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Development and Evaluation of Candesartan-Loaded Proliposomes for Improved Bioavailability

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Abstract | **Original Research Article**

This study focused on developing candesartan-loaded proliposomes to enhance the solubility and permeability of candesartan drug. Proliposomes were prepared using the thin film hydration technique. Formulations were developed by varying the ratio of the lipid HSPC and cholesterol, while same consistent quantity of carrier. These formulations were then evaluated to determine the optimal size, entrapment efficiency, and enhanced in vitro dissolution. Dynamic light scattering analysis showed the particles had a size range of 450.3±2.2 to 480.4±2.31 nm and a zeta potential between -39 and -38 mV. Fourier transform infrared spectroscopic analysis showed that the drug was compatible with the excipients, with no interactions detected. Powder X-ray diffraction analysis indicated that the pure drug was crystalline, but was transformed into an amorphous form within the formulation. The in vitro drug release study using a dialysis membrane displayed enhanced dissolution of the drug due to the hydrophilic carrier, followed by sustained drug release owing to the lipid mixture of HSPC and cholesterol.

Keywords: Candesartan, Proliposomes, Solubility Enhancement, Thin Film Hydration, Drug Delivery.

1. INTRODUCTION

Oral drug administration remains the predominant route for drug delivery. However, many of the new drugs synthe-sized through combinatorial chemistry have bioavailability issues. This is due to their poor solubility and stability in the gut, trouble getting across the GI barrier, and being broken down in the liver and intestines before reaching the bloodstream [1]. Various techniques have been adopted to improve the dissolution of poorly soluble drugs, such as complexation, chemical modification, solid state manipulation, incorporation of surfactants, increasing surface area through micronization or nanonization, spray drying, and microencapsulation. Although the drug's dissolution behavior has been improved, its systemic exposure remains poor, puzzling the formulation scientists. They aim to overcome the barrier function of the gastrointestinal tract and avoid first-pass metabolism [2]. Studies show that the absorption of poorly hydrophilic and, fat-soluble drugs can improve when taken with a fatty meal [3] [4].

There is a concept that Developing colloidal lipid carrier systems can improve drug solubilization and permeation across the gastrointestinal barrier [5].

Among different colloidal drug delivery systems, liposomes are unique compared to other traditional dosage forms, because the particles can serve as drug reservoirs and have their composition or surface modified to adjust the drug release rate or affinity for the target site. Liposomes are lipid-based vesicles that can encapsulate both polar and non-polar substances. Although liposomes have advantages, their limited success in oral delivery is due to physicochemical

stability issues such as sedimentation, aggregation, fusion, phospholipid hydrolysis, and/or oxidation. Furthermore, the large-scale production of liposomes remains an unresolved challenge [5]. The use of proliposomes provides a significant advantage in maintaining the stability, particularly during sterilization and storage, by utilizing a dry, free-flowing format. This dry powder approach effectively avoids many of the stability challenges that are associated with liquid formulations [6]

The pro-liposome formulation offers a versatile delivery system due to its ease of distribution, transfer, measurement, and storage. Proliposomal formulations are dry powders comprising water-soluble carrier particles coated with phospholipids, that can be quickly reconstituted as liposomal dispersions by briefly agitating in water. The liposomes formed following the dispersion process are similar to conventional liposomes and more uniform in size [7]. While some drugs encapsulated in liposomes may not be well absorbed, the use of liposomes can enhance the rate and extent of drug absorption in the gastrointestinal tract [8].

Liposome-entrapped drugs are delivered more effectively due to vesicle adsorption onto the cell surface followed by endocytosis. Furtherhome, the liposomes are also bioadhesive and biocompatible, allowing them to adhere to the surface of the gastrointestinal tract and facilitate absorption [9]. There is a hypothesis, that Positively charged vesicles may interact more effectively with the negatively charged epithelial cell surface, which leads to stronger electrostatic interactions and improved delivery. Many studies have explored the use of proliposomes to improve the solubility and bioavailability of poorly soluble drugs [10].

Candesartan is a tetrazole derivative (five-membered heterocyclic ring with 4 nitrogen atoms). It is used in the form of an ester pro-drug Candesartan cilexetil. Candesartan is an oral angiotensin II receptor blocker used to treat high blood pressure and cardiovascular disease. Due to its ability to lower blood pressure and reduce oxidative stress, candesartan has been used to help prevent stroke [11]. However, oral Candesartan has poor absorption due to its low water solubility and slow dissolution. In addition, hepatic first-pass metabolism decreases Candesartan's absorption [12].

