Research Article

Formulation and Evaluation of Self-emulsifying Drug Delivery System of Poorly Soluble Drug using Varying Chain Surfactants

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ABSTRACT

In the present study, the aim was to formulate self-emulsifying drug delivery system of mefenamic acid. Two homologous surfactants of Tween series, Tween 20 and Tween 40 were used as surfactants. The two surfactants were used to formulate a self-emulsifying system of mefenamic acid using a common co-surfactant ethanol. The clear microemulsion regions obtained in phase diagram of Tween 40 was larger than Tween 20; which indicates that Tween 40 has good emulsifying ability. Tween 20 has a hydrophobic chain length of 12 carbons, whereas Tween 40 has a hydrophobic chain length of 16 carbons, so increment in carbon chain length provides good self-emulsifying ability due to better shielding of the hydrophobic core. This inference is further consolidated after formulating six different formulations using the two surfactants and subjecting them to various evaluation parameters. The formulations containing Tween 40 were superior in all the evaluation parameters, including particle size, zeta potential, and drug release rate. The optimized formulation's particle size, zeta potential, and drug release rate (in 60 minutes) were 187.20 nm, -22.2 mV, and 90.42%, respectively.

INTRODUCTION

Oral drug delivery is the most common form of drug delivery and also the preferable one. One of the biggest challenges to deliver the drugs from the oral route is to deliver the drugs with poor aqueous solubility.[1] Around 40% of the available drugs are hydrophobic and have poor aqueous solubility, due to which their absorption from the gastrointestinal tract becomes dissolution rate limited. Due to improper dissolution and absorption, the bioavailability of these drugs considerably decreases if given orally.[2]

To overcome the poor absorption of hydrophobic drugs, a self-emulsifying drug delivery system is a promising technique. Self-emulsifying drug delivery systems are isotropic pre-mixtures of oil, surfactants, co-surfactants, and water. When these systems are exposed to the gastrointestinal fluid, they spontaneously form oil in water microemulsions. The fine dispersion thus formed can be directly absorbed through the lymphatic system.[3]

Surfactants are one of the vital components of a self-emulsifying drug delivery system. Surfactants were found to affect the self emulsification process with respect to different parameters. The structure of surfactants such as chain length also influences the process of self emulsification. This study has attempted to formulate and evaluate the self-emulsifying drug delivery system formulated with two Tween surfactants having different structures.[4]

Mefenamic acid is a non-steroidal anti-inflammatory drug with poor water solubility and is categorized as BCS class II drug. It exhibits low bioavailability after oral administration as its gastrointestinal absorption and dissolution rate are limited; hence, it is selected as model drug for formulating a self-emulsifying drug delivery system in the present study.[5]

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Polysorbates class of surfactants differ from each other concerning their fatty acid chain length.[6] This study will help investigate the effect of chain length of polysorbate class of surfactants on self emulsification of poorly soluble drug mefenamic acid. This study will help to estimate the most appropriate surfactant among Tween 20 and Tween 40 for formulating an optimized self-emulsifying formulation. This study prepared and evaluated the formulations with model drug mefenamic acid using Tween 20 and Tween 40 with varying fatty acid chain length, ethanol as co-surfactant, and an oil phase.

Materials and Methods

Mefenamic acid was obtained as a gift sample from Swiss Medicare Private Limited, India. Tween 20 and Tween 40 were purchased from Loba Chemie. Other chemicals were of reagent or analytical grade and used without further purification. In-house distilled was used in all preparations and dilutions.

Solubility Determination in Various Oils, Surfactants, and Co-surfactants

Excess amount of mefenamic acid was added to different vials containing 2 mL of different oils, surfactants, and co-surfactants. Continuous mixing in a mechanical shaker was done for 72 hours at room temperature. The drug-containing vehicles were then subjected to centrifugation. The supernatant was separated and dissolved in methanol and solubility was determined by UV Spectroscopy (Shimadzu, 1800) at 275 nm after dilution with methanol.[7]

Pseudoternary Phase Diagram Study

Based on solubility studies, almond oil as oil, Tween 20 and Tween 40 as surfactants, and ethanol as co-surfactant were selected to construct pseudoternary phase diagrams. The surfactant and the co-surfactant were mixed in 1:1 ratio as shown in Table 1. Tween 20 is mixed with ethanol in 1:1 ratio to form smix 1, and Tween 40 is mixed with ethanol in 1:1 ratio to form smix 2. The various ratios of oil : smix (1 and 2) taken are 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1. 2g of each ratio was taken and titrated with water till the final mixture contains more than 90% water of the total weight of the mixture.[8]

The pseudo-ternary phase diagram of oil (containing drug), surfactants, and water were constructed using SigmaPlot 13.0 software, and the self-emulsifying region was identified. The diagrams were further used to optimize the concentration of surfactants.

