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Formulation Development & *Invitro* Evaluation Of Felbamate Nanosuspensions By Using Anti Solvent Precipitation And Ultrasonic Method

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Abstract

The Felbamate nanosuspension formulation was prepared by using the anti-solvent precipitation and ultrasonic method. In this work the polymers like HPMC K4M, Poloxamer 188.Polyvinyl alcohol, Polyethylene Glycol 400, as anti-solvent acetone was used. total eight formulations were prepared by using different composition of the polymers based on the prepared formulations (F1 – F8) were evaluated for Drug content, Solubility determination, In vitro drug release study, ATR-FTIR spectroscopy, Particle size determination and poly dispersity index, Zeta potential determination and Morphology characterization by scanning electron microscopy. All the formulations were evaluated for drug content which was in the range 90.15 & to 98.95 %The solubility determination of all formulations in phosphate buffer pH 6.8 was found to be in the range of 0.0156 mg/ml to 0.0375 mg/ml. The results showed that the solubility of formulation was found to be higher in F1 (0.031 mg/ml) compared with other formulations. The solubility of all formulations improved (from insoluble to slightly soluble) compared to pure drug of Felbamate. The in vitro release was carried out for all formulations. The results showed that as the concentration of polymer was increased, the percentage drug release was decreased. Optimized formulations showed 98.69% and 96.49% drug release within 120 minutes, but pure drug released upto 22.46% only. The release rate kinetic data for the best as a F1 formulation showed that the formulation provided good linearity was observed with the zero order (R2 = 0.9), the zero-order kinetics explains the good release of the prepared nanosuspension over the period of 120 minutes. The data were fitted into the Korsmeyer-Peppas equation which showed good linearity and the slope of the Korsmeyer-Peppas plot (n= 0.969) were found to be more than 0.45 indicating the diffusion mechanism is Case II transport

Key words: Felbamate, dispersity index, Zeta potential, Kinetic studies

1. Introduction

A nanosuspension is a colloidal dispersion of drug particles that are submicron in size. The particles are stabilized by surfactants and polymers, and are dispersed in an aqueous vehicle. Nanosuspensions are used to deliver drugs that are poorly soluble in water. They can be administered through oral, topical, ocular, pulmonary, and parenteral routes.
Nanosuspensions can improve the bioavailability, dissolution, and aqueous solubility of drugs. They can also be converted into solid dosage forms like tablets, capsules, pellets, and powders. [1-3]
The most important characteristic of nanosuspensions is their particle size. Particle size determines the following characteristics:

- Dissolution rate
- Bioavailability
- Physical stability
- Drug saturation solubility

Some commonly used surfactants and polymers for the preparation of nanosuspensions include:

- Tween® 80
- Poluronics (F68 and F127)
- Poloxamar-188
- Polyethylene glycols (PEG)
- Polyvinyl alcohols (PVA)
- D-α-Tocopherol polyethylene glycol 1000 succinate or Vitamin E-TPGS

Nanosuspensions can be prepared by a variety of methods, including:

- Precipitation techniques
- Homogenization
- Dry co-grinding
- Wet milling or media milling
- High-pressure homogenization
- Emulsification-solvent evaporation
- Super critical fluid [4-5]

Felbamate is an anticonvulsant drug used in the treatment of epilepsy. In particular, in the adult patient population, it can be employed to treat partial seizures (with and without generalization). Alternatively, it is used to treat partial and generalized seizures associated with Lennox-Gastaut syndrome in children. It has a weak inhibitory effect on GABA receptor binding sites. It is chemically called as: (3-carbamoyloxy-2-phenylpropyl) carbamate [6].

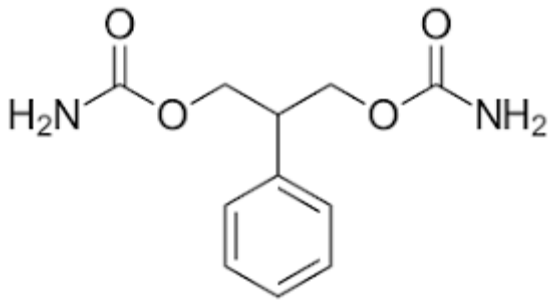

Figure1 Chemical structure of Felbamate

Experimental Work [7]

2. Materials and Methods:

Felbamate Sample from Pure Chem Pvt. Ltd, HPMC K4M , Poloxamer 188 was purchased form the Saimirra Innopharm, Chennai, Polyvinyl alcohol from S D Fine-Chemicals Ltd , Acetone Finar Chemicals, Chennai , Polyethylene Glycol 400 purchased from Merck specialities Pvt. Ltd , Potasium dihydrogen Phosphate and sodium hydroxide purchased from Lab Chemicals, Chennai. All instruments were used in this work were well calibrated.

METHODOLOGY [8-11]

Preformulation studies

Preformulation study is defined as "investigation of physical and chemical properties of the drug substance alone and combined with the excipients". Preformulation studies are the first step in the rational development of dosage form of drugs. It involves the application of biopharmaceutical principles to the physicochemical parameters of the drug with the goal of designing an optimum delivery system that is stable, bioavailable and can be mass produced.

Melting point by capillary tube method

The melting point of Felbamate was determined by the capillary tube method. A sufficient quantity of Felbamate powder was filled into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in an electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Felbamate in the tube passed into liquid phase.

Drug-Excipient Compatibility Studies

The drug and excipients selected for the formulation were evaluated for physical and chemical compatibility studies.

