WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Modification Optimization & Assessment of Ciprofloxacin Liposomes by Using the Technique of Thin Film Hydration

Dnyaneshwari A. Gunjal *[1], Janhavi R. Vispute*[2], Janhavi K. Lokhande*[2], Yogita S. Mahajan *[2]

[2]Student of Sumantai Institute of Pharmacy ,Bambrud Kh, Pachora ,Affilated by Dr. Babasaheb Ambedkar Technological University, Lonere, Department of Pharmaceutics, 424201, Maharashtra ,India .

[1]Assistant Professor of Sumantai Institute of Pharmacy ,Bambrud Kh, Pachora ,Affilated by Dr. Babasaheb Ambedkar Technological University, Lonere, Department of Pharmaceutics, 424201, Maharashtra ,India .

ABSTRACT:

The current study's goals were to Modification Optimization &Assessment of Ciprofloxacin Liposomes By Using the Technique of Thin film hydration using design of experiments (DOE) and investigate how process variables affect the complex liposomal's quality features. system of formulation. The slow commercialisation of liposome drug products over the past ten years may have been caused by a number of factors, including: 1) the challenges of determining the formulation and process design critical quality attributes of these complex systems, and 2) higher manufacturing costs as a result of low entrapment of therapeutic active agents and low preparation reproducibility As a result, the liposomal formulation was optimised using a central composite design (CCD). The drug:okra pectin ratio, hydration volume, hydration time, and sonication time were selected as input factors for the current investigation. a result, the liposomal formulation was optimised using a central composite design (CCD). Particle size, peak shape, polydispersity index, drug loading, entrapment efficiency, and redispersion behaviour were examined as quality attributes in the current study, while the hydration volume, hydration time, sonication time, and drug: okra pectin ratio were selected as input variables for the liposomal preparation. In order to comprehend the basic connections between input variables and quality criteria, contour plots and response surface plots were also used. When compared to the equal dose of Ciprofloxacin, in-vitro dissolution using the United States Pharmacopoeia (USP) apparatus II demonstrated improved dissolution for the full drug: okra pectin ratios. According to research, the input variables had a major impact on the liposomal formulation's quality qualities ratios of okra pectin to the corresponding quantity of ciprofloxacin. According to the contour plots and surface response plots, the input factors had a substantial impact on the liposomal formulation's quality features. The impact of process variables on the liposomal formulation's quality will be better understood thanks to this study. [1,5,6,4]

Keywords :- Liposomes, Thin film hydration, Phospholipid, Duration of action, Ciprofloxacin , Okra pectin ratio.

Introduction:-

A liposome is a microscopic vesicle or bubble composed of the same substance as the membrane of a cell. Drugs for cancer and other illnesses can be delivered via liposomes that are loaded with medication. The British haematologist Dr. Alec D. Bangham FRS initially described liposomes in 1961 at the Babraham Institute in Cambridge (published in 1964). They were found when Bangham and R. W. Horne added negative stain to dry phospholipids in order to test the institute's new electron microscopeThe Greek terms "Lipos," which means fat, and "Soma," which means body, are the origin of the phrase"liposome." Liposomes are concentric bleeder vesicles, meaning that a membraneous lipid bilayer completely encloses an aqueous volume. Phospholipids, which are molecules with a hydrophilic head group and a hydrophobic tail group, are typically used to make membranes. Water repels the tail, which is composed of a lengthy hydrocarbon chain, whereas it attracts the head. Natural phospholipids with mixed lipid chains, such as egg phosphatidylethanolamine, or pure surfactant components, such as DOPE (dioleoylphosphatidyl ethanolamine), can make up liposomes. Liposomes typically, but not always, include an aqueous solution core; lipid spheres devoid of aqueous material are known as micelles; conversely, reverse micelles can be created to encompass an aqueous environment. Up to 40% of newly developed medications by the pharmaceutical industry in recent years are thought to contain lipophilic or poorly soluble substances. making the steps of formulation more complicated. One of the main obstacles to developing novel compounds into oral dosage forms is their poor water solubility, as these compounds'

Absorption is restricted by their dissolution. Poor bioavailability, fed/fasted variation in bioavailability, lack of dose- response proportionality, suboptimal dosing, use of harsh excipients (co-solvents), use of extremely basic and acidic conditions to enhance solubilisation, uncontrollable precipitation after dosing, and patient non-compliance are some of the significant problems associated with poorly water-soluble compounds. By altering the drug's affinity for its receptor, changes made to the chemical structure to increase solubility have the potential to significantly alter pharmacological efficacy. Although creating water-soluble derivatives is expensive, this method has shown that new chemical species are safe and effective. Ciprofloxacin is not considered a hydrophilic drug, but rather a moderately hydrophobic one; clinically, it is used as a broad-spectrum antibiotic to treat a wide range of bacterial infections

