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Updated Review on Proniosomal Transdermal Drug Delivery System

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Abstract

Scientists worked to stabilise without having an impact on the noisome drug delivery method its marital characteristics, which led to the creation of the potential drug carrier proniosome. Drug delivery methods using niosomes and liposomes have disadvantages that proniosomes do not. Dry formulations of a non-ionic, water-soluble surfactant are called proniosomes and are applied to a carrier system. Proniosome hydration results in the formation of niosomes.

They have the potential to increase the dissolution, accessibility, and uptake of various medications by addressing the instability issues with niosomes and liposomes. In addition, they provide a flexible method of drug delivery for a variety of both hydrophilic and hydrophobic medicines. They can deliver medications using a number of techniques to the intended site of action, offering a controlled drug release of the medication and a reduction in any potentially harmful side effects. It's critical to be knowledgeable of each study's limitations, which each have their own benefits and drawbacks, in order to get the right study results. Ecological, prospective, retrospective, case-control, case-crossover, or cross-sectional cohort designs are all possible for observational studies. A vital subclass of observational experiments of the diagnosis research designs, which compare the accuracy of different diagnostic approaches and tests to other diagnostic measures, can be used to derive important findings. Only data collected utilising a valid scientific methodology and the appropriate statistical methods can be used in biomedical research to draw meaningful findings. As a result, it's critical to pick a solid study strategy in order to offer a just and impartial evaluation of the research concerns. This review focuses on a variety of proniosome-related topics including - advantages, preparation, mechanism of action, materials and their specification, study design, characterization &evaluation parameter.

Keywords: Proniosomes; Niosomal; Factorial designs; Relationship; TDS

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Introduction

In a dry formulation, proniosomes are surfactant-coated carrier with water solubility. When stirred in a hot water solution to form a noisome dispersion, they quickly rehydrate prior to application. Proniosomes maintain their physical stability while being stored and transported. Drugs that are encased in the vesicular structure of proniosomes have a longer shelf life in the bloodstream, have better tissue penetration, and are less toxic. From a technical perspective, niosomes are attractive drug carriers from a technical perspective since they have superior chemical stability and don't have the numerous drawbacks of liposomes, such as their high cost and issues with changeable phospholipid purity [1-5]. Proniosomes have drawn a lot of attention from researchers since the early 1980s due to the possibility of using them as pharmacological targets and carriers. In comparison to conventional medication delivery methods, these applications have a number of benefits while avoiding disadvantages [6].

Benefits of Proniosomes

(I) Non-ionic surfactants and phospholipids can both help with medication diffusion and act as penetration enhancers in proniosomes.

(II) Proniosomes have various advantages, including simpler distribution, storage, and dosage. (III) They avoid problems including leakage, aggregation, fusion, and physical instability that are connected to one or more aqueous dispersions.

(IV) Proniosomes avoid the problems associated with liposomes, such as oxidative or hydrolytic degradation, also decreased potential for fusion, agglomeration, or deposition while being stored. (V) Proniosomes not only offer a promising drug delivery technique, but they may also hasten epidermal barrier restoration [7-10].

Mechanism of Action

A dormant form of niosomes is called a proniosome that require hydration in order to become their active forms. The two ways to hydrate are: the first uses the skin's natural moisture, and the second uses solvents like water or a buffer. Transdermal medication delivery methods use a variety of skin penetration strategies. Due to their deformable characteristics, among them, like transfers, may get through the skin undamaged. Other types, like ethosomes, disrupt the epidermis' dense structure as they enter the body intact. Still other types, like proniosomes and niosomes, utilize surfactants to improve penetration into the skin. The SC and viable epidermis must first be crossed by the topically administered molecule [11-15].

There are three different routes by which this might occur: the path of appendages, the intercellular highway is used by cells and lipids to pass via sebaceous glands and hair follicles, or cells travel via the complex web of lipids to reach other cells [16]. Skin appendages are not a significant conduit because they account for only 0.1% of total skin surface. Multiple partitioning and diffusion phases are necessary to cross SC via the Trans cellular pathway. Drug molecules are thought to be transported mostly via the intercellular pathway. The fluidity and permeability of the SC are increased, which enhances drug penetration into the SC, and the highly reversible organisation of the highly thick intercellular lipid lamellae matrix is disturbed. Proniosomes moisturise the skin when they are applied to it, causing a gradient of thermodynamic activity to emerge at the interface, increasing the diffusion pressure for drug penetration through the SC [17-20]. In the vascular system, niosomes are endocytosis, and proteolytic enzymes break down their membranes, releasing the medication they carry. Proniosome activity involves penetration via the skin and systemic absorption and might be dermal, intracellular, or transdermal (**Figure 1**). In terms of physical characteristics, a drug intended for transdermal administration should have a molecular weight of less than 600 Da, optimum oil solubility, an ideal partition coefficient, a low latent heat of fusion, and a log p-value of 1-3. Molecular entities with a log p-value below one are too hydrophilic to successfully diffuse into SC by passive diffusion. If the log p-value of the particle is greater than 3, the particle's hydrophobicity will lead it to get stuck in the lipid matrix [21-25].

Materials

The following are the various substances employed and how they affected proniosomes preparation: (**Table 1**)

Methods of preparation

There are several ways to create proniosomes, such as spraying a non-ionic surfactant over water-soluble carrier particles, employing a slurry method, and coacervation phase separation [26], Provides an explanation of the preparation procedures and their sequential processes (**Table 2 and Figure 2**)

Study Design

Clinical epidemiology studies often concentrate on the relationship between an exposure, such as a treatment or environmental factor, and an outcome, like a disease or death. Numerous study designs can be used to answer these research topics. Both observational study types, such as cohort and case-control studies, and randomised controlled trials (rcts) are frequently employed in nephrology research [27] (**Figure 3**).

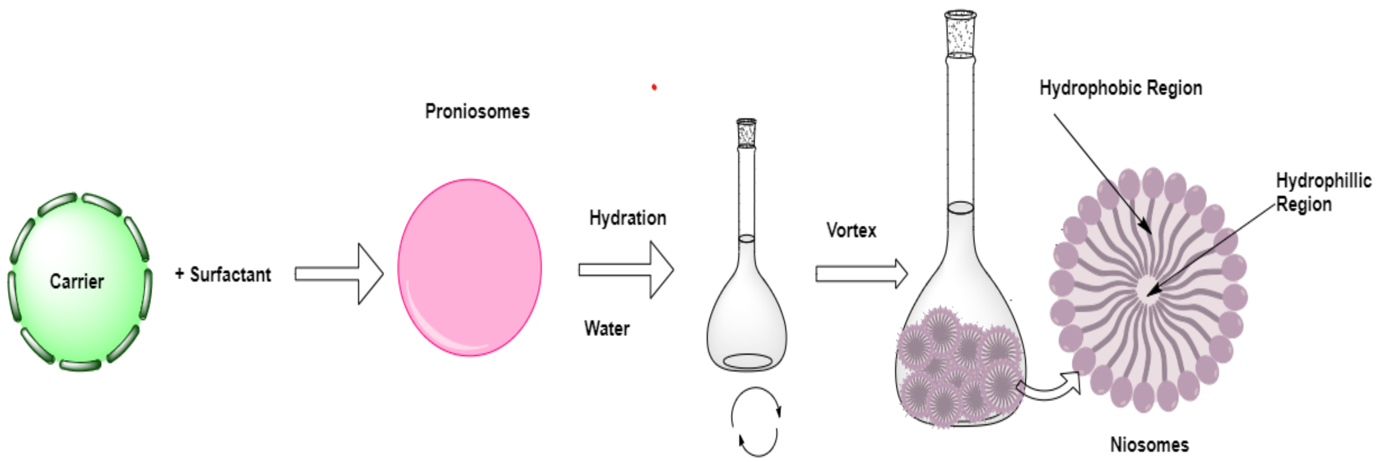

Figure 1 Proniosome hydration, as well as the hydrophilic and hydrophobic areas of niosomes.

