Research Article

DESIGN AND EVALUATION OF SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEMS OF ALVERINE FOR ENHANCEMENT OF SOLUBILITY

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ABSTRACT

Background: The aim of this study is to develop a liquid self-nano emulsifying drug delivery system for alverine (liquid-SNEDDS). Excipients in the alverine SNEDDS include Ethyl oleate as the oil phase, Tween 80 as a surfactant, and PEG600, Propylene glycol as a cosurfactant. The prepared eleven formulations of alverine SNEDDS were performed for emulsification time, percentage transmittance, particle size, drug release, in vitro dissolution and stability studies. The optimised alverine liquid SNEDDS formulation (D1) was studied for drug-excipient compatibility using infrared spectroscopy, as well as particle size, zeta potential, transmission electron microscopy, and stability. Alverine SNEDDS have a spherical shape with uniform particle distribution, according to their morphology. D1's optimised formulation's drug release percentage (96.6). The stability data revealed no discernible changes in drug content, emulsifying properties, drug release, or appearance. As a result, a potential SNEDDS formulation of alverine with improved solubility, dissolution rate, and bioavailability was developed.

Keywords: Alverine, Antispasmodics, Self-nano emulsifying drug delivery system, Solubility studies, Ethyl oleate, PEG 600, Tween 80, Propylene glycol

INTRODUCTION

Irritable bowel syndrome (IBS) is a long-term gastrointestinal condition characterized by abdominal pain/discomfort, bloating, and altered bowel patterns^{1,2}. Antispasmodics are a class of medications used to treat IBS. IBS patients have visceral hypersensitivity as well as hyper-reactive intestinal motility³. Smooth muscle contraction and endocrine secretion are mediated by voltage-gated calcium channels, which are the critical transducers of membrane potential changes into intracellular Ca²⁺ transients⁴. Alverine (ALV) is an antispasmodic drug that reduces the calcium sensitivity of smooth muscle contractile proteins. ALV selectively binds with 5-HT_{1A} receptors and acts as an antagonist that reduces the visceral pronociceptive effect of 5-HT. This action mode can account for its antinociceptive effects in post-inflammatory visceral hypersensitivity^{3,5}. ALV, in combination with simethicone, has demonstrated significant efficiency in the treatment of abdominal pain in IBS³. Alverine citrate 60/120 mg hard capsules and a 60 mg alverine citrate 300 mg simethicone combination in a soft capsule is commercially available under the brand name Spasmonal Forte. ALV is rapidly converted to its primary active metabolite, para hydroxy alverine (PHA), after oral administration, metabolized into two secondary metabolites⁶. The oral route is the most commonly used drug administration method because it is the most normal and comfortable. Because of the greater versatility in oral routes of administration, they have gained more attention in the pharmaceutical sector. However, the dosage type is different from the drug delivery design for other routes. Oral drug delivery is influenced by several factors, including the type of delivery mechanism used, the condition being treated and the patient, its duration, and the drug's properties⁷.

The main limitation of drug administration's oral route is that drugs taken orally for systemic effects have variable absorption rates and volatile serum concentrations. The discovery of new chemical entities that are potent enough and may also have concise biological half-lives has become a significant research area in the field of pharmaceutical drug delivery, as has the development of novel drug delivery for the oral method⁸. To deliver the drug to the gastrointestinal tract (GIT), most novel drug delivery systems (NDDS) rely on diffusion, dissolution, or combining the two mechanisms. Furthermore, most new chemical entities produced by drug development programs have low water solubility (BCS class II and IV). Insufficient oral bioavailability, irregular absorption profiles, high intra-, inter-subject variability, and a lack of dose proportionality are associated with such drugs⁹. The ability of nanoemulsion/SNEDDS to improve atorvastatin and ezetimibe oral bioavailability has been demonstrated; however, increased drug bioavailability does not always imply increased pharmacodynamic impact. When planning SNEDDS inquiries, one should carefully consider certain factors. Self-nano emulsifying drug delivery systems (SNEDDS) are anhydrous homogeneous liquid mixtures consisting of oil, surfactant, drug, co emulsifier, or solubilizer that, when diluted with water gently stirred, spontaneously form oil-in-water nanoemulsions of 200 nm or less in size¹⁰.