Physical compatibility study

The physical compatibility studies were conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drugs and excipients and placed at room temperature, 40ºC and 75% RH. Any colour change of the physical mixture was observed visually.

Chemical compatibility study by FTIR

Compatibility of Felbamate with excipients was confirmed by FTIR studies. FTIR study was conducted using KBr pellet method and recorded using FTIR measurement over the range of 4000-400cm-1. The procedure consists of dispersing the sample (drug alone, mixture of drug and excipients and the optimized formulation) in potassium bromide and compressing into discs by applying hydraulic pressure. The pellet was placed in light path and spectrum was recorded.

Table 1 Composition of drug and excipients for FTIR spectra

S. NO	INGREDIENTS
1	Drug
2	Drug + HPMC K4M
3	Drug + Poloxamer 188
4	Drug + PVA
5	Drug+ HPMC K4M + PVA
6	Drug + Poloxamer 188 + PVA

Solubility studies of pure Felbamate

Preformulation solubility analysis was done, which include the selection of suitable solvent, to dissolve the respective drug. The solubility was done by adding the solute in small incremental amounts to the fixed volume of solvents, after each addition, the system was vigorously shaken and examined visually for the undissolved solute particles. When some amount of the solute remains undissolved, the total amount added up to the point served as a good and rapid estimate of solubility.

Determination of absorption maximum (λ max) of Felbamate

Preparation of 0.2 M Phosphate Buffer pH 6.8

A stock solution is prepared by 50 mg of Felbamate was accurately weighed and transferred to a 50 ml volumetric flask. The drug was dissolved in 5 ml acetone and the volume was made up to 50 ml by using phosphate buffer pH 6.8 to obtain a stock solution of 1000 µg/ml. 1 ml of this stock solution was again diluted with phosphate buffer pH 6.8 up to 10 ml to obtain a solution of 100 µg/ml. The resulting solution was scanned at 200-400nm in UV-Visible spectrophotometer to attain the absorption maximum λ max.

Preparation of 0.2 M Potassium dihydrogen phosphate solution:
27.218 g Potassium dihydrogen phosphate was dissolved in distilled water and diluted with the same to make up to volume to 1000ml.

Preparation of 0.2 M Sodium hydroxide solution:
8 g of sodium hydroxide was dissolved in distilled water and diluted with the same to make up the volume to 1000ml.

Preparation of Buffer Solution of pH 6.8
The buffer was prepared by using distilled water following standard method. For the preparation of 1000ml buffer having pH6.8 at first 250ml of 0.2M potassium dihydrogen phosphate was taken in a 1000ml standard flask and adds 112ml of 0.2M Sodium hydroxide solution and mixed well, then distilled water to make the rest of the volume.

Standard curve for Felbamate
A stock solution of Felbamate was prepared by dissolving 50 mg of Felbamate in 5 ml of acetone in a 50ml volumetric flask and shaking the flask for few seconds. Then the final volume was made up to the mark with phosphate buffer pH 6.8 to obtain the stock solution concentration of 1000 µg/ml. From the above standard stock solution, 5ml was pipetted out into a 50mL volumetric flask and the volume was made up to the mark with phosphate buffer pH 6.8 to get a working standard of 100µg/ml. From the working standard solution 1ml, 2ml, 3ml, 4ml, 5ml were pipetted out into 50mL volumetric flasks and volume was made up to the mark with phosphate buffer pH 6.8. The absorbance of these solutions was measured by UV spectrophotometric method at 257nm against blank. Based on this information, the calibration curve was obtained by plotting concentration versus absorbance.

FORMULATION DEVELOPMENT
Felbamate nanosuspension is prepared by the bottom-up technique, employing the antisolvent precipitation-ultrasonication technique. Briefly, Felbamate is dissolved in a mixed solvent of PEG 400 and acetone (ratio of 1:1 v/v) to form organic solutions. PVA and polymer/ surfactant is dissolved in deionized water to obtain a series of anti-solvents with different concentrations. Both solutions are passed through a 0.45µm filter.
The anti-solvent is cooled to below 3ºC in an ice-water bath. Then, 2ml of organic solution is quickly injected slowly and drop wise with a syringe into the 10ml of precooled anti-solvent kept at a low temperature (3ºC) in an ice water bath. During injection, the mixture is stirred continuously by the magnetic stirrer at 500rpm for 2 hr. After the antisolvent precipitation, the volatile solvent is evaporated by subsequently stirred the mixture at 400rpm for 1 hr.
Then sample is transferred to another beaker and treated with an ultrasonic probe with a tip diameter of 6mm was immersed 10mm in the liquid by which waves are travelled downwards and upwards and the period of ultrasound burst is set to 2s with a pause of 2s between two ultrasound bursts. During the process, the temperature is controlled using an ice-water bath.