Table 1. The various substances Employed and how they affected Proniosomes preparation.

Material	Specification	Action	References
the span and tween	Surfactants	Maintains HLB level	[36,37,39,42]
	1. Spans 20, 40, 60, and 80 2. Tween-20,60		
	3. Span 85		
cholesterol & lecithin	stabilizers for membranes	Cholesterol: Has an impact on the permeability and stability of vesicles. Lecithin is a penetration-enhancing substance. Keep the vesicles' stability, permeability, and integrity intact. Improves penetration	[35,37,38, 39,40,41]
Glucose monohydrate, Sucrose stearate, Lac, Mannitol, Polyols, and Maltose	Carriers	Holds the drug	[35,37,38, 39,40]
Methanol, chloroform, ethyl alcohol	Organic solvents	influence on the drug's vesicle size and penetration	[35]

Table 2. Explanation of the Preparation Procedures and their Sequential processes.

Process of preparation	Philosophy	Product type	References
Method of coacervation phase separation	In order to create a translucent dispersion, lipids, a surfactant, and a medicine are mixed with a solvent and heated at 60 to 70 °C over a water bath.	Transparent gel	[18,19,20]
Slurry technique	An organic solution, cholesterol, surfactants, and a medication are combined, and the resulting mixture is poured over a carrying medium to create slurry. To create proniosomes that flow freely, rotary evaporators should be used to evaporate the solvent.		
	An organic solution, cholesterol, surfactants, and a medication are combined, and the resulting mixture is poured over a carrying medium to create slurry. To create proniosomes that flow freely, rotary evaporators should be used to evaporate the solvent.		
	An organic solution, cholesterol, surfactants, and a medication are combined, and the resulting mixture is poured over a carrying medium to create slurry. To create proniosomes that flow freely, rotary evaporators should be used to evaporate the solvent.	Powdered form	[21–22]
Method of spray coating	A spinning evaporator connected to a flask with a rounded bottom is used to spray organic cholesterol, surfactant, and medicine solutions one after the other onto a carrier material.	Powdered form	[23]

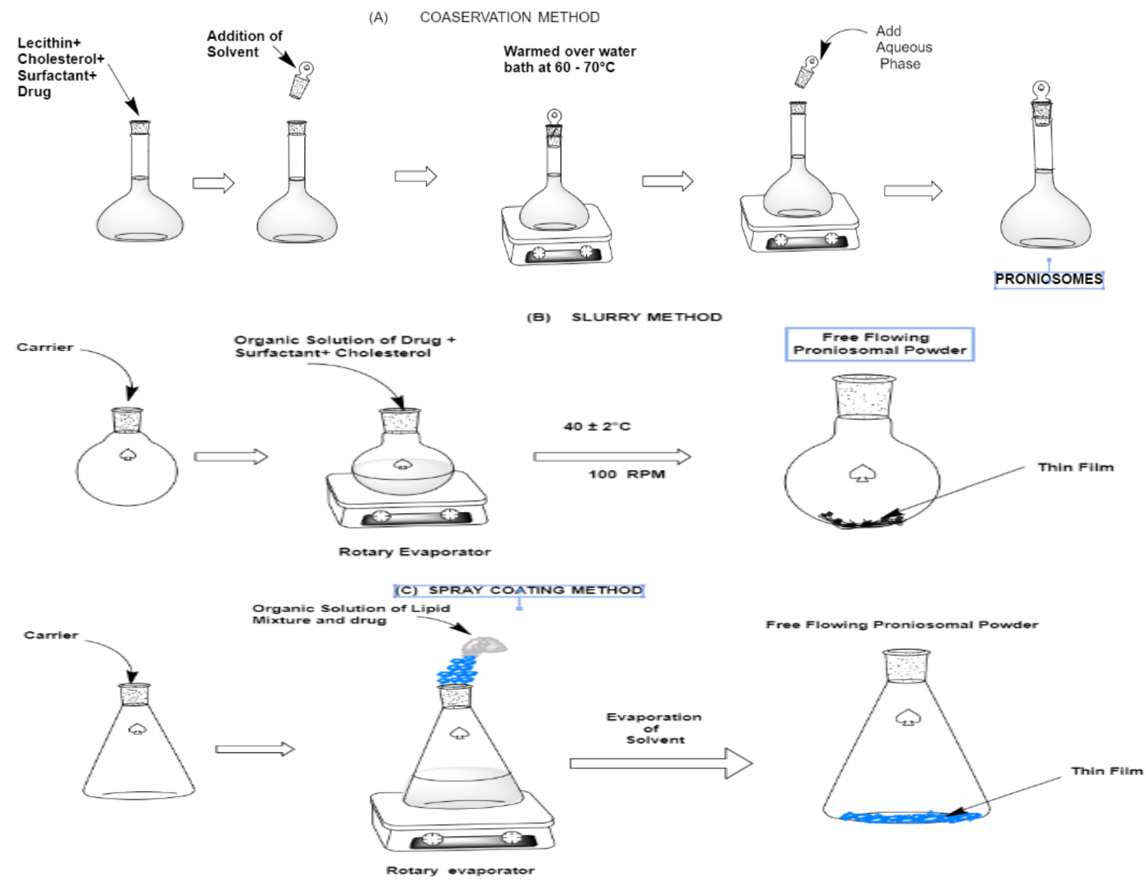

Figure 2 Various Methods of Preparation.

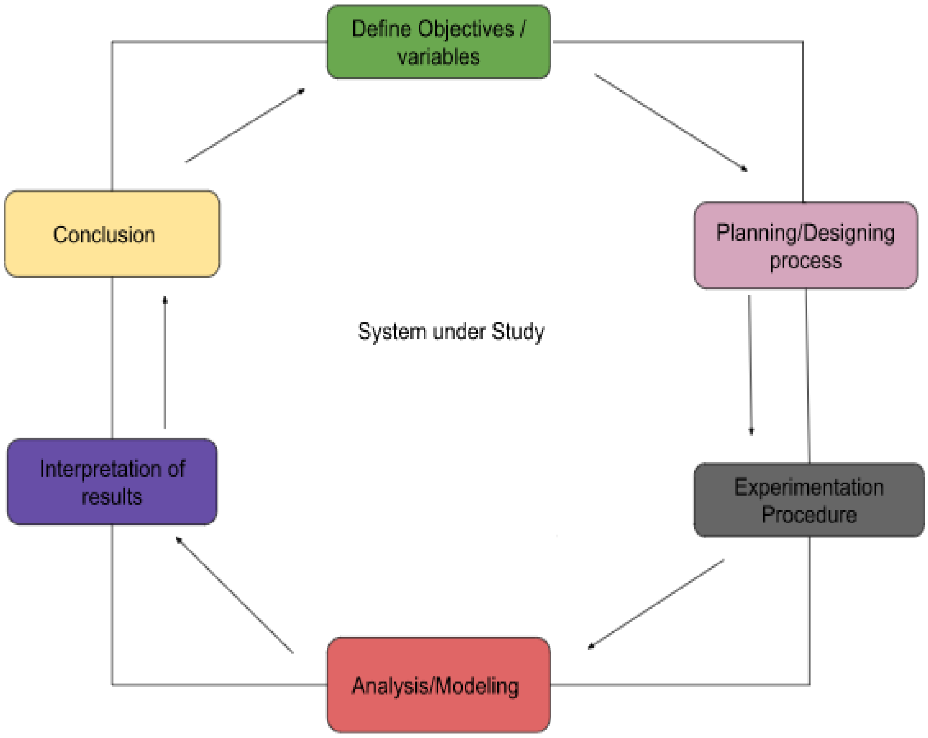

Figure 3 Analysis of System under Study

Types of experimental research design

The procedures used to collect data in experimental investigations are referred to as experimental design in the classic sense.