Alverine is a substance that is both hydrophobic (log P=5.46) and acidic (pKa = 10.44). It's a white crystalline powder that's insoluble in water, resulting in a wide range of absorption following oral administration. It's typically taken twice a day in one or two oral doses, for a total of 60-120mg twice a day¹¹. The selection of SNEDDS components is heavily influenced by physicochemical properties, drug solubilization ability, and physiological fate. Phase diagrams can optimize the composition of SNEDDS, while statistical experimental design can be used to

optimize SNEDDS further. According to preliminary research, encapsulating Alverine in a lipophilic vesicular structure (SNEDDS) can improve drug absorption from the GIT after oral administration and prolong its presence in systemic circulation due to the slow release of encapsulated drug¹². SNEDDS can increase Alverine oral bioavailability through a variety of mechanisms. It is necessary to convert liquid SNEDDS to solid oral dosage form or solid SNEDDS. SNEDDS can enhance patient compliance and reduce the issues associated with liquid with filled capsules SNEDDS. The self-nano emulsifying drug delivery system can also render extended-release drug delivery systems for poorly soluble drugs. As a result, the primary aim of this research is to provide and sustain sufficient drug concentration at the site of action, which is otherwise hindered by the existence of physiological barriers along the route of drug passage, resulting in low absorption of drugs with only small fractions of the administered dose reaching circulation, using a novel self-nano emulsifying formulation^{12,13}.

MATERIALS AND METHODS

Alverine was purchased from Sherincorps Solutions Inc. Indore (M.P). Ethanol was purchased from Changshu Hongsheng Fine Chemical PVT LTD, Propylene glycol, Tween 80, Ethyl oleate, PEG600 was purchased from Central drug house (P) LTD New Delhi. The institution provides the rest of the materials, which were of analytical grade.

Preparation of Alverine standard stock solution

To generate a 1000 g/ml solution, 10 mg of working standard Alverine was placed into a 10 ml volumetric flask and 1 ml of phosphate buffer pH 1.2 was added until the mark was reached. To achieve a solution concentration of 100 g/ml, the solution was diluted with phosphate buffer. At a maximum of 253nm, the sample was scanned. At the previously observed maximum, the absorbance of samples of various concentrations (at 253 nm). The absorbance and concentration were plotted on a graph. In the chosen concentration range, the graph followed Beer Lambert's law^{14,15}.

Solubility studies

The drug's maturation solubility in various oil, surfactant, and co-surfactant was setting by the shake flask method. First, 1ml oil, surfactant, and co-surfactant were shot in vials, an excess of alverine (appropriately 10mg) was added in each of the vials till its reach saturation point. Next, Alverine equilibrium solubility was determined in various lipids, including Ethyl oleate PEG 600, Tween 20, Tween 80, and Olive oil span 80¹⁶. Then, excess alverine was applied to each of the selected vehicles in each vial until was reached saturation point. Next, the vials were continuously stirred in a vortex mixer for 7 days at 37°C. After reaching equilibrium, the mixture was centrifuged for 10 minutes at 3000rpm, and the supernatant was filtered through a Whatman filter paper. A double beam UV/VIS spectrophotometer (Shimadzu, UV-1700) was used to measure the filtrate's spectrophotometric absorbance at a wavelength of 253 nm.

Pseudo ternary phase diagram

The phase diagram is based on the drug's solubility in various media excipients. Various oil, surfactant, and cosurfactant combinations were taken into consideration for the construction of the same¹⁷. The group's surfactant and cosurfactant (Smix) were blended in different weight ratios (1:1, 2:1, and 3:1). Smix ratios are chosen by comparing increasing surfactant concentration to increasing cosurfactant concentration, and vice versa. Glass vials were filled with various weight ratios of oil and

Smix ranging from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:3, 8:2, and 9:1). Aqueous titration method plotted pseudo ternary phase diagram, each Smix and oil samples were titrated with an aqueous phase. The results were tallied. Based on emulsion transparency and flowability, the system's physical state is represented by a pseudo-three component phase diagram. Emulsion with oil on one axis and surfactant on the other, with on the third axis, there is a cosurfactant¹⁸.

Measurement of percentage transmittance

Reconstituted Alverine SNEDDS with distilled water. Visually inspect the resulting emulsion for turbidity. The percentage transmittance was measured at 253 nm with a UV spectrophotometer.

Emulsification time

A present volume of the mixture (0.2 ml) was diluted with 300 ml of water at 37°C using a magnetic stirrer using the virtual test procedure. The emulsion forming tendency was discovered¹⁹.

Development of alverine SNEDDS formulations

PEG600, Tween 80, and Propylene glycol were employed as surfactant and cosurfactant in alverine SNEDDS formulations made with Ethyl oleate as the oil phase (Table 1). Alverine (60mg) was mixed with oil and heated to 40°C in a glass vial. Surfactant and cosurfactant thoroughly combined the oily mixture. For 15 minutes, the mixture was sonicated.

