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DEVELOPMENT AND CHARACTERIZATION OF NIOSOMAL TRANSDERMAL PATCHES OF BREXPIPRAZOLE

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ABSTRACT
Brexpiprazole is a type of atypical antipsychotic that can be used to treat schizophrenia and major depressive disorder (MDD) in addition to antidepressants. The current study's objective is to develop and assess Brexpiprazole niosomal transdermal patches. Cholestrol and Tween 60 in various ratios were used to formulate the niosomeal dispersions.
Among all BN3 and BN4 were shown to have the smallest particle sizes, the best zeta potential, and the best polydispersity index in niosomal dispersions employing different surfactants. Tween 60 was used as the surfactant in 15 different formulations (BNR1 to BNR15) after these formulations were further refined utilizing a central composite design. BNR8 was chosen to be included in the patch since it demonstrated the highest entrapment efficiency among them. Niosomal patches (BT1 through BT9) were subsequently evaluated, and the results showed that BT7 performed the best. All things considered, these results demonstrate the stability and appropriateness of niosomal patches of Brexpiprazole for future research and possible therapeutic uses, as well as their potential for sustained drug release.

Keywords:
Niosomes, Transdermal Patch, Dispersion, Brexpiprazole

1. INTRODUCTION:

1.1. Overview of Transdermal Drug Delivery Systems

Transdermal patches have emerged as a popular and effective method for delivering medications through the skin directly into the bloodstream. These patches are designed to adhere to the skin's surface and slowly release the active ingredients over a specific period, providing a sustained and controlled release of medication. Transdermal patches offer several advantages over traditional routes of drug administration, such as avoiding the hepatic first-pass effect, minimizing gastrointestinal side effects and providing continuous blood levels of the drug, resulting in improved therapeutic outcomes[1,2].

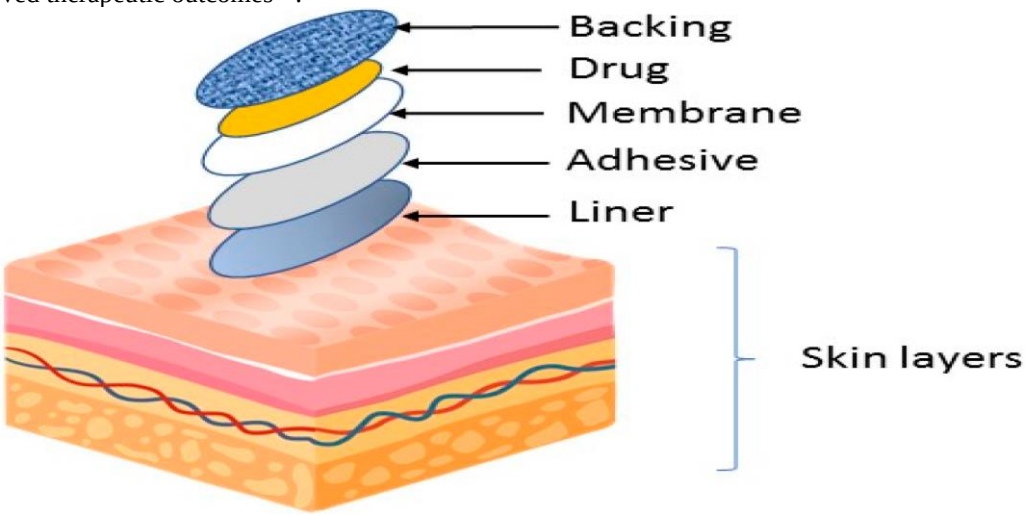

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Fig-1: Layers of Transdermal Patch

The performance of transdermal patches is largely dependent on the patch design and formulation. The selection of materials, such as the adhesive layer, drug reservoir, and backing membrane, plays a crucial role in determining the patch's effectiveness in delivering the medication. Formulation parameters, including drug release kinetics, patch thickness, and permeation enhancers, must be carefully optimized to ensure optimal drug delivery through the skin barrier. Additionally, factors such as patch application site, skin permeability, and patient variability also influence the patch's efficacy in delivering the desired drug dose[3].