Three sorts of experimental designs can be identified:

The following research designs are available:

- Design of the pre-experimental study
- True experimental or real-world experimental research
- Quasi-experimental.

The kind of research strategy to use depends on how you categories study subjects depending on circumstances or groupings.

1. **Design of the pre-experimental study:** An observational group or groups are preserved after the application of cause-and-effect elements. If these groups need to be the topic of additional research, this study will assist you in making that decision.

Three sorts of preliminary analysis can be identified:

- Individual Case Studies
- One-group pre-post-test-test study design; comparison of static groups.

1. **Real-world experimental research methods:** Statistics are used in real experimental study to confirm or deny a notion. It is therefore the most trustworthy sort of research. Only real design can demonstrate a cause-and-effect link within a set of participants among the several forms of experimental design. Three requirements must be met for an experiment to be valid:

Two groups will participate in the study:

- Comparison of the experimental group, which will experience changes, and the control group, which won't.
- A variable that a researcher can change
- Roughly distributed

This form of experimental inquiry is frequently employed in the physical sciences [28, 29-35].

1. **Design of a quasi-experimental study:** "Quasi" means "almost," which implies similarity. Though it is different from an experimental design, a quasi-experimental design is similar to one. Assigning a control group to each makes the difference between the two. The individuals of a group are not chosen at random; instead, an independent variable is altered in this study. When random assignment is unnecessary or unimportant, quasi-research is employed in field situations (**Table 3**).

RCT Subjects are randomly assigned to experimental or control groups. The gold standard for determining causes in therapeutic research suitable to investigate several interventions. It can be very expensive and time-consuming. Unsuitable for studying uncommon events may be improper Due to tight selection criteria, generalizability is frequently low [36-45].

Table 3. Design of a quasi-experimental study.

Research Plan	Essential Qualities	Toughness	Weakness
Case Report and Series of Cases	one or several subjects.	The earliest types of publications It is quick and affordable to produce hypotheses.	There is very little chance of proving selection bias has a causal effect.
	Without a control group, a thorough description of (a) and (s)		
Cross - sectional study / research	Exposure and results are measured simultaneously. Comparison of subjects with and without results	Quick and affordable hypothesis generation This is useful for describing the prevalence of illness.	There is very little chance of establishing causes and effects.
			bias in favour of survival and selection
Case-control research	In terms of exposure, cases—those who achieve the intended result—are compared to controls—those who don't.	Efficient Suitable for researching uncommon consequences and numerous exposures, reasonably affordable for creating theories.	There may be some opportunity to identify causes and effects, but All we can do is analyses One result Choosing a randomized controlled trial could be challenging.

Observational Designs

Case Report and Series of Cases

Without using a control group, Case Report and Series of Cases provide in-depth descriptions of cases. The probable association between the observed outcome and a case report or small group of patient histories and clinical evaluations are used to report a specific exposure (case series). These research techniques could be among the first to discover a brand-new disease or harmful health consequence of an exposure. For example, the first case reports on acute phosphate nephropathy-a type of acute renal failure-following the use of oral sodium phosphate products for stoma cleansing before colonoscopy were published in the English language literature in 1985 [46-48]. Following this preliminary research, numerous additional cases and series of instances were published, which provided further evidence of this unusual and important adverse event. Following the completion of these investigations, the oral sodium phosphate shouldn't be given to patients who have kidney disease, impaired kidney function or reperfusion, dehydration, or uncorrected electrolyte imbalances, according to an United states Food And drug caution [49].

Cross-Sectional Research

A specific outcome and the population's exposure status are both looked into simultaneously in a cross-sectional assessment. The likelihood and attributes of a result at a specific accent might be thought of as being "snapped" by cross-sectional investigations. Due to the simultaneous measurement of the exposure and the consequence, since it is frequently impossible to tell whether an exposure occurred before or after an event, cause and effect relationships are ambiguous. The bulk of cross-sectional studies that have been published talk on the treatment of certain patient populations or the prevalence of a disorder in a population. A cross-sectional study is well-exemplified by Bello et al. They looked into the prevalence of micro albuminuria in family members of individuals suffering from chronic kidney disease (CKD) in relation to the general population as part of a population-based surveillance system, a form of cross-sectional study. Researchers discovered that people with a CKD family history had significantly more cases of micro albuminuria than the sex- and age-comparison groups. It is evident in this case that knowing that there is a genetic predisposition of CKD happened before the onset of micro albuminuria, in contrast to the majority of cross-sectional research [50-59].

Case-control research

Finding probable contributing factors to a result is the aim of case-control research. In this kind of study, participants are chosen depending on the dependent variables and contrasted with participants who do not have the condition (controls). The patients and controls have already been compared with regard to exposure. When analyzing unusual outcomes, case control studies are very useful. End-stage renal disease is one illustration of such an unusual result (ESRD). Ibanez et al. investigated if the development of ESRD was associated with use of non-steroidal anti-inflammatory medications, aspirin, and other analgesics for an extended period of time (NSAIDs). They selected as cases those patients with ESRD who registered in the neighbourhood dialysis programme over a two-year period. They kept track of when the medications were used in the past. The selection of control individuals, who were hospitalized at the same hospital as the cases and had a similar age and sex distribution, and their drug use were also recorded. When the researchers compared the two groups, neither NSAIDs nor non-aspirin an increased risk of ESRD was linked to the use of analgesics. The researchers contrasted the two groups; however, aspirin use on a regular basis seems to be linked to a higher incidence of ESRD [60-64].

Cohort Studies/ Research

A study group (cohort) made up of individuals who are not exposed to the intended outcome is chosen by the researcher while conducting a cohort study. The goal of this study's design is to identify the factors that contribute to the occurrence of this result. Whether a subject was exposed or not before the investigation relies on their occurrence status (controls). Following that, People are observed over time to determine who will experience the consequence and who won't. Researchers can examine several results and widespread exposure variables in cohort research. In cohort research, a researcher selects a study group (cohort) made up of volunteers who are not exposed to the desired result. Finding the factors that affect the appearance of this outcome is the goal of the design of this study. The classification of subjects as exposed or unexposed depends on their exposure status prior to the investigation (controls) [65-68].

