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FORMULATION AND EVALUATION OF BIFONAZOLE-LOADED NANOCOCHLEATES

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ABSTRACT:-

The goal of the current invention is to create and evaluate a formulation for bifonazole nanoliposomes and nanocochleates. Over 70% of people will at some point in their lives experience dermatophytosis, a fungal infection that is common around the world and affects people of all ages and genders. Conventional dosage form which are available in market for treatment of tinea pedia are insufficient to supply drug to the site, they have side effects, poor permeability, toxicity and lower therapeutic index. In the current study, bifonazole-loaded nanocochleate was prepared in stages: Initially, ten batches of liposomes were made with varying ratios of phosphatidylcholine and cholesterol and 1:1 ratio of organic solvents like methanol and chloroform by using a modified thin-film hydration method, Next, PBS 6.8 was used to hydrate the liposomes. Ten batches of liposomes were evaluated for their percentage of drug entrapment efficiency, drug content, and percentage of in vitro drug release.The optimized formulation LF8 showed entrapment efficiency 88.74 %; drug content 90.30%; particle size, 152.6 nm and in vitro drug release, 89.41 % at the end of 8 hour. Entrapment efficiencies and drug content were found to increase with increase in phospholipid and cholesterol concentration. The SEM analysis of liposomes shows the spherical surface of the particles. The formulation of nanocochleates is done by trapping method using calcium chloride as a bridging agent. Three NC formulations are created by varying the bridging agent's concentration (cacl2). NCF2 formulation showed better results as compared to other. Stability studies revealed no significant changes in visual appearance in gel comparison to initial characteristics.

KEYWORDS: liposomes, thin film hydration, nanocochleates, trapping method.

INTRODUCTION:

Nanotechnology is the systematic engineering and manipulation of particulate matter into a physical state ranging from 1 to 100 nm, which may then be reassembled or rearranged to build nano-systems with improved functioning. Because of the development and application of nanotechnology. [1] Nano-carriers have the ability to improve the effectiveness of antifungals by attaching to the wall of fungal cell and so raising the drug concentration near fungus.[2] Because nanotechnology focuses on the targeted location and effectively delivers controlled

medication release, it is necessary for better medicine and drug formulations. Through the application of nanostructures and nanophases to enormous variety of scientific fields, nanotechnology has proven to be able to bridge the gap between the biological and physical sciences; this has proven especially beneficial for nanomedicine and nano-based drug delivery systems, where these particles play a major role.[3] Liposomes are defined architecturally as concentric bleeder vesicles, in which an aqueous volume is entirely surrounded by a membraneous lipid bilayer. Membrane construction usually involves the usage of phospholipids, which are molecules containing a hydrophilic head group and a hydrophobic tail group. Water repels the tail, which is composed of a lengthy hydrocarbon chain, whereas it attracts the head group.[4] liposomes have Low solubility, Short half-life and Sometimes phospholipid undergoes oxidation and hydrolysis-like reaction.[5]

Cochleates are employed in delivery of vaccines by transferring peptides and antigens. Cochleates are microstructures that resemble cigars that are created when divalent cations and tiny, negatively charged liposomes contact. The cation functions as a lipid bilayer bridging agent. Calcium aids in the formation of massive multilayer sheets by liposome fusion.[6] nanocochleates are more stable because of their reduced oxidation. They can be treated by freeze drying, which allows them to be kept for extended periods of time at room temperature. This would be advantageous prior to administration for international transportation and storage. Unlike liposomes, which have their structures broken by lyophilization, they can maintain their structure even after lyophilization. [7] They might show that they can effectively integrate into the lipid bilayer of hydrophobic medicines' cochleate structures. [8] Pellizzari was the first to describe tinea pedis in 1888, although it has been a problem for individuals for a very long time. The dermatomycotic disease known as "tinea pedis et manuum" or "Celal Muhtar" sickness was studied by renowned dermatologist Dje´laleddin-Moukhtar (1892). The infection was dubbed "trichophytosis" by Djelaleddin-Moukhtar (1892) who also provided information on its genesis, differential diagnosis, prognosis, and therapy. [9,10] Accurate diagnosis and successful treatment of tinea pedis are essential. Tinea pedis mimics several foot dermatological disorders. This illness commonly spreads by autoinoculation, which also causes tinea manuum, tinea inguinalis, and tinea unguium. Inappropriate treatment can lead to bacterial infections and a range of allergic issues. Tenia pedia is the most prevalent cause of bacterial entry for leg cellulitis and the most common cause of id reactions.[11]

Bifonazole [1-[[1,1’-biphenyl)-4-phenylmethyl]-1H-imidazole) (BFZ) is an imidazolic antifungal drug indicated against the skin. It has a wide range of antimicrobial action in vitro

against moulds, yeasts, dermatophytes, dimorphic fungi, and some Gram-positive bacteria. Bifonazole is a small-molecule drug that is classified as therapeutic in the biomedical fields of infectious diseases, skin diseases, and musculoskeletal diseases. It is effective against a variety of fungal diseases because it particularly targets fungal CYP51A1. such as tinea pedia.[12] Potential delivery vehicles for antifungal medications used to treat tinea pedia include liposomes and nanocochleates. However, nanocochleates may provide a longer-lasting, more regulated release of the antifungal medication and a higher dose frequency than liposomes. Compared to liposomes, nanocochleates may be more stable, especially when it comes to temperature fluctuations. This could help with shelf life and storage. Compared to typical gels, nanocochleates gel may offer regulated release and deeper penetration, which might increase the antifungal medication's overall efficacy.[13]

Materials Methods:-

Materials

Bifonazole was obtained as a gift sample form Vital Lab. Pvt. Ltd. Gujarat, Phosphatidylcholine was obtained from Lipidome Life Science Gujarat, and all other excipient used in the present study were of analytical grade.