Drug content determination

1ml of SNEDDS (60mg equal to the drug) was put at a volumetric flask and complete the volume with ethanol. Then permitted to equilibrate for 30min at room temperature with shaking in the thermostatic water bath. After cooling to room temperature, filtered the solution and assessed it spectroscopically at the specified wavelength by UV. Spectrophotometer at 253nm, the drug concentration was calculated regarding beer's storyline, and drug content was ascertained²⁰.

In vitro dissolution studies of alverine SNEDDS formulations

SNEDDS of ALVERINE 1 ml (equivalent to 6mg of alverine) with 1 ml PBS 6.8 pH was filled in dialysis membrane (formerly soaked overnight from the release medium) and shut both open ending sides by the thread. The liquid SNEDDS profile was investigated in vitro using United States Pharmacopeia (USP) XXIII devices II in 37± 0.5 °C with a rotating speed of 75 rpm in Phosphate buffer 6.8 pH as dissolution media. In addition, 5ml of aliquots were detached from the dissolving medium throughout the study and exchanged with fresh media at pre-determined time intermissions (1,2,4,6,8,12,24 hours). Finally, using the UV-1700 Pharmaspec Shimadzu spectrophotometer, the amount of drug released in the dissolution medium (Phosphate buffer 6.8 pH) was determined.

Characterization of alverine SNEDDS formulation

Drug compatibility studies

Infrared was used to verify drug compatibility. IR (infrared) spectroscopy method The infrared spectra were recorded using a Shimadzu IR Spectrophotometer with a total reflectance accessory. KBr disc was used to analyse alverine and physical combinations of the drug or excipients. Within a frequency range of 821,1260,650,1075,1442,1506 1554 cm⁻¹, eight scans were collected at a resolution of 4 cm⁻¹.

Viscosity

Viscosity is determined by Brookfield viscometer using spindle no.06 at 100 rpm. It's to push a spindle (that can be immersed in

the test fluid) through a calibrated spring, and the result of viscosity is provided in the table 6²¹.

Determination of droplet size

Photon correlation spectroscopy (Malvern Instrument UK) was used to determine the droplet size of alverine SNEDDS formulations, which measures the size range of 10 to 5000 nm. After dilution, the formulations were placed in an electrophoretic cell.

Determination of zeta potential

A zeta metre instrument was used to determine the zeta potential of the diluted alverine SNEDDS formulation. The SNEDDS were diluted at a 1:2000 (v/v) ratio and constantly mixed. The resulting emulsion's zeta-potential was measured with a Zetasizer.

Fig. 1: Structure of Alverine

Determination of shape and surface morphology

Transmission Electron Microscopy (model-FEI Philips Morgagni 268D) was used to examine the SNEDDS morphology. After diluting the SNEDDS samples with water (1:1000), a sample drop was stained for 30 seconds with a 2 per cent phosphotungstic acid solution and placed on a copper grid.

Stability studies

Given 60 mg drug-loaded self-nanoemulsion (Ethyl Oleate) surfactant/co-surfactant ratio had been stored in 50 ml borosil volumetric container in three different temperatures was 25 °C, 45 °C, and 5 °C in biological oxygen demand (BOD) for 3 months, samples were periodically removed for visual review to detect any physical and chemical modifications like turbidity and clarity, etc²².

Fig. 2: Determination Infrared spectroscopy spectrum of alverine pure drug

Fig 3: Ternary phase diagram of Ethyl oleate Tween 80, Polyethylene glycol for 1:1 ratio of Smix

Fig 4: Ternary phase diagram of Ethyl oleate Tween 80, Polyethylene glycol for 3:2 ratio of Smix

Fig 5: Ternary phase diagram of Ethyl oleate Tween 80, PEG600 for 1:1 ratio of Smix

Fig 6: Ternary phase diagram of Ethyl oleate Tween 80, PEG600 for 2:3 ratio of Smix

Fig 7: Dissolution profiles of optimized batch (D1, EE2) of SNEDDS

Fig 8: Particle size analysis of alverine SNEDDS formulation D1

Fig 9: Zeta potential analysis of alverine SNEDDS formulation D1

Fig 10: Transmission electron micrograph of SNEDDS

Fig 11 Alverine loaded SNEDDS formulation

Table 1: Composition of Ethyl Oleate, Tween 80, PEG 600,(w/w)