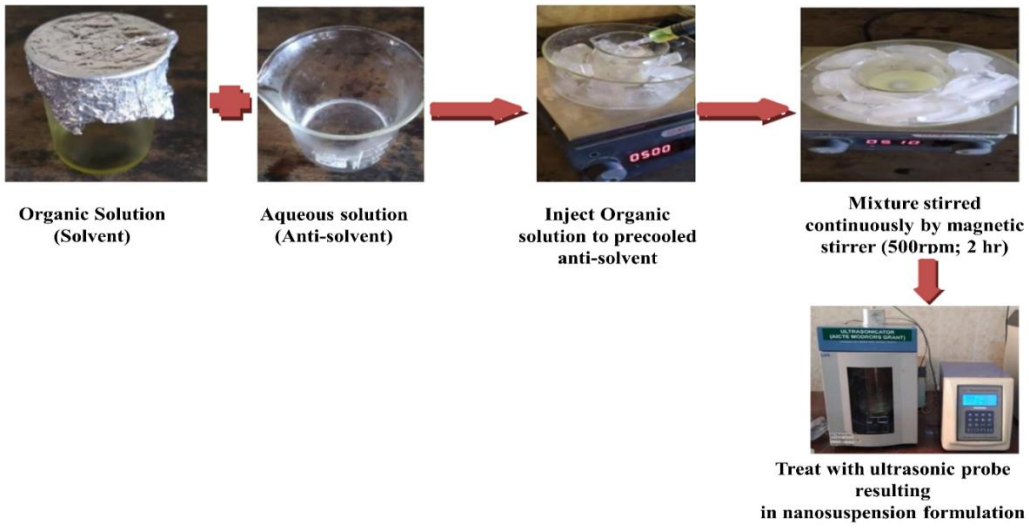

Figure2 Formulation Process of Felbamate Nanosuspension

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug: polymer ratio	01:01	01:01.5	01:02	01:02.5	01:01	01:01.5	01:02	01:02.5
Felbamate (mg)	120	120	120	120	120	120	120	120
Poloxamer 188 (%w/v)	0.1	0.15	0.2	0.25	-	-	-	-
HPMC K4M (%w/v)	-	-	-	-	0.1	0.15	0.2	0.25
Polyvinyl alcohol (%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Polyethylene glycol (ml)	1	1	1	1	1	1	1	1
Acetone	1	1	1	1	1	1	1	1
Distilled water (ml)	100	100	100	100	100	100	100	100

Table 3 Composition of nanosuspension formulation

EVALUATION OF FELBAMATE NANOSUSPENSION [12-14]

Determination of drug content

The drug content in various nanosuspension formulations was estimated. An amount equivalent to 5mg was first dissolved in acetone and was further diluted up to 100ml with phosphate buffer pH 6.8 and stirred well. After 2 hr, the solution was filtered and then the absorbance was measured spectrophotometrically at 257nm (UV-Visible spectrophotometer 1800) using phosphate buffer pH6.8 as the blank solution and the percentage drug content was calculated.

Solubility determination of Felbamate nanosuspension

Solubility of Felbamate nanosuspension formulations were tested in distilled water and phosphate buffer pH 6.8. An excess amount of Felbamate nanosuspensions formulation was added in 10ml of the pertinent media. The mixtures were stirred in a magnetic stirrer at speed of 100 rpm for 24 hours and the temperature was maintained at 37±0.5ºC. Visual inspection was carefully made to ensure there were excess Felbamate nanosuspensions in the mixture, indicating saturation had been reached. Then the mixtures were filtered using whatmann filter paper and filtrates were suitably diluted with same media and the absorbance of the solution measured at 257 nm in UV-Visible spectrophotometer.

In vitro drug release studies

The in vitro release of Felbamate nanosuspension was evaluated. To study the dissolution behaviour of formulation, 5 ml of nanosuspension was taken and transferred into the open ended test tube tied at one end with cellulose membrane filter. The test tube was dipped from membrane side in a beaker containing 300 ml phosphate buffer pH 6.8. The content of the beaker was agitated on a magnetic stirrer. The temperature and stirring rate were maintained at 37±0.5ºC and approximately 100 rpm, respectively. Samples were withdrawn 5 ml for 15, 30, 45, 60, 75, 90, 105, 120 minutes periodically and replaced with an equal volume of fresh phosphate buffer pH 6.8. The samples were analyzed spectrophotometrically at 257 nm wavelength using UV-Visible spectrophotometer.

ATR-FTIR Spectroscopy

The ATR-FTIR spectra of the liquid form nanosuspensions were measured using Access ATR single reflection spectrophotometer fitted with a ZnSe ATR crystal. The spectra were recorded across the range of 400 to 4000 cm– 1, using a 16 resolution and 20 scans.

Particle size and polydispersity index

Particle size and polydispersity index (PDI) were determined by dynamic light scattering (DLS) technique using a Horiba SZ-100 nanoparticle analyzer which allows the sample measurement in the range of 0.3nm-8µm. Each measurement was performed on the diluted suspension in low volume disposable sizing cuvette at 25ºC in triplicate.

Prior to measurements all samples were diluted using ultra–purified water to yield a suitable scattering intensity. The diluted nanosuspension dispersion was poured into disposable sizing cuvette which is then placed in the cuvette holder of the instrument and analyzed. Air bubbles were removed from the capillary before measurement.

Monodisperse samples have a lower PDI value, whereas higher PDI value indicates a wider particle size distribution and the polydisperse nature of the sample can be calculated by following equation:

PDI = Mw/Mn

Where,

Mw = Weight average molecular weight; Mn = Number average molecular weight

Determination of Zeta Potential of Nanosuspension

Zeta potential was evaluated by a Laser Doppler Anemometer coupled with Nanoparticle Analyzer SZ-100 (Horiba Scientific). The samples were properly diluted with deionized water and placed in the electrophoretic cell. Each sample was assessed three-times at 25ºC and the average values were employed for measuring the response.

Morphology of Nanosuspension by Scanning Electron Microscopy

Particle morphology was observed using scanning electron microscopy (SEM-Tescan Vega 3). The sample's small drop of the suspension was air dried followed by oven drying and was fixed on an SEM stub using double-sided adhesive tape and coated with gold layer.