Methods

Preparation of Liposomes by thin lipid film hydration technique

Using a rotary flash evaporator and the thin film hydration process, ten liposome formulations were created. The process of thin film hydration was used to create liposomes. In overall, soy lecithin and cholesterol was dissolved in varying ratio in a 1:1 chloroform-methanol solution, and then Bifonazole was added. A 250 ml round-bottom flask containing the drug solution was connected to the rotating vacuum evaporator. The flask was maintained submerged in a water bath with a thermostat that was set at 40°C and revolved at a speed of around 100 rpm. The procedure was kept going until the flask wall was covered with a dry lipid coating and all of the liquid had evaporated from the solution. Phosphate buffer with a pH of 6.8 was added to the round-bottom flask after the thin layer had developed. After 15 minutes of vortex agitation, the suspension was subjected to an hour of sonication. [14]

Table 1: Formulation of liposomes

Ingredients	Formulation Codes									
	LF_1	**LF_2**	**LF_3**	**LF_4**	**LF_5**	**LF_6**	**LF_7**	**LF_8**	**LF_9**	**LF_{10}**
Bifonazole (mg)	100	100	100	100	100	100	100	100	100	100
Phosphatidylcholine (mg)	100	200	300	400	200	400	500	800	900	700
Cholesterol (mg)	100	100	100	100	200	200	200	300	300	300
Chloroform (ml)	10	10	10	10	10	10	10	10	10	10
Methanol (ml)	10	10	10	10	10	10	10	10	10	10
PBS 7.4 (ml)	15	20	20	20	20	22	25	25	25	30

Preparation of Nanocochleates by trapping method

The trapping approach was utilized to create nanocochleate filled with Bifonazole. Each of the solutions of calcium chloride (0.1M) was added dropwise while being vortexed into a separate 25 ml of optimized liposomal suspension. The production of nano-cochleate caused the solution to become turbid instantly. The produced nanocochleate suspensions were refrigerated for about six hours or overnight in order to stabilize them. A nanocochealates sediment was created by centrifuging the prepared nanocochleates suspension for 15 minutes at 20,000 rpm at -4°C. This sediment was then lyophilized and stored. [15,16]

Evaluation / Characterization :

A. Preformulation studies:

1) The calibration curve had been generated using a UV-Vis spectrophotometer.

a. Bifonazole Standard Stock Solution

The 10 mg of drug were precisely weighed, and dissolved in methanol 100 ml, and then 10 ml of this stock solution were taken out and put into a 100 ml volumetric flask. Methanol was used to create a volume in order to obtain a standard stock solution with 10 µg/ml.[17]

b. Bifonazole Standard Graph

Methanol was used to generate a series of dilutions (2, 4, 6, 8, 10 µg/ml) from this standard stock solution. The absorbance of these solutions was determined spectrophotometrically using

a 1 cm quartz cuvette in a UV-visible spectrophotometer (Shimadzu UV 1800) against a blank of methanol at 254 nm for bifonazole. Plotting absorbance measurements against their corresponding concentration allowed for the establishing a typical calibration curve. [17]

2) FTIR-Based Drug-Excipient Compatibility Study:

In order to choose appropriate, chemically compatible excipients, IR spectroscopy may be utilized to analyze and forecast any physicochemical interactions between various components in a formulation. The current investigation set out to see whether the medicine and carriers interacted in any way. The subsequent infrared spectra were captured:

- Bifonazole
- Combination of calcium chloride, phospholipid, drug, methyl paraben, propyl paraben, glycerine, methanol, chloroform, propylene, glycol, and Carbopol.

The Perkin Elmer FTIR instrument was used to conduct the FTIR investigation. Excipients and medication were consumed in the same ratio (1:1). After that, the FTIR graphs were examined in the near-infrared band, or between 4000 cm-1 and 400 cm-1. [18,19]

B. Evaluation Of Liposomes:

1)Determine the Entrapment Efficiency: Liposome drug entrapment effectiveness The centrifugation technique was used to determine the liposome entrapment efficiency. One millilitre of aliquots of liposomal dispersion was centrifuged at 3500 rpm for 90 min using a laboratory centrifuge (Remi). To isolate the non-entrapped bifonazole, the clear supernatants solution were carefully removed, and the absorbance at 254 nm was measured. The phosphate buffer pH 6.8 was used to dilute the sediment in the centrifuge tube to a volume of 100 ml, and the absorbance of this solution was measured at 254 nm. Total bifonazole in 1 ml dispersion was determined by measuring the quantity of the drug in the sediment and supernatant. The percentage of drugs entrapped was computed using the formula.[20]

2)Microscopic Determination: Using an optical microscope, a drop of liposomal dispersion was placed on a glass slide, cover slip was placed on the drop and inspected under the microscope to estimate the particle size of the liposomal formulation.

3)Zeta Potential Determination: Zeta sizer was utilized to ascertain the improved formulation's zeta potential. The materials were mixed on a magnetic stirrer for one minute after being diluted 1:100 with an appropriate solvent (PBS). Every study was conducted three times. The zeta potential is obtained by passing a voltage over two electrodes at opposite ends of a particle-dispersed cell. The electrode with the opposite charge attracts charged particles.[21]

4)In vitro drug release study: A 250 ml beaker containing 100 ml of phosphate buffer was used for the release investigations. A 250 ml beaker was filled with 100 ml of phosphate buffer at a pH of 6.8. The medium was brought to room temperature (37±5 ^{0}C.) and the beaker was put together utilizing a magnetic stirrer. After removing the dialysis membrane, one end of it was sealed. Following the release of the non-entrapped bifonazole, the dialysis membrane was filled with liposome dispersion and the opposite end was sealed. The sample-containing dialysis membrane was submerged in the medium. At predetermined intervals, 10 ml aliquots were removed, filtered, and the device was promptly refilled with the same amount of brand-new buffer medium.[22]