Table 1: Ideal properties for the drug for transdermal drug delivery

Parameters	Ideal properties
Dose	< 50 mg
Half life	< 10 hrs
Molecular weight	< 500 Daltons
Oral bioavailability	Low
Partition coefficient	1 – 4
Melting point	< 250^{0}C
Therapeutic index	Low

Evaluation of transdermal patches is essential to assess their performance, safety, and efficacy. In vitro studies, such as drug release testing and skin permeation assays, provide valuable insights into the patch's drug delivery characteristics and skin compatibility. In vivo studies, including pharmacokinetic and pharmacodynamic evaluations, help to determine the patch's bioavailability, systemic exposure, and therapeutic effects. These evaluations are crucial for ensuring the quality, reliability, and consistency of transdermal patches in delivering medications[3].

The development of innovative transdermal patch technologies, such eservoirr systems, matrix systems, and drug-in-adhesive patches, continues to advance the field of transdermal drug delivery. These advancements aim to enhance drug delivery efficiency, expand the range of drugs that can be delivered through the skin, and improve patient convenience and adherence to treatment regimens. With ongoing research and development, transdermal patches hold great promise in revolutionizing drug delivery by providing a safe, effective, and convenient option for administering medications for various medical conditions[4].

The **skin** is very effective as a **selective penetration barrier**. The epidermis provides the major control element for drug penetration.

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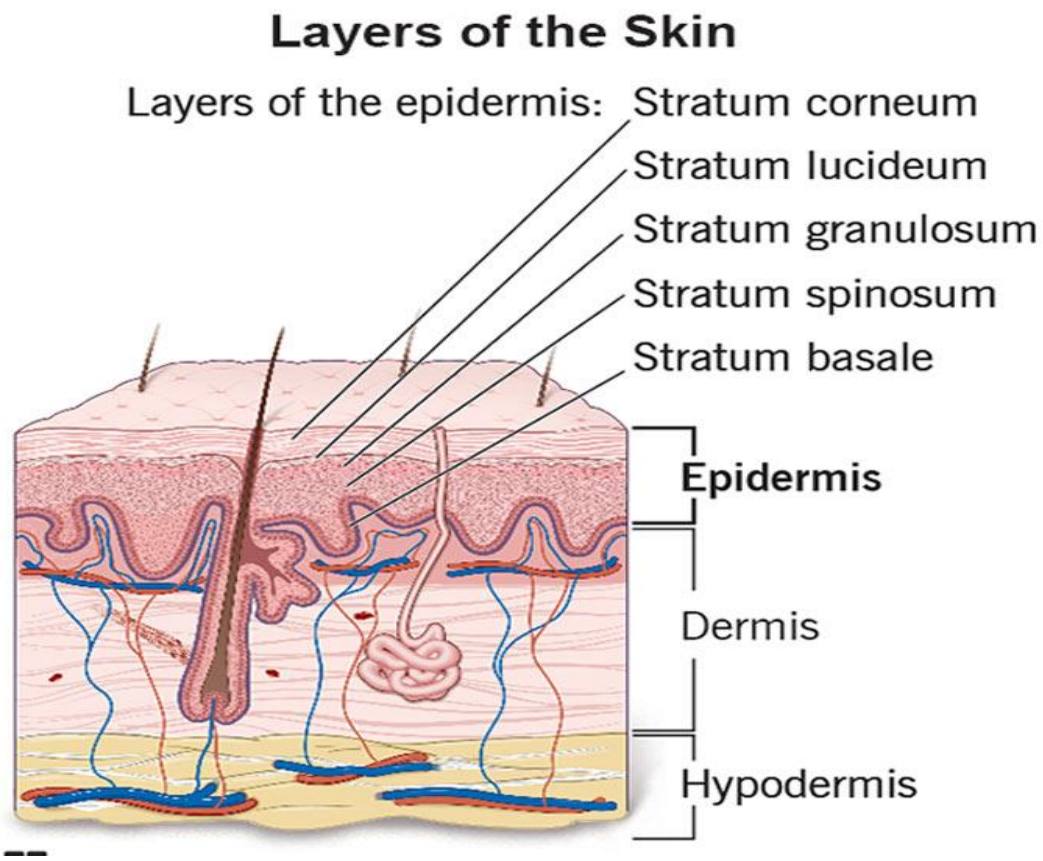

