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Proliposomal Dry Powder Inhalation: Design and Development for Pulmonary Antihypertensive Drug Delivery

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Abstract: The present study aimed to create a dry powder proliposomal inhaler that would administer a medication for hypertension to the lungs. The pulmonary method of administration also has many benefits because the alveolar membrane is very thin and highly permeable, which lets different APIs be absorbed by the lungs. After getting information from the *in vitro* drug penetration, RSM analysis was used to find out how each measure affected the results. The best mix of cholesterol and soya phosphatidylcholine (SPC) was picked from the different amounts. Five grammes of SPC, six grammes of cholesterol, and a stirring speed of 210 rpm (F5) were picked as the amounts. It shows 94.81% *in vitro* permeability for 12 h with the improved preparation. Several different kinetic models are used to display the drug release kinetics data from *in vitro* drug release research. We were able to comprehend the drug's release mechanism thanks to the curve fitting findings of the generated formulae' rate of entrance. We employed non-Fickian diffusion to account for the medication release. Based on the "n" number of 0.6300, this suggested both a diffusion and growth process. Also, Higuchi gave the best answer for how the drug was released, as shown by the plots' highest level of regularity ($r^2 = 0.9990$) and Higuchi's best fit for the drug release. In the improved composition, particles with a size of 683 nm were seen. Based on the above findings, atenolol proliposomes show potential as a way to give medicine to treat high blood pressure.

Keywords: Antihypertension, Proliposomal, Pulmonary antihypertensive drug delivery, Dry powder inhalation

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Introduction

Proliposomes consist of the medication, phospholipids, and a water-soluble porous powder. They are unquestionably dry, free-moving particles. When water is introduced, the particles become moist, forming a liposomal combination (Gomez *et al.*, 2020). Proliposomes may be prepared into many various dosage forms, including tablets, pellets, transdermal distribution, and vaginal delivery (Reddy *et al.*, 2023). Proliposomes, which are dry liposomal materials, seem to be more practical and simpler to utilise than freeze-dried alternatives (Srichana *et al.*, 2022). Proliposomes may be made in a variety of methods, including as the fluidized bed approach, the spray drying method, the film-deposition on carriers method, and the crystal-film method. Stable formulations for the digestive system and industrial production processes, however, are still not without problems (Aher *et al.*, 2023).

Proliposomes are among the most popular and affordable techniques. Because they are easily obtained in the form of dry powder, which makes them easy to preserve, disperse, and transfer, they may be employed in a variety of settings (Reddy *et al.*, 2022).

Liposomes can be made either in a lab, with the help of the right soaking fluid before transport, or inside the body, with the help of organic fluids. Making proliposomal formulas may help with the absorption and metabolism problems of some medicines (Khan *et al.*, 2023).

Liposomes are small circular bubbles, one or more cylindrical lipidic bilayers surround a water space inside. The layer of a liposome is made up of natural or man-made lipids that do not cause immune reactions, break down naturally, and work well with living things. Because they are made up of two layers, liposomes can dissolve both in water-soluble and lipophilic chemicals (Yeola *et al.*, 2023). There are hydrophilic

chemicals inside the inner liquid chambers. Lipid bilayers are the main way that lipophilic medicines are stored (Malamatari *et al.*, 2020).

The biological features that make liposomes appealing are that they are biocompatible and biodegradable. As active vectors, they show promise because they can make drugs more stable and dissolve better. They can also move capsule drugs to specific target areas and keep the drugs working for longer (Reddy *et al.*, 2019). The subatomic size of these particles makes them more bioavailable in living things because they can be absorbed more easily inside cells than other particle systems (Elhissi, 2017). Liposomes also have other benefits, such as causing less tissue pain, being safe because they contain phospholipids, encapsulating drugs very well even though they dissolve easily, and protecting drugs from things like light and pH that break them down (Bahiram *et al.*, 2023).

Still, liposomes in watery dispersion form have major stability problems because of phospholipid breakdown, fusion, and clumping, which could make them go bad faster (Sonawane *et al.*, 2023). Even though freeze drying is the most common way to make liposomes last longer, it still has some problems because it leaves behind some water and the lyoprotectants used can make chemicals less stable (Khalandar *et al.*, 2018).

Because it goes through the lyophilization step, this method is more expensive and takes a lot more energy during the making process (Pawar *et al.*, 2020). When liposomes are made on a large scale, the needed product properties should be taken into account, along with how efficient and viable the production method is (Sonawane *et al.*, 2023). The present study aimed to create a dry powder proliposomal inhaler that would administer a medication for hypertension to the lungs.