Our Previous research shows, proniosomes and proliposomes have ability to enhance dissolution and permeation, respectively. The study aimed to combine the benefits of proliposomes and surface charge to enhance oral delivery of Candesartan. The Candesartan-loaded proliposome powders were prepared and analyzed. The physical properties and structure of Candesartan in the proliposome powders were examined using solid-state analysis [13] [14].

2. MATERIALS AND METHODS

2.1. Materials

Candesartan was received as a kind donation sample from Wilshire Laboratories (Pvt) Ltd, Lahore. Cholesterol was purchased from AppliChem, Chemica Synthesis Services, and Germany. Chloroform, methanol and ethanol of analytical grade were purchased from Sigma-Aldrich, USA. Double distilled water was obtained from Drug Testing Laboratory, Bahawalpur (Thesis).

2.2. Preparation of proliposomal formulation

Proliposomes were prepared by using different quantities of phospholipid and cholesterol, while hydrophilic carrier (sorbitol) was kept constant. The thin film hydration with few modifications was implied by taking various combinations of phospholipids and cholesterol. Accurately weighed amounts of lipid mixture (250 µM) containing HSPC and cholesterol at various molar ratios (7:3, 6:4, 5:5, 4:6, 3:7, 2:8 respectively) and drug (8 mg) was dissolved in 15 mL mixtur.e of chloroform and methanol (1:2), respectively as shown in table 1. The resultant solution was incorporated into the round bottom flask containing sorbitol to form slurry and subsequent removal of organic solvent by rotary evaporator under vacuum at reduced pressure at a temperature at 45 ± 2 ˚C and 60 rpm for four hours. The Proliposomal powder obtained was then dried overnight in oven [15]. The Proliposomal formulations were then passed through sieve 60 to obtain free flowing powders. The obtained proliposomal powder is filled in glass vials and stored at 5 ±3 ˚C for further studies [16].

Table 1. Composition of Candesartan Loaded Proliposomes

Codes	Lipid: Cholesterol (250µmol)	HSPC (mg)	Cholesterol (mg)	Candesartan (mg)	Sorbitol (mg)	Chloroform (ml)	Methanol (ml)
FCP1	7:3	137.2	28.95	8	500	10	5
FCP2	6:4	117.6	38.6	8	500	10	5
FCP3	5:5	98	48.25	8	500	10	5
FCP4	4:6	78.4	57.9	8	500	10	5
FCP5	3:7	58.8	67.55	8	500	10	5
FCP6	2:8	39.2	77.2	8	500	10	5

2.3. Physico-chemical characterization of proliposomal powder

2.3.1. Flow properties of proliposomes powder

The flow properties of Proliposomal powder formulation were calculated by fixed funnel method. The Proliposomal powder was poured into the funnel fixed at 10 cm height from surface of the petri dish. Then the powder was allowed to flow through the funnel and angle of repose was calculate by measuring the height of the heap and diameter of its base [17].

2.3.2. Determination of percentage yield

The percentage yield was calculated to determine quantity of material wasted during the process and indirectly determining the efficiency of the formulation process [18]. The actual yield was determined by weighing dried proliposomes according to the equation no

$$\% \text{ yield} = \frac{\text{Total weight of formulation obtained}}{\text{total weight of drug } + \text{all excipients}} \times 100 \quad 2.1$$

2.3.3. Scanning electron microscopy (SEM) analysis

The morphology and surface attributes of candesartan loaded powder proliposomes were studied by using scanning electron microscope. The trivial quantity of Proliposomal powder was mounted on a chip and plated with thin layer of gold on the surface to improve conductivity through the sample. The formulation was visualized under various resolutions and scans were taken at accelerated voltage of 3.0kV [19].

2.3.4. Fourier transform infrared spectroscopic studies (FTIR) analysis

FTIR study of pure drug, phospholipid, cholesterol, sorbitol, and physical mixture and optimized formulation were done. FTIR of pure formulation was done determine the physical compatibility among the ingredients of formulations. Pure drug, phospholipid, cholesterol, sorbitol were analyzed from interferogram constructed between wavenumber and percentage transmittance to evaluate the characteristics peak and to determine the possible interactions among them. The sample was analyzed in the wavelength region of 4000 to 400cm -1 and percentage transmittance in the range from 85 to 100% [19] [20].