5)Drug Content: UV spectroscopy was used to evaluate the drug content of the liposome. After two minutes of vigorous shaking, liposomes were dissolved in the methanol and phosphate buffer (pH 6.8) combination. A milliliter of the resulting solution was collected, dissolved in methanol, and diluted with PBS 6.8 to a volume of 10 ml. A UV spectrophotometer was then used to record the absorbance at 254 nm, and the concentration was calculated using the standard calibration curve calculation.[23]

C. Evaluation Of Bifonazole Nanocochleate

1. **Determination of Entrapment Efficiency:** A centrifuge tube composed of polypropylene was filled with 100 µL of bifonazole-loaded nanocochleate. The tube was spun at 6000 rpm for 20 minutes at 40 °C, and the sediment and supernatant separated. To enable the release of Bifonazole from the cochleates, 60 µL of EDTA (pH 9.5) was introduced into the BN sediment. To extract the medication even further, one ml of ethanol was included in the combination above. Using a UV spectrophotometer (Shimadzu UV1800), the clear solution that resulted was suitably diluted with phosphate buffer pH 6.8. The absorbance was then measured at 254 nm. EE was determined by measuring the conc. of the free (untrapped) drug in the supernatant. [24,25]

$$(\%)\ EE = (\text{Amount of drug entrapped})/(\text{Total amount of drug present}) \times 100$$

2. **Determination of Zeta Potential:** Zeta sizer was used to calculate the improved formulation's zeta potential. The materials were mixed on a magnetic stirrer for one minute after being diluted 1:100 with an appropriate solvent (PBS). Every study was conducted three times. Applying voltage across a pair of electrodes at either end of a cell containing particle

dispersion yields the zeta potential. The electrode with the opposite charge attracts charged particles. [25,26]

3. **Determination of Particle Size and Poly-dispersity Index:** Particle size and PDI were measured at 25°C using a Zeta sizer device. The mean particle diameter and particle size distribution are obtained using this method. Malvern Instruments provided the software that was used for the analysis. Samples were kept in a refrigerator at 4°C before to analysis.
4. **In Vitro study**: 100 millilitres of phosphate buffer were contained in a 250-millilitre beaker for the release experiments. A 250 ml beaker was filled with 100 ml of phosphate buffer at a pH of 6.8. The medium was brought to room temperature (37±5 ^{0}C) and the beaker was put together utilizing a Magnetic stirrer. After removing the dialysis membrane, one end of it was sealed. The dialysis membrane was filled with nanocochleates dispersion after the non-entrapped bifonazole was separated, and the opposite end was sealed. The sample-containing dialysis membrane was submerged in the medium. At predetermined intervals, 10 ml aliquots were removed, filtered, and the device was promptly refilled with the same quantity of brand-new buffer medium.[27,28]
5. **Drug Content:** At 25°C, the dispersed nanocochleate suspension is centrifuged for 40 minutes at 15,000 rpm. The complimentary medication After an appropriate dilution, the concentration in the supernatant can be measured using a technique like UV-Vis spectrophotometry.

$$\text{Drug Content} = \frac{sample\ absorbance}{standard\ absorbance} \times 100$$

6. **Scanning Electron Microscopy:** Scanning electron microscopy (SEM) was employed to assess the morphology of the surface. (roundness, smoothness, and aggregate formation) of nanocochleates with carriers. Samples for the SEM were X 2000 magnified and put on metal studs.[28,29]

RESULT AND DISCUSSION:

A. Preformulation Studies:

1. Physical Characteristics:

a. Physical Appearance of drug:

The drug sample have white colour, odourless and crystalline powder nature which is as per specification of EP/BP.

b. Melting Point:

Bifonazole's melting point was discovered to be 149 ℃, which was in conformity with the reported range 147-151 ℃.

c. Solubility of drug: Solubility of drug is insoluble in water, slightly soluble in Ethanol and Chloroform, soluble in Methanol and PBS 6.8.

2. Standard calibration curve of drug in UV spectrophotometer

The UV absorbance of bifonazole standard solutions in a range of 2-10 µg/ml of drug in Methanol showed linearity at λ max 254 nm. The linearity was plotted for absorbance (A) against concentration (C) with R^2 value 0.9985 and with the slope equation y=0.0663x + 0.0909. The absorbance values and standard curve was given in below figure.

3. FTIR studies of Drug and Excipients

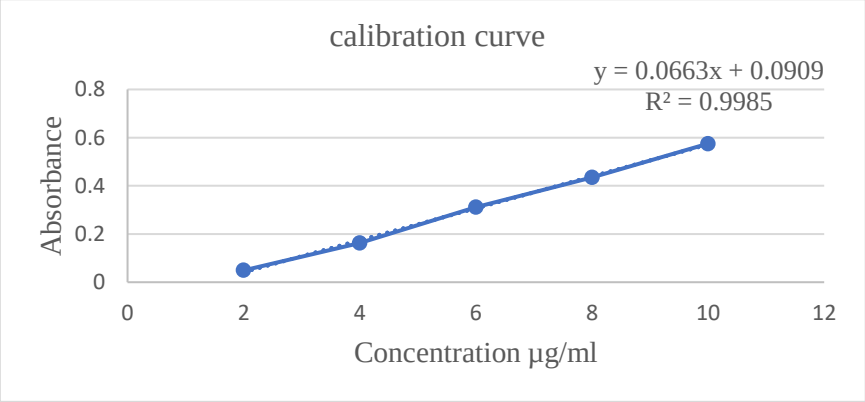

Figure 1: Calibration curve of Bifonazole

The compatibility study between the drug and other excipients was evaluated using FTIR. FTIR spectra was compared and checked for any shifting in functional groups peaks and non-

involvement of functional group. From the spectra it was cleared that no interaction between selected drug and phospholipid and other excipient was observed. Hence the selected excipient were found to be compatible for nanocochleate gel formulation.

