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FORMULATION AND EVALUATION OF LIGAND TARGETED AMOXICILLIN NANOPARTICLE EMULSION

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ABSTRACT

Emulsion technology is very old and distinct from the more modern liposome technology. This is exemplified by the prolific research and patent literature involving liposomes since the 1963 report by Bangham (Physical structure and behavior of lipids and lipid enzymes. Prolonged association of the emulsion particles with the surface of the targeted cell or tissue is in contradistinction to the transient interaction that an unbound particle, existing free in extracellular body fluids, would achieve. By binding the particle to the cell surface, the continued circulation of the nanoparticle through the body is halted. the experimental results it can be concluded that, Ligand targeted perflourocarbon nanoemulsion of Amoxicillin trihydrate canbe prepared by Sonication method using Perfluorochemical fluid, surfactant commixture mentioned. A suitable method of analysis of drug by UV spectrophotometry was developed. Amoxicillin trihydrate showed maximum absorption at a wavelength 334 nm in pH 1.2 buffers (0.1N HCl) and Phthalate Buffer. The value of regression coefficient (r2) was found to be 0.999, which showed linear relationship between concentration and absorbance.

Key Words: Amoxicillin trihydrate, Perflourocarbon nanoemulsion, Regression coefficient.

INTRODUCTION

An emulsion is a heterogeneous system, consisting of at least one immiscible liquid intimately dispersed in another in the form of droplets, whose diameters, in general, exceed 0.1μ. Such systems possess a minimal stability, which may be accentuated by such additives as surface-active agents, finely-divided solids, etc." In accordance with the present invention, it has now been found that improved compositions for use in delivering a bioactive agent to targeted tissues or cells may be formulated by combining (a) a site-specific targeting ligand; (b) a lipid encapsulated oil in water emulsion; and (c) a bioactive agent in or on the surface of the outer lipid monolayer of the emulsion [1].

The present invention thus relates to ligand-targeted emulsions that incorporate biologically active agents on or in the outer monolayer of the lipid-based emulsion particle surface [2]. These novel emulsions are particularly useful for the treatment of disease with biological agents that have improved risk/benefit profiles when applied specifically to selected cells, tissues or organs [3]. Site directed, lipid encapsulated emulsions provide a unique opportunity to deliver potent bioactive agents, such as chemotherapeutic agents, nucleic acid-based therapy, protein-or peptide therapy and the like, with enhanced efficiency to targeted tissues through a unique form of bioactive agent transfer into target cells, i.e. contact facilitated delivery. Contact facilitated delivery of bioactive agents by targeted lipid encapsulated emulsions reflects the prolonged association and increased contact of the ligand-bound, lipid-encapsulated particles with the lipid bilayer of the target cell [4].

The affixed particle is able to interact with the target cell surface over an extended period of time. The exact amount of time may be variable, but is meant to exceed that of more transient nontargeted contact between

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particles and cell surfaces by orders of magnitude [5].

MATERIALS AND METHODS

Methods of Preparation of Ligand Targeted Emulsions

Sonication

This method can be used to produce kinetically stable nanoemulsions. Probe sonicator is brought in contact with dispersion of liquids with surfactants, cosurfactants to generate mechanical vibration and cavitation,which provides the necessary energy input for formation of small sized droplets.Sonication can be widely used to prepare nanoemulsions on small scale however care must be taken to prevent shear induced coalescence [6].

While preparation of emulsions by Sonication has been acceptable, some degree of variability in particle size distribution may be observed. An alternative method of making the emulsions involves directing high pressure streams of mixtures containing the aqueous solution, a "primer" material or the specific binding species, the oil or fluorocarbon liquid and a surfactant (if any) so that they impact one another to produce emulsions of narrow particle size and distribution. The Microfluidizer™ apparatus (Microfluidics, Newton, Mass.) can be used to make the preferred emulsions. The apparatus is also useful to post-process emulsions made by sonication or other conventional methods. Feeding a stream of emulsion droplets through the Microfluidizer™ apparatus yields formulations of small size and narrow particle size distribution [7].

High And Low Energy Methods

High and low energy methods are used for the preparation of nanoemulsions.In high energy methods, large disruptive forces are provided by the use of mechanical devices such as ultrasonicators, microfuidisers and high pressure homogenizers which produces small sized droplets. In low energy methods, no external force is provided; instead it makes use of the intrinsic physiological properties of the systemfor production of nanoemulsions.These are based on stored energy of the system and nanoemulsions are produced by alteration of parameters such as temperature, composition of the system [8].