F. No	Oil (ml)	Water (ml)	Smix	Smix Ratio	Drug (mg)	Oil (%)	Water (%)	Smix (%)	Transmittance (%)
A1	9	1	8.5	1:1	60	45.9	4.81	60.1	Transparent
B1	9	1	10.6	1:2	60	43.6	4.53	53.7	Transparent
C9	1	9	15.6	2:1	60	4.79	42.7	52.3	Transparent
D1	9	1	7.6	2:3	60	55.2	5.75	49.8	Transparent
E2	8	2	11.5	3:2	60	38.7	9.62	51.7	Transparent

Table 2: Composition of Ethyl Oleate, Tween 80, Propylene glycol,(w/w)

F. No	Oil (ml)	Water (ml)	Smix	Smix Ratio	Drug (mg)	Oil (%)	Water (%)	Smix (%)	Transmittance (%)
AA1	1	9	9.6	1:1	60	4.62	42.4	52.9	Transparent
BB9	9	1	10.8	1:2	60	39.8	4.4	55.5	Transparent
CC2	2	8	11.10	2:1	60	9.7	38.6	51.4	Transparent
DD1	1	9	11.6	2:3	60	4.9	41.6	53.9	Transparent
EE1	1	9	11	3:2	60	5.6	47.3	47.7	Transparent
EE2	2	8	14.6	3:2	60	10.4	41.4	48.5	Transparent

Table 3: Solubility of alverine in different oils, surfactant, cosurfactant

S.no.	Component	% Release(mg/ml)	Solubility
1	Ethanol	48.41	Soluble
2	Ethyl oleate	82.52	Soluble
3	Olive oil	32.58	Very slightly soluble
4	Phosphate buffer 6.8	46.1	Soluble
5	Tween 80	90.11	Soluble
6	Span 80	42.55	Slightly soluble
7	Polyethylene glycol	50.67	Soluble
8	PEG 600	70.56	Soluble
9	Distilled water	12.68	Very slightly soluble

Table 4: Dissolution profiles of an optimized batch of SNEDDS

Time (h)	CDR% D1	CDR% EE2
1	10.75	11.68
2	25.12	27.31
4	55.66	60.50
6	87.98	95.63
8	123.98	134.76
12	163.54	234.66
16	208.90	226.55

Table 5: Droplet size analysis, zeta potential, and Polydispersity index of alverine SNEDDS

S.NO	Droplet size	Polydispersity index	Zeta potential
A1	30.6	0.391	-19.69
D1	21.6	0.352	-18.60
BB9	58.0	0.339	

Table 6: Study Stability, viscosity, drug content, and emulsification time of SNEDDS

F. No	Storage Condition 5°C	Storage Condition 25°C	Storage Condition 45°C	Viscosity (cps)	Drug content (mg/g)	Emulsification Time (s)
A1	Accepted	Accepted	Accepted	1450	75.75	42.32
D1	Accepted	Accepted	Accepted	1230	96.6	70.12
E2	Rejected	Rejected	Rejected	1420	63.6	48.98
AA1	Accepted	Accepted	Accepted	1380	81.8	72.58
BB9	Accepted	Accepted	Accepted	1260	75.7	62.41
C9	Rejected	Rejected	Rejected	1280	69.69	52.33
EE1	Accepted	Accepted	Accepted	1140	72.2	48.96
EE2	Accepted	Accepted	Accepted	1350	92.89	55.68

RESULTS AND DISCUSSION

Solubility studies

The solubility in the oil phase was critical for keeping the active components solubilized and preventing the active component of emulsification from depositing in the intestinal lumen. The higher the solubility, the less oil is required in the formulation, and thus the amount of surfactant and co-surfactant necessary for emulsification time is reduced. Alverine solubility in oils phases was investigated. Ethyl oleate has a maximum solubility of 82.54 mg/ml. For alverine SNEDDS formulations, this was chosen as the oil phase. Tween 80 had a maximum solubility of 90.11 mg/ml as a surfactant phase, and PEG600 and Propylene glycol had a maximum solubility of 70.56, 50.67 mg/ml cosurfactant phase. For the SNEDDS formulation, they were chosen as surfactant and cosurfactant.

Pseudoternary phase diagram

Ethyl oleate was chosen as the oil, Tween 80 as the surfactant, and Polyethylene glycol PEG 600 as the cosurfactant for the SNEDDS formulation based on solubility experiments. According to a ternary phase diagram, the self-emulsifying zone grows as the concentration of surfactant and cosurfactant with oil increases. Thus, with an increase in surfactant concentration, self-emulsification efficiency improves.