Table 1: The formulation of proliposomes

Formulation	Atenolol (mg)	SPC	Cholesterol	Starch	RPM
F1	20	3	3	20	230
F2	20	5	3	20	210
F3	20	3	5	20	200
F4	20	5	5	20	210
F5	20	3	6	20	200
F6	20	5	6	20	210

Materials and Methods

Preparation of Calibration curve:

20 mg of the atenolol reference standard was diluted with 0.1N HCl to obtain 20 µg/ml of the atenolol reference standard (Bharat *et al.*, 2017). To make 20–100 µg/ml of atenolol reference standard, methanol was added to this stock solution, and the absorbance at 275 nm was measured. The standard curve was prepared between concentration and absorption (Keservani *et al.*, 2017).

Developing Proliposomes loaded with Atenolol using the Slurry Method:

The slurry method was used to make proliposomes, and starch was used to carry the carbohydrates. One mole of soya phosphatidylcholine (SPC) and one mole of cholesterol were used together as the lipid phase. The drug atenolol was added during the fat phase. The lipid phase, which contained cholesterol, atenolol, and SPC, broke down in pure ethanol (Keservani *et al.*, 2020). The ethanolic solution was poured over the carbohydrate carrier in a 100-ml glass beaker that had starch in it to make sure that the lipid phase and medicine were evenly spread across the carrier particles (Ahire *et al.*, 2023). This made a mush. The organic liquid was left to drain for an hour while a magnetic stirrer turned the beaker at 270 turns per minute in a 45°C water bath. Dried Proliposomes were

collected and stored at -18°C in a glass jar that kept air out so they could be used in further studies. Table 1 shows the formulation of proliposomes (Ahire *et al.*, 2022).

In Vitro Drug Release:

The Franz Diffusion method was used to study skin entry *in vitro*. The cells were kept at 37°C. The goat lung mucosal membrane stood between the donor and target areas as a wall. After the phosphate buffer had been degassed, it was added to the receptor chamber and magnetically stirred all the time (Jain *et al.*, 2023).

The right amounts of recommended proliposomes were spread out in phosphate buffer to get atenolol at a concentration of 5 mg/ml. It took 5 ml of these dispersions to put them in the donation section (Jarouliya *et al.*, 2015). A 2 ml sample was taken out of the receptor section and new medium was put in its place after 5 to 360 min. UV spectrophotometry at 275 nm was used to measure the amount of atenolol in the sample (Surana and Mahajan, 2022).

Results and Discussion

Preparation of Calibration curve:

The concentration and associated absorbance were used to create the atenolol curve. The equation for the line of greatest fit, as determined by the values of linear regression analysis, is $y = 0.0894x + 0.0794$. In the concentration range of

Table 2: Calibration curve value

S. No.	Concentration	Absorbance
1	20	0.046
2	40	0.170
3	60	0.320
4	80	0.505
5	100	0.664

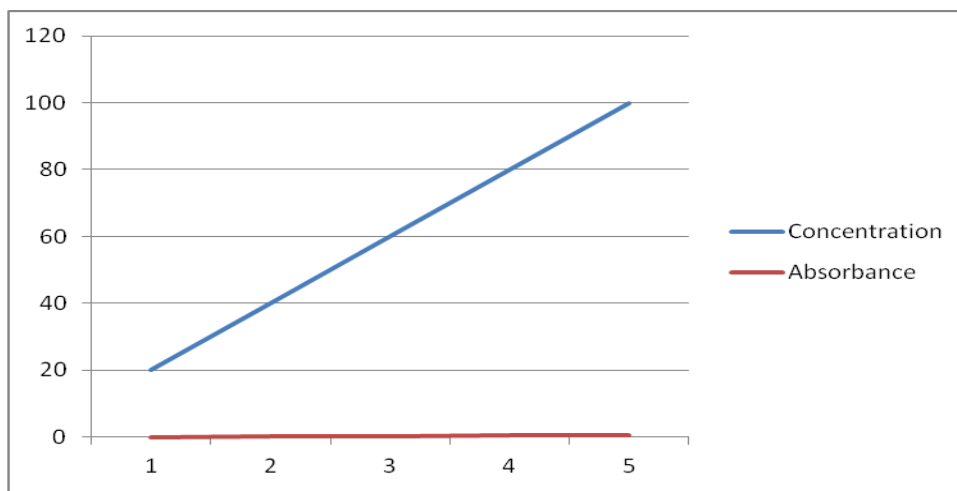


Fig. 1: Calibration curve of Atenolol.

Table 3: Drug release in permeation study

Time(h)	F1	F2	F3	F4	F5	F6
0	00	00	00	00	00	00
2	34.52	39.12	30.21	57.63	29.10	33.49
4	37.32	43.64	33.52	60.11	31.56	37.66
6	40.81	50.54	37.33	61.12	35.26	49.71
8	44.61	53.57	42.11	64.56	37.29	53.58
10	47.12	55.23	44.69	69.32	41.52	57.25
12	62	64.82	49	79.10	46.82	66.60

20–100 $\mu\text{g/ml}$, linearity was seen. Table 2 shows Calibration curve value. Figure 1 shows Calibration curve of Atenolol.

