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SCREENING OF SURFACTANTS IN IVERMECTIN PRONIOSOMES USING QUALITY BY DESIGN APPROACH

Pharmaceutics

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ABSTRACT

Pro-niosomes emerge as superior vesicular carrier among them. Pro-niosomes are dry formulations of carrier system coated with water-soluble nonionic surfactant that immediately hydrates to form niosomes. They have potential to improve drug solubility, bioavailability, and absorption by overcoming instability issues associated with niosomes and liposomes. Additionally, they provide flexible drug delivery strategy for wide range of hydrophilic and hydrophobic drugs. They can effectively deliver drugs to specific site of action through variety of routes to achieve controlled release action and reduce drug-induced toxic effects. IVM is low-solubility BCS II drug that works by paralyzing and eliminating parasites. Additionally, drug's Log P value of 5.83 indicates that it is suitable for skin route and highly lipophilic. These topical preparations probably function through IVM absorption through skin barrier to diseased sites. Because it was discovered to be safe, tolerable, and effective. The Concept of QbD is a systemic approach to development that begins with predefined objectives and process control, based on sound and quality risk management.

KEYWORDS

Ivermectin, Vesicals, Pro-Niosomes, Surfactant, Span 60, Cholesterol, Quality by Design, Entraptment Efficacy, Drug Release.

INTRODUCTION

Niosomes are water-soluble carrier particles that are dried to form a niosomal dispersion in hot aqueous media. Proniosomes are a dehydrated product called this. The resulting niosomes are very similar to conventional niosomes and are of higher size uniformity. The proniosomal approach reduces the issues associated with dry, free-flowing product, which is more stable during storage and sterilization. Because of their ease of distribution, measuring, transfer, and storage, the proniosomes are a versatile delivery system.[1,2]

The field of nanotechnology has been focusing on vesicular drug delivery systems. Among them, the proniosomes become the superior over other vesicular carriers. Dry formulations of nonionic surfactant-coated carrier system that immediately forms niosomes upon hydration are called proniosomes.[3,4]

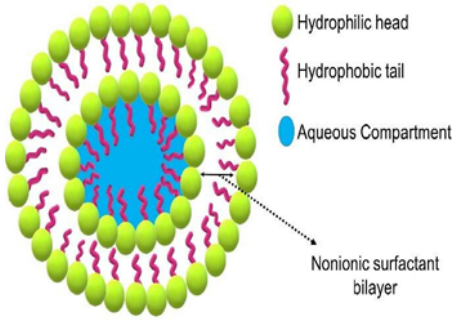

Figure: Structure of Pronisomes

They have the potential to improve solubility, bioavailability, and absorption of various drugs by overcoming instability problems associated with niosomes and liposomes. Furthermore, they provide a flexible drug administration strategy for a substantial array of hydrophilic and hydrophobic substances. They have the potential to deliver drugs effectively through different routes at specific sites of action to achieve controlled release action and reduce toxic effects associated with drugs. They have the potential to deliver drugs effectively through different routes at specific sites of action to achieve controlled release action and reduce toxic effects associated with drugs.[5-7]

IVM is a BCS II drug with low solubility and belongs to a pharmacological class of drugs known as antihelmintics, and it works by paralyzing and killing parasites. IVM is believed to enter the circulatory system and reach the skin via the sebaceous glands after ingestion.[8-10]

Numerous formulation and processing factors can affect how well the finished product performs during proniosome preparation. As a result, the investigation of these factors in proniosome preparation will contribute significantly to the scientific data pertaining to these carriers. The quality by design (QbD) methodology involves the design and development of a product that satisfies predetermined product requirements through manufacturing processes. Beyond the conventional quality by testing (QbT) approach, which primarily tests the quality of the finished product, it is a methodical recommendation that quality be ingrained into the process and product during development. It can be used to investigate the impact of multiple factors that affect responses at the same time by conducting a small number of trials. [11-13]