including urinary tract infections, respiratory infections, skin and bone infections, and certain types of gastrointestinal infections due to its activity against both Gram-positive and Gram-negative bacteria. Ciprofloxacin is Lipophilic drug belong to category quinolone antibiotic and ,its slightly soluble in acetic acid , methanol , and acetone practically insoluble in water and some cases they readily soluble , and they belong to BCS class IV low solubility and low permeability , their half life is 4-6 hr. and shelf life is 24 month from the manufacturing date , and its bioavailability is 70-80 %. A reason behind to prepare 7 & formulate ciprofloxacin liposomes , this formulation may improve tolerability increase compliance by reducing the dose frequency and enhance penetration of biofilm and treatment of intracellular infection . e.g like Lipoquin ® ,Pulmaquin ® and route of administration of liposomes is ocular, oral , pulmonary , and transdermal , parenteral , so selecting antibiotic category drug for formulation of liposomes they provide better , effect , as compare to oral dosage form , and parenteral liposomes goes into systemic circulation and blood to provide better therapeutic effect in short time as compare to traditional dosage form , and liposomes is a Novel approach of formulation . As medication carriers, liposomes are a flexible technology that offers more benefits than alternative delivery methods, including as the following retention and permeability are enhanced, medication toxicity is significantly reduced, biocompatible and biodegradable, and therapeutic efficacy is significantly increased. Liposomes can incorporate both hydrophilic and lipophilic drugs into their phospholipid ability to concurrently encapsulate additional active chemicals into its complex formulation is an additional benefit. As a result, we optimised the liposomal formulation using central composite design (CCD). Response surface methodology (RSM), another name for central composite design (CCD), is a quick process used to empirically establish a useful relationship between the set of input variables/designs and the trial result. It establishes the ideal range of experimental parameters required to obtain the intended response. An input variable with a well-defined value that can be fixed during an experiment is called a factor. The points (level) chosen for the factors change the value of the output (response) variable, which is a measured quantity. A four-factor, face-centered central composite design was used in the current investigation to create the liposomal suspension and determine the crucial parameters. [2,6,8,14, 9]

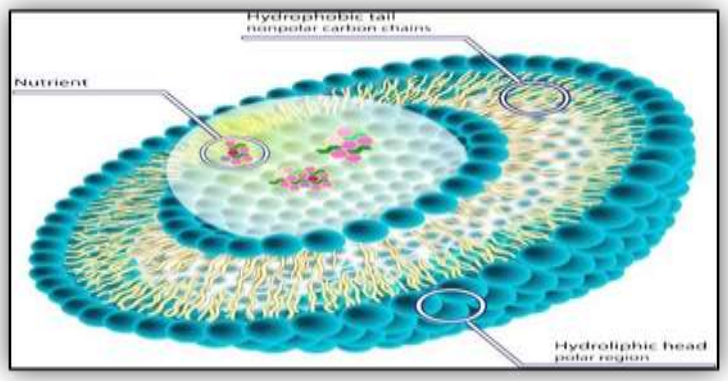
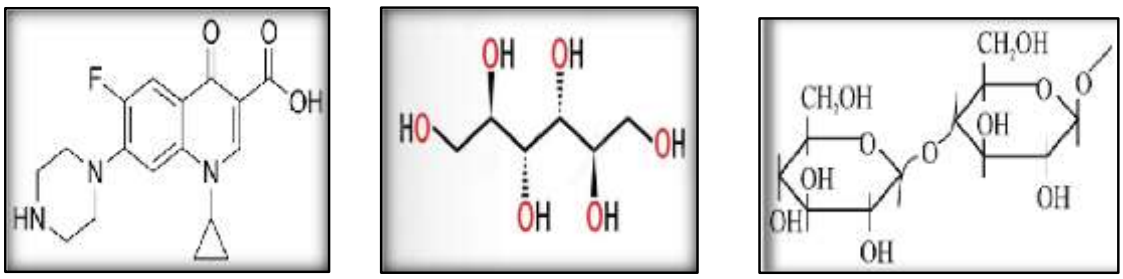


Fig No.1 A Schematic representation of Liposomes

Materials and Methods :-

Materials: - Ciprofloxacin was obtained from Aiping Pharma Inc. Hauppauge , New York .okra pectin was purchased from Global Pharma solution partner Envision pharma united kingdom ,Mannitol was purchased from Roquette America Inc. (Sodium lauryl sulfate (SLS) was obtained from spectrum pharmaceuticals (New Brunswick, NJ). All materials were used as received. 1,7,4,9