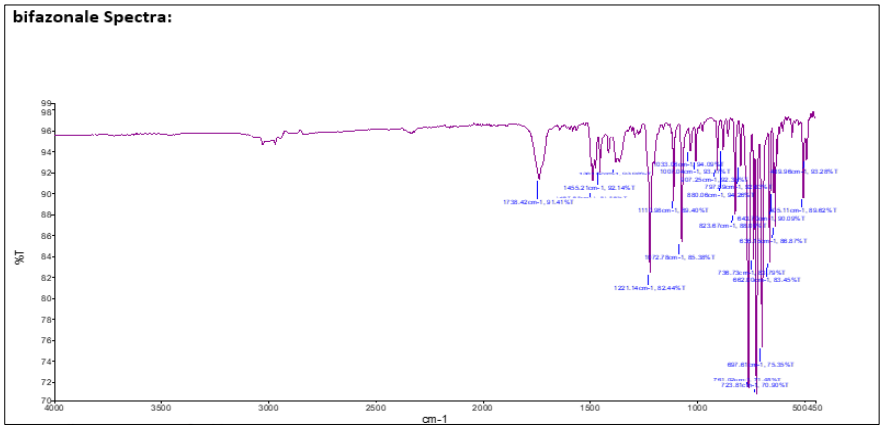

Figure 2: FTIR graph of bifonazole

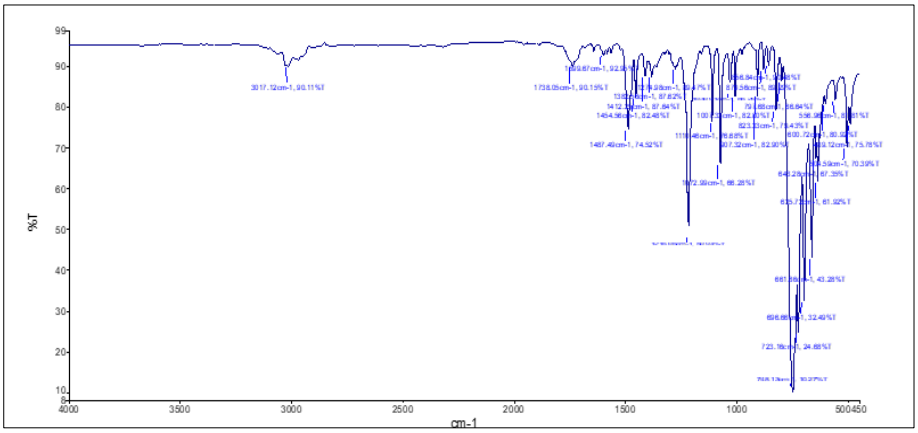

Figure 3: FTIR graph of bifonazole + All excipient

B. Evaluation of liposomes:

1. **Physical appearance, pH, drug content, Drug Entrapment Efficiency of liposomal formulation:**

Table 2: Physical appearance, pH, %drug content, Entrapment Efficiency of liposomal formulation

Formulations	**Physical Appearance**	**pH**	**Drug Content (%)**	**Percentage of drug Entrapment Efficiency (%EE)**
LF1	Yellowish white	6.15	68.29	65.52
LF2	White	6.20	77.70	68.22
LF3	Yellowish white	6.23	80.72	74.97
LF4	Slightly Yellowish white	6.30	81.02	79.44
LF5	Yellowish white	6.32	79.90	81.27
LF6	Yellowish white	6.38	82.12	80.67
LF7	Yellowish white	6.46	81.27	79.19
LF8	Yellowish white	6.48	90.30	88.74
LF9	Yellowish white	6.43	81.08	80.01
LF10	Yellowish white	6.40	78.17	76.64

All formulations were observed visually and was found to be yellow-white dispersion having pH in range of 6.8. The drug content of all batches was in range of 68.29-90.30 % where the highest drug content showed by the F8 batch i.e.,90.30% Entrapment efficiency of ten liposomal batches were performed by centrifugation method and drug entrapment efficiency of all batches were found in range of 65.52% - 88.74 %the batch F8 shows highest entrapment efficiency i.e., 88.74% while F1 shows lowest entrapment efficiency i.e.,65.52%