In Vitro Diffusion:

Table 3 illustrates the drug absorption data for different forms of atenolol proliposomes.

Figure 2 shows how the Atenolol Proliposomes versions let drugs pass through them. Between 62.82% and 46.82% of medicine was found to have diffused in formulas F1, F3, and F5. It was found what the total amount of drug spread was for versions F2, F4, and 79.10%. The amount of F6 in the mix was 66.60%. This shows

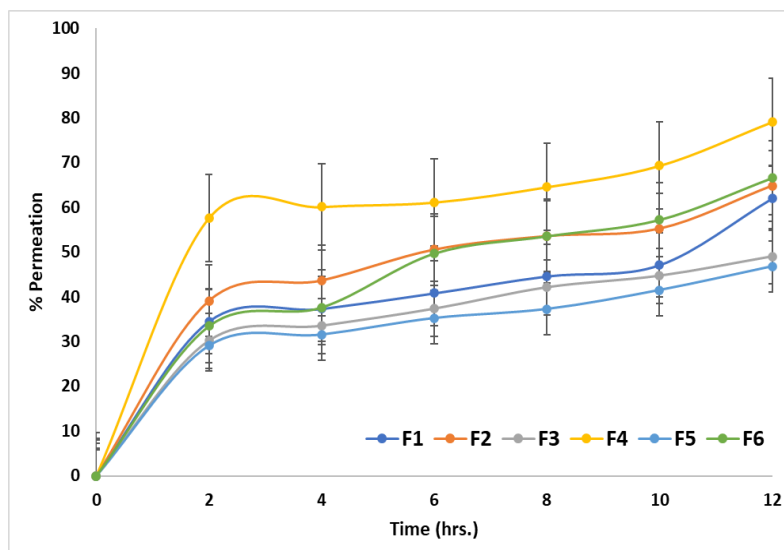


Fig. 2: *In vitro* drug permeability plot.

Table 4: Drug release kinetics values of r^2 for optimized formulation

Optimized Formulation	Zero-order kinetics		First-order kinetics		Higuchi		Korsmeyer-Peppas	
	K	r^2	K	r^2	K	r^2	K	N
	12.21	0.9490	-0.141	0.071	52.63	0.9990	1.94	0.6300

that increasing the amount of SPC (5 g), cholesterol (6 g), and proliposome particle size decreases medicine release higher.

In Vitro Drug Release Kinetics:

The correlation coefficient (R^2) number shows that the drug got into cells from Atenolol proliposomes in their best form (F6) through a diffusion process. Plotting data from *in vitro* drug release experiments in various kinetic models may be used to determine the rate of drug release. We were able to comprehend how the medication was released after curve fitting findings of the rate of entrance of the developed formulae. Based on the "n" number of 0.6300, it was found that the drug release happened through non-Fickian diffusion. Also, Higuchi gave the best answer for how the drug was released, as shown by the plots' highest level of regularity ($r^2 = 0.9990$) and Higuchi's best fit for the drug release. Table 4 shows Drug release kinetics values of r^2 for optimized formulation.

Conclusion

The lung epithelium has a lot of blood vessels and covers a lot of space. Also, there are not many efflux transporters, which helps the body absorb medicines. Using atenolol proliposomes to make a custom drug delivery system that targets heart tissue directly and lowers overall exposure could be a good alternative. This route starts to work pretty quickly, and it has fewer digestive enzymes than the liver pathway. So, the medicine may be taken even if its physical and chemical properties are different. The pulmonary method of administration also has many benefits because the alveolar membrane is very thin and highly permeable, which lets different APIs be absorbed by the lungs. The best version was picked based on how well the atenolol proliposomes let drugs pass through and how big the particles were. After getting information from the *in vitro* drug penetration, RSM analysis was used to find out

how each measure affected the results. The best mix of cholesterol and SPC was picked from the different amounts. Five grammes of SPC, six grammes of cholesterol, and a stirring speed of 210 rpm (F6) were picked as the amounts. It shows 94.81% *in vitro* permeability for 12 h with the improved preparation. Several different kinetic models are used to display the drug release kinetics data from *in vitro* drug release research. We were able to comprehend the drug's release mechanism after curve fitting findings of the generated formulae' rate of entrance. We employed non-Fickian diffusion to account for the medication release. The "n" value of 0.6300 indicated the presence of both a growth and diffusion process. Also, Higuchi gave the best answer for how the drug was released, as shown by the plots' highest level of regularity ($r^2 = 0.9990$) and Higuchi's best fit for the drug release. Based on the above discovery, atenolol proliposomes show potential as a way to give medicine to treat high blood pressure.

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