A scanning electron microscope with a secondary electron detector was used to obtain digital images of the samples at an accelerating voltage of 15kV. The processed images were recorded and individual formulated Nanosuspension diameter was measured to obtain average particle size.

Release Kinetics of Optimized Formulation [15-17]

The drug kinetics release mechanism achieved from hydrophilic matrices and the dissolution outcome of the respectively nanosuspension batch was processed with various kinetic equations, known as zero and first-order kinetics, Higuchi, Hixson-Crowell and Korsmeyer-Peppas model. To find out the kinetics release, information got from in vitro drug release readings plotted in different models of kinetic.

Zero order kinetic model– Cumulative % drugs released versus Time.
First order kinetic model–Log cumulative percent drug remaining versus Time.
Higuchi's model– Cumulative percent drug released versus square root of Time.
Hixson Crowell model- Cube root of log cumulative percentage of drug remaining vs. log Time.
Korsmeyer equation–Log cumulative percent drug released versus log Time.

Based on the highest regression values for correlation coefficients for formulations, the best-fit model was decided.

Diffusion Coefficient (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anamolous (non-fickian diffusion)
n>0.89<1	Case II transport
n>1	Super case II transport

Table 4 Diffusion exponents and solute release mechanism

Stability testing studies:[18-21]

Stability testing plays a crucial role in the drug development process. The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of different environmental factors such as temperature, humidity and light to recommend shelf life for the drug product and recommended storage conditions.

Stability studies were carried out on the optimized formulation according to ICH guidelines. Three temperature conditions were applied in the stability study of the optimized nanosuspensions: 4ºC (refrigerator), 25ºC±2ºC (room temperature). Physical stability of the nanosuspensions was evaluated after one month of storage. The formulation was evaluated before and after at periodic intervals for change in appearance, drug content and in vitro drug release.

3. Results And Discussion

PREFORMULATION STUDIES

Melting point by capillary tube method

Melting point of Felbamate was observed for quality determination, it matches with standard values.

Table 5 Melting point of pure drug

Drug	Standard value	Experimental value
Felbamate	151.5- 153.2 ^{O}C	153^{O}C

Drug-Excipient Compatibility Studies
Physical Compatibility Study
Table 6 Physical Compatibility of Drug and Excipients

S.No	Drug and Excipient	Initial	Description and condition					
			At Room Temperature			At 40 oC ±2o and 75 % RH ± 2% (in days)		
			10	20	30	10	20	30
1	Felbamate	Light yellow Crystalline Powder	NC	NC	NC	NC	NC	NC
2	HPMC K4M	White fibrous granular powder	NC	NC	NC	NC	NC	NC
3	Poloxamer 188	White Free flowing Prilled Granules	NC	NC	NC	NC	NC	NC
4	PVA	White coloured granular powder	NC	NC	NC	NC	NC	NC
5	CPN + HPMC K4M	Light Yellow Crystalline Powder	NC	NC	NC	NC	NC	NC
6	CPN + Poloxamer 188	Light Yellow coloured granules	NC	NC	NC	NC	NC	NC
7	CPN+PVA	Light Yellow granular powder	NC	NC	NC	NC	NC	NC

*NC-No Change

Inference
The Physical compatibility of The drug and excipient were evaluated for 10, 20 and 30 days at room temperature and at 40˚C±2˚C/75±5% Relative Humidity. There was no change in colour.
Therefore, the drug and excipients are physically compatible with each other. The excipients which are compatible with the drug were selected for the formulation

Chemical compatibility study by FTIR
FTIR spectroscopy gives the possible information about the interaction between the drug and polymers. It shows no shift and no disappearance of characteristic peaks of drug and hence suggests that there is no interaction between the drug, Poloxamer 188 and PVA.

Solubility study of pure Felbamate
The solubility of Felbamate was checked in different solvents such as deionized water, acetone, ethanol and the results are given in Table 9.9.
Table 7Solubility of Felbamate in various solvent

S.No	Solvent	Solubility
1	Deionized water	Insoluble
2	Acetone	Freely Soluble
3	Ethanol	Soluble

Inference
Felbamate was found to be insoluble in demineralized water, freely soluble in acetone and soluble in ethanol.

Determination of absorption maximum (λ max) of Felbamate
The absorption maximum of Felbamate was determined. The maximum absorbance of Felbamate was found to be at 257 nm. Hence the wavelength of 257 nm was selected for estimation of drug content and analysis of drug in dissolution media.

Standard curve for Felbamate
The UV-Visible spectrophotometric method was used to analyse Felbamate at wavelength of 257 nm. The solution of Felbamate in phosphate buffer pH 6.8 was suitably diluted to give concentration ranging from 0.2-1 µg/ml. The absorbance was measured at 257 nm and the values are given in Table 9.10. The calibration curve is shown in Fig 9.7.