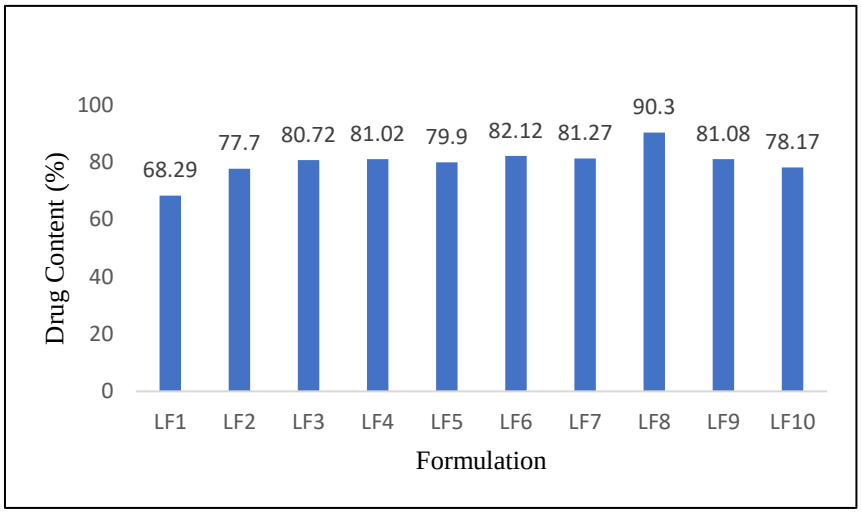

Figure 4: All liposomal batches Drug content

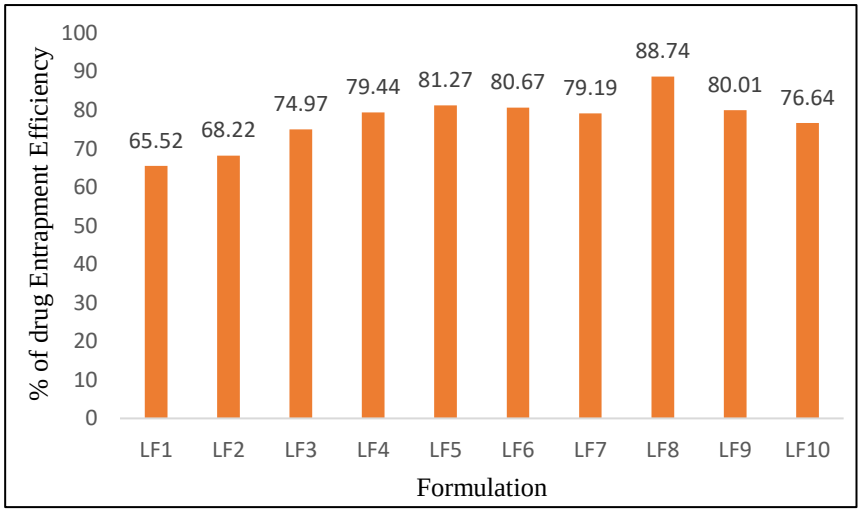

Figure 5: % Drug Entrapment Efficiency of all liposomal batches

2. In vitro drug release:

Table 3: In vitro drug release of LF1 to LF10

3.

Time	% Cumulative drug release									
	LF1	**LF2**	**LF3**	**LF4**	**LF5**	**LF6**	**LF7**	**LF8**	**LF9**	**LF10**
0	0	0	0	0	0	0	0	0	0	0
1	4.11	5.25	5.59	6.24	6.75	5.99	7.35	8.28	7.15	6.15
2	10.93	14.07	12.41	15.06	17.57	16.57	18.07	21.43	18.76	13.66
3	28.99	30.13	32.47	34.12	37.63	25.63	34.03	38.69	31.36	29.72
4	40.29	44.43	48.77	51.42	50.93	52.17	49.33	55.79	50.66	40.02
5	53.1	54.24	57.58	58.04	60.47	61.98	56.14	64.6	58.47	58.83
6	62.64	64.78	61.12	70.77	68.28	65.52	68.52	77.14	67.01	70.37
7	71.14	72.28	68.62	75.27	76.68	73.81	70.18	85.64	80.51	74.87
8	74.93	78.07	75.41	82.01	80.27	82.02	81.7	89.41	82.3	81.06

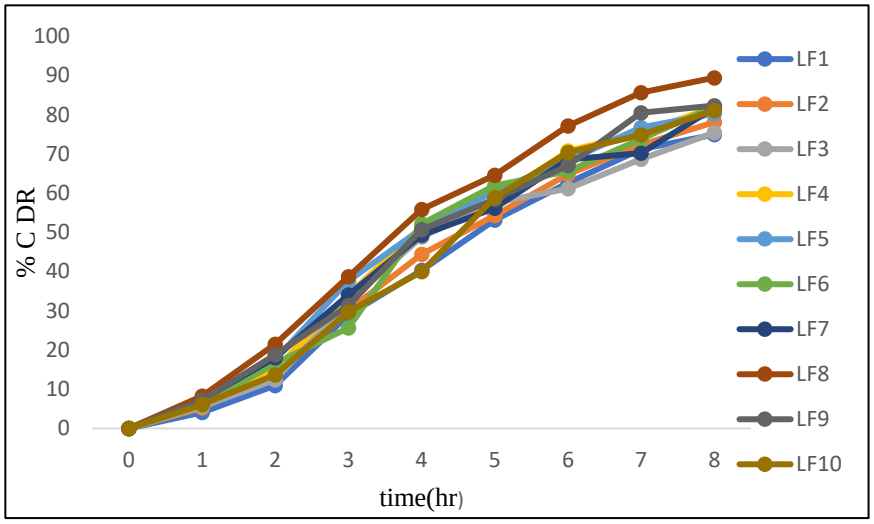

Figure 6: Percentage of drug release of LF1 to LF10

The in vitro release of ten Bifonazole liposomal formulations were performed and measured the release at 1 hr., 2 hr., 3 hr. upto 8 hrs. After examining percentage cumulative drug release graph of all formulations, the formulation F8 shows highest In- vitro drug release i.e., 89.41 % . From the all-liposomal formulations, F8 shows high drug content, entrapment efficiency and in vitro drug release on basis of these LF8 batch it was optimized. This optimized formulation further evaluation study like particle size, SEM and zeta potential were reported. The optimized formulation of liposomes was selected for further Nanocochleate formulations.

4. Microscopic Determination:

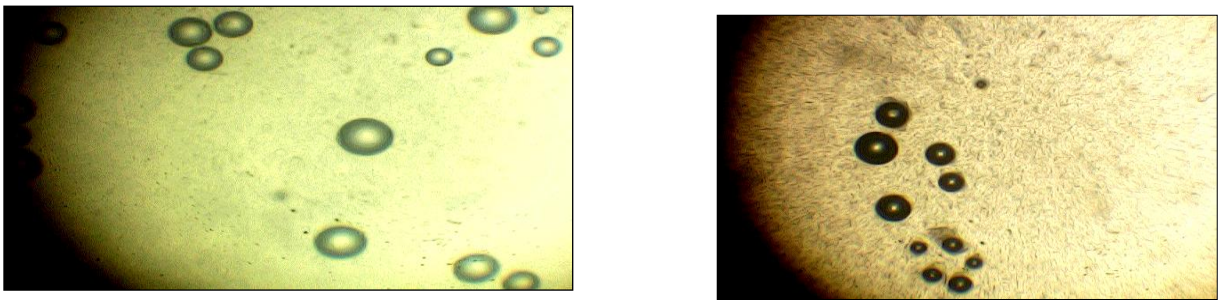

Figure 7: Microscopic image of optimized batch

5. Scanning-Electron Microscopy:

The shape and surface morphology of Liposomes droplet was determined using SEM showing the intact nature. The SEM images of optimized batch (LF8)showed that a formulated liposomes was spherical in shape**.**