High pressure homogenisation

This methodis widely used for the producing nanoemulsions utilizing several forces such as hydraulic shear, intense turbulence and cavitation. In this method, piston or high pressure homogeniser is used and two liquids along with surfactants, cosurfactants are made to pass through a small orifice at high pressure (500-5000 psi) to produce nanoemulsions. At first, emulsion is formed with large volume fraction of dispersed phase, which may be diluted later on. The problem of coalescence can be reduced by adding surfactants in excess amount. High pressure homogenisation is a highly efficient method, available at both laboratory and large scale but consumes a large amount of energy and temperature usually increases during processing which might deteriorate the components [9].

Microfluidisation

This mixing technique makes use of high pressure displacement pump (500 – 20000 psi) to produce fine nanoemulsions. Liquids (oil and water) from two opposite microchannels are made to collide with each other at a common impingement area at high pressure to create tremendous shear. Coarse emulsion is made to pass repeatedly through the interaction chamber microfluidiser till desired size of droplets is obtained [10].

Phase inversion temperature technique

Phase transition is brought about either by alteration in temperature at constant compositionor keeping the temperature constant and alerting the composition. In this technique a mixture of oil, water and nonionic surfactants at room temperature exhibiting a positive curvature are taken .On increasing the temperature, the polyethoxylated surfactant becomes lipophilic (due to dehydration) and gets solubilized in the oily phase. This results in the phase inversion and o/w emulsion changes to w/o emulsion exhibiting a negative curvature. It must be noted here that at intermediate temperature (HLB temperature) highly unstable emulsions are formed as the curvature approaches zero. A quick change in temperature (increase or decreasing HLB temperature by 25-30o C) prevents coalescence and produce stable nanoemulsions [11].

Solvent displacement method

In this method nanoemulsions can be produced at room temperature by pouring the organic phase containing oil dissolved in a solvent like acetone or ethanol into aqueous phase having surfactants. Emulsification occurs spontaneously by diffusion of organic solvent, which may be removed later by vacuum evaporation. A high ratio of solvent to oil is needed to prepare small sized droplets .The method requires additional effort for removal of the solvent.

Spontaneous emulsification

Nanoemulsions can be produced by this method at room temperature without the use of any special device. Water is added stepwise into solution of oil and surfactant at constant temperature and stirred gently to produce o/w nanoemulsions. The spontaneity of the emulsification process depends mainly on: interfacial tension, interfacial and bulk viscosity, phase transition region and surfactant structure and its concentration [12]

Formulation of ligand targeted amoxicillin nanoparticle emulsion

Targeting of Amoxicillin therapeutic emulsions may be achieved with a three-step process for

- Pretargeting a Ligand or Protein.
- Subsequent binding of a targeted emulsion to a molecular Epitope.
- The emulsion itself is produced by incorporating Ligand conjugated phosphatidylethanolamine into the outer lipid monolayer of a perfluorocarbon microemulsion. But this invention is limited to preparation of therapeutic emulsion with a surfactant layer providing place for the targeting ligand and encapsulating the drug within or on the perflourocarbon core [13].

The emulsion comprises

1. Perfluorooctylbromide (40% w/v, PFOB, 3M),
2. A surfactant co-mixture (2.0%, w/v) and
3. Glycerin (1.7%, w/v).

The surfactant co-mixture includes

a) 74 mole% lecithin
b) 35 mole% cholesterol and
c) 1 mole% N-(7-(biotinoyl)amino) hexanoyl)-dipalmitoyl-L-alpha-phosphatidyl-ethanolamine, (Pierce Inc.) Which are dissolved in chloroform.

METHOD OF PREPARATION

1. Amoxicillin is suspended in methanol 500mg in 5ml and added in titrated amounts between 0.01 and 5.0 mol % of the 2% surfactant layer, preferably between 0.2 and 2.0 mol %.
2. The chloroform-lipid mixture is evaporated under reduced pressure, dried in a 50° C. vacuum oven overnight and dispersed into water by Sonication.
3. The suspension is transferred into a Blender Cup (Dynamics Corporation of America) with perfluorooctylbromide and distilled, deionized water and emulsified for 30 to 70 seconds.
4. The emulsified mixture is transferred to a Microfluidics Emulsifier (Microfluidics Co.) and continuously processed at 20,000 PSI for three minutes.
5. The completed emulsion is vialed, blanketed with nitrogen and sealed with stopper crimp seal until use.
6. A control emulsion can be prepared identically excluding amoxicillin from the surfactant commixture.
7. Unincorporated drug can be removed by Dialysis Or Ultrafiltration Techniques.