Table 8 Calibration data of Felbamate at pH 6.8

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	0.2	0.142 ± 0.012
3	0.4	0.312± 0.124
4	0.6	0.485± 0.214
5	0.8	0.66 ±0.541
6	1	0.822± 0.254

*Mean ± SD (n=3)

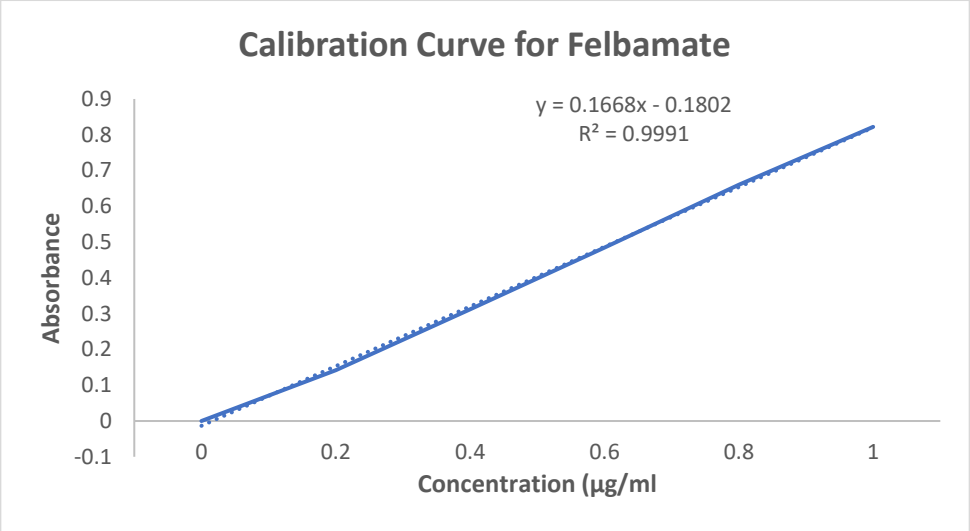

Figure3 Calibration curve of Felbamate in phosphate buffer pH 6.8 Inference

It was found that the solutions show linearity (R2 = 0.997) in the concentration of 2 - 10 µg/ml and obeys Beer Lambert's law.

FORMULATION OF FELBAMATE NANOSUSPENSION

The prepared formulations (F1-F8) of Felbamate nanosuspension were tabulated

EVALUATION OF FELBAMATE NANOSUSPENSION

Drug content of Felbamate nanosuspension

Table 9 Drug content of Felbamate nanosuspension

Formulation code	Drug content (%)
F1	98.95 ± 0.214
F2	95.64 ± 0.124
F3	96.12 ± 0.321
F4	94.85 ± 0.147
F5	95.15 ± 0.845
F6	97.11 ± 0.115
F7	93.14 ± 0.124
F8	90.15 ± 0.541

*Mean ± S.D (n=3)

Inference

The drug content of the Felbamate nanosuspension formulations were determined which were observed in the range between 90.15 % to 98.95 %.

The amount of drug present in the formulation was found to be higher in F1 98.95 % compared to other formulations

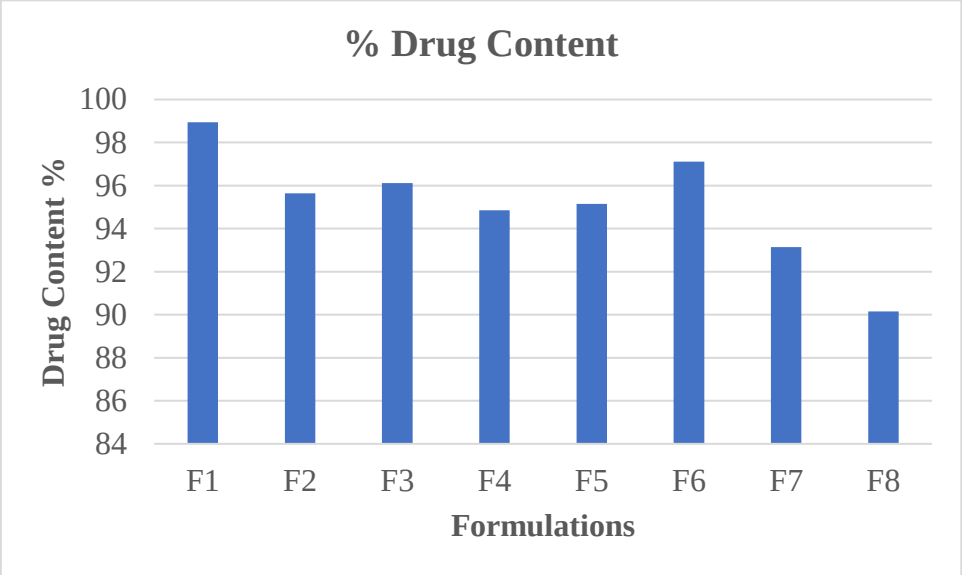

Figure 5 Graphical representation of Drug content of nanosuspension formulation

Solubility Studies of Felbamate Nanosuspension

Solubility of drug and nanosuspensions in deionized water and phosphate buffer pH 6.8 were studied and the values are given in Table 9.12.

Table 10 Solubility studies of pure drug and Felbamate nanosuspension

S.NO.	Formulation code	Deionized water(mg/ml)	Phosphate buffer pH 6.8(mg/ml)
1	Drug	0.001	0.0241
2	F1	0.0164	0.0331
3	F2	0.0155	0.0315
4	F3	0.0145	0.0321
5	F4	0.0154	0.0328
6	F5	0.0157	0.0386
7	F6	0.0142	0.0276
8	F7	0.0121	0.0292
9	F8	0.0137	0.0276

Inference

The solubility of pure drug and all formulations in the Phosphate buffer pH 6.8 was found to be in the range of 0.0276 to 0.0386 mg/ml as mentioned in Table 9.12.

Among all the formulations F1 show higher solubility in Phosphate buffer pH 6.8.

Among all the formulations F1 shows a higher solubility of 0.0331 mg/ml.