As a result, this method can drastically cut down on the time and expenses related to the development and production of drugs. Additionally, it offers a comprehensive understanding of the process and product behaviors and is helpful in determining the composition of the best possible formulation. Understanding how crucial material properties and process parameters impact product quality and subsequent optimization parameters in relation to the final specifications is a crucial component of this methodology. The International Conference on Harmonization (ICH) and the Food and Drug Administration are actively pushing this cutting-edge strategy. Furthermore, QbD components are now mandated by regulation for submissions. [14-16]

In order to characterize the formulations for the drug content, entrapment efficiency, In vitro drug Release and to identify the critical material attributes (CMAs) and critical process parameters (CPPs) that impact the key characteristics of drug-loaded proniosomes using a systematic QbD approach, the research prepared Ivermevtin loaded proniosomes using a Slurry method. According to this investigation's experimental findings, the amounts of surfactant and cholesterol, mixing parameters, and addition rate all have a critical impact on proniosomes.[17]

MATERIALS & METHODOLOGY

Materials

Drug was received as a gift sample from kivi Labs limited, Gujarat, india. All others materials were purchased from local suppliers.

Methodology

Preparation Of Standard Calibration Curve For Ivermectin [19]

The 100mg Ivermectin was dissolved in a small amount of Methanol, sonicated for a few minutes, and then diluted with 100 ml of phosphate buffer (pH 7.4) to create a Ivermectin stock solution. The highest concentration of the stock solution was established after it was serially

diluted to produce solutions with concentrations between 10-50 µg/ml. In a UV-visible spectrophotometer, the absorbance of various diluted solutions was measured at 245 nm. The relationship between drug concentrations and absorbance was plotted to construct a calibration curve.

Preparation Of Proniosomes [20,21]

Pronisomes was prepared by using Slurry method.The necessary quantity of components that form vesicles, such as cholesterol and surfactants, are dissolved in the appropriate solvent (ether, methanol, or chloroform) in an RBF that is put inside a rotating evaporator. At room temperature, or between 40 and 45°C, the organic solvent evaporates, leaving behind a thin film that deposits on the container walls.

Setting Up Quality Target Product Profile (qtpp) And Selection Of Formulation And Process Variables By Preliminary Trial Batches Of Ivermectin Proniosomes [23,24]

To determine the impact of cholesterol and span 60 concentrations on the parameters of prepared proniosomes, preliminary trials were conducted. In order to develop the QbD approach, ivermectin proniosomes were formulated using different RPM speeds, temperatures, and pressures. These parameters were then assessed for drug content, %CDR, and entrapment efficiency.

Formulation Of Ivermectin Proniosomes By Using Factorial (doe) Approach [25]

Design space can represent formulation and process understanding, i.e., characteristics linked to drug composition, equipment, materials, intellectual property, and quality of final product. In order to achieve this, a risk assessment was conducted using parameters related to the formulation of proniosomes quality and process understanding. For high risk parameters, preliminary research and subsequently Design of Experimentation (DoE) were conducted. A suggested design space for achieving robust formulation was made based on the impact of the target product profile's critical quality attributes. Proniosomes were characterized for a number of parameters.

Characterization Of Proniosomes

Entrapment efficiency [26]

To measure the encapsulation efficiency of ivermectin-stacked proniosomes, the proniosomal dispersion was centrifuged at 8000 rpm for 1 hour at 50C using a cooling rotator. The unentrapped ivermectin in the supernatant can be isolated and measured using a developed UV method at 245 nm after being diluted with mobile phase. The formula used to calculate it was as follows:

Entrapment efficiency = Amount of entrapped drug *100/ (Total amount of drug)

In-Vitro drug release study [27-28]

A Franz diffusion cell was utilized for conducting in vitro drug release investigations. The dialysis membrane was positioned with its epidermal surface facing the donor compartment between the donor and receptor compartments. A pH 7.4 phosphate buffer was employed as the dissolution medium. In the space between the donor and receptor compartment, promiosomal dispersion was added. The water jacket circulated to keep the cell's temperature at 37 ˚C±0.5 ˚C.

A magnetic bead was used to continuously stir the solution while the entire assembly was held on a magnetic stirrer. The sample (5 ml) was taken out at appropriate intervals, diluted with the same solvent to a maximum of 10 ml, and then replaced with the same volume of brand-new dissolving media.