Ciprofloxacin Mannitol Okra Pectin

Fig No .2 Chemical structure of API and Excipient

Method :- Preparation of Ciprofloxacin Liposomes

Buchi rotavapor R 200 was used in the thin film hydration process to create Ciprofloxacin liposomes Formulations for liposomes were created by varying the Okra pectin and drug concentrations (2:0.1, 3.5:0.1, and 6:0.1) in roughly 50 millilitres of chloroform , After that, the mixture was transferred to a 500 ml round-bottom flask. To create a thin layer, chloroform was evaporated at 63 °C using a rotating evaporator (R10 Rotavapor, Buchi) under 100 mmHg of vacuum. About 15 minutes were spent on evaporation till a dry residue was obtained. This process produces a thin coating on the flask's inside

surface by gradually removing the organic solvent. The films were vacuum-dried for a whole night in order to guarantee that the organic solvent evaporated completely. The film was then spun for varying hydration times (15, 30, and 45 minutes) at 45°C, after being Okra pectin (Fibre obtain from ladyfinger) hydrated with varying volumes (90, 105, and 120 millilitres) of phosphate buffer (pH 7.4) solution containing 1g of mannitol. To achieve full lipid hydration, the liposomal suspension was stored at 4 oC for the whole night.[9,10, 12, 15]

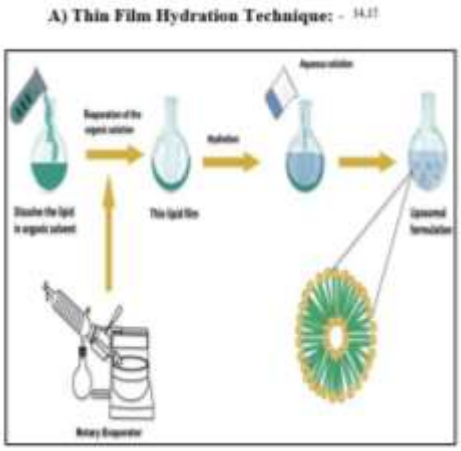


Fig No. 3 Thin film hydration technique

- **Action of Liposomes :-**

Liposomes, spherical vesicles composed of phospholipid bilayers, act as versatile drug delivery systems by encapsulating both hydrophilic and lipophilic compounds, enhancing solubility, and enabling targeted delivery to specific cells or tissues.

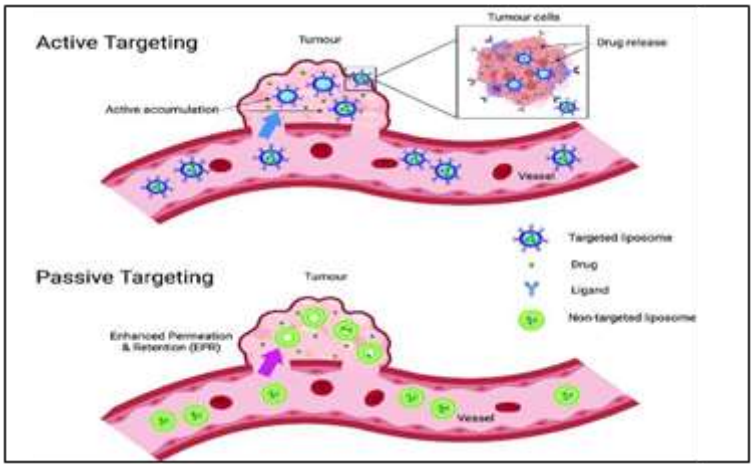


Fig No. 4 Targeting Action of Liposomes

- **Pre-compression parameters** :-

1. **Size Reduction by sonicator :-**

This technique made use of a Fisher Scientific sonic dismembrator (model F50) equipped with a probe sonicator. The strength supplied to the solution, which was maintained at 40%, can be chosen as the percentage amplitude. At room temperature, the liposomal suspension was sonicated for varying durations (14, 21, and 28 minutes) using a probe sonicator set to 40% amplitude and a depth of 19 mm measured from the vessel base.[3, 5,8]

2. **Calculating the polydispersity Index and Particle Size :-**

Photon correlation spectroscopy was used to measure the particle size at 25 ºC. equipped with a 4 mW He-Ne laser (633 nm) on a Malvern Zetasizer Nano Z® equipment The dispersant viscosity and refractive index were set to 0.8872 CP and 1.330 at 25 oC, respectively, after the samples were placed in a transparent disposable cuvette. Malvern Instruments' Dispersion Technology Software was used to analyse particle size. Before being characterised, all materials were stored in a refrigerator at 4 °C. [2,4]

3. Zeta potential Determination :-

The liposomal formulation's zeta potential was measured using a dynamic light scattering device. Using a dispersant refractive index of 1.33, the sample was examined at 25 °C. Disposable folded capillary cells were used in the current investigation to assess the liposomal formulation's zeta potential. Bubble-free samples are necessary for precise zeta potential measurement. At 25°C, measurements were made using a Malvern nano series zeta size device.[1,4]

