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EVALUATION OF IBUPROFEN - IN SELF EMULSIFYING DRUG DELIVERY SYSTEM

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Abstract:

SEDDS (Self Emulsifying Drug Delivery System) is an isotropic mixture of oil, surfactant, solvent and co - solvent/surfactants that can be used to design formulations for oral administration of highly lipophilic drugs. SEDDS can be administered orally in soft/hard gelatin capsules. SEDDS form fine (or micro) emulsions in GIT with mild gastric agitation. Many parameters such as surfactant concentrations, oil / surfactant ratio, emulsion polarity and droplet size/charge play an important role in oral drug absorption from SEDDS. This formulation improves bioavailability by increasing drug solubility and minimizes gastric irritation due to the hydrophobic nature of nearly 40% of new drug compounds.This formulation can be used to enhance oral absorption of drugs that are not soluble orally, such as Ibuprofen. The purpose of this study is to formulate SEDDS for Ibuprofen and to evaluate its anti inflammatory properties in vitro and in vivo. The following evaluations were performed on the SEDDS formulations: Visual Isotropicity, Emulsification Time, Drug Content, In vitro Drug Release, Post Dilution Drug Precipitation, and In vivo Anti Inflammation Testing. All batches passed the Visual Isotropic test, Emulsification time was less than 1 minute, and the drug release was rapid. Infinite Aqueous Dilution showed no Phase separation and no phase separation. In vivo anti inflammatory studies showed significantly higher anti inflammatory activity ($p < 0.05$). Ibuprofen powder

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INTRODUCTION:

One of the most time-consuming tasks of the formulation scientist is to find a way to increase the bioavailability of drugs that are poorly soluble drugs. Almost always solubilized with GIT before being absorbed through the mucosa. Obviously, poor water solubility can lead to incomplete and inconsistent absorption. Therefore, some therapeutic molecules such as poorly soluble drugs suffer from problems of low bioavailability, high intra- and inter-subject variability, and lack of dose proportionality when administered orally.

The poorly soluble drugs suffer from the problem of low bioavailability, high inter and intra-subject variability and lack of dose proportionality when per orally administered. Here, drug dissolution is the rate limiting step in the absorption process. The major limitation of lipophilic drugs vis-a-viz solubility and dissolution in GIT could be overcome if formulated into self-emulsifying drug delivery system (SEDDS).

SEDDS is an ideal isotropic mixture of oil, surfactant, and cosurfactant that spontaneously emulsifies in the aqueous phase and produces an oil-in-water or water-in-oil emulsion upon gentle agitation.

After preparation and evaluation of self-emulsifying drug delivery system (SEDDS) of ibuprofen using peanut oil and they composed of concentrations of peanut oil , tween 80 (surfactant) and span 20 (co-surfactant). Observe the globule size of surfactant and co-surfactant of dissolution rate test by using dissolution apparatus 2 . Self-emulsifying capsules dissolution rate is faster than conventional tablet. The perfect SEDDS released approximately above 80% - 85% of ibuprofen within 30mins, but the conventional tablet released within 30mins .as the result ibuprofen emulsion is more soluble than conventional tablet .

Advantages:

- SEDDS dramatically increases the solubility of poorly soluble drugs.
- They can reduced food effect by food intake .
- Improved patient compliance, because of different formulations of SEDDS (such as soft gels, liquids, tablets and capsules) and they can makes easier administration.
- Protection from degradation of enzymes in GIT, leading to increases efficacy and stability .
- Versatility.
- Simple to manufacture.

Disadvantages:

- SEDDS typically require a high concentration of surfactants for perfect emulsification, this may lead to side effects in GI tract (Nausea, vomiting and diarrhea, especially in individuals).
- Low drug loading capacity
- Liquid SEDDS can be susceptible to physical and chemical instability.
- SEDDS formulations, especially solid forms may require specialized processes or expensive equipment, potentially increasing production costs .
- Cost effectiveness by using the high- quality oils, surfactants, and other excipients of SEDDS formulation.

Ibuprofen:

- Ibuprofen is a Non - steroidal Anti-inflammatory drug , Anti pyretic and analgesic .
- It is discovered by **Steward Adams and John Nicholson** in 1961.
- Ibuprofen was initially marketed as Ibuprofen.

Brand names:

- Advil®
- Midol®
- Motrin
- Nurofen

Uses of ibuprofen:

- It is used for treatment of moderate pain and inflammation
- It can also help reduce the fevers and relieve arthritis pain.
- Commonly used as analgesic.

Experimental:

Materials:

- Ibuprofen powder (raw material)
- Peanut oil
- Tween 80
- Span 20

Preparation of sedds:

- Weigh 500mg of ibuprofen powder for five batches (Each batch contain 100mg (0.1g) of drug).
- Amount of ibuprofen was dissolved in the mixtures of oil, surfactant and co-surfactant.
- Dissolve the mixtures under 25ºC
- The mixture was vortexed until a clear and perfect solution (SEDDS) was attained.
- The oil phase is laterally used for some evaluation studies of SEDDS.