Fig-2: Layers of skin

1.2. Introduction to Niosomes as Drug Delivery Vehicles

Niosomes have gained considerable attention in the field of drug delivery as promising alternatives to liposomes and other vesicular carriers. These vesicles are composed of non-ionic surfactants and cholesterol, offering distinct advantages such as improved stability, reduced toxicity, and simplified manufacturing processes compared to traditional liposomes. Niosomes have demonstrated the ability to encapsulate a wide range of drug molecules, including hydrophilic and hydrophobic compounds, making them versatile delivery vehicles for various therapeutic applications[5,6].

The unique structural characteristics of niosomes, including their flexible bilayer membrane and aqueous core, enable efficient encapsulation of drugs and controlled release kinetics. Niosomes can protect drug molecules from degradation, enhance their solubility, and improve their bioavailability, leading to enhanced therapeutic outcomes. Additionally, the surface properties of niosomes can be modified with targeting ligands, stabilizing agents, or permeation enhancers to optimize drug delivery efficiency and specificity to target tissues or cells[7].

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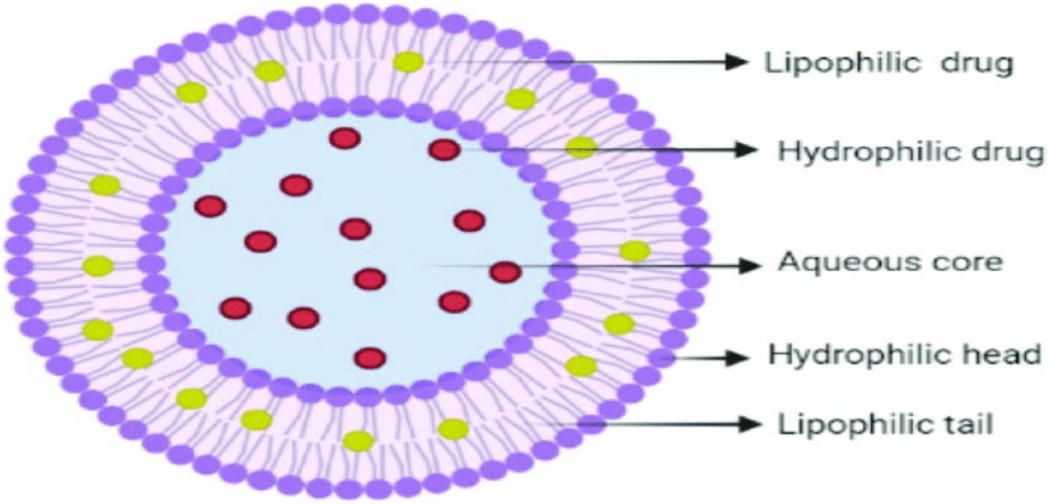

Fig-3: Structure of Niosomes

Niosomes have shown promising potentials for transdermal drug delivery applications due to their ability to enhance skin permeation and drug absorption. When formulated into transdermal patches, niosomes can facilitate the delivery of drugs across the skin barrier, minimizing systemic side effects and providing sustained release profiles. The encapsulation of drugs within niosomes protects them from enzymatic degradation and promotes their accumulation in the skin layers, allowing for prolonged drug retention and controlled release at the target site[7].