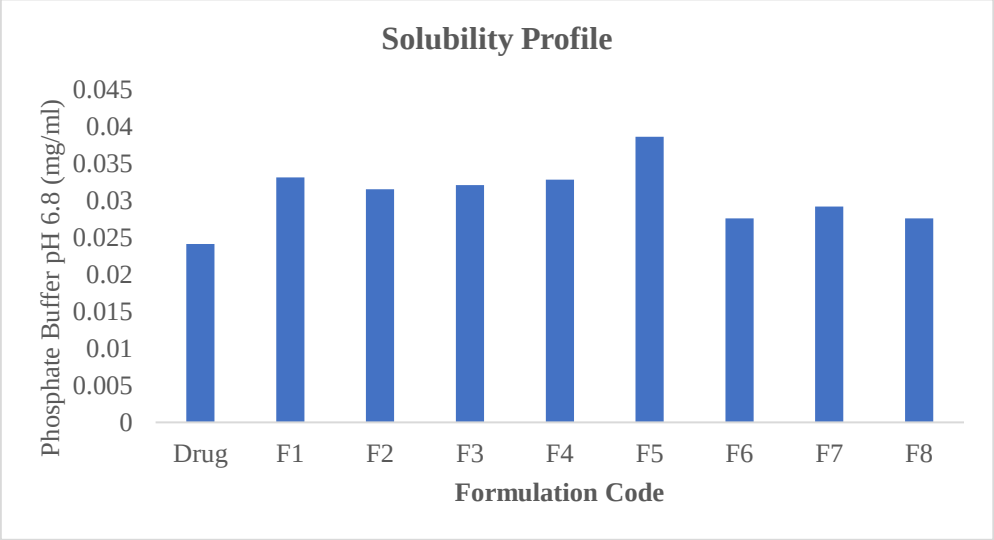

Figure 6Graphical representation of solubility studies of drug and nanosuspension formulations

In vitro drug release studies

An in vitro drug release of all the formulation was studied and the percentage of drug release were tabulated.

Table 11 In vitro drug release study of formulations F1-F8 And Pure Drug

S.No	Time (minutes)	Cumulative percentage drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	Pure drug
1	0	0	0	0	0	0	0	0	0	0
2	15	5.59	4.52	3.12	4.25	7.65	5.74	5.12	4.58	1.24
3	30	14.25	11.23	10.28	11.25	12.15	11.45	10.14	9.52	4.12
4	45	21.02	18.52	17.15	19.25	36.52	34.12	33.12	29.85	6.89
5	60	30.12	26.25	24.25	26.52	45.6	44.12	43.12	42.12	11.21
6	75	54.55	51.22	50.25	51.25	58.14	52.24	50.12	48.12	13.45
7	90	69.95	65.54	64.15	63.12	72.15	69.52	63.12	58.12	16.87
8	105	82.23	79.5	77.68	81.12	83.12	81.2	75.62	72.12	19.82
9	120	99.14	86.52	88.52	90.12	97.12	92.3	89.12	86.52	23.14

Inference

From the in vitro drug release studies of the nanosuspension formulations (F1 – F8), it was observed that only the formulations F1 shows the higher in vitro release when compared to other formulations.

Formulation F1 containing Poloxamer (0.1% w/v) and PVA (0.5% w/v) showed 98.69% of drug release at the end of 120 minutes.

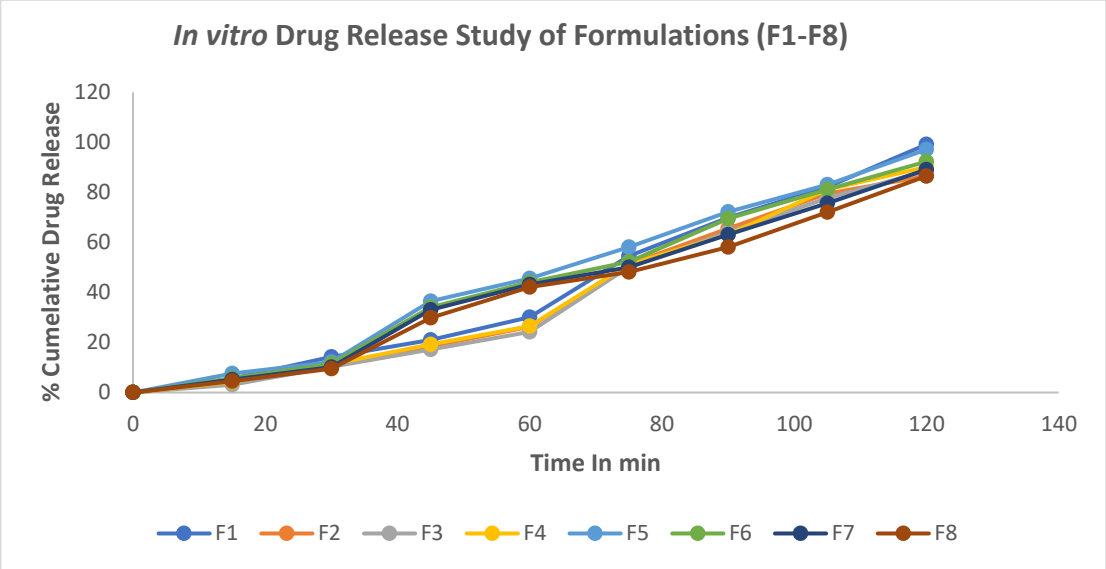

Figure7 In vitro release of optimized formulations and pure drug

The in vitro release data of optimized formulations F1 and F5 are compared with pure drug and the results are shown in Table 9.14.