Visual observation

The visual observation approach was used to test the emulsion formation tendency. The surfactant and cosurfactant ratios (Smix) were kept at 1:1, 2:1, and 3:1, respectively²¹. Smix 1:1, 7:3, 8:2, 9:1, 1:9, and 2:8 of Smix 2:1, and 5:5, 6:4, 7:3, 8:2, and 9:1 of Smix 3:2 all showed quick emulsion production with a clear appearance in a short time. The ratios for the formulation of SNEDDS were chosen based on this information. SNEDDS of alverine 0 produced utilising Ethyl oleate (oil), Tween 80 (surfactant) and Polyethylene glycol PEG600 (cosurfactant). Every one of the eleven-formulation produced was discovered to be clear and translucent, and their completeness was confirmed analyzed composition.

The selected formulation's viscosity was determined to be 1450. Because Tween 80 has a high viscosity, adding PEG 600 could help with self-emulsification. Because of the smaller droplet size, SNEDDS has a reduced viscosity.

Stability study

The stability tests revealed no substantial phase separation or effect of temperature fluctuation on the formulations' physical appearance. Furthermore, even after centrifugation freeze-thaw cycles, no significant visual changes were found. Therefore, the thermodynamically stable formulations were chosen for further investigation²³.

Transmittance measurement

The transmittance (% T) of a material is a measurement of its clarity and transparency emulsions. Formulation F11 has a % transmittance rating of more than 99 %. Transmittance values of 99% indicate that emulsions are less clear²⁴.

Drug content of Alverine SNEDDS

The formulated alverine SNEDDS has a drug content ranging from 75.7 to 81.96 percent. However, in formulation D1, a high of 96.56 per cent was discovered.

In-vitro dissolution studies of alverine SNEDDS

According to drug dissolution experiments, the drug release from D1 is higher than that of the EE2 formulations and the pure drug.

Characterization of alverine SNEDDS

Droplet size analysis, zeta potential, and Polydispersity index of alverine SNEDDS

The droplet size distribution after self-nano emulsification is an essential factor to consider when assessing a self-nanoemulsion system²⁵. The ability of the current technology to generate nanoemulsions with larger interfacial surface area needed for drug absorption was demonstrated by the mean globule size of selected SNEDDS formulations of Alverine, which was A1-30.6 and D1-21.6 nm, and BB95.8 nm. Because of the parallel decrease in the s/cos proportion, an increase in the oily phase (Ethyl oleate oil) ratio resulted in a proportional increase in particle size. The s/cos (surfactant to cosurfactant) ratio was increased, which resulted in a reduction in mean droplet size. The optimized SNEDDS developed the smallest mean particle diameter of 58 nm with the highest proportion of surfactant (55.5 percent w/w Tween 20) at a fixed volume of oil (39.8 percent w/w). This could be due to a higher proportion of surfactant compared to cosurfactant. The improved SNEDDS had a high absolute zeta potential of -19.69, 18.60 mv. The magnitude of the surface charge has a clear relationship with emulsion stability. The coalescence of nanoemulsion droplets is generally prevented by increasing electrostatic repulsive forces between droplets. A decrease in electrostatic repulsive forces, on the other hand, would result in phase separation. Table 5 shows the effects of zeta potential and drug quality estimation.

Transmission Electron Microscopy (TEM)

The nanoemulsion showed a bright spot with a spherical shape and uniform droplet size (Figure 10). Different and non-aggregated nanoemulsion droplets indicated physically stable nanoemulsion²⁶.

Stability studies

For three months, the stability of an optimised alverine SNEDDS formulation was investigated. For the stability tests, the product was packed in a borosil volumetric container. The tests found no significant differences in drug release, drug content, physical qualities, or emulsifying properties²⁷.

CONCLUSION

Alverine SNEDDS formulation was successfully produced using irritable bowel syndrome (Antispasmodics), Ethyl oleate as oil, surfactant, and cosurfactant, respectively. The region producing microemulsion was found using a ternary phase diagram. Alverine was effectively designed as an enhanced SNEDDS formulation with increased solubility and dissolution rate, consisting of ALV (60mg), ethyl oleate oil (55.2 percent w/w), Tween 80 and PEG 600 (49.8% w/w), and water (5.75 percent w/w). The ALV SNEDDS has a mean nanoparticle size of 21.6 nm and other desirable properties for a faster dissolution rate. When compared to the two batches, the optimised SNEDDS formulation of ALV demonstrated a considerable increase in dissolution rate and oral absorption. As a result, our research found that the SNEDDS formulation can be utilised as an alternative to the conventional oral ALV formulations to improve dissolution rate and bioavailability.

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