RCTs

For evaluating treatment or other interventions, the RCT is considered the gold standard. RCTs are capable of removing selection bias and prognostic selection (often referred to as confounding by indication), providing them a clear advantage over observational studies in establishing a causal relationship [69]. Randomization, in which patients are admonished at random to either the experimental group (which would receive the intervention under study) or the control group, is the main concept. The relationship between the therapy recommended by the doctor and the patient's prognosis is broken via randomization. The outcome of the experimental and control groups are then compared after being followed up on for a predetermined amount of time. The ADEMEX trial [70] is a prime nephrology RCT illustration. For this process, 965 Mexican peritoneal dialysis patients were randomly split into two groups: to increase peritoneal creatinine clearance, a modified prescription was given to the experimental group, while the control group received their regular peritoneal dialysis prescriptions. The two group's initial traits following randomization were comparable, with a few minor exceptions, for example, a somewhat greater degree of diabetes in the comparison group. But rather than being a result of the investigator's decision, this divergence was the result of chance [71]. Following a comparison of death rates between the two groups over the course of at least two years, the researchers came to the conclusion that an increase in peritoneal small-solute clearance did not clearly improve survival. Despite the fact that RCTs are useful tools, there are certain disadvantages [72, 73]. They cost a lot more than observational studies, first and foremost, however it will be impossible to evaluate every healthcare intervention in an RCT due to the sheer quantity of them. Additionally, it is frequently considered unethical to subject patients to a treatment that is ostensibly (but not yet demonstrably) superior to the standard of care. RCTs are technically possible but are not the best method for detecting adverse outcomes that are uncommon or take years to emerge [70-74].

Factorial Designing

In factorial designs, input variables are purposefully and simultaneously changed in accordance with an established matrix of potential sequences of factor values. They vary most from what is typically determined in this regard since each factor can be altered independently of the others. A, B, C, and other capital letters are frequently used to represent factors, while +1 and -1 stand for a factor's lower and upper levels, respectively. In the event that there is a middle level, this is defined as (0). This clearly represents the levels in a coded manner, but the following equation shows that it also represents the real values of the parameters:

Xcoded = (Xactual - Xmean)/ [(Xhigh – Xlow)/2]

All possible factor level configurations are included in full factorials. The following equation indicates how many tests are necessary:

Number of experiments = Levels Factors

For instance, 23=8 experiments are needed to complete a two-level factorial with three elements. Straightforward two-level factorial models for factors with two and three are shown in (**Figure 3**).

Partial factorial designs, which are a portion of the pertinent full design, often, represent half or a fourth of the complete factorial. They are typically used for screening purposes if there are more than 4 criteria. As was already established, confusion, or the aliasing of key effects and interactions, is their fundamental problem. Resolution refers to a design's ability to accurately assess impacts and interactions absent any potentially confusing factors. These resolution rating are the most widely used. Two-factor interactions can be used to alias main effects; however, Resolution III designs state that while some two-factor interactions may be achieving to other main effects, others are not. When there are significant two-factor interactions that influence it, the answer can be inaccurate.

Three-factor interactions can be utilized to alias primary effects, according to Resolution IV designs, as opposed to other significant effects or two-factor interactions. Additionally, there is overlap between two-factor interactions. They are an appropriate screening option since the primary impacts won't reveal any two-factor interactions [75-78].

Resolution V (or greater) models effectively cut down on the number of experiments required while still offering performance that is almost on par with full factorials. These results show that no aliased major implications or two-factor interactions with the other key variables or two-factor interactions exist. One possible name for the latter is interactions among three factors. All significant effect and two-factor correlations can be roughly predicted if 3 (and above) interactions are neither statistically significant nor improbable to occur. Evidently, the interpretation of the findings is made more difficult whenever the design resolution is lowered. **Figure 4** shows a two-level factorial with a half-fraction for four factors. Each of the cubes at the fourth element's two levels, D, stands in for one of the three first components, A, B, or C (**Figure 4**).

It is obvious that just eight of the appropriate full factorials total 16 points—or roughly half of the design—is used in this instance (circled points). A DoE's primary goal is, as was previously said, to develop mathematical equations that connect the causes to the effects. Both the direct impacts of the constituents and their interactions are necessary for the latter. The mean difference in reaction that occurs as a component rises from a low to a very high level is what matters most in terms of an effect. It can be calculated by contrasting the general trend at the higher factor level with the typical reaction at the relatively low level for the identical factor. Interactions between the elements are frequently observed in addition to the principal impacts and should be carefully taken into account. The degree to which two factors A and B interact, denoted by the letters AB, and determines how much of an impact factor A has on the solution. In this instance, factor B's low and high ratings for component are used to calculate

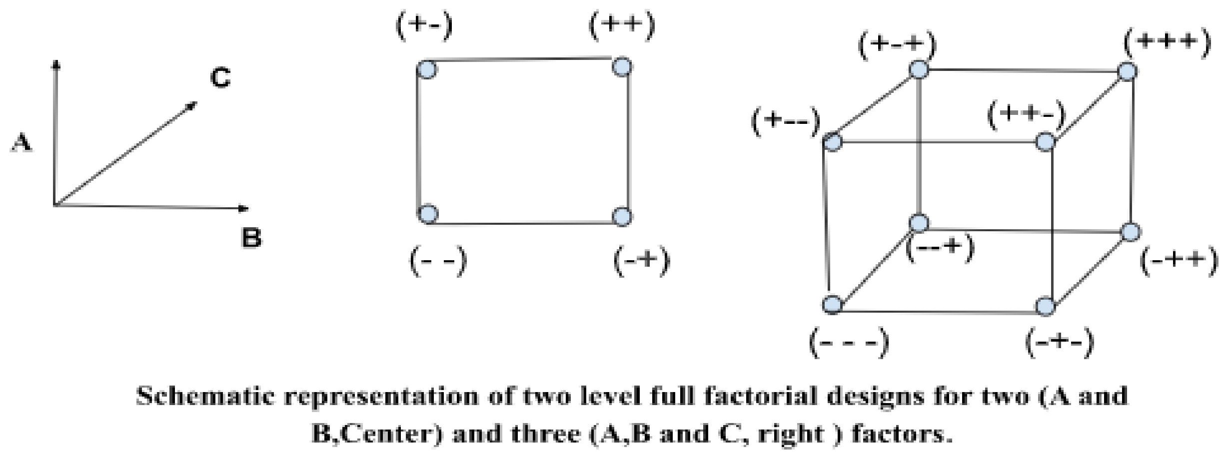

Figure 4 Schematic representation of two level full factorial designs for two (A and B, Center) and three (A, B and C, right) factors.

the interaction as the variation in response between them [79].

These are the most approach in favour schemes.

- Three-level factorial arrangements.
- Design Center for Composites (CCDs): Since cubic or higher models are incredibly rare in practice, they are the most typical choice to represent the operations under investigation (**Figure 5**).

Instead of employing cognitive subtraction, the experiment's design might be modified to process the cognitive circumstances in a factorial approach, allowing assessments of interactions between the various elements [80]. To properly pinpoint the task components, this strategy relies on neuropsychological data and, if available, supplementary behavioral data. The goal is to get the subject to do a function in which the cognitive elements (or dimensions) are combined in certain situations and divided in others (**Figure 6**).

The strategy is based on the premise that the BOLD responses resulting from the circumstances are linear, even though a non-linear approach is possible. Otherwise, unexpected interactions can contaminate some of the results. However, this method is quite beneficial for analyzing cognitive interactions [81].