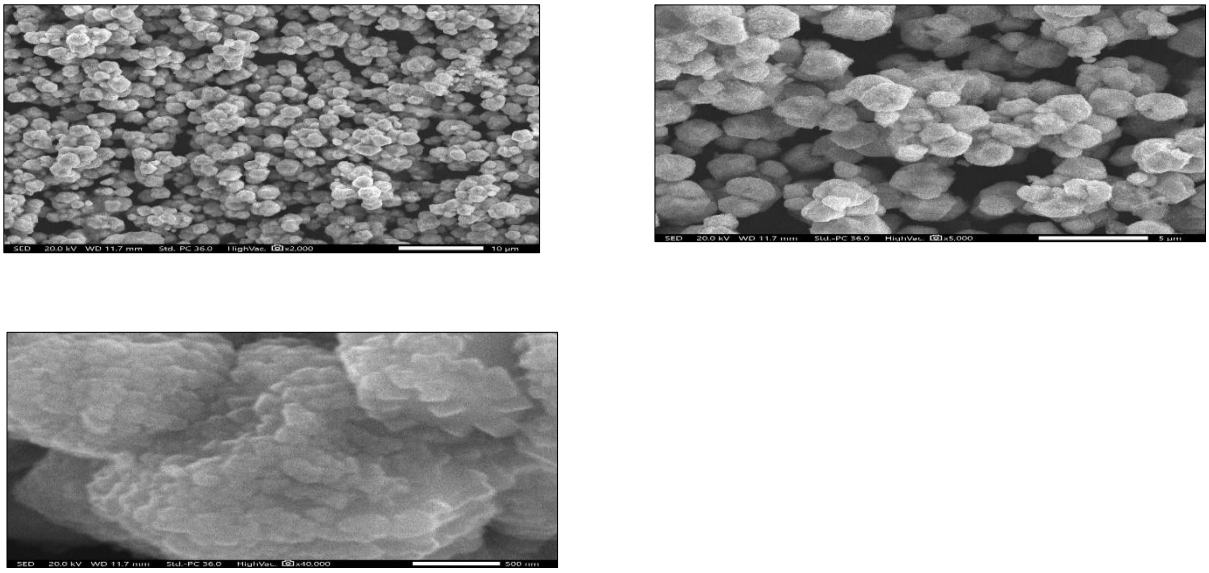

Figure 8: SEM images of liposomes

6. **Particle size and polydispersity index:**The particle size of optimized batch is found to be 152.6 nm (Fig7.11) and polydispersity index was determined to be 0.415. A low polydispersity index indicates particle size uniformity within the formulation. The particles size of liposomes should be in between 10-500 nm. The nanometer particle sizes of the liposomes formulation influences the good antifungal activity by increasing solubility of drug which increases the bioavailability of drug.

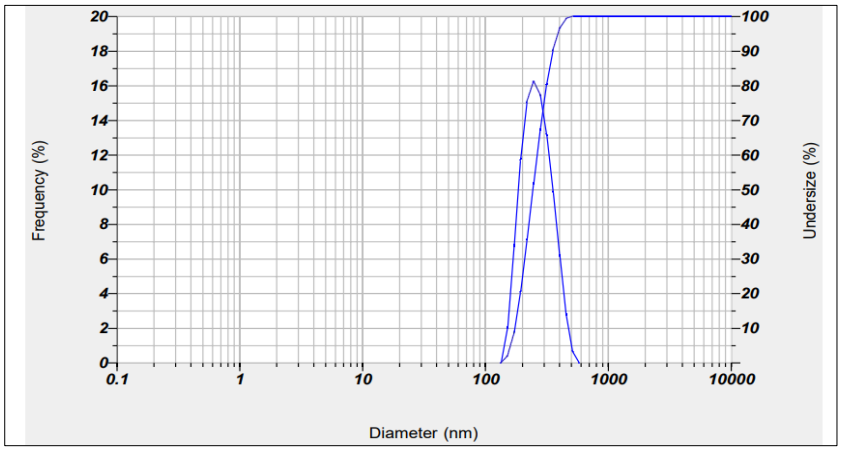

Figure 9: Particle size of optimized batch of liposomes

7. **Zeta Potential:**

The stability of liposomes were determined form zeta potential. Zeta potential of liposomes was shown in fig.7.11. Zeta potential value of LF8 was determined to be -24.0 mV. The surface charge on nanoparticles was determined by Zeta potential. Values in a range of -30 mV to +30 mV of either charge characterize stable formulations.

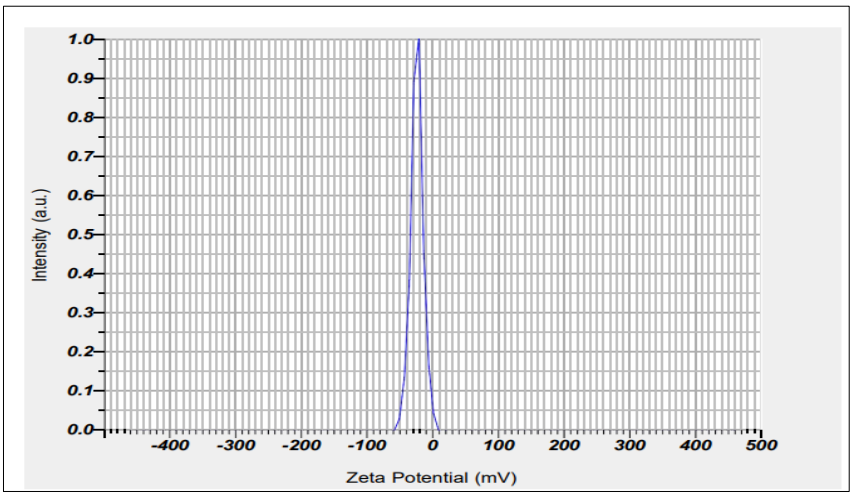

Figure 10: Zeta potential of an optimized batch of liposomes

C. Evaluation of Nanocochleates:

a) Physical appearance, pH and drug content, Entrapment Efficiency and In-vitro release of nanocochleates:

Table 4: physical appearance, PH and drug content, Entrapment Efficiency and in- vitro of nanocochleates

Formulations		NCF1	NCF2	NCF3
Physical Appearance		Yellowish white	Yellowish white	Yellowish white
pH		6.0	6.42	6.46
Drug Content (%)		90.80	92.08	89.78
Drug Entrapment Efficiency (%EE)		88.04	90.36	87.54
In Vitro Drug Release	0 hr	0	0	0
	1 hr	8.31	10.46	7.04
	2 hr	21.11	25.72	18.03
	3 hr	30.25	43.86	38.15
	4 hr	47.4	59.27	51.75
	5 hr	60.01	70.74	58.04
	6 hr	64.65	80.49	71.46
	7 hr	75.86	87.41	79.34
	8 hr	86.34	92.13	83.13

The drug content of the nanocochleates formulation (NCF2) was 92.08 and their physical appearance was a yellowish white dispersion with a PH of 6.42. Entrapment efficiency of three NC batches were performed by centrifugation method and drug entrapment efficiency of all batches were found in range of 87.54% - 90.36 % the batch NCF2 shows highest entrapment efficiency i.e., 90.36% while F3 shows lowest entrapment efficiency i.e.,87.54%

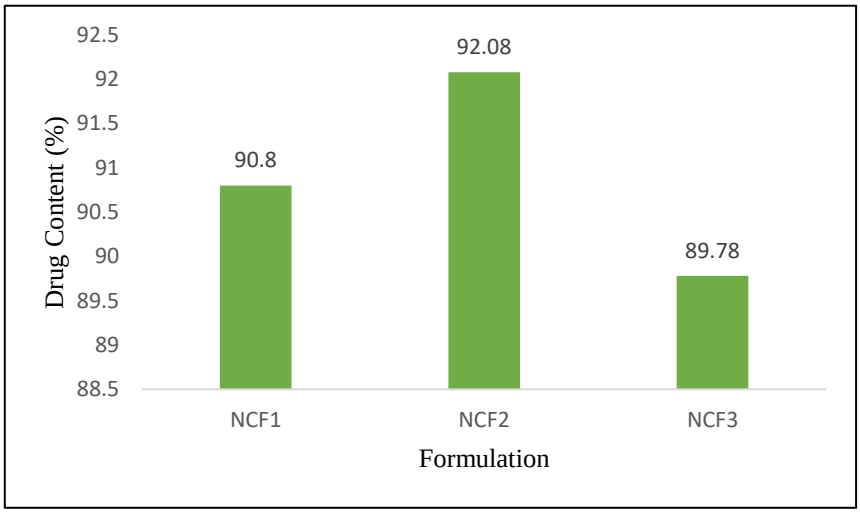

Figure 11: % drug content of nanocochleates batches

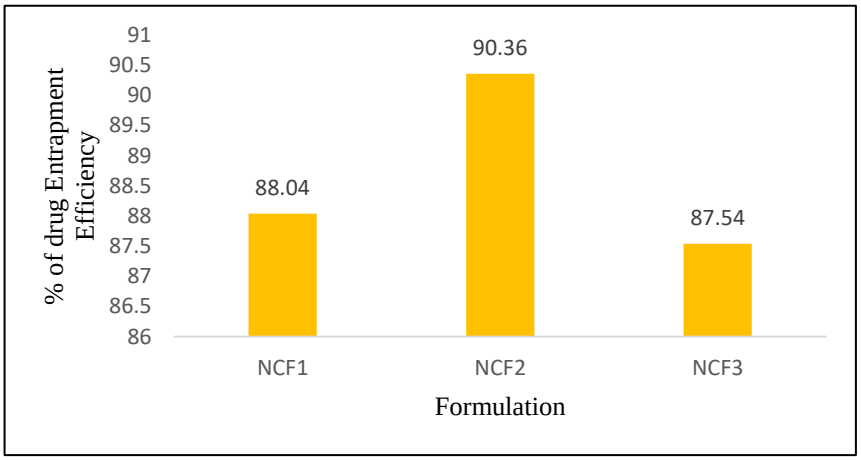

Figure 12: Percentage entrapment efficiency of nanocochleates

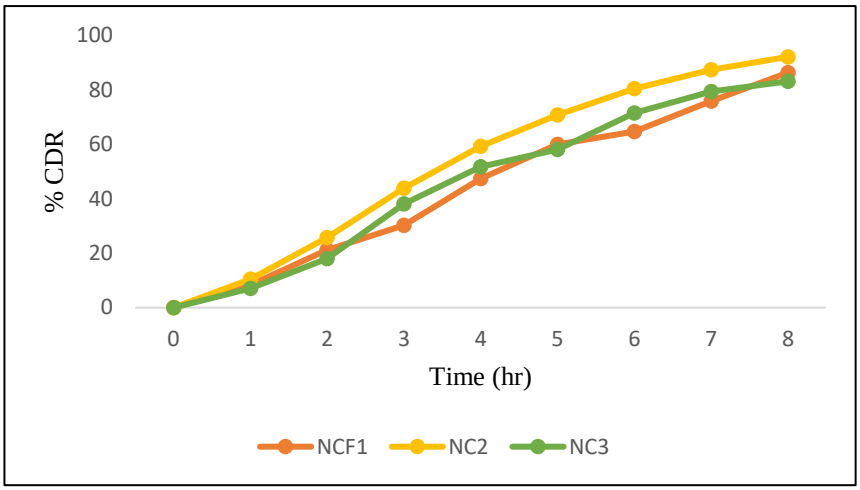

Figure 13: In-vitro drug release of nanocochleates

The In-vitro release of three nanocochleates formulations were performed and measured the release at 1 hr., 2 hr., 3 hr. upto 8 hrs. After examining percentage cumulative drug release graph of all formulations, the formulation NCF2 shows highest drug release i.e.,92.13 % which is high. From the all nanocochleates formulations, NCF2 shows high drug content, entrapment efficiency and In-vitro drug release. This optimized formulation further evaluation study like particle size, SEM and zeta potential were reported. The optimized formulation of Nanocochleate were selected for further Nanocochleate gel formulations.

b) Scanning-Electron Microscopy:

The shape and surface morphology of nanocochleates droplet was determined using SEM showing the intact nature.