Evaluation Studies

Standard Calibration Curve, Visual Observation, Particle size analysis , Transmission electron microscopy (TEM), Microscopic Evaluation, pH , Density , Viscosity, Electrical Conductivity, Thermodynamic stability tests, Heating cooling cycle, Centrifugation, Freeze thaw cycle, Dispersibility tests, Polydispersity, Dilution test, Refractive index and percent transmittance, Dye test, Zeta potential, Fluorescence test, Filter paper test, Invitro dissolution studies, Entrapment efficiency

RESULTS AND DISCUSSION

Standard calibration curve amoxicillin trihydrate

Particle size analysis

The particle size or the globule size of selected formulations F1A, F1B, F1C, F2A, F2B, F2C, were analyzed using zeta-size analysis. Particle sizes are determined in triplicate at 37° C. with a laser light scattering submicron particle size analyzer and their average was tabulated. All the formulations indicate tight and highly reproducible size distribution with average diameters less than 400 nm.

Transmission electron microscopy (TEM)

TEM analysis was done to the formulation (F2C) with good entrapment efficiency.

pH

Initially the pH meter was calibrated with suitable calibration solution of pH 4.4 and 7.9 by water. All the formulations F1A, F1B, F1C, F2A, F2B, F2C, were with pH ranging between 4.5 and 7.5 Thus the prepared formulation were neither too acidic nor too basic.

The density of the prepared O/W emulsion formulations was determined using a typical Picnometer. The viscosity of the emulsion formulations F1A, F1B, F1C, F2A, F2B, F2C, was determined by Brookfield Viscometer using spindle no.18. The viscosity of the emulsion formulations was determined at various 100rpm operating at 37ºC.

Selected formulations were subjected to different thermodynamic stability tests.

Heating cooling cycle

Freeze thaw cycle

Between -21^{o} C and +25.6 ^{o}C three freeze thaw cycles with storage at each temperature for not less than 48 h was done for the formulations, which passed these thermodynamic stress tests, were further taken for the Dispersibility tests.

Dispersibility tests

Dispersibility tests were done using a dissolution apparatus 2. 1mL of each formulation was added to 500 mL of water at 37±0.5^{o}C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. In vitro performance of the formulation was visually assessed using the following grading system.

The formulations that passed the thermodynamic stability and also Dispersibility tests in Grade A and B were selected for further studies.

Dilution test

All the Prepared Therapeutic emulsions were diluted with water and with oil.

Refractive index and percent transmittance

The refractive index of the system was measured by an Abbe refractometer by placing 1 drop of nanoemulsion on the slide. The percent transmittance of the system was measured at 272 nm using UV spectrophotometer (Shimadzu, Japan) keeping distilled water as blank.

Dye test

Water-soluble dye is added in an o/w nanoemulsion the nanoemulsion takes up the colour uniformly. This is revealed immediately by microscopic examination of the emulsion.

Zeta potential

Zeta potential is measured to find out charge on the surface of droplet in emulsion. All the Formulations F1A, F1B, F1C, F2A, F2B, F2C.were measured and the Zeta Potential Values were tabulated below.

Fluorescence test

Many oils exhibit fluorescence when exposed to UV light. When a w/o nanoemulsion is exposed to a fluorescence light under a microscope, the entire field fluoresces. If the fluorescence is spotty, the nanoemulsion of o/w type.

The prepared Formulations F1A, F1B, F1C, F2A, F2B, F2C nanoemulsion spread out rapidly when dropped onto filter paper. This reveals the formulated formulations were oil in water type.

In-vitro Dissolution studies

Among the formulations, were selected on the basis of transparency, pH, Density, Viscosity and Conductivity were subjected to in-vitro dissolution in order to analyze the release pattern of the selected O/W Targeted emulsion formulations in the dissolution apparatus using a dialysis membrane. The other dissolution parameters include temperature of 37ºC at 50 rpm. The dissolution process is carried out for 6 hours and the samples taken at regular intervals and replaced with the same quantity of fresh media to maintain the sink condition and the samples were analyzed spectrophotometrically at 334.5 nm for Amoxicillin. The percentage drug release was calculated using standard calibration curve and the graphs were plotted by taking percentage drug release along the Y-axis and time along X-axis to compare release with respect to time.

