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A Proniosomal Drug Delivery System for Targeting the Brain: Design, Development, and Formulation

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Abstract

When someone gets sick with Plasmodium falciparum, they can get cerebral malaria, which is a major public health problem. The patient died, became unconscious, and went into a coma because brain malaria infected his red blood cells, platelets, and white blood cells. Artemether has artemisinin in it, which kills Plasmodium falciparum parasites very well. The artemisia annua plant makes artemether, which is a chemical that is used to treat cancer. Artemisinin, one of its products, is approved to treat some types of colon cancer, melanoma, leukemia, and breast cancer. Artemether is also used to treat parasitic infections in the brain. It is a Bcs Class IV drug because its half-life is only three to five hours and it doesn't dissolve well in water. So, to get around this problem, look into other ways to use ARM to send drugs from the nose to the brain. Normal ways of giving this medicine don't work for treating cerebral malaria because they send the medicine into the bloodstream instead of straight to the brain. Because of this, it doesn't work to treat CM. It is necessary to send ARM for CM through the nose to the brain in order for it to work well. According to a recent study, three different carriers are used to put drugs inside a proniosome. This makes sure that the drugs are the right size for best release and success in trapping the drug. We use lactose that has had its surface changed, along with a certain carrier called Neusilin. Surface modification is a good thing that can change the qualities of adhesion and cohesion, improve the performance of aerosols, change how particles stick together, and reduce the contact area of lactose. Neosilin is employed to enhance the flow properties and desiccate the powder for producing proniosomes.

Keywords: Adhesion aerosol, cerebral malaria, neurological, intramuscular.

Introduction

Nanotechnology has come a long way, and it has helped a lot in creating new nanocarriers for controlled drug transport. Niosomes were made by proniosomes, which is a lasting predecessor. Their technology has been around for twenty years. Several research papers have been written about the study of how to use Proniosomes to make a controlled drug delivery system (Khatoon *et al.,* 2017). But in order to fully understand and research the many uses of this approach—using prometheosomes as a nasal drug delivery system—it is important to look at and talk about the newest and quickly rising reported trials, along with the theories behind them. This article shows a thorough study that uses pictures to look into how nanotechnology can be used to make protosomes. The first thing that was looked at was the physicochemical makeup of the additives and non-ionic detergents that were making prometheosomes. A close study of recent works has looked at many aspects of how Proniosomes are made, how drugs are loaded onto them, how they are administered, how they are characterized, how toxic they are, and how drugs are released (Djupesland, 2013; Bragagni *et al.,* 2012).

A niosome is a multilamellar vesicular structure that is made by a surfactant that is not charged with electricity. Niosomes are mostly made up of cholesterol or its products and non-ionic surfactants that are hydrated. Because they are made in a special way, nanosomes can hold both lipophilic and hydrophilic molecules (Ahire *et al.,* 2023). This can be done by separating molecules that are attracted to fat into the bilayers' fat-loving area or by enclosing substances that are attracted to water in a vesicular water core. Thin lipid films, which are sometimes called "lipid cakes," become fluid, spread, and change into liposomes when liquid crystalline bilayers are hydrated. When agitation happens, wet lipid sheets separate, which lets them join together to form vesicles. Water can't connect with the edges of the bilayers' hydrocarbon cores because of this process. This makes promniosomes form (Tiozzo *et al.,* 2018; Keservani *et al.,* 2020).

In addition, the Proniosomes work better than the Niosomes. The proniosomal way of delivering medicine: Peptidosomes are better than other ways of delivering drugs because they can hold drugs and are drawn to specific areas because they are made of cholesterol and surfactants. That being said, there are still a lot of problems with using liposomes and niosomes to deliver drugs. Liposomes have problems with breaking down, oxidizing, sedimenting, fusing, and sticking together. Also, these substances are chemically and physically stable, which makes it hard to make, sterilize, and store large amounts of them (Imam, *et al.,* 2015; Khulbe *et al.,* 2023). To make a lot of proniosomes, you don't need any special conditions, the wrong chemicals, or extra safety measures. The stuff is a loose, powder-like mix of a surfactant-coated stuff that is easy to revive by stirring it really hard in hot water or a buffer solution. This makes a solution of multi-lamellar Niosomes that can be taken by mouth or sent to the body in some other way. A lot of different active substances can be moved by adaptable delivery methods (Ahire *et al.,* 2020; Jadhav *et al.,* 2008).