2.3.5. Powdered X-ray diffraction (XRD) analysis

The powder X-ray diffraction of candesartan, phospholipid, cholesterol, sorbitol, and physical mixture and optimized formulation by using powder X-Ray diffractometer. The measurement was done using Cu-Kα radiation, nickel filtered graphitic monochromator at 40 KV voltage and 30 mA current. The scanning rate employed was 10 min-1 over 10-50º diffraction angle [21].

2.3.6. Optical microscopy

The proliposomes were hydrated with distilled water and observed under optical microscope to confirm liposome formation. The liposomal suspension was mounted on a glass slide ,placed over a cover slip on it and observed under magnification lens of 100x and images were taken by camera and analyzed for liposome formation [22].

2.3.7. Vesicular diameter, colloidal stability, and PDI analysis

The diameter of vesicles, zeta potential and polydispersity index of liposomes formed after hydration of powder proliposomes was determined by Zetasizer (ZS-90, Malvern Instrument, Malvern, Worcestershire, UK) through dynamic light scattering technique. The zeta potential determines the electrostatic forces of attraction and repulsion among liposomal vesicles. The size of vesicle is important in determining the properties of system and zeta potential is important for determining the colloidal stability of dispersion, aggregation properties of vesicles and dispersion stability [23].

2.3.8. Determination of encapsulation efficiency

The encapsulation efficiency of candesartan proliposomes were determined by indirect method. The liposomal dispersion formed by hydration of phosphate buffer of pH 6.8, and subsequent vortex mixing. The dispersion formed was then subjected to ultracentrifugation at 10000 rpm for 40 minutes (In triplicate). The supernatant layer was collected and absorbance was measured using UV-Visible spectrophotometer (IRMECO, U2020, Germany). The unknown concentration of free drug were determined at 254nm. The entrapment efficiency were calculated by using following equation [24].

2.3.9. Dissolution analysis

The in-vitro release profile of drug loaded Proliposomal were performed by using USP dissolution type II Paddle apparatus (Pharma test W00 4895, Hainburg, Germany). The pre-calculated amount of liposomal formulation containing equivalent of 2mg of candesartan was taken in dialysis membrane and dipped in 900ml of phosphate buffer of pH 6.8 to maintain sink conditions. The temperature was maintained at 37 ± 2˚C and at 50 rpm stirring speed of peddle. The samples were taken at 0.25hr, 0.5hr, 0.75hr, 1hr, 1.5hr, 2hr, 3hr, 4hr, 5hr, 6hr, 9hr and 12 hr. The sample taken each time consisted of 5ml and was replaced with fresh phosphate buffer of pH 6.8. The sample collected were analyzed at 254nm [25].

2.3.10. Kinetics of drug release

The kinetic models are showed the mechanism and order of release drug from liposomes. The data obtained from release profile was fitted to the kinetic model; zero order, first order, Higuchi and Korsmeyer-Peppas model. The value of correlation coefficient R2 for

all kinetic models was determined by using DDsolver.xla [19].

3. RESULTS AND DISCUSSION

3.1. Flow properties of proliposomes powder

The formulation of proliposomal powder were evaluated for their flow properties and the results were shown in below table 2. Angle of repose of different formulation was in the range from 30 to 35.2 which show excellent flow properties [26].

Table 2. Angle of repose of all formulations.

Sr. No	Codes of Formulations	Angle of Repose (θ)
1	FCP1	33.5
2	FCP2	35.2
3	FCP3	32.5
4	FCP4	31.0
5	FCP5	28.5
6	FCP6	27.0

3.2. Determination of percentage yield

Percentage yield of different candesartan proliposomes formulations were determined. The maximum recovery of candesartan proliposomes formulation obtained by extra care during the weighing of different components of formulations and mixing of components and specially recovery of Proliposomal powders from the round bottom flak after evaporating the organic solvents. The percentage yield of each candesartan Proliposomal formulation was given in below table and was found in the range 81% to 87% as shown in table 3 [27].