Spectrophotometric analysis of the samples was performed at 245 nm, and the cumulative percentage of drug release was computed.

Drug Content [29]

UV spectrophotometer is used for measurement of drug content in proniosomes. The prepared proniosomal formulations was taken in a test tubes and to this 30 mL of methanol was added so that the proniosomes can be broken up to release the entrapped drug.

The amount of drug released was determined by using U.V-visible spectrophotometer at 245 nm.

RESULT AND DISCUSSION

Determination Of Calibration Curve Of Ivermectin

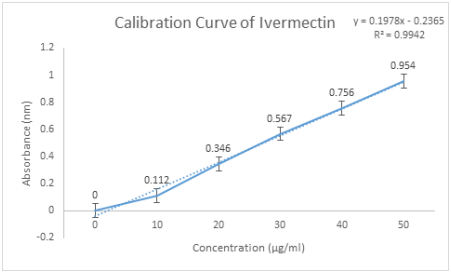

Figure: Calibration Curve

Table: Preliminary Trial Batch of Ivermectin Proniosomal

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ivermectin(mg)	10	10	10	10	10	10	10	10	10
Cholesterol(mg)	25	25	25	25	25	25	15	15	15
Soya Lecithin(mg)	50	50	50	50	50	50	50	50	50
Span 40(mg)	250	-	-	-	-	-	150	-	-
Span 60(mg)	-	250	-	-	-	-	-	150	-
Span 80(mg)	-		250	-	-	-	-	-	150
Tween 20(mg)	-	-	-	250	-	-	-	-	-
Tween 60(mg)	-	-	-	-	250	-	-	-	-
Tween 80(mg)	-	-	-	-	-	250	-	-	-
Ethanol(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Phosphate buffer saline(ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

- Preliminary batches of proniosomes were prepared by taking different concentration of cholesterol and surfactant as per above table.

Characterization of trial batch

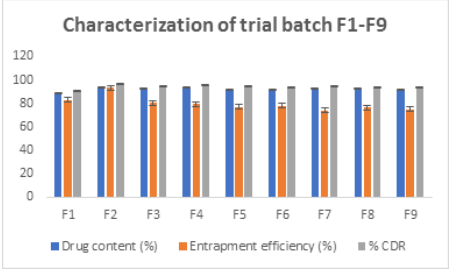

Figure: Characterization of trial batch F1-F9

- As a result of preliminary batches % Drug content was found in the range of 88% to 94%, % EE was found in the range of 74% to 93%, % CDR was found in the range of 90% to96%.

Risk Assessment of Critical Quality Attributes from Preliminary trial Batches to Develop QbD Approach:

The critical quality attributes are categorized in high, medium and low risk parameters based on knowledge space to check influence of formulation and process parameters. Usually, high risk parameters are considered important for Design of Experiments as they are having more effect than others and need to be in accepted multivariate ranges.

Table: Risk Assessment of Critical Quality Attributes from Preliminary trial Batches to Develop QbD Approach

Drug Product CQAs	Surfactant Concentration	Cholesterol Concentration	RPM	Temperature	Pressure
%Entrapment Efficiency	HIGH	HIGH	MEDIUM	MEDIUM	LOW
%CDR	HIGH	HIGH	MEDIUM	LOW	LOW
%Drug content	HIGH	HIGH	LOW	LOW	LOW

Risk assessment was carried out to check the influence of independent variable on the %EE, %CDR, %Drug content.

CONCLUSION

Proniosomal formulations offer a promising approach for enhancing the topical delivery of Ivermectin, a broad-spectrum antiparasitic agent. By encapsulating Ivermectin within proniosomal vesicles, the

proniosomal gel improves drug stability and facilitates penetration through the skin layers, potentially enhancing therapeutic efficacy. The proniosomes formulation may enable modify release of Ivermectin over an extended period, prolonging its local action at the site of application.

This modify release profile could contribute to improved treatment outcomes and reduced dosing frequency, enhancing patient compliance.

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