Table 1: Different ratios of surfactants and co-surfactants used

S. No.	Surfactant	Co-surfactant	Ratio of surfactant: co-surfactant (Smix)
1.	Tween 20	Ethanol	1:1
2.	Tween 40	Ethanol	1:1

Development of Mefenamic Acid Self-emulsifying Formulations

Different self-emulsifying systems containing mefenamic acid were developed based on pseudoternary diagram studies, as shown in Table 2. The fixed quantities of oil and smix were taken and homogenized using a magnetic stirrer. The drug was slowly added to the mixture and continuously stirred till it gets completely dissolved. Different batches were prepared and subjected to evaluation.[9]

Evaluation of Mefenamic Acid Self-emulsifying Formulations Homogeneity

The prepared self-emulsifying formulations were evaluated for their color and homogeneity in appearance through visual examination.

pH

The prepared formulations were subjected to pH measurement by using a digital pH meter. The measurements were done in triplicate, and the average value was determined.

Ease of Dispersibility

1 mL of the prepared formulations was taken in a USP type II dissolution apparatus containing 900 mL of phosphate buffer pH 6.8. The rotations per minute were set to 50, and the time in which a homogeneous dispersion is formed is noted.[10]

Optical Transparency

1 mL of the prepared self-emulsifying preconcentrate was taken and diluted up to 100 mL with distilled water. The resulting dilutions were then analyzed by UV-visible spectrophotometer at 655 nm.[11]

Particle Size and Polydispersity Index

1 mL of the prepared self-emulsifying formulation was taken and diluted up to 100 mL with distilled water. The diluted preparations were subjected to particle size analysis using Malvern zetasizer at 25°C.[12]

Zeta Potential Analysis

1 mL of the prepared self-emulsifying formulation was taken and diluted up to 100 mL with distilled water.

Table 2: Composition of different self micro-emulsifying formulations

Batch	Drug	Oil	Tween 20	Tween 40	Ethanol
F1	100 mg	0.30	0.30	-	0.20
F2	100 mg	0.30	0.40	-	0.20
F3	100 mg	0.30	0.60	-	0.20
F4	100 mg	0.30	-	0.30	0.20
F5	100 mg	0.30	-	0.40	0.20
F6	100 mg	0.30	-	0.60	0.20

The diluted preparations were subjected to zeta potential analysis using Malvern zetasizer at 25°C.[13]

Refractive Index

The refractive indices of the prepared formulations were determined using Abbe's refractometer at room temperature. All the readings were taken in triplicate, and the mean was calculated.[14]

Viscosity

The prepared formulations were subjected to rheological analysis by Brookfield viscometer DV-II+ using spindle SC4-34LV at 25°C.[15]

In-vitro Dissolution studies

The drug release studies from the prepared formulations were carried out using a paddle-type dissolution apparatus at 37°C. 900 mL of phosphate buffer pH 6.8 was used as a dissolution medium. The dissolution speed was kept at 30 rpm. The samples were withdrawn at 5-minute intervals and analyzed by a UV-visible spectrophotometer at 275 nm. The release rates of drugs from various prepared formulations were compared with plain drugs.[16]

Statistical Analysis

Statistical analysis was conducted by one-way analysis of variance and in all analysis, a p value of less than 0.05 was considered significant.

RESULTS AND DISCUSSION

Pseudoternary Phase Diagram Study

The Pseudoternary phase diagrams were constructed using almond oil, Tween 20 and Tween 80 combined with the same co-surfactant ethanol in a fixed ratio. The region obtained after delineation confirms that the self-emulsifying region obtained with Tween 40 is comparatively larger than the self-emulsifying region obtained with Tween 20 when common surfactant ethanol is used (Figs. 1 and 2). This leads to the inference that Tween 40, having a hydrophobic chain length of 16 carbons, is a better emulsifier than Tween 20, having a hydrophobic chain length of 12 carbons. Also, it has been observed that more transparency is observed in Tween 40 containing systems, which indicates the formation of a finer dispersion compared to Tween 20. The reason for this observation can be that as the chain length increases, the folding of chains of surfactant occurs, which protect the hydrophobic core from hydration.[17]

Homogeneity

The prepared self-emulsifying formulations were oily viscous preparations and found to be homogeneous in appearance after visual examination.

pH

The pH of all self-emulsifying pre-concentrates and all dilutions were found to be in the range of 6.9 ± 0.3 to 7.3 ± 0.2, which resembles the pH range of the physiological fluids.[15]

Ease of Dispersibility

It has been found that Tween 40 incorporated formulations got spontaneously dispersed within 5–10 minutes. However, Tween 20 containing formulations took more than 20 minutes to form a homogeneous dispersion. The quickest dispersion is formed in the case of formulation F5, which got dispersed within 5 minutes. So it can be inferred that 40% of Tween 40 can solubilize 30% of oil most efficiently when ethanol is used as a co-surfactant spontaneously.