Table 3. Percentage yield of proliposomal formulation

Formulation Code	Percentage yield (%)
FCP1	83.96
FCP2	81.75
FCP3	81.93
FCP4	81.33
FCP5	87.02
FCP6	87.76

3.3. Scanning electron microscopy (SEM) analysis

Scanning electron microscopy is used to determine morphology and surface characterization of proliposomal formulation. Scans imagination of of optimized candesartan proliposomal formulation was examined at various resolution. The SEM analysis showed that candesartan-loaded proliposomes had a rough and non-porous surface structure [19].

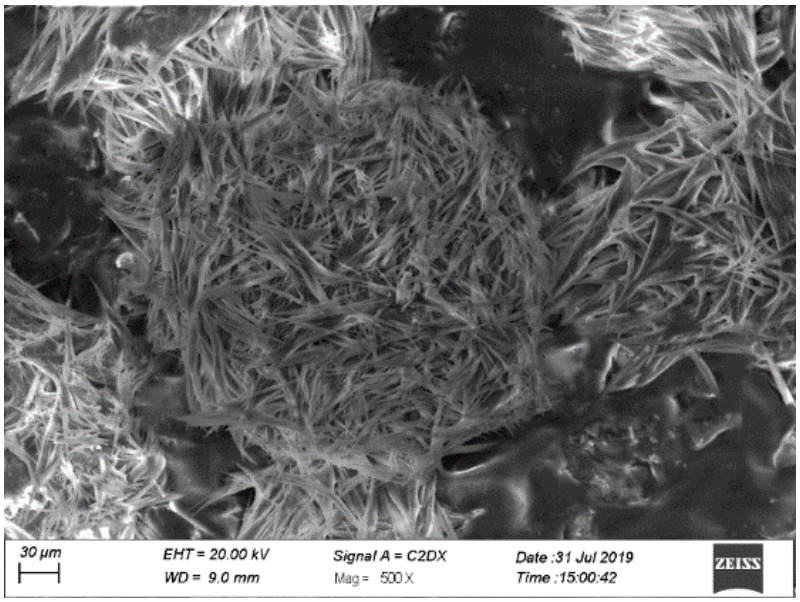

Fig.1. Scanning electron microscope images of FCP-2

3.4. Fourier transform infrared spectroscopic studies (FTIR) analysis

FTIR analysis was conducted on the pure drug, phospholipid, cholesterol, sorbitol, physical mixture, and optimized formulation. No interactions were found between the ingredients and excipients, indicating the formulation is compatible [28].