Characterization of Proniosomal Transdermal Drug delivery system: (Figure-7)

Entrapment efficiency

Proniosomal gel weighing in a glass tube was mixed with prepared phosphate buffer having a pH 7.4 and 0.1 g. Then aqueous suspension was sonicated by using an ultrasonicator for five minutes. Centrifugation at 9000 rpm for 45 minutes was used to separate the produced niosomes carrying lornoxicam from entrapped medication. Using a UV spectrophotometer (Shimadzu), Spectrophotometric analysis of the supernatant was performed at 375 nm, against the solution. Following equation determine the drug's level of entrapment:

Entrapment effectiveness (%) = Entrapped Drug x100/ Drugs added in total

Proportion of drug diffusion

Diffusion investigations were performed in a Franz cell. The diffusion cell was equipped with a dialysis membrane. On one part of the dialysis membrane, proniosomal gel was placed in a precise amount. Phosphate buffered saline with a pH of 7.4 was present in the receptor compartment (PBS) in 10 ml. The fluid in the donor compartment was continually swirled using a Teflon-coated magnetic bead at a speed of 100 rpm. Every 60 minutes, 1 ml of sample should be taken from the sample cell and continue for 24 hours from the starting time. The sample that was collected will be analyzed at 375 nm in an UV-visible spectrophotometer. Replace the same amount of receptor compartment sample with fresh 7.4 pH phosphate - buffered saline [82-88].

Size of the particles and PDI index

After being hydrated with PBS pH 7.4, drug-loaded proniosomal gel's average particle size and size distribution were measured. Using photon correlation spectroscopy (PCS) on Nanophox at room temperature, to avoid multicasting activities, Water that had been filtered and twice-distilled was used to homogenize the produced noisome dispersion. Using the following equations, the PDI revealed the range of the size distribution.

PID ¼ ð Þ X90 – X10 X50

Scanning Electron Microscopy

Following soaking using a pH 7.4 buffer, the proniosomes' morphology examined five minutes of gold ion coating and scanning electron microscopy [89].

Zeta potential analysis

Potential on the surface of drug-loaded compartments was

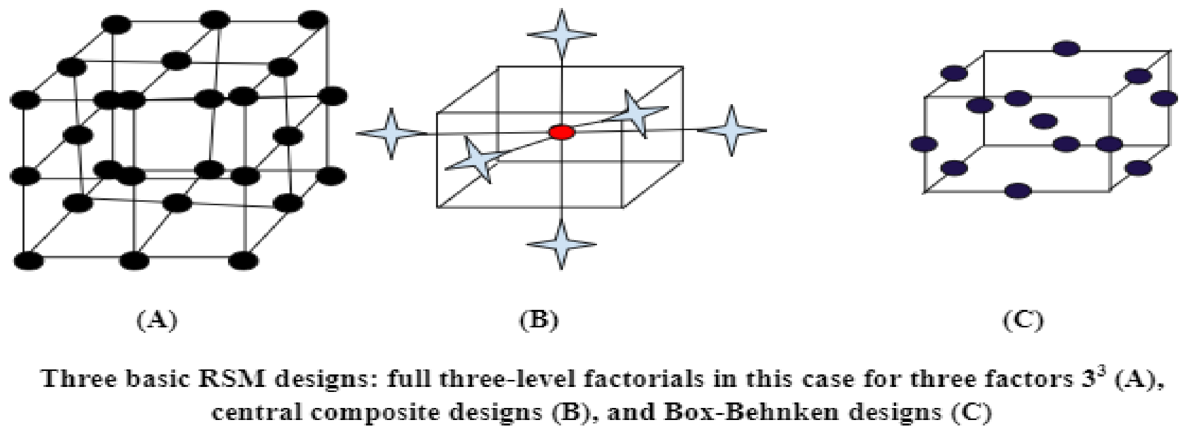

Figure 5 Three basic RSM designs: full three-level factorials in this case for three factors.

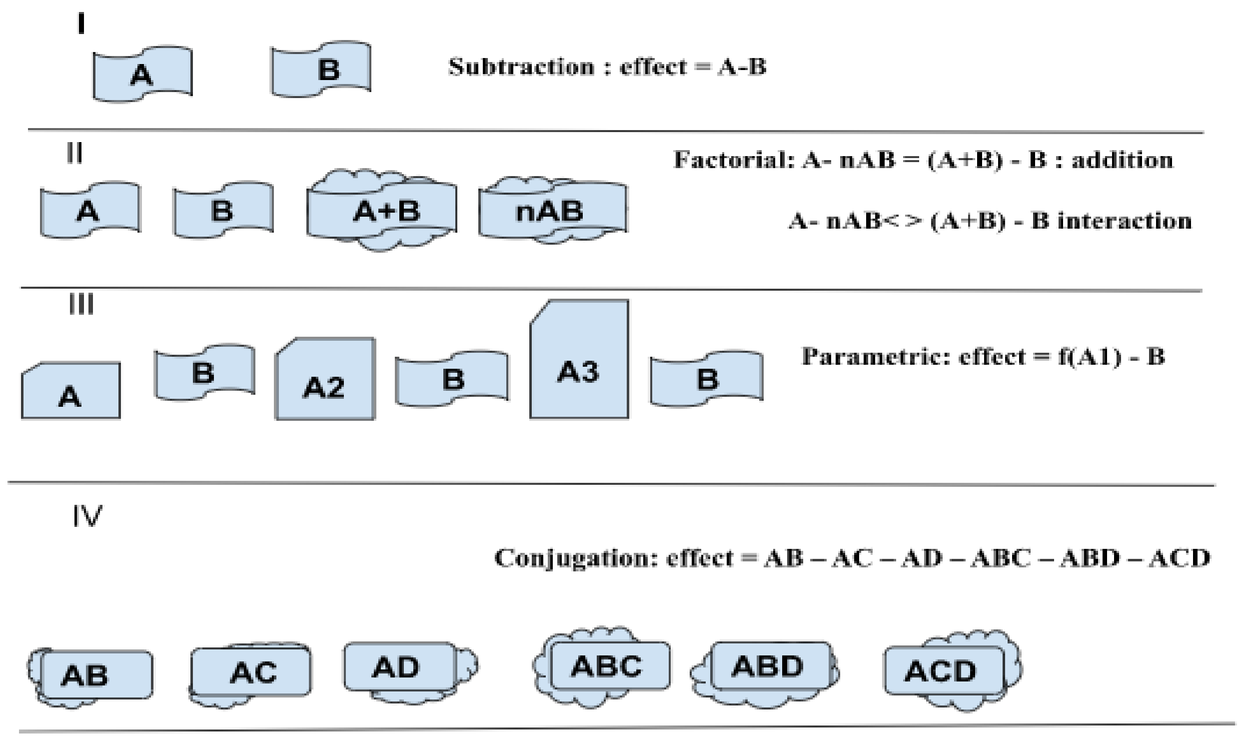

Figure 6 Cognitive comparison strategies.

found using a Zeta potential analyzer. (Brookhaven Instrument Corporation). PH 7.4 after PBS resuscitation, at 25 °C, the typical proniosomes preparation zeta gradient and charges were determined across three runs. The analysis time was set to 60 seconds [90].