Table 1. List of Instruments

S.No	Instrument name	Manufacturer
1.	Micro fluidics Emulsifier	Microfluidics Co.
2.	Blender Cup	Dynamics Corporation of America
3.	Sonicator	-
4.	Vacuum oven	-
5.	Malvern Zetasizer	Malvern Instruments Ltd,Southborough, Mass.
6.	Homogenizer	Remi
7.	Ultracentrifuge	-
8.	Freeze dryer	-
9.	SEM	-
10	TEM	-
11	Optical microscope	-
12	USP Dissolution apparatus Type	-
13	UV-Visible Spectrophotometer	-
14	Stability chamber	Remi Electro technik Ltd.,Vasai
15	Digital pH meter	Servewell Instruments and Equipments Pvt.Ltd.,Banglore
16	Dissolution Apparatus	Electrolab DissolutionTester TDT-08L,Mumbai
17	Conductivity meter	-
18	Abbe refractometer	Bausch and Lomb optical company, NY

Table 2. List of Chemicals with Name of Suppliers

S.No	Chemical name	Manufacturer
1.	Amoxicillin	Sigma Aldriech
2.	Perfluorooctylbromide	Sigma Aldriech
3.	Glycerin	Sigma Aldriech
4.	Lecithin	Sigma Aldriech
5.	Cholesterol	Sigma Aldriech
6.	N-(6-(biotinoyl)amino) hexanoyl)-dipalmitoyl-L-alpha-phosphatidyl-ethanolamine,	Pierce Inc.
7.	Methanol	Sigma Aldriech

8.	Chloroform	Sigma Aldriech
9.	Glycerin	Sigma Aldriech

Table 3. List of Ingredients and formulation

Ingredients	Formulation Code					
	F1A	**F1B**	**F1C**	**F2A**	**F2B**	**F2C**
Drug	500mg	500mg	500mg	500mg	500mg	**500mg**
Perflouro octyl bromide	30%	35%	40%	30%	35%	**40%**
Lecithin (Soya): Cholesterol	1:1	1:1	1:1	2:1	2:1	**2:1**
Chloroform	QS	QS	QS	QS	QS	**QS**
Glycerin	1.7%w/v	1.7%w/v	1.7%w/v	1.7%w/v	1.7%w/v	**1.7%w/v**
Water	QS	QS	QS	QS	QS	**QS**

Table 4. Solubility of amoxicillin trihydrate in aqueous and organic solvents

S.No	Name of solvent Solubility	(µg/ml)[a]
1.	Distilled water	52±1.2
2.	Ethanol	58±1.3
3.	Chloroform	56±1.4
4.	Acetone	55±1.5
5.	Simulated gastric fluid (pH=1.2)	50±1.8
6.	Phthalate buffer solution (pH 3.4)	51±1.4

a = mean ±SD (n=3)

Table 5. Absorbance of Amoxicillin Trihydrate for Preparation of Standard Calibration Curve in Simulated Gastric Fluid (PH 1.2)

	In Simulated Gastric Fluid (1.2 PH)		
S.No	**Concentration (µg/ml)**	**Absorbance (average)**	**Standard deviation (n=3)**
1	2	0.02	±0.034
2	5	0.022	±0.0058
3	8	0.025	±0.0034
4	11	0.035	±0.0038
5	14	0.044	±0.0042
6	17	0.053	±0.0058
7	20	0.059	±0.0072
8	23	0.062	±0.0038
9	26	0.071	±0.0028
10	29	0.082	±0.0034
11	32	0.092	±0.0023
12	35	0.099	±0.0028
13	38	0.124	±0.0056
14	40	0.168	±0.0048

Table 6. Absorbance of Amoxicillin Trihydrate for Preparation of Standard Calibration Curve in Phthalate Buffers Solution (PH 3.4)

	In Phthalate Buffer (3.4 PH)		
S.No	**Concentration (µg/ml)**	**Absorbance (average)**	**Standard deviation (n=3)**
1	2	0.018	±0.0053
2	5	0.019	±0.0068
3	8	0.036	±0.0059
4	11	0.047	±0.0046
5	14	0.058	±0.0093
6	17	0.069	±0.0067
7	20	0.072	±0.0059