4. HPLC Analysis :-

Reverse-phase gradient high-performance liquid chromatography was used to quantitatively analyse Ciprofloxacin . An Agilent 1100 System fitted with an X Terra TM RP18 (5 µm 4.6 * 250 mm column was used for the analysis. For Ciprofloxacin , UV detection was performed at 287 nm, while the column temperature was maintained at 25 ^{0}c A 70:30% v/v mixture of acetonitrile (ACN) and water solvent made up the mobile phase. Ten microlitres was the injection volume. Nine minutes was the allotted run duration, and the flow rate was 1.5 mL/min. It was discovered that the retention time was 6.5 minutes. For Ciprofloxacin the gradient approach yielded good peak characteristics and baseline resolution. Agilent Chemstation® analytical software 28 was used to analyse the peak area in order to quantify the drug concentrations. [14,15]

5. Using differential scanning calorimetry (DSC) to characterise liposomes:-

The purpose of the differential scanning calorimeter was carrying out thermal analysis. At a flow rate of 50 ml/min, nitrogen is utilised as a purging gas, giving the DSC cell exceptional sensitivity. Indium with 99.99% purity is utilised to calibrate the device meant for temperature and cell constant. For the baseline and heat capacity calibrations of sapphire and empty cells, respectively, heat was applied. Standard aluminium pans with pin holes were used to hermetically enclose powder samples weighing between 5 and 10 mg. When a pin hole is put in the lid of each pan, constant pressure is maintained throughout the analysis. Samples underwent a DSC heating protocol that heated them from 30 to 220 degrees Celsius at a rate of 50c/ min. [6,8,9]

6. Fourier Transform Infrared Spectroscopy :-

Spectral analysis is performed using a Nicolet iS5 Fourier transform infrared spectrophotometer equipped with an iD5 ATR diamond attachment. As a background, a little amount ofthe sample was combined with inert potassium bromide (KBr). Using a mortar and pestle, 500 mg of KBr and 5 mg of the dried liposomes are completely triturated before being squeezed into a semi-transparent film. In the spectrophotometer, the film was scanned with an average scan of 64 and 2 cm-1 resolution over a 400–4000 cm-1 region. The depths associated with the functional groups found in the sample molecules were further examined in the resulting spectrum.

- **Post –Compression Parameter :-** 1,3,9

1. Drug Loading Determination :-

HPLC was used to determine drug loading. 10 mL of a methanol &water combination (ratio 7:3) was used to dissolve 1 mL of the liposome formulation. After that, the solution was briefly sonicated. 0.22 µm filters are then used to filter the resultant solution. HPLC analysis was then performed on the filtrate. Depending on the drug to okra pectin ratio 29, different formulations displayed varying drug loading.

2. Entrapment Efficiency Measurement:-

Using remi, a the liposomal mixture was centrifuged for 18 minutes at 4000 rpm and 4 °C. To separate the free drug, use a cooling centrifuge. The liposomes in the suspending stage and the free medication on the centrifuge tube wall are both present in the supernatant. The supernatant was centrifuged one again for 38 minutes at 4 °C and 12,000 rpm. Consequently, a translucent mixture of liposome pellet and supernatant was obtained. Before further research, the liposome pellet was re-dispersed in distilled water. After 5 minutes of sonication, the liposomes free of unentrapped free drug were combined with 10 millilitres of a methanol:water combination (7:3 v/v). Sonication caused the liposomes to become disturbed and release. The medication was released by disrupting the liposomes by sonication. The drug entrapment caused by the discharge was identified. The HPLC system was used to estimate the quantity of ciprofloxacin . Using the formula Wc / Wt × 100, the percentage entrapment efficiency was calculated. represents the quantity of drug content (entrapped) in the liposomes, while Wt represents the total amount of drug in the dispersion. [4,7]

$$\text{Entrapment Efficiency Percentage} = Wc / Wt \times 100$$

3. Redispersibility:-

Using a remi cooling centrifuge , the liposomal formulation was centrifuged at 4000 rpm for 18 minutes at 4 °C to separate the free drug. The resulting transparent solution of supernatant and liposome pellet was then diluted to 10 ml with deionised water, and the solution was then taken in 14 ml Eppendorf tubes and vortexed on a vortex mixture at speed 3 for 5 minutes. Following vortexing, the solution was then placed in transparent cuvettes, and particle size was measured after 10ml while using deionised water. After that, the solution was transferred into 14 ml Eppendorf tubes and vortexed for five minutes at speed 3 on a vortex mixture. The solution was vortexed, then placed in clear cuvettes, and after ten minutes, the particle size was measured. [9]

4. Studies on In-vitro Dissolution:-

In-vitro release studies were carried in USP Type- II (Paddle)dissolution apparatus was used to perform in-vitro dissolutions studies for the liposomes. The release behavior of the liposomal formulation and pure drug was studied in distill water (containing 0.3 gmof sodium lauryl sulfate). The media was conditioned at 37 ºC with rotation speed of 75 rpmto confirm sufficient wetting. A sample of 10 mlfrom the liposomal formulation was taken in dissolution

medium and is sustained at a temperature of 37 ± 0.5 ºC with rotation speed of75 rpm.Small aliquots (5ml) of sample with help of stainless steel cannula were taken from each dissolution vessel at regular time intervals of 5, 10,15, 30, 45, 60, 90 and 120min.