Differential Scanning Calorimetry

By means of a calorimeter with differential scanning, evaluated the Proniosomes' thermal properties after being hydrated with phosphate-buffer saline pH 7.4, one milligram proniosomal gel samples encapsulated in common aluminium pans were used for the study. A plot of proniosomes and bulk medication was obtained using a scan range of 10 °C/min and a mean temperature between 30 and 300 °C [91].

Diffraction of X-rays

After being hydrated with PBS, lornoxicam proniosomes were examined using X-ray diffraction analysis to identify their solid-state properties. Using an X-ray diffractometer and an X-ray producer operating at a 40 kV voltage and 20 mA current, drug-loaded proniosomal disperse were scanned at a scanning speed of 2 °/min [92].

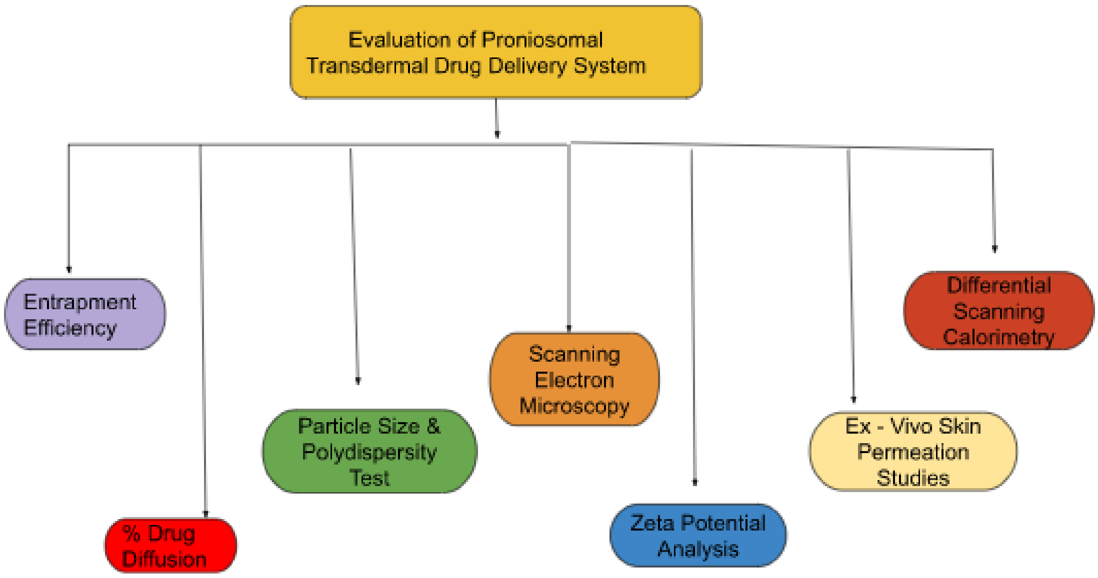

Figure 7 Evaluation of Proniosomal Transdermal Drug Delivery System

Skin permeation research in *ex vivo*

By using Franz diffusion cell for studies of *ex vivo* skin penetration was carried out. A male albino with rat abdominal skin is used for the test. The test was conducted on a Wistar rat weighing 250–20 g. The clamping method brought the skin's dermal side into interface with the receptor medium. Receptor medium was placed inside the receptor chamber, which has a cross-sectional size of 4.32 cm2. After the rat's membrane on the dorsal surface had been evenly coated with gel, a donor chamber was attached. With a tolerance of 0.5°C at 100 rpm, at 37 C, the temperature held steady. During specified 18-hour periods, a sample of 1 ml was gathered, and the amount of medication which has migrated from the formulation into the receptor was measured using UV spectrophotometer assessment at 375 nm [93].

Conclusion

Proniosomes are water soluble carrier particles that are coated with a surfactant and can be hydrated immediately before used to yield to aqueous noisome dispersion. They are more stable than the noisome and liposomes. They can incorporate both lipophilic as well as hydrophilic drugs. They have emerged as challenging carriers for drug delivery via transdermal route. It has become useful dosages form for transdermal drug delivery due to the simple and cost-effective scale up production procedure. Proniosomes have enabled to overcome all the stabilities problems associated with a noisome and liposomes such as fusion, aggregation on storage.

References

1 Radha GV, Rani TS, Sarvani B (2013) a review on proniosomal drug delivery system for targeted drug action. J Basic Clin Pharm 4: 42-48.

2 Arunothayanun P, Bernard MS, Craig DQ, Uchegbu IF, Florence AT et al (2000) the effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from a hexadecyl diglycerol ether. Int J Pharm 201: 7-14.

3 Mittal T, Chaudhary S, Chaudhary A, Kumar A, Ankit S, et al. (2020). Proniosomes: the effective and efficient drug-carrier system. Therapeutic Delivery 2019: 65–68.

4 Paolino D, Cosco D, Cilurzo F (2012) Improved *in vitro* and *in vivo* collagen biosynthesis by asiaticoside-loaded ultradeformable vesicles. J. Control Rel 162: 143-151.

5 Celia C, Cilurzo F, Trapasso E (2011) Ethosomes and transfersomes containing linoleic acid: physicochemical and technological features of topical drug delivery carriers for the potential treatment of melasma disorders. Biomed. Microdevices 14:119-130.

6 Paolino D, Celia C, Trapasso E (2012) Paclitaxel-loaded ethosomes: potential treatment of squamous cell carcinoma, a malignant transformation of actinic keratoses. Eur J Pharma Biopharm 81: 102-112.

7 Carafa M, Marianecci C, Rinaldi F (2014) Ammonium glycyrrhizinate-loaded niosomes as a potential nanotherapeutic system for anti-inflammatory activity in murine models. Int. J. Nanomed 9: 635-651.

8 Di Marzio L, Marianecci C, Cinque B (2008) pH-sensitive non-phospholipid vesicle and macrophage-like cells: binding, uptake and endocytotic pathway. Biochim Biophys Acta 1778: 2749-2756.

9 Donnelly RF (2017) how can micro needles overcome challenges facing transdermal drug delivery? Ther Deliv 8: 725-728.

10 Brambilla D, Luciani P, Leroux J (2014) Breakthrough discoveries in drug delivery technologies: the next 30 years. J Control Rel 190: 9-14.

11 McCrudden MT, Singh TR, Migalska K, Donnelly RF (2013) Strategies for enhanced peptide and protein delivery. Ther Deliv 4: 593-614.

12 Muzzalupo R, Tavano L (2015) Niosomal drug delivery for transdermal targeting: recent advances. Res. Rep. Transdermal Drug Delivery 4: 23-33.

13 Maryam K, Fakhar Ud D, Shefaat Ullah S, Naz D, Ahmad N, et al. (2017). Proniosomes derived niosomes: recent advancements in drug delivery and targeting. Drug Delivery 24: 56-69.

14 Yasam VR, Jakki SL, Natarajan J, Kuppusamy G (2014) A review on novel vesicular drug delivery: proniosomes. Drug Deliv 21: 243-249.

15 Ammar H, Ghorab M, EL-Nahhas S, Higazy I (2011) Proniosomes as a carrier system for transdermal delivery of tenoxicam. Int J Pharm 405: 142-152.

16 Ahmad MZ, Mohammed AA, Mokhtar Ibrahim M (2017) Technology overview and drug delivery application of proniosome. Pharm Dev Technol 22: 302-311.