8	23	0.084	±0.0065
9	26	0.092	±0.0039
10	29	0.124	±0.0046
11	32	0.132	±0.0057
12	35	0.146	±0.0059
13	38	0.154	±0.0033
14	40	0.162	±0.0078

Table 7. Regression data of the calibration lines for quantitative determination of amoxicillin trihydrate by UV method

S.No.	Parameters	Values (Simulated gastric fluid;1.2 pH)	Values (Phthalate buffer; 3.4 pH)
1	Λmax (nm)	334.5	334.5
2	Beer's law limits (µg/ml)	2-40	2-40
3	Regression equation	Y = 0.075x +0.069	Y = 0.084x + 0.032
4	Y-Intercept	0.069	0.032
5	Slope	0.075	0.084
6	Correlation coefficient (r)	0.9812	0.9808
7	Standard deviation (SD ±)	0.042	0.046
8	Limit of Detection (LOD; µg/ml)	1.68	1.64
9	Limit of Quantification (LOQ; µg/ml)	5.60	5.47

The prepared formulations F1A, F1B, F1C, F2A, F2B, F2C, were analyzed by Visual observation. All the formulations shows good transparency, no phase separation was seen.

Table 8. Data showing results of Visual Observation of all formulated Emulsions

S.No	Formulation Code	Transparency	Phase separation
1	F1A	Clear	No
2	F1B	Clear	No
3	F1C	Clear	No
4	F2A	Clear	No
5	F2B	Clear	No
6	F2C	Clear	No

Table 9. Data showing results of Average Particle Size at 37^{o}C in nm of all formulated Emulsions

S.No	Formulation Code	Average Particle Size @ 37^{o}C in nm
1	F1A	379±3.56nm
2	F1B	385±2.69nm
3	F1C	356±4.5nm
4	F2A	361±7.6nm
5	F2B	369±6.3nm
6	F2C	337±0.7nm

Table 10. Data showing results of pH of all formulated Emulsions

S.No	Formulation Code	pH
1	F1A	5.5
2	F1B	5.9
3	F1C	6.4
4	F2A	4.4
5	F2B	4.6
6	F2C	5.9

The density of the prepared O/W emulsion formulations was determined using a typical Picnometer. The viscosity of the emulsion formulations F1A, F1B, F1C, F2A, F2B, F2C, was determined by Brookfield Viscometer using spindle no.18. The viscosity of the emulsion formulations was determined at various 100rpm operating at 37ºC.

Table 11. Data showing results of Viscosity and Density of all formulated Emulsions

S.No	Formulation Code	Viscosity	Density gm/c^3
1	F1A	106.9	1.26
2	F1B	112.9	1.45
3	F1C	111.5	1.87
4	F2A	104.2	1.57
5	F2B	108.5	1.68
6	F2C	106.9	1.93

Table 12. Data showing results of Electrical Conductivity of all formulated Emulsions

S.No	Formulation Code	Electrical Conductivity (Micro Siemens [µS].)
1	F1A	3.3
2	F1B	3.5
3	F1C	3.7
4	F2A	3.4
5	F2B	3.6
6	F2C	3.7

Table 13. Data showing results of Heating cooling cycle of all formulated Emulsions:

S.No	Formulation Code	H/C Cycle
1	F1A	Passed
2	F1B	Passed
3	F1C	Passed
4	F2A	Passed
5	F2B	Passed
6	F2C	Passed

All the Formulations F1A, F1B, F1C, F2A, F2B, F2C, were stable at these temperatures. No Phase separation was seen and were further subjected to centrifugation.

Those formulations that passed were centrifuged at 3500 rpm for 30 min by using centrifuge. All the Formulations F1A, F1B, F1C, F2A, F2B, F2C ,were stable, No Phase separation was seen .The formulations that did not show any phase separated were taken to further tests.