Materials and methods

A free sample of astamethrin was offered by the research and development business. Span 60 was provided by Loba Chemicals, a research lab in Mumbai. The lactose, cholesterol, dichloromethane, and methanol that were HPLC grade came from Research Lab Fine Chemicals Industries in Mumbai. Fuji Chemical Industries and Gangawal Chemicals, both in Mumbai, were the places where the neusilin carrier grades US2 and USF2 were bought. It was bought from Loba Chemie Pvt. Ltd., which is also based in Mumbai.Reverse osmosis was used to clean the water (MilliQ. Millipore, USA). The chemicals used were all laboratory grade and

were used without being changed in any way.

Preparation of Proniosomes

The slurry method was used to make the proteosome powder. The number was looked at using different carriers, as shown in Table 1 and 2. The process involved dissolving the drug in a 20 ml solvent that contained methanol, chloroform, and exactly measured amounts of Span60 and cholesterol in different amounts. During the process, RBF is linked to a Rota evaporator, and in the next step, modified lactose is used to make the proniosome powder. The dried product was put through a sieve with a mesh opening of 60# to get a finely divided material that is easy to move. After that, the material was put in containers that could not be opened and kept at a temperature of 4°C for further study (Alsarra, 2009; Khatoon *et al.*, 2019).

Table 1: Formulation composition

Code	Span 60 : Chol ratio	Cholesterol (mg)	Span 60 (mg)	Methanol (ml)	Chloroform (ml)
Batch 1	1:1	50.0	52.0	7.0	12.0
Batch 2	1.4:1	37.5	63.0	7.0	12.0

Table 2: Bunches containing a carrier for processing

Ratio	Batch No.	Drug (gm)	Span 60 (gm)	cholesterol (gm)	Solvent (%)	NUS 2 (gm)	NUFL 2 (gm)	lactose (gm)
1:1	B3	14.5	0.562	0.950	2:2	1.56	-	-
1:1	B4	14.5	0.570	0.950	2:2	-	1.56	-
1:1	B5	14.5	0.570	0.950	2:2	-	-	1.56
1.5:1	B6	14.5	0.626	0.375	2:2	1.56	-	-
1.5:1	B7	14.5	0.626	0.375	2:2	-	1.56	-
1.5:1	B8	14.5	0.626	0.375	2:2	-	-	1.56
1:1.5	B9	14.5	0.425	0.580	2:2	1.56	-	-

Evaluation of Proniosome Powder

Physical Properties

An study was done to look at the shapes, sizes, and colors of all the different types of Artemether floating microspheres that were made.

Micromeritics properties

Each batch of prometheosome powder that was made was looked at in terms of its angles of repose, Carr's index, Hausner's ratio, bulk density, and tapping density.

Percentage yield

Quantification of drug content and evaluation of how well drugs are trapped. The medicine's concentration was found using a UV spectrophotometer (V-630, Shimadzu Co Ltd., and Japan) at a wavelength of 228 nm, after it had been dampened with dichloromethane as needed.

Surface characterization

To look at the surface of the Proniosome powder, scanning electron microscopy was used.

In- vitro drug release study

A dialysis membrane was used to measure how much Artemether was produced from Proniosome powder at 200 rpm. The temperature was kept at 370°C, and 50 mL of phosphate buffer (pH 6.8) was used as the solution. Five-ml samples were taken at 30, 60, 90, 120, 150, 180, 210, and 240 minute intervals. Whatman filter paper was used to filter the samples, and then UV research was used to look at them. It was measured and written down what percentage of drugs were released over time. They looked at how the mixture and the standard Artemether capsule broke down and saw which one was better (Ray *et al.,* 2018; Thombre *et al.,* 2022).

Result and Discussion

Drug-Excipients Compatibility Study

A 14-day evaluation of physical and chemical compatibility was conducted in a stability chamber at 45º C with and without moisture. With the aid of FT-IR analysis, the drug-excipient mixtures were examined for chemical and physical incompatibilities, including color change, liquefaction, caking, and gas production. The following table 3 presents the findings for each day when moisture was present and absent (Ahirrao *et al.,* 2022).