Optical Transparency

The maximum transmission from UV-visible spectroscopy is 93.2% of formulation F5, indicating fine microemulsion formation. The transmission from other formulations
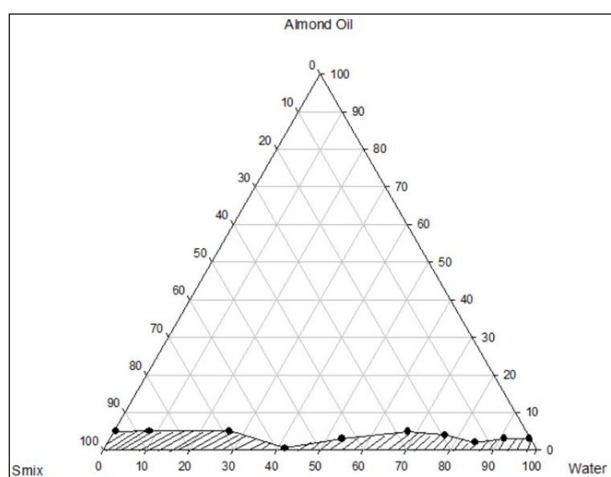

Fig. 1: Pseudoternary phase diagram showing oil in water microemulsion (shaded region) of almond oil, smix (Tween 20: ethanol in 1:1 ratio) and water.
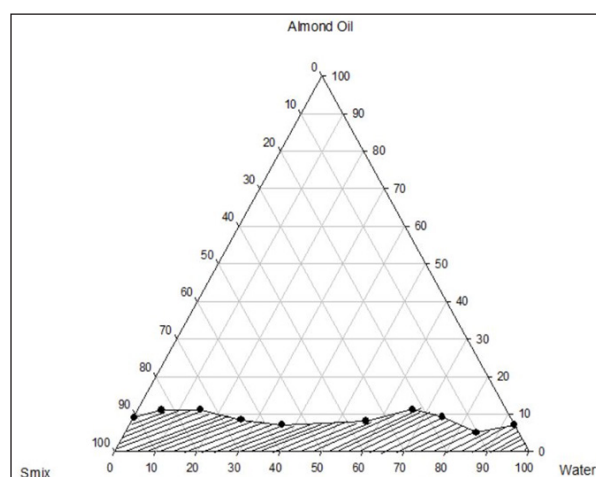

Fig. 2: Pseudoternary phase diagram showing oil in water microemulsion (shaded region) of almond oil, smix (Tween 40: ethanol in 1:1 ratio) and water.

ranges between 89.8–93.2%, as shown in Table 3. The transmission values indicate that the drug has completely solubilized in vehicles and a fine microemulsion formed on dilution.

Particle Size and Polydispersity Index

The particle size of the optimized formulation F5 is found to be 187.2 ± 0.032 nm, and polydispersity index is found to be 0.321 ± 0.003, which indicates the formation of a uniform, homogeneous dispersion. The size distribution by intensity is shown in Fig. 3.

Zeta Potential Analysis

The zeta potential of the optimized formulation F5 is -22.2 ± 0.012 mV, which indicates the formation of the stable microemulsion. The zeta potential distribution is shown in Fig. 4.

Refractive Index

The refractive indices of the prepared formulations were found to be in the range of 1.5 to 1.4, as shown in Table 4. As the refractive index of the prepared formulations

was found close to the refractive index of water (1.33), it can be inferred that the prepared formulations were isotropic.

Viscosity

The viscosity of the optimized formulation is 321 ± 3 centipoises at 100 rotations per minute and a torque value of 22%.