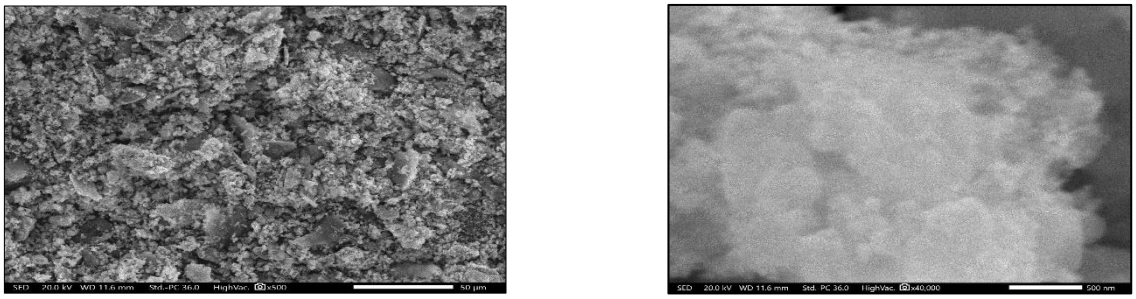

Figure 14: SEM images of nanocochleates

c) Particle size: The particle size of optimized batch (NCF2) is found to be 108.2 nm (Fig7.16) and polydispersity index was found to be 0.828. The particles size of liposomes

should be less than 500 nm. The nanometer particle size of the nanocochleates formulation influences the good antifungal activity by increasing solubility of drug which increases bioavailability of the drug.

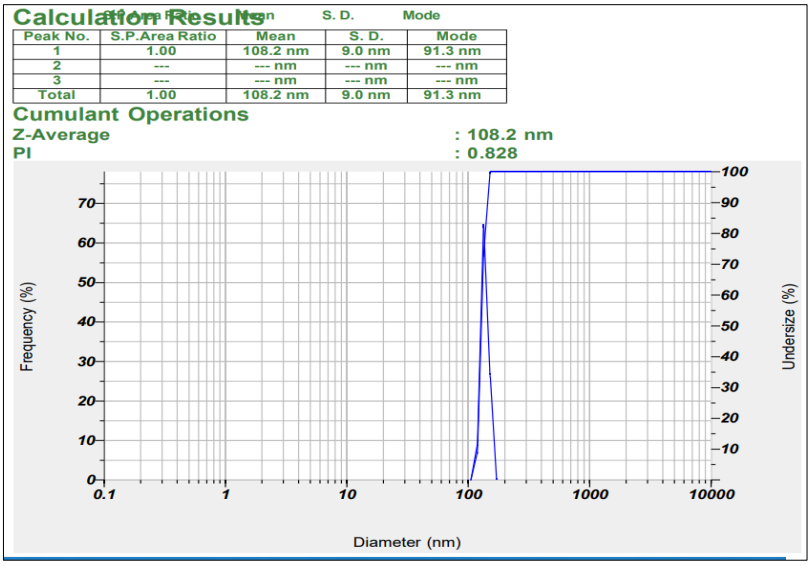

Figure 15: Particle size of optimized batch of nanocochleates

d) Zeta Potential:

The stability of nanocochleate were determined form zeta potential. Zeta potential of nanocochleate was shown in fig.7.17. Zeta potential value of NCF2 was determined to be -10.1 mV. The surface charge on nanoparticles was determined by Zeta potential. Values in range of -30 mV to +30 mV of either charge characterize stable formulations.

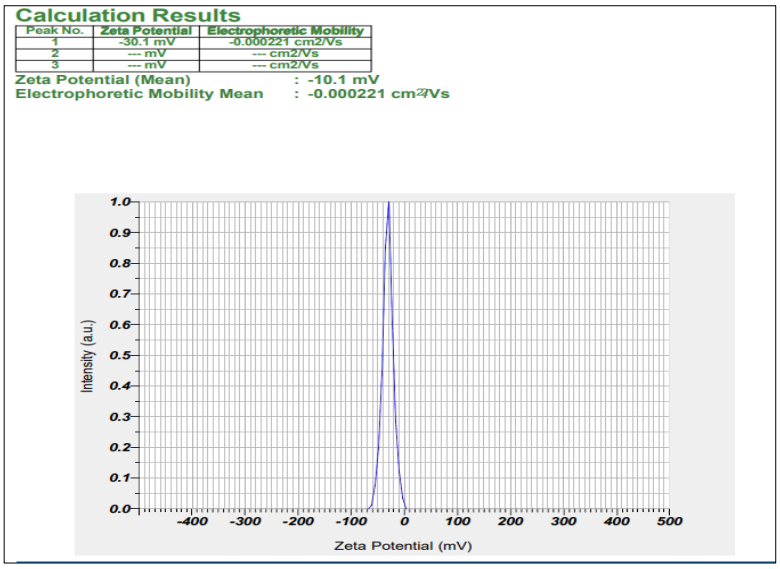

Figure 16: Zeta potential of an optimized batch of nanocochleates

CONCLUSION:

It is clear from the current study that the drug Bifonazole, which has been studied, is used to treat tinea pedia. A potential novel drug delivery method for the treatment of tinea pedis, or athlete's foot, is represented by nanocochleates. The benefits of these treatments over traditional topical therapies may include continuous drug release, tailored administration of antifungal medicine to the infection location, and increased effectiveness. A variety of nanocochleate formulations were developed and assessed based on factors such as drug content, entrapment efficiency, and In-vitro drug release. It was discovered that as the conc. of calcium chloride increased, and so did the entrapment efficiency and drug content. The intact nature of nanocochleates is revealed by SEM examination.

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