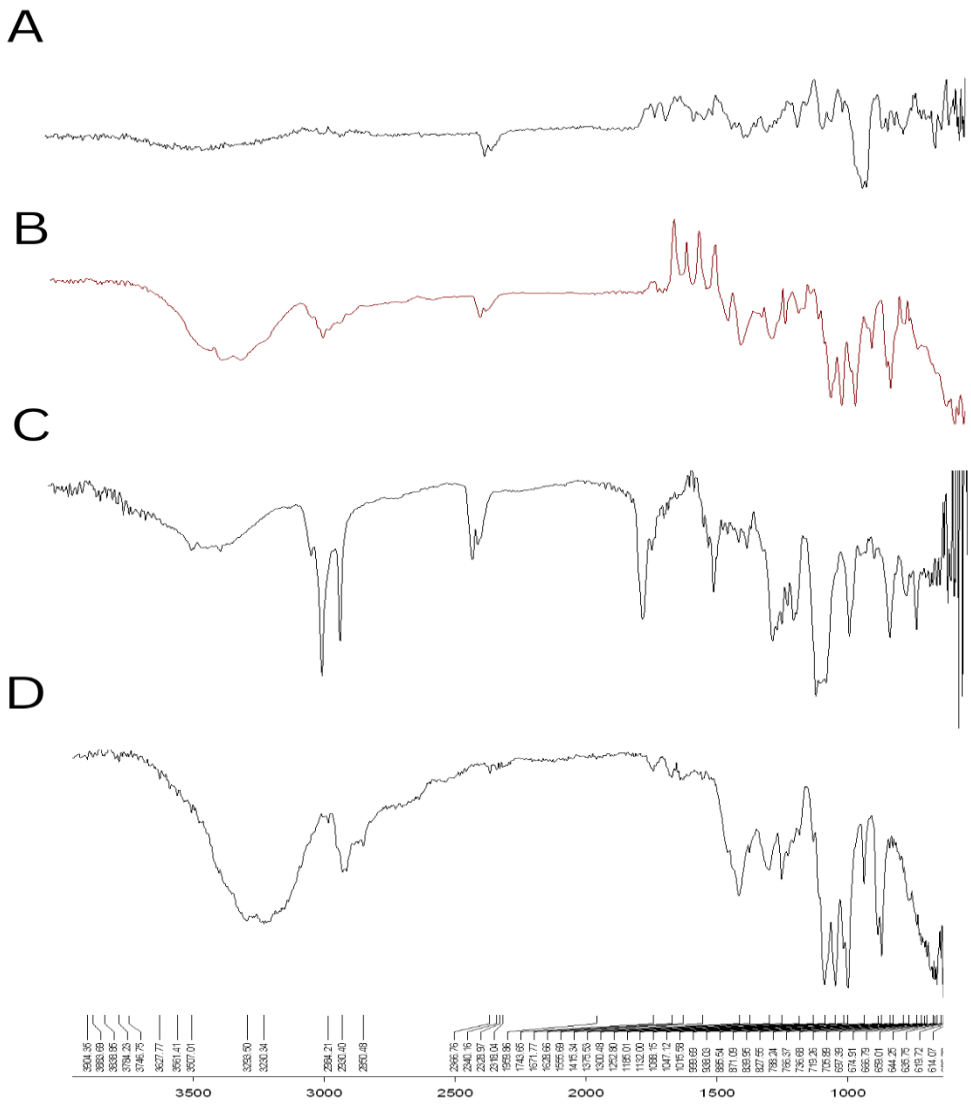

Fig. 2. FT-IR of (A) Drug, (B) Sorbitol (C) HSPC and formulation FCP-2

3.5. Powdered X-ray diffraction (XRD) analysis

The X-ray diffraction analysis of the Candesartan-loaded pro-liposomal formulation demonstrated the absence of Candesartan crystalline peaks, suggesting successful encapsulation within the pro-liposomes as shown in Figure 3 [21].

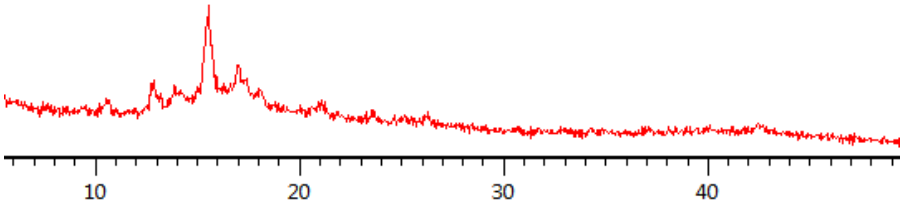

Fig. 3. Powder X-ray diffraction of FCP-2

3.6. Optical microscopy

Liposomes are formed by hydrating proliposome powder. Analysis using a light imaging microscope reveals that the liposomes are spherical in shape as shown in Figure 4. The size of the liposomes can be controlled by adjusting the flow rate and pressure. Optical microscopy showed that proliposomal powders rapidly transform into liposomes when hydrated.

Candesartan-loaded proliposomes became a semi-transparent mixture within 30 seconds of contact with water.