The formulation of niosomal transdermal patches involves the selection of appropriate surfactants, cholesterol ratios, and drug-to-vesicle ratios to optimize the encapsulation efficiency, stability, and release properties of the formulation. Various methods, such as thin-film hydration, sonication, and solvent evaporation, are utilized to prepare niosomes and incorporate them into transdermal patches with desired characteristics. The physicochemical properties of niosomes, such as vesicle size, surface charge, and membrane integrity, play a crucial role in determining their skin penetration capabilities and drug delivery efficiency[8].

Overall, niosomes hold great promise as drug delivery vehicles for transdermal applications, offering a versatile and effective platform for enhancing the therapeutic potential of various drugs. The integration of niosomes into transdermal patches represents a promising approach to improve drug delivery efficiency, reduce side effects, and enhance patient compliance in the treatment of various medical conditions. Continued research and development in niosomal transdermal delivery systems are essential to harness the full potential of niosomes for targeted and controlled drug delivery[8].

1.3. Importance of Niosomal Transdermal Patches in Drug Delivery

Niosomal transdermal patches represent a significant advancement in drug delivery technology, offering a targeted and efficient approach to administering medications through the skin. These patches incorporate niosomes, lipid-based vesicles composed of non-ionic surfactants and cholesterol, which can encapsulate a wide range of drug molecules and enhance their stability and bioavailability. By delivering drugs through the skin barrier, niosomal transdermal patches bypass the gastrointestinal tract and liver metabolism, allowing for sustained release of medication and minimizing systemic side effects[9].

The development of niosomal transdermal patches holds great importance in drug delivery due to their ability to improve drug permeation across the skin and achieve targeted delivery of therapeutic agents. These innovative drug delivery systems offer controlled release kinetics, enhanced skin penetration efficiency, and prolonged drug retention at the application site, leading to improved drug efficacy and patient compliance. Niosomal transdermal patches have the potential to revolutionize the way medications are administered, providing a safe, convenient, and effective option for delivering a wide range of drugs for various medical conditions[10].

1.4. Factors Influencing the Formulation of Niosomal Transdermal Patches

The formulation of niosomal transdermal patches involves several key factors that impact the design, performance, and efficacy of the drug delivery system. These factors must be carefully considered and optimized to ensure the successful delivery of medications through the skin[11,12].

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1. Selection of Surfactants: The choice of non-ionic surfactants plays a crucial role in the formation and stability of niosomes. Different surfactants have varying properties, such as critical micelle concentration, vesicle size, and membrane fluidity, which can influence the drug encapsulation efficiency and release kinetics of niosomal transdermal patches. The compatibility between the surfactants and the drug molecules should be evaluated to ensure optimal encapsulation and bioavailability.
2. Cholesterol Ratio: Cholesterol is an essential component of niosomes that helps to stabilize the vesicle structure and regulate membrane fluidity. The ratio of cholesterol to surfactants in niosomes can impact the membrane integrity, drug loading capacity, and release profile of the transdermal patches. By optimizing the cholesterol content, the permeability and stability of niosomes can be enhanced, improving the skin penetration and drug delivery efficiency.
3. Drug-to-Vesicle Ratio: The ratio of drug molecules to niosomal vesicles in the formulation is critical for achieving the desired drug loading capacity and release characteristics. Balancing the drug-to-vesicle ratio can influence the encapsulation efficiency, drug distribution within the niosomes, and drug release kinetics from the transdermal patches. Careful consideration of this factor is essential to ensure uniform drug distribution, sustained release profiles, and enhanced therapeutic efficacy.
4. Formulation Method: Various techniques, such as thin-film hydration, sonication, and solvent evaporation, are employed to prepare niosomes and incorporate them into transdermal patches. Each formulation method can affect the vesicle size, shape, lamellarity, and drug entrapment efficiency of niosomes, thereby influencing their skin permeation properties. Selection of the appropriate formulation method is crucial to achieving reproducible and optimized niosomal transdermal patches for efficient drug delivery.
5. Permeation Enhancers: The addition of permeation enhancers, such as penetration enhancers or lipids, can improve the skin permeation and penetration of drugs across the stratum corneum barrier. These enhancers enhance the fluidity and hydration of the skin, facilitating the diffusion of drugs through the skin layers and increasing their bioavailability. The selection and concentration of permeation enhancers in niosomal transdermal patches should be carefully optimized to enhance the skin permeation properties and maximize the drug delivery efficiency[13].