To maintain a constant total volume of dissolving media after sample removal, an equivalent volume of fresh media was added. After passing through 0.22 µm syringe filters, the dissolution samples were prepared for HPLC analysis. Calculations become easier as a result of maintaining the media's steady volume. The release profile of the liposomal formulations was examined in triplicate, and the mean was taken as the absolute value (n=3).[1,3]

- **Design of Experiments (DOE):**

Drug: okra pectin ratio ratio, hydration volume, hydration time, and sonication time were chosen as independent variables in order to assess the impact of liposomal formulation process factors on different product qualities. [14,15]

Table 1: The input variable and their ranks and units Levels of independent variables

	Levels		
Independent variable	**Low**	**Medium**	**High**
Drug : Okra pectin ratio	0.1:2	0.1:3:5	0.1:6
Time spent hydrating (min)	15	30	45
Volume of hydration in ml	90	105	120
Sonication duration (min)	14	21	28

Table 2 : composite design central with independent input variables composition

Composition	**Hydration volume (ml)**	**Hydration time (min)**	**Drug : okra pectin ratio**	**Sonication time (min)**
1	108	25	0.1:3:5	20
2	120	40	0.1:2	13
3	80	40	0.1:2	25
4	80	40	0.1:6	25
5	108	25	0.1:3:5	20
6	80	30	0.1:3:5	20
7	108	30	0.1:6	20
8	80	15	0.1:6	13
9	120	15	0.1:6	25
10	120	40	0.1:6	13
11	105	30	0.1:2	20
12	105	30	0.1:3:5	25
13	120	15	0.1:2	25
14	105	40	0.1:6	20
15	105	30	0.1:3:5	13
16	**120**	**30**	**0.1:3:5**	**20**
17	80	15	0.1:2	13

Results And Discussion:

Contour Plots And Surface Response Plots Examine The Impact Of Process Parameters On Quality Attribute

Table 3: The Liposomal Formulations' Results For Every Quality Attribute

1. **Effect Of Process Parameters On Particle Size**

Composition	Particle size (nm)	PDI	Peak shape	% Drug Loading	Drug % Entrapment efficiency	Redispersion (nm)
1	186	0.412	2	107.95	**78.19**	140
2	168	**0.674**	3	74.96	55.31	142
3	135	0.39	3	75.74	63.17	105
4	**99.5**	0.160	1	**88.45**	2.91	105
5	199	0.220	1	93.91	57.78	245
6	208	**0.135**	1	111.52	43.82	166
7	184	0.312	2	104.36	18.79	173
8	234	0.350	1	96.21	18.80	125
9	169	0.192	1	168.98	26.00	180
10	121	0.225	3	97.04	56.20	132
11	134	0.501	2	90.48	75.72	110
12	169	0.502	3	92.32	50.70	154
13	121	0.395	2	91.80	50.47	105
14	134	0.380	2	74.56	77.40	106
15	187	0.390	3	108.12	77.32	142
16	164	0.342	2	108.22	75.45	138
17	**290**	0.427	3	**91.84**	57.32	155