Table 12 In vitro drug release of optimized formulations (F1) and pure drug

S.No	Time in min	Cumulative % Drug Release	
		F1	Pure drug
1	0	0	0
2	15	5.59	1.24
3	30	14.25	4.12
4	45	21.02	6.89
5	60	30.12	11.21
6	75	54.55	13.45
7	90	69.95	16.87
8	105	82.23	19.82
9	120	99.14	23.14

Inference

The in vitro drug release profile for optimized formulations F1 and pure drug of Felbamate is shown in Fig 9.13. The results of optimized formulations F1 shows 99.14 % release up to 120 minutes, but pure drug (raw crystals) shows only 23.14 % drug release during the same period.

The results demonstrate that the rate and extent of drug dissolution was markedly enhanced in the nanosuspensions. The increased dissolution rate of Felbamate nanosuspensions could be attributed to the pronounced reduction in particle size, the corresponding increased surface area, the enhanced solubility and the amorphous nature of the drug in the preparation.

The optimized formulations F1 was characterized for particle size analysis, zeta potential and surface morphology.

ATR-FTIR Spectroscopy

A decrease in the bands intensity was observed, probably due to the presence of water molecules in Fig 9.14. The results demonstrated that there were no significant changes in the IR spectra of the pure drug and the liquid nanosuspension F1.

Particle size and polydispersity index Inference

The particle size analysis of optimized F1 formulation was measured. The average particle size was found to be 189.6 nm.

PDI indicates the particle size distribution, which ranges from 0 to 1. Theoretically, a monodisperse population indicates PDI equal to zero. The low value of PDI signifies the uniformity of particle size within the formulations.

Polydispersity of optimized F4 formulation was found to be 0.469 indicating uniformity of particle size within formulation

Determination of Zeta Potential of Nanosuspension Inference

The zeta potential of the optimized formulation F1 was found to be -30.1 mV which shows that the formulation is stable

The zeta potential of the optimized formulation F5 was found to be – 6.0 mV which shows that the formulation is stable.

Morphology of Nanosuspension by Scanning Electron Microscopy

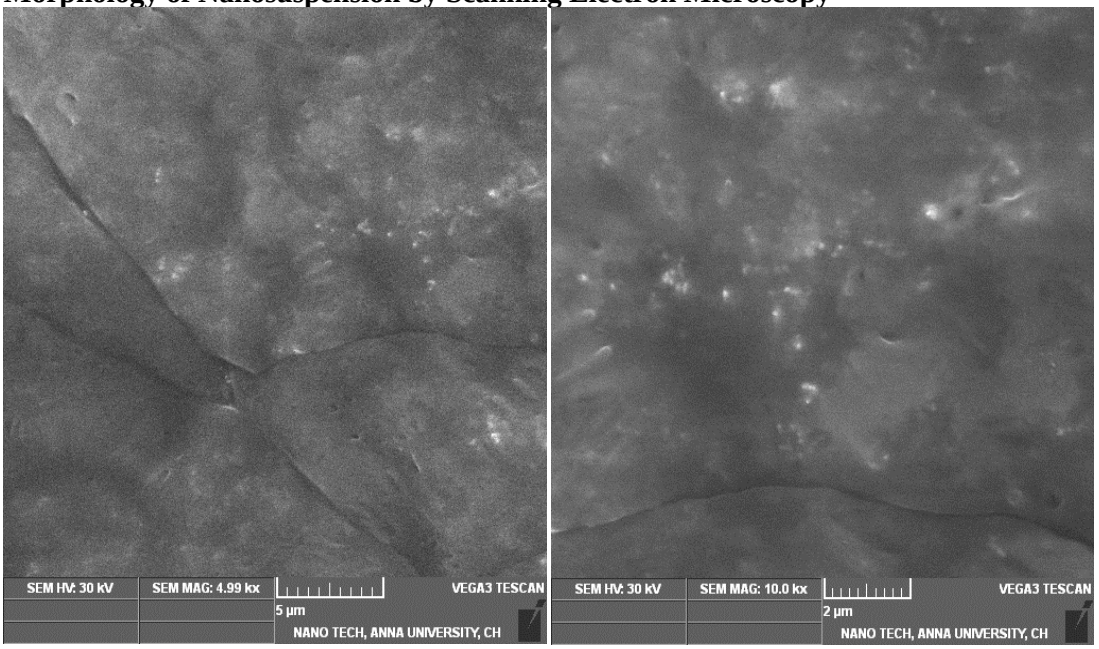

Figure 8 SEM Image of optimized formulation F1 (a) and F1 (b)

Inference

The shape and surface morphology of optimized formulations F1 were observed in scanning electron microscope. The morphology of precipitated drug particles in the suspension is obtained by air drying at room

temperature. Figure presents a regular shape and homogenous size of F1 that is different from that of the other formulations.

RELEASE KINETICS OF OPTIMIZED FORMULATION

Table 13 Release kinetics of optimized formulation (F1)

Time (min)	Cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt)
0	0	100	0.000	0.000	0.000	0.000	100	4.642
15	5.59	94.41	3.873	1.975	1.176	0.747	5.59	4.553
30	14.25	85.75	5.477	1.933	1.477	1.154	8.66	4.410
45	21.02	78.98	6.708	1.898	1.653	1.323	6.77	4.290
60	30.12	69.88	7.746	1.844	1.778	1.479	9.1	4.119
75	54.55	45.45	8.660	1.658	1.875	1.737	24.43	3.569
90	69.95	30.05	9.487	1.478	1.954	1.845	15.4	3.109
105	82.23	17.77	10.247	1.250	2.021	1.915	12.28	2.610
120	99.14	0.86	10.954	-0.066	2.079	1.996	16.91	0.951

The coefficient of determination (R2) was taken as criteria for choosing the most appropriate model

Table 14 r2 values of various Kinetic Models

Kinetic Models	Coefficient of determination (r2) F1
Zero order	0.9558
First order	0.872
Higuchi	0.8046
Korsmeyer and Peppas	0.564

Inference

The release rate kinetic data for the best as a F1 formulation in Fig 9.26 – 9.30. Good linearity was observed with the zero order (R2 = 0.9558), the zero-order kinetics explains the good release of the prepared nanosuspension over the period of 120 minutes.