By understanding and optimizing these factors in the formulation of niosomal transdermal patches, researchers and developers can enhance the efficacy, stability, and performance of these innovative drug delivery systems for targeted and controlled delivery of therapeutics.

1.5. Significance of Formulation and Evaluation in Enhancing Drug Delivery Efficiency

Formulation and evaluation play a crucial role in enhancing drug delivery efficiency by optimizing the properties of drug delivery systems, improving drug stability, bioavailability, and targeting specific sites of action[14,15]. Here are some key aspects highlighting the significance of formulation and evaluation in enhancing drug delivery efficiency:

1. Targeted Drug Delivery: Formulation design allows for the incorporation of targeting ligands, such as antibodies, peptides, or nanoparticles, to facilitate specific drug delivery to the site of action. Evaluation studies help in determining the efficacy of targeted drug delivery systems in reaching the desired target tissues or cells, thereby enhancing therapeutic outcomes while minimizing systemic side effects.
2. Controlled Release Systems: Formulation strategies enable the development of controlled release drug delivery systems that regulate the release rate and duration of drug action. Evaluation studies assess the release kinetics, drug release profiles, and release mechanisms to optimize the formulation for sustained or pulsatile drug delivery, improving patient compliance and reducing dosing frequency.
3. Enhanced Bioavailability: Formulation optimization can improve the solubility, stability, and absorption of poorly soluble or poorly permeable drugs, enhancing their bioavailability. Through in vitro and in vivo evaluation studies, researchers can analyze the drug pharmacokinetics, tissue distribution, and plasma profiles to ensure efficient drug absorption and distribution, leading to improved therapeutic efficacy.
4. Stability and Shelf-life: Formulation development focuses on enhancing drug stability and shelf-life by selecting appropriate excipients, protective coatings, and manufacturing processes. Evaluation studies, including accelerated stability testing, provide insights into the physical and chemical stability of drug delivery systems under various storage conditions, ensuring product quality and efficacy over an extended period.
5. Biocompatibility and Safety: Formulation and evaluation of drug delivery systems involve assessing the biocompatibility, toxicity, and safety profiles of formulations to ensure patient safety and reduce adverse effects. In vitro cell viability assays, histopathological examinations, and skin irritation tests are conducted to evaluate the

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compatibility of drug delivery systems with biological tissues, enhancing the overall safety and tolerability of the formulations.

6. Physicochemical Properties Optimization: Formulation optimization aims to tailor the physicochemical properties of drug delivery systems such as particle size, surface charge, morphology, and drug loading capacity. Evaluation techniques like dynamic light scattering, zeta potential analysis, and microscopy help in characterizing these properties and understanding their impact on drug release, stability, and pharmacokinetics, thereby enhancing drug delivery efficiency.

In conclusion, the formulation and evaluation of drug delivery systems are integral steps in enhancing drug delivery efficiency by improving targeting capabilities, controlled release behavior, bioavailability, stability, safety, and physicochemical properties. By systematically formulating and rigorously evaluating drug delivery systems, researchers can develop optimized formulations that meet therapeutic requirements, improve patient outcomes, and advance the field of drug delivery science.