Table 3: Compatibility study of drug and excipients

Drug and Excipients	Span 60	Cholesterol	Lactose	Neusilin
1	*	*	*	*
2	*	*	*	*
3	*	*	*	*
4	*	*	*	*
5	*	*	*	*
6	*	*	*	*
7	*	*	*	*
8	*	*	*	*
9	*	*	*	*

No change (*); caking (#)

Evaluation of Proniosomes

Physical Appearance

For the mixture to change into a Proniosome, it needs to get rid of all the conditions that are needed.

Micromeritic Properties

We checked the micromeritic properties of all the batches that were made. These included the bulk density, the tapped density, Carr's index, Hausner's ratio, and the angle of repose. We looked at the micromeritic features of the formulation and found that its bulk density is between 0.3581 and 0.4648 g/cm3 and its tapped density is between 0.3848 and 0.5134 g/cm3. The composition has great flow properties, as shown by the Hausner's ratio being between 1.1180 and 1.1256 and the Carr's index being between 5.99 and 8.22 (Sharma *et al.,* 2010).Table 4

showing the results of the micromeritic characteristics of the mixture.

Percentage yield

It was found out what amount of peptidosomes Artemether made. Formulations B1 through B9 had percentage returns that were between 98.12% and 99.11%, which is a good range.

Table 4: Micromeritic characteristics of the mixture

Batch code	Bulk density (gm/ml) ± SD	Tapped density (gm/ml) ± SD	Carr's index ±SD	Hausner's ratio ± SD	Angle of Repose (º)
B1	0.4962 ±0.004	0.4347±0.0061	7.81 ± 0.062	1.0821± 0.0044	32.0º
B2	0.3745 ±0.005	0.3548± .0358	0.5134± 0.008	1.0657± 0.0055	32.00º
B3	0.4462 ±0.006	0.3348± 0.055	0.4914± 0.007	1.0238± 0.0087	33.65º
F4	0.3755 ±0.007	0.3519± 0.058	0.5621± 0.008	1.0798± 0.0055	32.78º
B5	0.4470 ±0.006	0.3345± 0.050	0.4945± 0.007	1.0347± 0.006	33.91º
B6	0.4859 ±0.036	0.3614±0.035	5.3634± 0.040	1.0648±0.012	35º.1
B7	0.3842 ±0.990	0.4836±0.040	8.1234± 0.055	1.0961± 0.034	38.34º
B8	0.4624 ±0.059	0.4431±0.040	8.2678± 0.031	1.7057± 0.021	36.12º
B9	0.3134 ± 0.033	0.3946±0.070	8.3847±0.029	1.0978 ± 0.033	36.78º
Placebo	0.3824 ±0.058	0.3512±0.040	5.1634± 0.030	1.5143± 0.028	31.8º

The amount of drugs and how well they are trapped

The proniosomes were broken up using sound waves in a phosphate buffer with a pH of 6.8. They were then screened. A UV spectrophotometer was set to the right concentration by diluting it with phosphate buffer at pH 6.8. The drug content was recorded at 228 nm. To find the percentage of drug content and the percentage of entrapment effectiveness, a formula was used. Formulations B1 through B9 had percentage returns that ranged from 98.28% to 99.33%, which is a normal range. All of the made formulations were found to have between 94.24% and 97.88% drug present. Because of this, the drug's content stayed the same in all versions. All of the mixtures were able to trap drugs between 91.33% and 94.66% of the time [17-19].

Surface characterization

Scanning electron microscopy was used to look at the Proniosomes' surface features. After being stuck to metal rings with double-sided tape, the Proniosomes were vacuum-coated with gold. Studying the particles with scanning electron microscopy (SEM) showed figure 1 that the formulation's particle size had a rough and uneven surface while keeping its round shape.