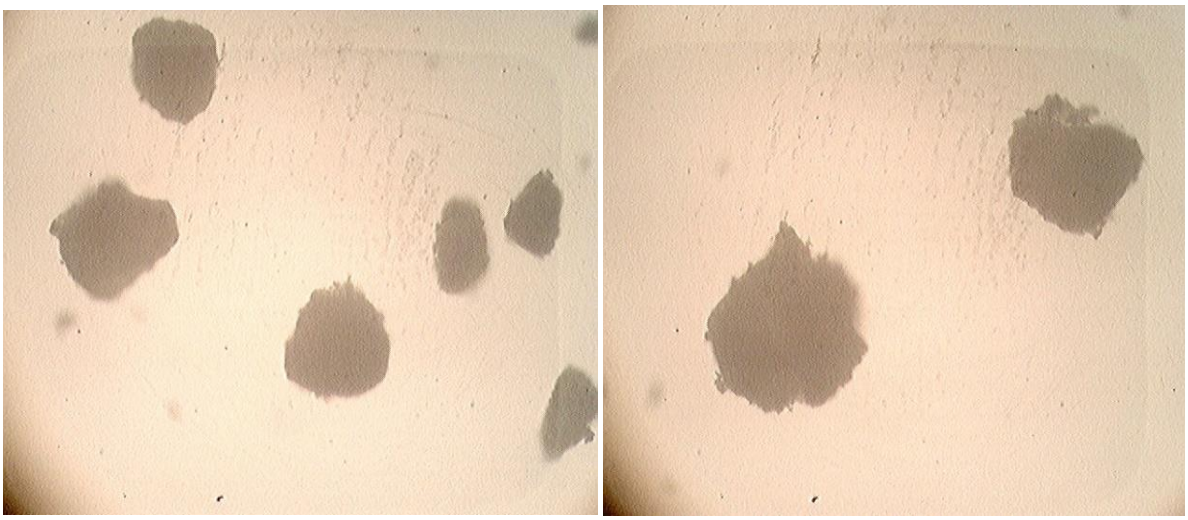

Fig. 4. Optical microscopy of FCP-2

3.7. Vesicular diameter, colloidal stability, and PDI analysis

The size, polydispersity index, and zeta potential of the Candesartan-loaded liposomes are showed. The liposomes have particle diameters ranging from 450.3±2.2 nm to 480.4±2.31 nm as shown in table 4. The minimum particle size was 450.3±2.2nm for the formulation FCP-1 with the lowest HSPC concentration, while the maximum particle size was 480.4±2.31nm for the formulation FCP-6 with the highest HSPC concentration.

The PDI of all formulations of had range of 0.244 to 0.267, indicating the phospholipid vesicles had a narrow size distribution. The formulations had a high zeta potential range of ---34 to -38 mV, which enhances the stability of the colloidal system by increasing repulsion between the particles.

Table 3: Zeta Size, zeta potential and PDI of proliposomal formulation

Code	Particle size (nm)	PDI	Zeta potential (mV)
FCP1	450.3±2.2	0.244	-36
FCP2	454.2±1.5	0.254	-34
FCP3	462.3±2.0	0.265	-36
FCP4	467.5±2.0	0.267	-29
FCP5	472.8±4.31	0.265	-38
FCP6	480.4±2.31	0.257	-37

3.8. Dissolution analysis

The in vitro release study showed that, under simulated gastric conditions without enzymes, around 20% of the drug was released from the system within 2 hours. The maximum drug release from the system FCP-2 (>90%) was observed after 16 hours, using a phosphate buffer of pH 6.8 without enzymes as a model for intestinal conditions.

In contrast, the pure Candesartan drug exhibited a release of 18% within the first two hours at pH 1.2 and 31% over 16 hours at pH 6.8. Similar trends were also observed. Initially, all the formulations displayed enhanced dissolution, leading to improved solubility and rapid drug release from the system due to the inclusion of a hydrophilic carrier. This was followed by sustained drug release attributed to the presence of a lipid mixture.

Table-4: In vitro dissolution profiles of Candesartan loaded liposomal formulation from proliposome powders

Time (hr)	FCP1	FCP2	FCP3	FCP4	FCP5	FCP6	Drug
0.00	0	0	0	0	0	0	0
0.25	5.710	5.240	3.880	6.610	4.790	2.960	2.510
0.50	7.110	7.550	7.540	10.28	6.630	9.360	6.170
0.75	12.63	10.32	11.21	13.96	11.66	10.76	9.390
1.00	17.73	14.47	14.89	17.20	15.35	13.98	11.71

Time (hr)	FCP1	FCP2	FCP3	FCP4	FCP5	FCP6	Drug
1.50	23.76	18.65	17.22	20.90	19.05	18.13	13.96
2.00	26.18	21.93	22.29	26.44	21.39	20.47	18.16
3.00	29.97	26.13	25.56	32.00	25.11	24.19	20.98
4.00	36.53	30.36	32.03	33.93	27.93	26.55	24.27
5.00	45.87	33.70	37.60	39.52	31.67	29.83	25.74
6.00	52.51	54.83	47.61	51.50	43.17	33.57	29.05
9.00	56.91	70.44	66.15	62.61	59.27	55.57	31.00
12.00	70.46	91.14	86.89	77.86	75.65	74.67	47.58