2. LITERATURE REVIEW

S.no	Author and year of publication	Title of publication	Journal name	Key points in publication
1.	Singh, N., & Pillai, S.	Recent advances in transdermal drug delivery system	2019	Transdermal drug delivery systems have gained significant attention in recent years due to their potential advantages such as improved patient compliance, reduced side effects, and sustained drug release.
2.	Mitragotri, S., & Langer, R.	Transdermal drug delivery: Opportunities and challenges	2012	The authors explore the opportunities for innovation in transdermal drug delivery technology, emphasizing the development of novel delivery systems, advanced materials, and strategies to enhance drug permeation through the skin. However, they also acknowledge the challenges associated with transdermal drug delivery, such as the limited permeability of the skin barrier, variability in drug absorption rates, and the need for optimized formulation approaches. Mitragotri and Langer underscore the importance of addressing these challenges through ongoing research and innovation to enhance the effectiveness and efficiency of drug delivery through the skin.
3.	Vidhi Malika et al.	Nano-Carrier for Accentuated Transdermal Drug Delivery	2014	Nanocarriers were characterized by various parameters. The skin permeation of optimized formulation was found to be significantly higher than the drug in solution. Hence, drug loaded nano-Niosomes accentuates its transdermal flux and can be used as a nano-vehicle.
4.	Haider, M., & Abdin, S. M.	Formulation and Evaluation of Niosomes	2017	The evaluation methods discussed in the article include physical characterization, drug encapsulation efficiency, drug release studies, and stability testing, which are crucial for assessing the performance and efficacy of niosomal drug delivery

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				systems. Furthermore, the potential applications of niosomes in drug delivery are highlighted, showcasing their ability to improve the bioavailability of poorly water-soluble drugs, target specific tissues, and reduce drug toxicity. Overall, the article sheds light on the versatility and effectiveness of niosomes in advancing drug delivery technology.
5.	Akbari, J., Saeedi, M., Morteza-Semnani, K., & Ghafourian, S.	Preparation of niosome as a transdermal carrier for psoralen	2016	The researchers detail the preparation process of niosomes as carriers for psoralen, which involves encapsulating the drug in non-ionic surfactant vesicles. The study likely covers aspects such as formulation optimization, characterization of niosomes, and evaluation of their ability to facilitate the transdermal delivery of psoralen.
6	Clemow DB, Walker DJ, Burrell A, Cui D	Clinical pharmacokinetics and pharmacodynamics of brexpiprazole, a novel serotonin-dopamine activity modulator	2019	Brexpiprazole is a medication that belongs to the class of atypical antipsychotics. It is used to treat conditions such as schizophrenia and major depressive disorder. Brexpiprazole works by acting on neurotransmitters in the brain, helping to restore the balance of these chemicals and improve symptoms.
7.	Citrome, L. for this newly approved antipsyhotic	Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile	2015	The study likely synthesizes findings from clinical trials and research studies to evaluate the effectiveness and safety of brexpiprazole in managing symptoms of schizophrenia and major depressive disorder. The comprehensive review offers insights into the potential benefits and risks associated with brexpiprazole treatment, aiding healthcare providers and clinicians in making informed decisions regarding the use of this antipsychotic medication for schizophrenia and depressive disorders.
8	Andhale, K. K., & Belsare, K. S.	Estimation of Brexpiprazole in Bulk by using UV-Spectroscopy Method	2022	Linearity was studied by analyzing five standard solutions covering the range of 0.5-7.5 µg/ml of Brexpiprazole. From the primary stock solution 0.5ml,2.5ml,5.0ml,6.2ml,7.5ml of solution pipette into 10 ml volumetric flasks individually and made up to the mark with methanol to give a concentrations of 0.51µg/mL , 2.53µg/mL ,5.05µg/mL ,6.26µg/mL and 7.58 µg/mL of Brexpiprazole.
9	Gupta, M., & Taneja, D.	Recent developments in the application of Fourier transform infrared spectroscopy for study of drug-excipient compatibility	2017	This review likely delves into the principles of FTIR spectroscopy, its applications in analyzing chemical bonds and functional groups, and the significance of assessing drug-excipient interactions in pharmaceutical formulations. The authors might discuss how FTIR spectroscopy can provide valuable insights into the physicochemical properties, stability, and compatibility of drug-excipient combinations, which are crucial for formulating safe and effective pharmaceutical products.