In-vitro Dissolution Studies

The dissolution rate of mefenamic acid from various formulations was determined. The dissolution rate of mefenamic acid from various formulations is shown in Table 5. The highest release rate is observed in the case of formulation F5. However, the release rate of mefenamic acid from all the formulations was higher than that of plain mefenamic acid. The result indicates that a self-emulsifying system can be considered for increasing the drug release rate of mefenamic acid. Also, it was observed that the highest drug release happens when the amount of surfactant and cosurfactant amounts is kept at approximately 40% and 20% in the formulation. The data
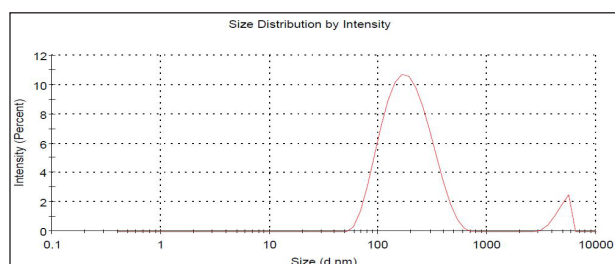

Fig. 3: Intensity distribution of particle size of formulation F5
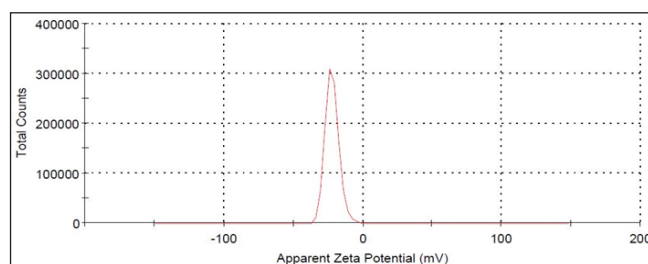

Fig. 4: Zeta potential distribution of formulation F5

Table 3: Optical transmission of different self-emulsifying formulations

S. No.	Batch	Percentage transmission (%)
1.	F1	89.80 ± 0.32
2.	F2	90.24 ± 0.21
3.	F3	91.42 ± 0.11
4.	F4	93.04 ± 0.23
5.	F5	93.20 ± 0.64
6.	F6	92.86 ± 0.31

Table 4: Refractive indices of prepared mefenamic acid microemulsions

Formulation code	Refractive index
F1	1.514±0.003
F2	1.515±0.002
F3	1.516±0.002
F4	1.519±0.003
F5	1.464±0.002
F6	1.465±0.003

Table 5: *In vitro* release of mefenamic acid from different self-emulsifying formulations.

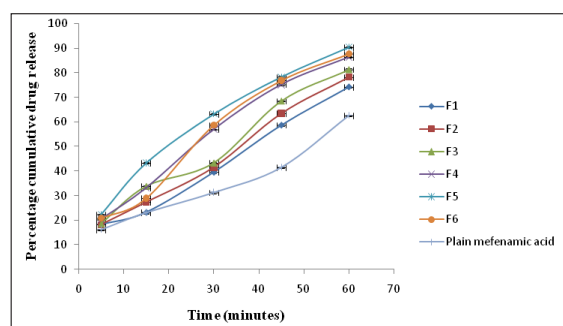| Time (minutes)	%Cumulative Drug Release*				
Formulation code	5	15	30	45	60
F1	18.30 ± 0.2	23.30 ± 0.3	39.60 ± 0.4	58.70 ± 0.3	74.21±0.3
F2	18.30 ± 0.2	27.40 ± 0.4	41.60 ± 0.3	63.50 ± 0.4	78.22±0.2
F3	18.50 ± 0.3	33.80 ± 0.4	43.32 ± 0.3	68.54 ± 0.3	81.34±0.4
F4	20.32 ± 0.3	33.12 ± 0.3	56.93 ± 0.4	75.21 ± 0.4	86.35±0.3
F5	22.40 ± 0.3	43.30 ± 0.3	63.20 ± 0.3	78.32 ± 0.4	90.42±0.3
F6	20.82 ± 0.5	28.92 ± 0.6	58.64 ± 0.5	76.89 ± 0.3	87.73±0.4
Plain Mefenamic acid	16.20 ± 0.4	23.11 ± 0.4	31.31 ± 0.5	41.50 ± 0.4	62.56±0.3

Fig. 5: Percentage cumulative drug release of mefenamic acid from the self-emulsifying formulations and plain mefenamic acid.

is presented in Table 5 and the graphical representation in Fig. 5.

Conclusion

In this study, six self-emulsifying formulations were developed using two different surfactants of tween series, i.e., Tween 20 and Tween 40, and the same co-surfactant ethanol. Based on various evaluation parameters, it has been observed that Tween 40 containing formulations were found to be better than Tween 40 containing formulations. Based on Pseudoternary diagram studies, it has been observed that the self-emulsifying capability of Tween 40 is better compared to Tween 20. The reason may be the long hydrocarbon chain of Tween 40 compared to Tween 20, leading to slight folding of chains and protecting the hydrophobic core from hydration. Among Tween 40 containing formulations, the finer particle size and best release rate are obtained when Tween 40 is around 40%. On this basis, it can be concluded that as the chain length increases in the case of tween surfactants, their emulsifying ability also increases.

Acknowledgement

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