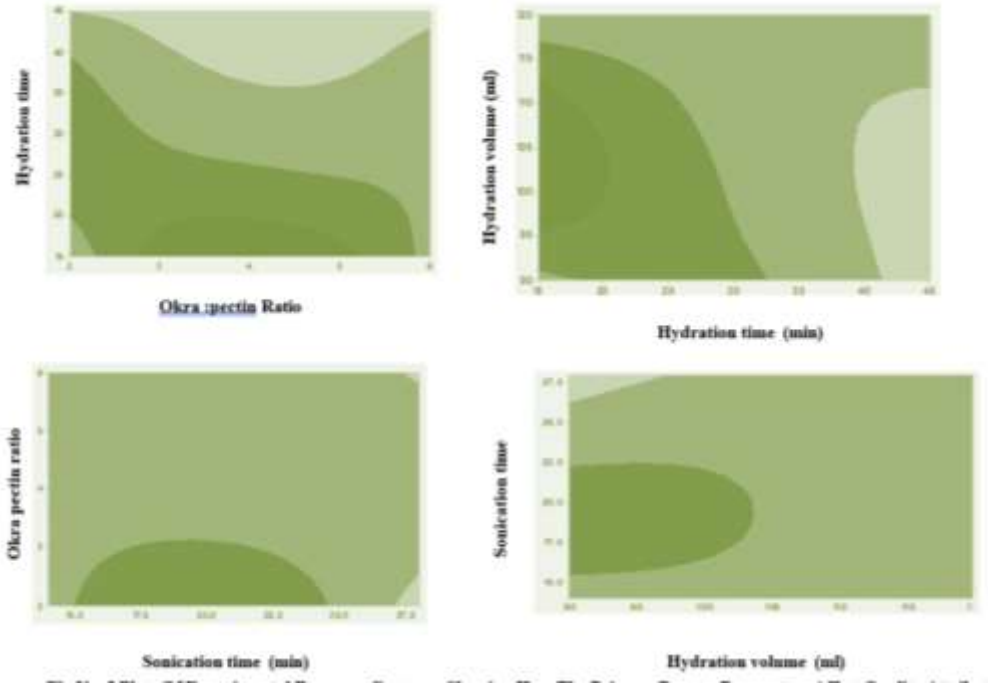


Fig No. 3 Plots Of Experimental Response Contours Showing How The Primary Process Parameters Affect Quality Attributes, Specifically Particle Size

2. Process parameters' Impact on Entrapment Efficiency:-

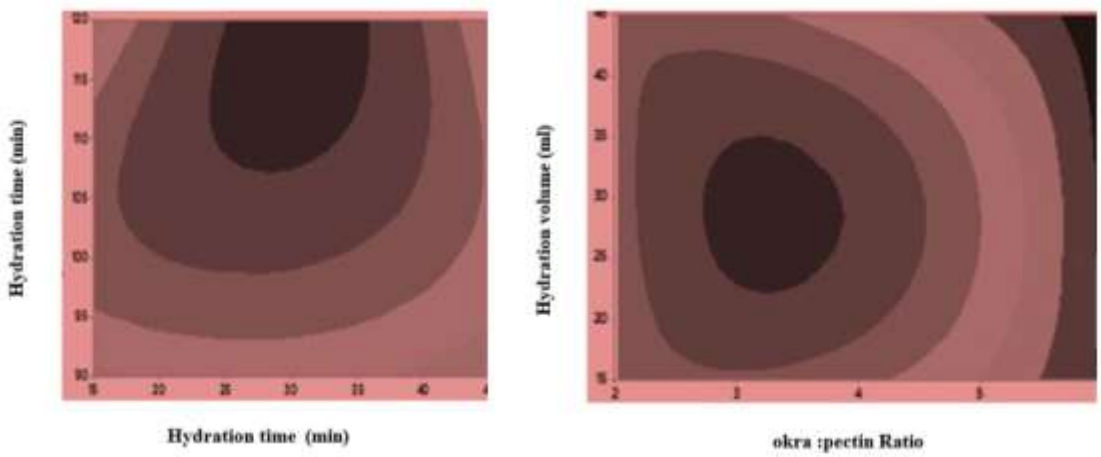
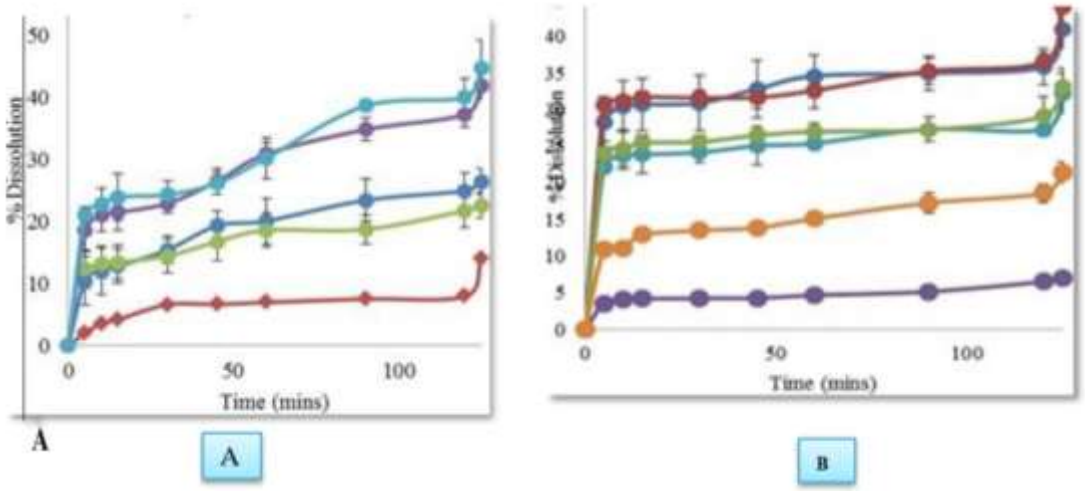


Fig No.4 Experimental Response Contour Plots Depicting The Influence Of The Main Process Parameters On Quality Attribute Entrapment Efficiency

