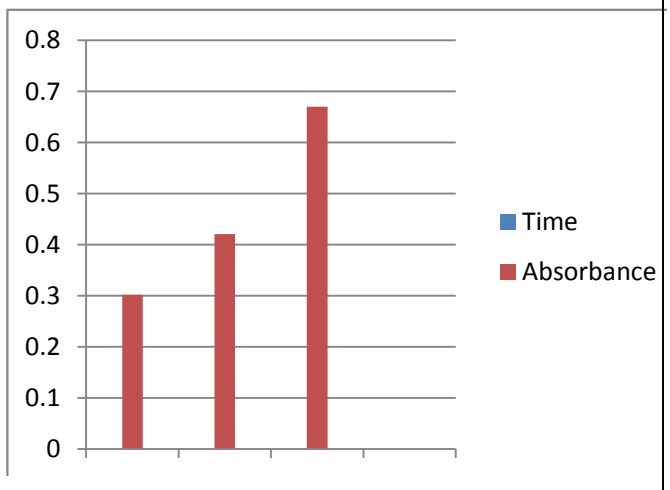


Fig. 6. Sample pH: 7.4



CONCLUSION

Diclofenac sodium drug was basically poor soluble drug, so it is formulated as multiple emulsion in order to increase its absorption and bioavailability. Two formulations were made F1 and F2 using different emulsifying agents (liquid paraffin and Arachis oil) and buffer 7 and 7.4 medium. The best results were achieved in F2 using arachis oil as emulsifying agent and 7.4 phosphate buffer medium. When compared to liquid paraffin emulsifying agent and at 7 phosphate buffer medium. Emulsifying agents are added to emulsify the drugs and to reduce interfacial tension between oil phase and aqueous phase.

REFERENCES

1. Gohel MC, Panchal MK: A novel mathematical method for quantitative expression of deviation from Zero order drug release. *Pharm. Tech*., 2001, 62-73.
2. Liberman HA, Martin R, Gilbert R, Banker S: Pharmaceutical Dosage Forms: Disperse system: Marcel Dekkar. Volume II, 1994, p. 47- 97, 261 – 310, 183- 239.
3. Davis SS: The Emulsion: obsolete dosage form or novel drug delivery system and therapeutic agent. *J. Clin. Pharm*., 1976, 11- 27.
4. Martindale: The complete drug reference, Sean C. Sweetman: Pharmaceutical press, 32th ed.; 2002. P. 1452-1460.
5. Chong-Kook Kim. Seong-Cheol Kim, Hee-Jong Sin, Kyoung MI KimYong-bok Lee. In-Joon Oh: Preparation and characterization of cytrabine-loaded W/O/W multiple emulsion. *International Journal of Pharmaceutics*, 124, 1995, 61-67.
6. Yoshiaki K, Tomiaki H, Hirofumi T, Toshiyuki N and Katsuhiko H, Rheological Study of W/O/W emulsion by cone-and-plate viscometer: Negative thixotropy and shear induced phase inversion. *International Journal of Pharmaceutics*, 72, 1991, 65-77.
7. Omotosho JA, Florence AT, Whately TL: Absorption and lymphatic uptake of 5-flurouracil in the rat following oral administration of W/O/W emulsions. *International Journal of Pharmaceutics*, 61, 1990, 51-56.
8. Jim J, Diane B, Rheology and Stability of Water-in-Oil-in- Water Emulsions Containing Span 83 and Tween 80: *AAPS Pharma. Science*, 2003, 7.
9. Nielloud F, Marti-Mestres G, Laget JP, Fernandez C, Maillos H. Emulsion Formulations: Study of the influence of parameter with experimental designs. *Drug Development and Industrial Pharmacy*, 22(2), 1996, 159-166.