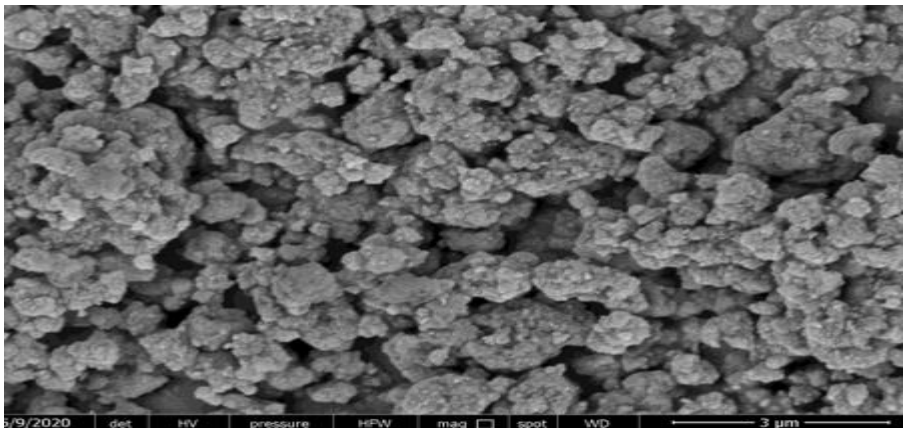

Figure 1: shape of the formulation's surface

In vitro drug release study

A high drug release of 92.33% was seen in the B2 batch. In addition, the research showed that the makeup of Proniosomes could make the medicine stay in the body for a long time. Formulations B1 through B9 show longer drug release in their drug release patterns. The B2 formulation had the fastest rate of release after four hours out of the four formulas. An in vitro study was done to look at how different versions of the medicine were released. Table 5 and figure 2 showing the results of the same study.

Table 5: Different batches of the formulation's drug release in a lab setting

Time (Min.)	B1	B2	B3	B4	B5	B6	B7	F8	B9
0	0	0	0	0	0	0	0	0	0
30	16.45 ± 0.042	17.55 ± 0.040	25.44±0.061	16.64 ± 0.022	16.78 ± 0.022	16.66 ± 0.024	14.89 ± 0.066	15.23 ± 0.064	11.28 ± 0.014
60	25.81 ± 0.033	27.88 ± 0.033	29.72 ±0.012	25.12 ± 0.033	25.88± 0.054	25.89 ± 0.033	25.87 ± 0.062	40.12 ± 0.033	20.12 ±0.035
90	49.34 ± 0.048	52.33 ± 0.070	54.86 ±0.066	47.78 ± 0.054	49.65 ± 0.070	49.78 ± 0.055	49.57 ± 0.074	43.78± 0.028	40.98 ±0.018
120	68.42 ± 0.050	71.30 ± 0.051	65.66 ±0.066	66.44 ± 0.055	66.96 ± 0.078	66.44 ± 0.025	68.59 ± 0.023	62.81 ± 0.063	55.51 ±0.033
150	80.33 ± 0.040	81.33 ± 0.040	82.55 ±0.044	78.33 ± 0.028	78.31 ± 0.042	78.31 ± 0.047	77.33 ± 0.022	73.65 ±0.047	65.67 ±0.034
180	82.50 ± 0.050	85.52 ± 0.078	83.45 ±0.247	81.78 ± 0.011	80.50 ± 0.046	79.50 ± 0.023	79.50 ± 0.055	78.88±0.012	74.42± 0.023
210	83.66 ± 0.030	88.66 ± 0.033	85.42 ±0.027	84.66 ± 0.034	82.66± 0.023	83.61 ± 0.088	82.64 ± 0.012	81.12 ±0.048	80.12± 0.023