3.In-vitro Dissolution Studies: -

One of the principal factors affecting oral absorption is the dissolution rate. According to Noyes-Whitney equation, increase in the surface area of particles by size- reduction enhances evaluate the effect of changing process parameters on the dissolution rate of Ciprofloxacin liposomal formulation. Dissolution studies performed for pure Ciprofloxacin in water having SLS showed dissolution profiles having 21.90%, 13.98% and 7.00% drug release. All the formulations with the equivalent amount of drug showed improved dissolution in comparison to pure drug release. This significant enhancement in the dissolution rate is addition to decrease in the particle size.All the Compositions having drug: okra pectin ratio 0.1: 3.5 has shown percentage drug release ranging from 22.61 % to 44.69 % in the composition 14 has shown 44.69% drug release and composition 6 has shown 22.61% drug release. Thus, it can be interfered that percentage drug release of liposomal formulation is increased in comparison to the pure Ciprofloxacin which was 13.98%. It can be inferred from composition 14 which has shown the best dissolution that the formulation which has highest hydration time showed more dissolution. The particle size in range of 120 - 190 nm showed better dissolution. While from composition 6 which showed slowest dissolution, it can be inferred that the lower hydration time affects the dissolution The particle size is the other factor affecting the dissolution.



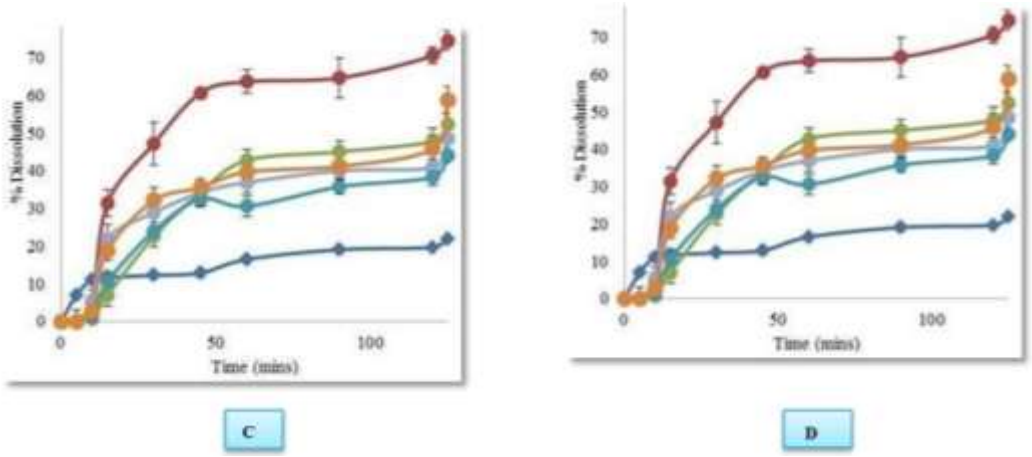


Fig No.5 dissolution profiles of liposomal formulations having different drug: okra pectin ratio in deionized water (0.3 gm sls) rpm 75 a) ratio 0.1: 3.5 b) ratio 0.1: 3.5 c) ratio 0.1: 6 d) ratio 0.1: 2