17 Mujoriya RZ, Bodla R (2011) Niosomes–challenge in preparation for pharmaceutical scientist. Int J App Pharm 3: 11-15.

18 Mujoriya RZ, Bodla R (2011) Niosomes–challenge in preparation for pharmaceutical scientist. Int J App Pharm 3: 11–15.

19 Noordzi J, Dekker M, Friedo W, Zoccali C, Kitty J, et al. (2009) Study Designs in Clinical Research. Nephron Clinical Practice 113: 218-221.

20 Biberstein M, Parker BA (1985) Enema-induced hyperphosphatemia. Am J Med 79: 645-646.

21 Rohack JJ, Mehta BR, Subramanyam K (1985) Hyperphosphatemia and hypocalcemic coma associated with phosphate enema. South Med J 78: 1241-1242.

22 Bello AK, Peters J, Wight J, de Zeeuw D, El Nahas M, et al. (2008) A population-based screening for microalbuminuria among relatives of CKD patients: the Kidney Evaluation and Awareness Program in Sheffield (KEAPS). Am J Kidney Dis 52: 434-443.

23 Ibanez L, Morlans M, Vidal X, Martinez MJ, Laporte JR, et al. (2005) Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. Kidney Int 67: 2393-2398.

24 Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, et al. (2003) Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Int 64: 339-349.

25 Stel VS, Jager KJ, Zoccali C, Wanner C, Dekker FW, et al. (2007) The randomized clinical trial: an unbeatable standard in clinical research? Kidney Int 72: 539-542.

26 Tripepi G, Jager KJ, Dekker FW, Wanner C, Zoccali C, et al. (2008) Bias in clinical research. Kidney Int 73:148-153.

27 Paniagua R, Amato D, Vonesh E, CorreaRotter R, Ramos A (2002) Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 13: 1307-1320.

28 Jager KJ, Stel VS, Wanner C, Zoccali C, Dekker FW, et al. (2007) The valuable contribution of observational studies to nephrology. Kidney Int 72: 671-677.

29 Jyotsana R, Nitesh P, Kamal D (2016). Formulation and evaluation of proniosomes containing lornoxicam. Drug Delivery and Translational Research 6:511-518.

30 Radha GV, Rani TS, Sarvani B (2013) A review on proniosomal drug delivery system for targeted drug action. J Basic Clin Pharm 4: 42-48.

31 Ahmad MZ, Mohammed AA, Mokhtar Ibrahim M (2017) Technology overview and drug delivery application of proniosome. Pharm Dev Technol 22: 302-311.

32 Abd-Elbary A, El-laithy HM, Tadros MI (2008) Sucrose stearate-based proniosome-derived niosomes for the nebulisable delivery of cromolyn sodium. Int J Pharm 357: 189-198.

33 Fang JY, Yu SY, Wu PC, Huang YB, Tsai YH (2001) *In vitro* skin permeation of estradiol from various proniosome formulations. Int J Pharm 215: 91-99.

34 Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D, et al. (2007) Design and development of a proniosomal transdermal drug delivery system for captopril. Trop J Pharm Res 6: 687-693.

35 Solanki AB, Parikh JR, Parikh RH (2007) Formulation and optimization of piroxicam proniosomes by 3-factor, 3-level Box–Behnken design. AAPS PharmSciTech 8: 86.

36 Vora B, Khopade AJ, Jain NK (1998) Proniosome based transdermal delivery of levonorgestrel for effective contraception. J Control Release 54: 149-165.

37 Politis S, Colombo P, Colombo G, Rekkas D (2017) Design of experiments (DoE) in pharmaceutical development. Drug Dev Ind Pharm 43: 889-901.

38 Amaro E, Barker GJ (2006) Study design in fMRI: basic principles. Brain Cogn 60: 220-232.

39 Friston KJ, Price CJ, Fletcher P, Moore C, Frackowiak RS, et al. (1996) The trouble with cognitive subtraction. NeuroImage 4: 97-104.

40 Hall DA, Haggard MP, Akeroyd MA, Summerfield AQ, Palmer AR, et al. (2000) Modulation and task eVects in auditory processing measured using fMRI. Hum Brain Mapp 10: 107-119.

41 Stark CE, Squire LR (2001) When zero is not zero: the problem of ambiguous baseline conditions in fMRI. Proc Natl Acad Sci U S A 98: 12760-12766.

42 Gurd JM, Amunts K, Weiss PH, Zafiris O, Zilles K, et al. (2002) Posterior parietal cortex is implicated in continuous switching between verbal Xuency tasks: an fMRI study with clinical implications. Brain 125:1024-1038.

43 Florence AT (1993) Non-ionic surfactant vesicles: preparation and characterization. In: Gregoriadis G, editor. Boca Raton, FL: Liposome Technology. CRC Press 19: 157-176.

44 Donnelly RF (2017) How can micro needles overcome challenges facing transdermal drug delivery? Ther Deliv 8: 725-728.

45 Danaei M, Dehghankhold M, Ataei S, Davarani F, Javanmard R, et al. (2018) Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics 10: 1-17.

46 Mokale VJ, Patil HI, Patil AP (2015) Formulation and optimisation of famotidine proniosomes: an *in vitro* and *ex vivo* study. J Exp Nanosci 11: 97-110.

47 Madni A, Rahim MA, Mahmood MA, Jabar A, Rehman M, et al. (2018) Enhancement of dissolution and skin permeability of pentazocine by proniosomes and niosomal gel. AAPS PharmSciTech 19: 1544-1553.

48 Mir M, Ishtiaq S, Rabia S, Khatoon M, Zeb A, et al. (2017) Nanotechnology: from *in vivo* imaging system to controlled drug delivery. Nanoscale Res Lett 12: 500.

49 Caddeo C, Pons R, Carbone C, Fernàndez-Busquets X, Cardia MC, et al. (2017) Physico-chemical characterization of succinyl chitosan-stabilized liposomes for the oral co-delivery of quercetin and resveratrol. Carbohydr Polym 157: 1853-1861.

50 Din FU, Choi JY, Kim DW, Mustapha O, Kim DS, et al. (2017) Irinotecan-encapsulated doublereverse thermosensitive nanocarrier system for rectal administration. Drug Deliv 24: 502-510.

51 Verma P, Prajapati SK, Yadav R, Senyschyn D, Shea PR (2016) Single intravenous dose of novel flurbiprofen-loaded proniosome formulations provides prolonged systemic exposure and anti-inflammatory effect. Mol Pharm 13: 3688-3699.

52 Tripepi G, Jager KJ, Dekker FW, Wanner C, Zoccali C (2008) Bias in clinical research. Kidney Int 73: 148-53.

53 Stel VS, Jager KJ, Zoccali C, Wanner C, Dekker FW (2007) The randomized clinical trial: an unbeatable standard in clinical research? Kidney Int 72(5): 539-542.

54 Goud BA, Raju J, Rambhau D (2012) Improved oral absorption of carbamazepine from sorbiton monolaurate based proniosome systems containing charged surface ligands. Int J Biol Pharm Res 3:37-42.

55 Akhilesh D, Bini KB, Kamath JV (2002) Comparative study of carriers used in proniosomes. Int J Pharm Chem Sci 3: 6-12.