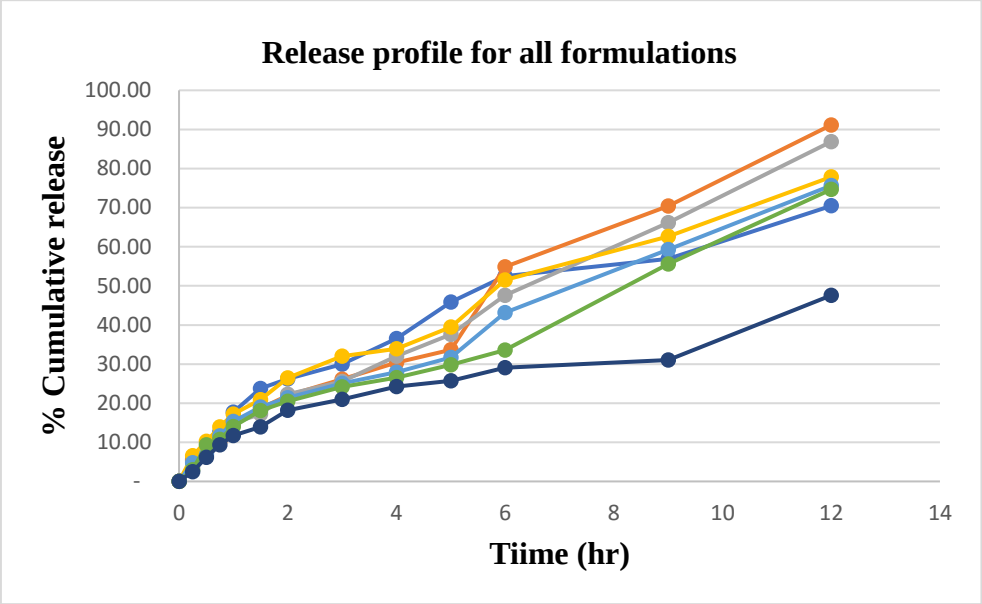

Figure. 5. In vitro dissolution profiles of Candesartan loaded all Candesartan loaded proliposomal formulation

3.9. Kinetics of drug release

The data of R2 indicates the Korsmeyer-Peppas model is the most appropriate fit for the system. The release mechanism for all formulations was above 0.45, suggesting a non-Fickian transport mechanism and indicating that a boundary region was affecting the passive drug diffusion process.

Table 5: Kinetic drug release of all Candesartan loaded proliposomal formulation

Formulation Code	Zero Order	1st Order	Higuchi Model	Korsmeyer-Peppas model	
FCP1	0.8020	0.954	0.975	0.9860	0.580
FCP2	0.9680	0.945	0.874	0.9805	0.851
FCP3	0.9710	0.966	0.9002	0.9922	0.812
FCP4	0.8771	0.966	0.9651	0.9920	0.637
FCP5	0.9402	0.961	0.9167	0.9818	0.747
FCP6	0.9380	0.9401	0.8925	0.9660	0.779

4. DISCUSSION AND CONCLUSION

The study showed significant improvements in enhancing the bioavailability of candesartan, a drug with poor solubility and limited absorption due to liver metabolism. The study used the thin film hydration method to formulate candesarten-loaded proliposomes, varying the ratios of HSPC and cholesterol while keeping the hydrophilic carrier constant. The study found that the vesicles had optimal sizes between 450.3 ± 2.2 nm and 480.4 ± 2.31 nm, suitable for effective drug delivery. The zeta potential measurements showed the dispersion was stable, with values around -39 to -38 mV, suggesting the liposomal vesicles would not aggregate. The Fourier Transform Infrared Spectroscopy and Powder X-ray diffraction studies showed that no interaction was found between the drug and excipients, so drug was compatible with the excipients. The formulation transformed to an amorphous state from crystalline state, which typically improves solubility and dissolution rates. The in vitro dissolution studies confirmed the effectiveness of the proliposomal formulations, especially FCP-2. This formulation significantly increased the drug release rate compared to pure candesartan, releasing over 90% of the drug within 16 hours under simulated intestinal conditions. The hydrophilic carrier and lipid mixture enabled sustained drug release. The formulation technique showed efficient flow properties and high percentage yields, ranging from 81% to 87%, indicating

a successful preparation process. Optical microscopy observations confirmed the formation of liposomes upon hydration, validating the efficacy of the methodology.

The findings support that proliposomes enhance dissolution and bioavailability of poorly soluble drugs like candesartan. They also provide a stable and effective delivery system that overcomes barriers of traditional oral formulations.

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