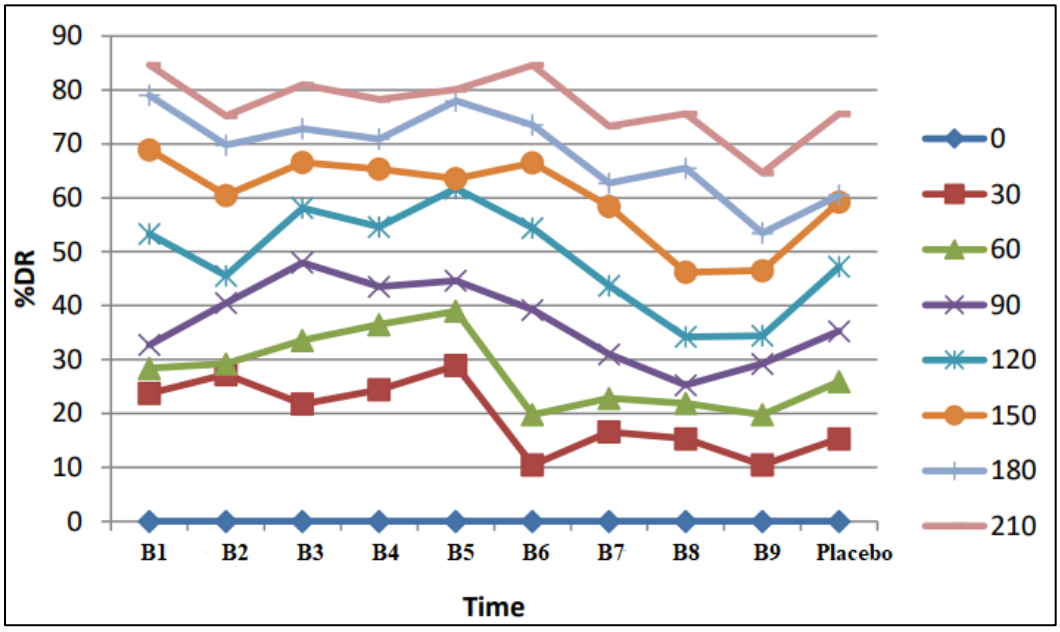

Figure 2: The way drugs are released from versions B1 to B9

Stability study

After three months of keeping at accelerated conditions, the prometheosomes that were made did not change, as shown by the three-month accelerated stability studies that were done at 400C ± 20C and 75% ± 5% RH. The formulation's color and appearance didn't change, and its FTIR spectrum also didn't show any changes, which supported this finding. Based on these results, the B2 version is stable for three months when conditions are sped up. After three months, the FTIR spectrum of Formulation Batch B2 had all of its distinct peaks. The samples were taken out and put through the tests shown in the table after one, two, and three months. Table 6 and figure 3 showning the results.

Table 6: Details of the study on stability for the B2 batch

Test	Before	After		
	0 month	1 month	2 month	3 month
Drug release	92.12 ± 0.126%	92.67±0.578%	94.12±0.357	95.88±0.578
Floating lag time	>12 hrs	>12hrs	>12hrs	>12hrs

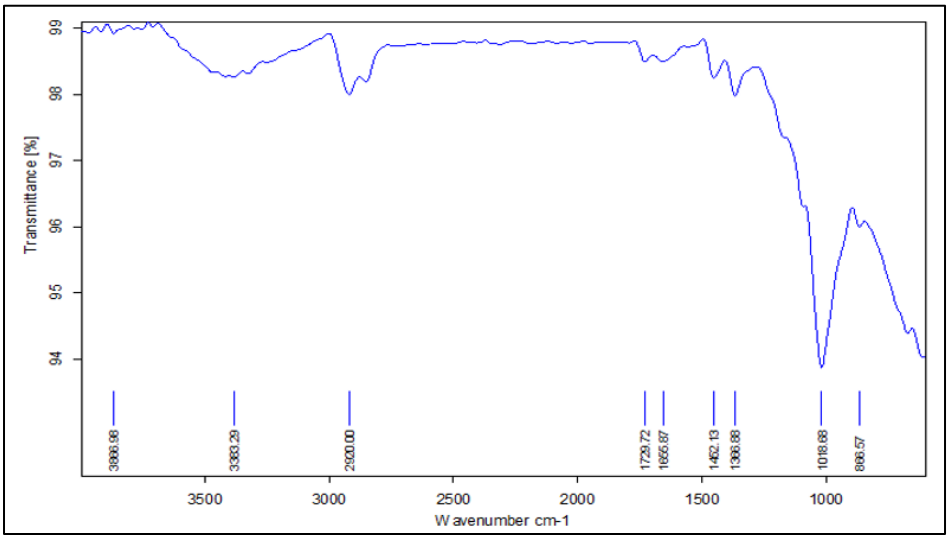

Figure 3: FTIR Report of Batch B2

Conclusion

It was possible to make a better Proniosome powder that has a vesicle size that lets Artemether be delivered through the nose and a high encapsulation efficiency. By using intranasal administration, the Artemether showed much better stability and penetration, as well as better control over drug release over a longer period of time. So, we can say that Proniosome powder with artemether for intranasal administration might be a good way to give drugs because it increases bioavailability by keeping the drugs in the nasal cavity for longer. It's based on the reviews. Better results were seen with the improved Proniosome powder from batch B2. Better results were seen in the batch that used Neusilin NUFL2 grade compared to other carriers.

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Conflict of Interest
None

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