Thus, the release kinetics of the optimized formulation showed zero order drug release with the transport is anomalous (non-Fickian) model.

STABILITY STUDIES

The optimized formulations F1 subjected to stability studies as per ICH guidelines and the results were shown in

Table 15 Stability data for Optimized Formulation

Stability condition		Physical appearance		Drug content (% w/w)	
		Initial	After 15 days	Initial	After 15 days
25±2oC /40±5%RH	F1	NC	NC	97.32	96.96
4±2oC	F1	NC	NC	97.32	97.08

*NC- No Change

Inference

No significant changes in physical appearance and drug content at storage condition of 25°C ± 2°C / 40 ± 5% RH & 4±2oC after the end of 0 and 15 days were observed

SUMMARY

The present study was aimed to develop a novel method for improving the oral bioavailability by enhancing the solubility of poorly water drug Felbamate and to improve the patient compliance.

Felbamate is a poorly water-soluble drug with a short half-life, thus selected for developing Nanosuspension formulation with improved in the solubility for enhancing oral bioavailability.

Felbamate nanosuspension was formulated by Anti-solvent precipitation and Ultrasonication method using poloxamer 188, HPMC K4M and Poly vinyl alcohol as a stabilizer.
Melting point of drug was determined. It matches with standard value.
Physical compatibility study showed that the drug and excipients are physically compatible with each other.
Chemical compatibility study was performed using FTIR spectroscopy and its studies revealed that there was no change in major peaks, thus confirming no interaction between the drug and excipients.
Solubility of pure drug was determined. Felbamate was found to be insoluble in demineralized water.
Calibration curve of Felbamate was constructed in phosphate buffer pH 6.8 and it obeys Beer Lambert's law.
8 formulations (F1 - F8) of Felbamate nanosuspension were prepared by Antisolvent precipitation and Ultrasonication using varying concentration of different polymers such as Poloxamer 188, HPMC K4M along with PVA (0.5% w/v) as the stabilizer.
The prepared formulations (F1 – F8) were evaluated for Drug content, Solubility determination, In vitro drug release study, ATR-FTIR spectroscopy, Particle size determination and poly dispersity index, Zeta potential determination and Morphology characterization by scanning electron microscopy.
All the formulations were evaluated for drug content which was in the range 90.15 & to 98.95 %
The solubility determination of all formulations in phosphate buffer pH 6.8 was found to be in the range of 0.0156 mg/ml to 0.0375 mg/ml. The results showed that the solubility of formulation was found to be higher in F1 (0.031 mg/ml) compared with other formulations. The solubility of all formulations improved (from insoluble to slightly soluble) compared to pure drug of Felbamate.
The in vitro release was carried out for all formulations. The results showed that as the concentration of polymer was increased, the percentage drug release was decreased. Optimized formulations showed 98.69% and 96.49% drug release within 120 minutes, but pure drug released upto 22.46% only.
Based on higher solubility and increased in vitro drug release, F1 selected as optimized formulations. The optimized formulations were characterized by ATR-FTIR spectroscopy, particle size determination and poly dispersity index and zeta potential determination.
The ATR-FTIR study demonstrated that there were no significant changes in the IR spectra of the pure drug and the liquid nanosuspensions F1.
The particle size and poly dispersity index were determined using Horiba scientific nanoparticle analyzer. The particle size of formulation F1 was 189.6 nm (within nanometric range).
The polydispersity of formulations F1 was found to be 0.469, indicating uniformity of particle size within formulation.
The zeta potential study was determined by Horiba scientific zeta sizer. The zeta potential for the optimized formulations F1 was found to be -30.1 mV which showed that the formulation is stable.
The shape and surface morphology of optimized formulations were observed by scanning electron microscopy. It shows that F1 formulation of nanosuspension has regular shape and homogenous size and has morphology that is different from that of the other formulations.
The release rate kinetic data for the best as a F1 formulation showed that the formulation provided good linearity was observed with the zero order (R2 = 0.9), the zero order kinetics explains the good release of the prepared nanosuspension over the period of 120 minutes.
The data were fitted into the Korsmeyer-Peppas equation which showed good linearity and the slope of the Korsmeyer-Peppas plot (n= 0.969) were found to be more than 0.45 indicating the diffusion mechanism is Case II transport.
The stability studies indicated that the optimized formulation F5 was stable and did not show any significant changes in the physical appearance and drug content at the end of 15 days and further carry out the stability studies on the formulations.

4. Conclusion

The overall results indicate that in the formulation of Felbamate nanosuspension, the increased dissolution rate for the nanosuspension is primarily due to the reduction in the particle size. These findings indicate the suitability of formulation procedure for preparation of nanosized poorly water-soluble drug with significantly improved in vitro dissolution rate and thus enhance fast onset of therapeutic drug effect.

The results obtained in the study suggest that Felbamate nanosuspension may improve the patient compliance due to ease of administration. Hence, the developed formulation would be a possible alternative delivery system to conventional oral formulation to improve its bioavailability.

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