56 Kish-Trier E, Hill CP (2013) Structural biology of the proteasome. Annu Rev Biophys 42: 29-49.

57 Rattanapak T, Young K, Rades T, Hook S (2012) Comparative study of liposomes, transfersomes, ethosomes and cubosomes for transcutaneous immunisation: characterisation and *in vitro* skin penetration. J Pharm Pharmacol 64: 1560-1569.

58 Najlah M, Hidayat K, Omer HK (2015) Facile approach to manufacturing non-ionic surfactant nanodipsersions using proniosome technology and high-pressure homogenization. J liposome Resources 25: 32-37.

59 Abdelbary GA, Aburahma MH (2015) Oro-dental mucoadhesive proniosomal gel formulation loaded with lornoxicam for management of dental pain. J Liposome Res 25: 107-121.

60 Imam SS, Aqil M, Akhtar M, Sultana Y, Ali A (2015) Formulation by design-based proniosome for accentuated transdermal delivery of risperidone: *in vitro* characterization and *in vivo* pharmacokinetic study. Drug Deliv 22: 1059-1070.

61 Shruthi PA, Pushpadass HA, Magdaline Eljeeva Emerald F, Surendra Nath B, Laxmana Naik N, et al. (2021) Formulation and characterization of catechin-loaded proniosomes for food fortification. J Sci Food Agric 101: 2439-2448.

62 Farooqui NA, Kar M, Singh RP, Jain S (2017) Development of Proniosomal Gel: *in vitro, ex vivo* and *in vivo* Characterization. Indian J Pharm Educ Res 51: 758-764.

63 Mel MMRD, Gunathilake KDPP, Fernando CAN (2020) Formulation of microencapsulated rutin and evaluation of bioactivity and stability upon *in vitro* digestive and dialysis conditions. Int J Biol Macromol 159: 316-323.

64 Rahman Z, Zidan AS, Khan MA (2010) Non-destructive methods of characterization of risperidone solid lipid nanoparticles. Eur J Pharm Biopharm 76: 127-137.

65 Aboelwafa AA, El-Setouhy DA, Elmeshad AN (2010) Comparative study on the effects of some polyoxyethylene alkyl ether and sorbitan fatty acid ester surfactants on the performance of transdermal carvedilol proniosomal gel using experimental design. AAPS PharmSciTech 11: 1591-1602.

66 Schlich M, Lai F, Pireddu R, Pini E, Ailuno G, et al. (2020) Resveratrol proniosomes as a convenient nanoingredient for functional food. Food Chem 310: 125-950.

67 García-Manrique P, Machado ND, Fernández MA, Blanco-López MC, Matos M, et al. (2020) Effect of drug molecular weight on niosomes size and encapsulation efficiency. Colloids Surf B Biointerfaces 186: 110-711.

68 Minakshee G, Bhushan R, Wrushali A, Ashish B, Jagdish V, et al. (2021) An overview of characterizations and applications of proniosomal drug delivery system. GSC Adv Res Rev 7: 025-34.

69 Abdul NK, Thimmaraju DR (2019) Proniosomes: innovative vesicular drug delivery system: a review. Int J Pharm Sci Rev Res 59: 44-51.

70 Sammour RMF, Taher M, Chatterjee B, Shahiwala A, Mahmood S (2019) Optimization of aceclofenac proniosomes by using different carriers, part 1: Development and characterization. Pharmaceutics 11:7.

71 Soujanya C, Satya L, Navyas Y (2020) A review on novel vesicular drug delivery system: proniosomes. Manipal J Pharm Sci 6:94-100.

72 Upadhye S, Rafik IN (2020) Proniosomes: A novel vesicular drug delivery system. Am J PharmTech res 10: 260-273.

73 Goud BA, Raju J, Rambhau D (2012) Improved oral absorption of carbamazepine from sorbiton monolaurate based proniosome systems containing charged surface ligands. Int J Biol Pharm Res 3: 37-42.

74 Lankalapalli S, Sphingosomes DM (2012) Applications in targeted drug delivery. Int J Pharm Chem Biol Sci 2: 507-516.

75 Zidan AS, Rahman Z, Habib MJ, Khan MA (2010) Spectral and spatial characterization of protein loaded PLGA nanoparticles. J Pharm Sci 99: 1180-92.

76 Ravaghi M, Sinico C, Razavi SH, Mousavi SM, Pini E (2017) Proniosomal powders of natural canthaxanthin: preparation and characterization. Food Chem 220: 233-241.

77 Lai F, Schlich M, Pireddu R, Fadda AM, Sinico C, et al. (2018) Nanocrystals as effective Delivery 18 systems of poorly water-soluble natural molecules. Curr Med Chem 23: 56-59.

78 Singh SK, Makadia V, Sharma S, Rashid M, Shahi S, et al. (2017) Preparation and in-vitro/in-vivo characterization of trans-resveratrol nanocrystals for oral administration. Drug Deliv Transl Res 7: 395-407.

79 Ge X, Wei M, He S, Yuan WE (2019) Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics 11: 55.

80 Debnath A, Kumar A (2015) Structural and functional significance of niosome and proniosome in drug delivery system. Int J Pharm Eng 3: 621-637.

81 Bomma G, Harika SM, Babu AM, Bakshi V (2017) Formulation development and evaluation of proniosomal powder of candesartan. Anaal Chem Lett 7: 567-577.

82 Lohumi A (2012) a novel drug delivery system: niosomes review. J Drug Deliv Ther 2:5.

83 Veerareddy PR, Bobbala SKR (2013) Enhanced oral bioavailability of isradipine via proniosomal systems. Drug Dev Ind Pharm 39: 909-917.

84 Barry BW (2001) Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 14:101-114.

85 Bayindir ZS, Yuksel N (2010) Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery. J Pharm Sci 99: 2049-2060.

86 Karatzas AA, Politis SN, Rekkas DM (2017) Development of rapidly dissolving pellets within the Quality by Design Approach. Drug Dev Ind Pharm 43: 770-779.

87 Belotti S, Rossi A, Colombo P, Bettini R, Rekkas D, et al. (2015) Spray-dried amikacin sulphate powder for inhalation in cystic fibrosis patients: the role of ethanol in particle formation. Eur J Pharm Biopharm 93:165-172.

88 Wurth C, Demeule B, Mahler HC, Adler M (2016) Quality by design approaches to formulation robustness – an antibody case study. J Pharm Sci 105:1667-1675.

89 Abdelbary GA, Aburahma MH (2015) Oro-dental mucoadhesive proniosomal gel formulation loaded with lornoxicam for management of dental pain. J Liposome Res 25: 107-121.

90 Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, et al. (2009) Formulation and *in vitro* assessment of minoxidil niosomes for enhanced skin delivery. Int J Pharm 377: 1-8.

91 Rinaldi F, Hanieh PN, Chan LKN, Angeloni L, Passeri D, et al. (2018) Chitosan glutamate-coated niosomes A proposal for nose-to-brain delivery. Pharmaceutics 10: 38.

92 Obeid MA, Khadra I, Mullen AB, Tate RJ, Ferro VA, et al. (2017) The effects of hydration media on the characteristics of non-ionic surfactant vesicles (NISV) prepared by microfluidics. Int J Pharm 516: 52-60.

93 Salem HF, Kharshoum RM, Abo El-Ela FI, F AG, Abdellatif KRA, et al. (2018) Evaluation and optimization of pH-responsive niosomes as a carrier for efficient treatment of breast cancer. Drug Deliv Transl Res 8: 633-644.