- Formulation of SEDDS is gently filled in the 550mg of stable formulation of hard gelatin capsules (size 0) by manually and studied to examine the dissolution profile.
- Five formulation were prepared which varied in concentration of oil, surfactant and co-surfactant, but the drug amount was kept constant for each formulations.

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Composition of five formulations has been summarized in table 1.

Batches	Drug (mg) (Ibuprofen)	Oil(mg)	Surfactant (mg)	Co surfactant (mg)	Amount of capsule	× 30
P 1	100mg	450	30	10	550	16500
P 2	100mg	420	24	6	550	16500
P 3	100mg	435	10	5	550	16500
P 4	100mg	410	25	15	550	16500
P 5	100mg	438	7	5	550	16500

Solubility studies:

Solubility studies are used for screen the solubility of a drug in a different oil. It is measured by the maximum amount of solute that can dissolve in a solvent at given temperature. solubility is dependent on the solvent, temperature, and solvent in the solution.

On SEDDS, the Solubility investigations were carried out by introducing an excessive quantity of ibuprofen into 10 ml of each of the following substances: water, phosphate buffer 6.8, oil, surfactant, and c -surfactant. The amalgamation was subjected to heating at 60ºc on a water bath to aid in the process of solubilization, and then vortexed for a duration of 48 hours using a vortex mixer. Subsequently, the solutions were subjected to filtration. The oil solutions underwent filtration using a vacuum filter. Portions of the filtered solutions were diluted with methanol and subjected to analysis using a double beam UV spectrophotometer at a wavelength of 264 nm.

Evaluation of sedds of ibuprofen:

Some evaluation were conducted for formulations. such as

- Visual observation
- Drug content
- Disintegration time
- Globule size determination
- Particle size analysis
- Viscosity determination
- Percent transmittance

Visual observation: The evaluation of emulsification effectiveness was conducted by employing a standard USP dissolution apparatus II. Each formulation was gradually added, in the form of drops, to 100 ml of phosphate buffer with a pH of 6.8 at a temperature of 37 ± 2OC. The stainless-steel dissolution paddle, rotating at a speed of 50 rpm, gently agitated the mixture. The formation of a transparent emulsion was considered satisfactory, while te absence or poor formation of the emulsion was deemed unsatisfactory.

Drug cont okent:

The purpose of the content uniformity test is to guarantee that each capsule contains the intended amount of drug substance with minimal variation among capsules in a batch. To determine the percentage of drug content, a self-emulsifying capsule was introduced into a conical flask containing 100 mL of methanol. The flask was left overnight and gently shaken using a mechanical shaking device. The solution obtained was then filtered using Whatman filter paper, appropriately diluted, and the absorbance of the resulting solution was measured using a PC based double beam UV spectrophotometer at a wavelength of 264 nm, with methanol serving as a blank.

Disintegration time:

The stable formulation, which is self-emulsifying and contains ibuprofen equivalent to 100 mg, was carefully filled into hard gelatin capsules. These capsules were then placed into a USP dissolution vessel that contained 900 ml of phosphate buffer with a pH of 6.8. The paddle of the apparatus was set to rotate at a speed of 100 rpm. The time it took for the capsule shell to burst and release its contents into the dissolution

media, also known as the disintegration time, was carefully recorded.

Globule size determination:

The globule size in emulsion can be determine by visual inspection of optical microscopy provides a direct measure of globule size and globule size distribution, which may be an indicator of the physical stability of the emulsion and observe consistency of the emulsion.

Particle size analysis:

The Zeta sizer was used to analyze the size of the stable formulations (P1, P2, P3, P4, and P5). The size analysis study concluded that initially, as the amount of surfactant increases, the size of the globules decreases. This is due to an increase in the adsorption of surfactants around the oil-water interphase of the droplets and a decrease in interfacial tension. However, after reaching a certain amount of surfactant, further increase in the amount of surfactant leads to an increase in globule size. This could be attributed *to the excess adsorption of surfactant on the interphase, which hinders the efficiency of emulsification and requires more energy to produce an emulsion.

Viscosity Determination:

The viscosity of the emulsions ranged from 1500 ± 0.00 to 2500 ± 0.01 m. All emulsions retained the same viscosity after 4 weeks of storage. It showed good stability**.**

Percent transmittance:

The refractive index of the system was measured using Abbe's refracto meter. The percent transmittance of the system was measured using UV spectrophotometer, keeping distilled water as blank at 221 nm15.

Miscibility test:

In this test the emulsion is mixed with a liquid that is miscible with the continuous phase. Ex: Dilution of emulsion with water, if no destruction occur, this indicates its o/w, while test is determine by visual evaluation more precious methods for determination include chromatographic analysis like spectroscopy, viscometry and calorimetry.