Table 14. Data showing results of Centrifugation of all formulated Emulsions:

S.No	Formulation Code	Centrifugation
1	F1A	Passed
2	F1B	Passed
3	F1C	Passed
4	F2A	Passed
5	F2B	Passed
6	F2C	Passed

Table 15. Data showing results of Freeze thaw cycle of all formulated Emulsions

S.No	Formulation Code	Freeze thaw cycle
1	F1A	Passed
2	F1B	Passed
3	F1C	Passed
4	F2A	Passed
5	F2B	Passed
6	F2C	Passed

Table 16. Data showing results of Dispersibility tests of all formulated Emulsions:

S.No	Formulation Code	Dispersibility
1	F1A	GRADE A
2	F1B	GRADE A

3	F1C	GRADE A
4	F2A	GRADE A
5	F2B	GRADE A
6	F2C	GRADE A

Table 17. Data showing results of Dilution tests of all formulated Emulsions

S.No	Formulation Code	Diluting with oil	Diluting with Water	Inference
1	F1A	Globules formed	Clear, Homogenous	Oil in Water Emulsion
2	F1B	Globules formed	Clear, Homogenous	Oil in Water Emulsion
3	F1C	Globules formed	Clear, Homogenous	Oil in Water Emulsion
4	F2A	Globules formed	Clear, Homogenous	Oil in Water Emulsion
5	F2B	Globules formed	Clear, Homogenous	Oil in Water Emulsion
6	F2C	Globules formed	Clear, Homogenous	Oil in Water Emulsion

Test reveals that formulated novel Therapeutic Emulsion Formulations F1A, F1B, F1C, F2A, F2B, F2C , was an Oil in water Type of Emulsion.

Table 18. Data showing results of % Transmittance of all formulated Emulsions

S.No	Formulation Code	% Transmittance
1	F1A	89.2%
2	F1B	87.6%
3	F1C	84.5%
4	F2A	87.8%
5	F2B	84.3%
6	F2C	81.8%

Table 19. Data showing results of Zeta potential of all formulated Emulsions

S.NO	Formulation code	Zeta potential
1	F1A	-44.9±3.9
2	F1B	-42.3±0.8
3	F1C	45±0.59
4	F2A	48±0.45
5	F2B	51±0.49
6	F2C	45±0.21

Table 20. Data showing results of Zeta potential of all formulated Emulsions

S.NO	Formulation code	Spreadability
1	F1A	RAPID
2	F1B	RAPID
3	F1C	RAPID
4	F2A	RAPID
5	F2B	RAPID
6	F2C	RAPID

Fig 1. Electron Microscopic image of formulation F2C

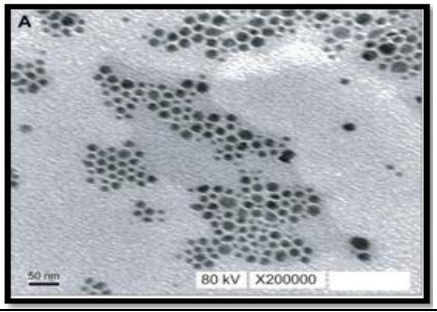
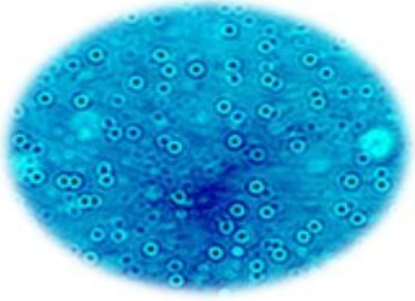


Fig 2. Dye Test of the Formulation F2C.



SUMMARY AND CONCLUSION

The present study has been a satisfactory attempt to formulate Ligand targeted perflourocarbon nanoemulsion of Amoxicillin trihydrate, with a view of improving its Drug entrapment efficiency for targeted drug release. From the experimental results it can be concluded that, Ligand targeted perflourocarbon nanoemulsion of Amoxicillin trihydrate canbe prepared by Sonication method using Perfluorochemical fluid, surfactant commixture mentioned. A suitable method of analysis of drug by UV spectrophotometry was developed. Amoxicillin trihydrate showed maximum absorption at a wavelength 334 nm in pH 1.2 buffers (0.1N HCl) and Phthalate Buffer. The value of regression coefficient (r2) was found to be 0.999, which showed linear relationship between concentration and absorbance. All the prepared emulsion formulations were found to be good without Phase separation.

From this study, it was concluded that the concentration of Lecithin:cholesterol @ 1:2% provides good Drug entrapment efficiency. Formulations F2C displayed zero order release kinetics, and drug release follows non-Fickanian diffusion mechanism. the Formulation F2C provides drug good drug encapsulation. The work can be extended for its incorporation of ligand molecule on to the surface of surfactant co-mixture. The formed perfluorocarbon core can be gateway for the wide range of drugs to the targeted therapeutics

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Nil

CONFLICT OF INTEREST

No interest

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