3. Fourier Transform Infrared Spectroscopy (FTIR):-

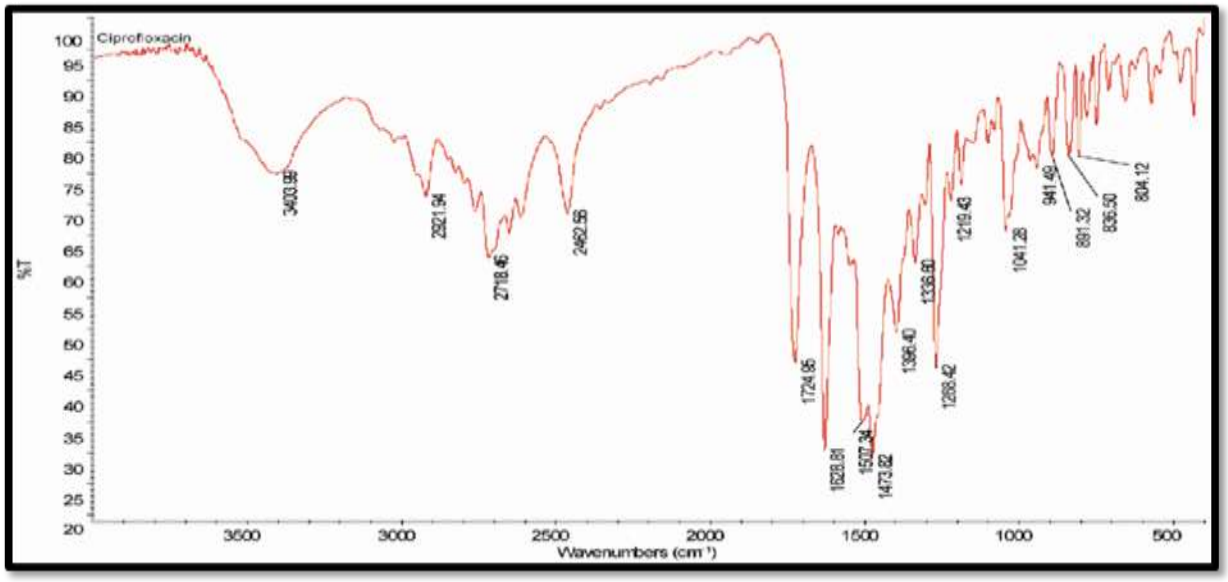


Fig No. 6 FTIR Analysis of Drug (Ciprofloxacin) Liposomes Formulation

Wave number (cm^{-1})	**Types of Vibration**	**Functional group**
3403.99	O-H	Alcoholic , Phenolic Hydroxyl group
2718.46	C-H	Methyl and methylene
1724.95	C=O	Carboxylic acid
1628.81	C=C	Aromatics
1473.82	C-H	Amorphous polysaccharides
1288.42	C-OH	Cellulose and Hemicellulose
1041.28	C-C-O	Lignin, Hemicellulose .

4. Differential Scanning Calorimetry (DSC):-

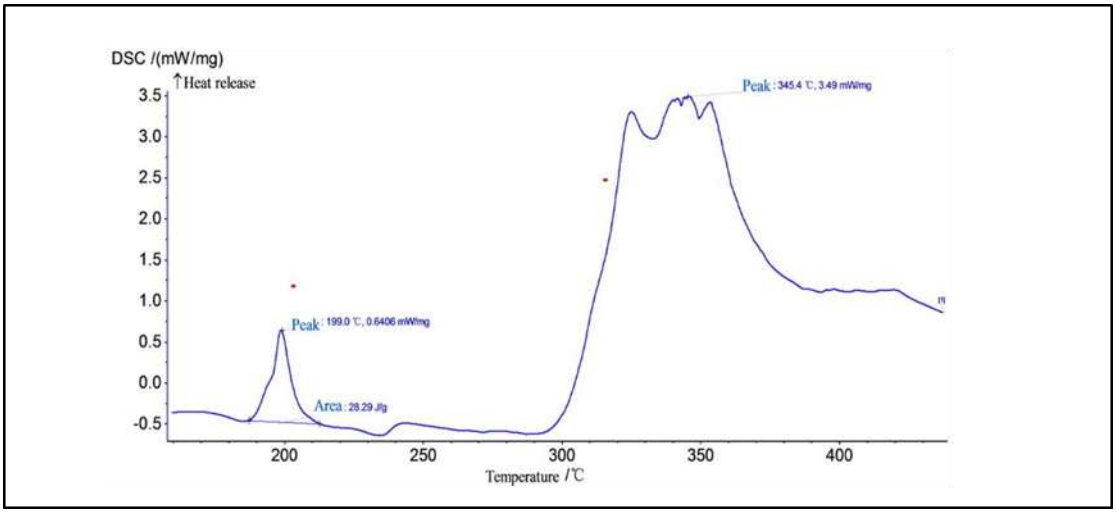


Fig No. 7 DSC Analysis of Ciprofloxacin Liposomes Formulation

The DSC curve of Ciprofloxacin show sharp endothermic peak (345.4 0c) corresponding to its melting point , Indicating its pure in nature .The melting point of Ciprofloxacin 323.15 0c matches with the Standard value and show no any interaction between drug and polymer.

Conclusion :-

The current study demonstrated the usefulness of the application of design of experiments to gain a comprehensive under- standing of formulation and processing parameters affecting liposomes formulations prepared via thin film hydration technique .The particle size of the liposomal formulation was found to be between ranges of 99.5 nm to 290 nm The entrapment efficiency was found to be 2.4% to 77.41% for the liposomal formulations. Entrapment efficiency is greater than 70 with drug: Okra pectin ratio 0.1: 3.5 and higher hydration volumes DSC thermogram of Ciprofloxacin, showed sharp endothermic peak however, the Ciprofloxacin loaded liposomes showed of melting peak for Ciprofloxacin, indicating the molecularly dispersion of Ciprofloxacin in liposomes and significant physical interaction between Ciprofloxacin and lipid components formulations having higher hydration time and less particle size showed enhanced drug release in comparison to the drug release of equivalent amount of Ciprofloxacin. The drug to Okra pectin ratio and hydration volume has significant impact on drug entrapment capacity of the formulation and in- vitro dissolution rate.

Acknowledgement :-

The authors are grateful to the Sumantai Institute of Pharmacy, Bambrud kh, Pachora dist- Jalgaon for providing facilities and assisting us through the process

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