RESULTS AND DISCUSSION:

Solubility studies:

Solubility test was conducted in ibuprofen, it was carried with water, methanol, phosphate buffer P^H 6.8, chloroform, acetone, ether,ethanol and glycerol …

No.	Solvents	Solubility
1	Water	Poor water- soluble
2	Methanol	Soluble
3	Phosphate buffer	Highly Soluble
4	Chloroform	Partly soluble
5	Acetone	Highly soluble
6	Ether	Soluble
7	Ethanol	Highly soluble
8	Glycerol	Low soluble

By performing the solubility test , water is poorly soluble compare to other solvents because the ibuprofen soluble in aqueous alcohol mixtures and also the ibuprofen contains polar carboxyl functional groups and non –polar alkyl groups .so the polarity can be reduces the ibuprofen molecule. Therefore, ibuprofen is poor soluble in water Ibuprofen is highly soluble in ethanol and acetone. Chloroform is partly soluble. However, ibuprofen is low soluble in glycerol at low temperature, they enhance using mono phasic esterification reaction. These reactions take advantage of glycerol viscous and liquid nature. Ibuprofen's solubility also depend on the P^H and especially low in the acidic environment of the stomach .

Visual observation:

The visual observation was carried out in five batches , Out of five ,three is stable another two is unstable .From the study ,amount of surfactant increasing beyond 10mg , the formulation became unstable due to adding excess amount of surfactant .Excessive amount of surfactant is settled at base of emulsion. (Table. 4)

BATCHES	OBSERVATION
P_1	Unstable
P_2	Stable
P3	Stable
P_4	Unstable
P_4	Stable

Table: 4 This shows visual observation out comes..

Drug content:
The drug content of each SEDDS batches are shown in Table; 5. There within compendia limits 96% - 105 % for ibuprofen.

BATCHES	DRUG CONTENT %
P^1	98.12 ± 0.26
P^2	99.02 ± 0.08
P^3	99.80 ± 0.20
P^4	98.12 ± 0.04
P^5	99.87 ± 0.17

Table: 5 This table shows absolute drug content percentage.

Disintegration time: All the capsules are disintegrated completely within 4 to 5 minutes .as shown in Table. 6

BATCHES	DISINTEGRATION TIME (nm)
P^1	3.8
P2	3.6
P3	3.4
P4	4.1
P5	3.7

Table. 6 This shows disintegration time ..

Globule size determination:

The extremely important factor in the self-emulsification process of the emulsion rate and influence of drug absorption and the size of the formulations were in the micrometer range. The globule size of the emulsion is in the form of minute droplets ranging diameter from 0.1µ to 100 µ. This method is carried out in five batches. It has been shown in Table.7 .

BATCHES	GLOBULE SIZE (nm)
P^1	131.6
P^2	158.7
P^3	139.5
P^4	141.5
P^5	162.4

Table .7 shows globule size of stable emulsion

Particle size analysis :

According to this analysis , the emulsion were subjected to size analysis by Zetasizer .

The amount of surfactant increases, globule size decreases due to increasing in adsorption of surfactants around the oil water interphase of a droplets and a decrease in interfacial tension. In the present study batch P^3 had least amount of surfactant and particle size of this batch P^3 **±618.7 nm.** Initially, as the amount of surfactant increased in the batches P^1, the globule size of the emulsion is decreased to **± 537.2 nm.** Further increasing the co -surfactant /surfactant on batches P^2 and P^4 ,the particle size started to increases the size**± 635.8nm** and **± 624.6nm**.

The particle size increases, they used to improving handling, reduce material losses, enhancing appearance and also improve flow ability of the product. The particle sizes analysis has been shown in the Table .8

NO.	BATCH	PARTICLE SIZE (nm)
1	P_1	± 537.2
2	P_2	± 635.8
3	P_3	± 618.7
4	P_4	± 624.6
5	P_5	± 616.8

Table .8 Results for particle size study...

Viscosity determination:

When the viscometer is determining the forces that must be overcome when fluids are used in the lubrication. It is useful to control the quality of emulsion. The amount of viscosity increases during homogenization is good indicator of emulsion quality. The viscosity of formulation related to the concentration of oil and surfactant used .The result as shown in Table .9

FORMULATION	VISCOSITY
P1	21.1 ± 0.2
P2	22.3 ± 0.4
P3	22.4 ± 0.2
P4	24.6 ± 0.5
P5	27.3 ± 0.3

Viscosity determination as been shown…

Percent transmittance:
The percent transmittance of the system by using UV spectrometer keeping distilled water at 353 nm.

FORMULATIONS	TRANSMITTANCE %
P1	98.7
P2	95.5
P3	96.7
P4	97.8
P5	97.0

The percent transmittance as been shown in Table 10..

Miscibility test :
The miscibility test shows a oil in water type , because it will mix easily with water that is miscible with continuous phase and form a homogenous solution and also it shows the temperature such as 25 ºc, 37ºc and 40ºc.

CONCLUSION:
In the emulsion totally depending on the varies size of the droplets in the emulsion and the ibuprofen release rate from SEDDS was found to be higher than that of conventional ibuprofen tablets. By utilization of SEDDS, the delivery and bioavailability of ineffectively water dissolvable, medications can be expanded. Ibuprofen SEDDS demonstrated better absorption and dissolution rates.

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