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10	Thabet Y, Elsabahy M, Eissa NG.	Methods for preparation of niosomes: A focus on thin-film hydration method	2022	The thin-film hydration method involves the formation of a thin lipid film followed by hydration, resulting in the formation of niosomes. The article likely discusses the steps involved in this method, the factors influencing niosome characteristics, and the advantages of using the thin-film hydration method for niosome preparation. This study contributes to the understanding of different niosome preparation techniques and their potential applications in pharmaceutical and biomedical research.

3. AIM AND OBJECTIVES

AIM

The aim of present study is to formulate and evaluate Niosomal transdermal patches of Brexpiprazole

OBJECTIVES

- To develop Calibration curve.
- To perform Drug excipient interaction studies by FTIR.
- To perform the solubility studies of Brexpiprazole in different solvents and surfactants.
- To formulate Niosomes of Brexpiprazole.
- To Characterize the prepared Niosomal dispersion of Brexpiprazole.
- To formulate niosomal transdermal patches of Brexpiprazole using various polymers.
- To evaluate the optimized niosomal transdermal patches for various physicochemical and mechanical properties.
- To perform *in vitro* drug release studies of the optimized niosomal transdermal patches of Brexpiprazole.
- To perform stability studies of the optimized niosomal transdermal patches of Brexpiprazole

4. MATERIALS AND METHODS

4.1 MATERIALS

4.1.1 List of Equipments

Table 2: List of Equipment

S. NO	EQUIPMENT	MANUFACTURE'S NAME AND MODEL NO.
1	**UV Visible Spectrophotometer**	Shimadzu company - UV 1800
2	**FTIR Spectroscopy**	Bruker company - Bruker alpha
3	**FTIR Pellet Press**	PerkinElmer – UTAR TWO
4	**Digital Weighing Balance**	Essae teraoka pvt. Ltd - 0.1g Sensitivity
5	**Electronic Water Bath**	Wincom Company
6	**Hot air oven**	Magma Technologies
7	**Screw gauge**	Vibration meter suppliers - EJS model

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8	**Bath Sonicator**	Ultra Auto sonic LLP
9	**Magnetic Stirrer**	REMI company - 1 MLH
10	**Rotary evaporator assembly**	Rotavapor Company - R-018
11	**Franz Diffusion cell**	Vertical Franz diffusion cell – JFDC 06-030
12	**Particle size analyzer**	Malvern Zeta Sizer
13	**Stability Chamber**	Meck pharma Techs
14	**Refrigerator**	LG Refrigerator
15	**pH meter**	Alpha - α 112
16	**Shaking Incubator**	Remi Electro Technick – RQ1291
17	**Cyclomixer**	REMI lab company - CM-101

4.1.2 Materials used in the Formulation of niosomal transdermal patches of Brexpiprazole.

Table 3: API and Excipients

S,No	Material/Chemical	Company	Category
1	Brexpiprazole	Aurobindo Pharma Ltd.	Active Pharmaceutical Ingredient
2	Cholestrol	Hetero Laboratories Ltd.	Stabilizer
3	Methanol	SLC Chemicals	Solvent
4	Potassium Bromide	Deepak Pharma	IR ingredient
5	Span-40	Nirman Chemicals	Surfactant
6	Tween-60	Vasudha Chemicals	Surfactant
7	Tween-80	Nirman Chemicals	Surfactant
8	HPMC E5	Ottokemi Company	Polymer

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9	HPMC 15 CPS	Ottokemi Company	Polymer
10	PEG 200	Clariant Pharma	Plasticizer
11	Glycerine	SLC Chemicals	Plasticizer
12	Chloroform	SDFCL company	Solvent
13	Potassium dihydrogen phosphate		Buffer component
14	Dipotassium hydrogen phosphate		Buffer component

5. DRUG PROFILE

5.1 Brexpiprazole

Brexpiprazole is a medication that belongs to the class of atypical antipsychotics. It is used to treat conditions such as schizophrenia and major depressive disorder. Brexpiprazole works by acting on neurotransmitters in the brain, helping to restore the balance of these chemicals and improve symptoms[16].

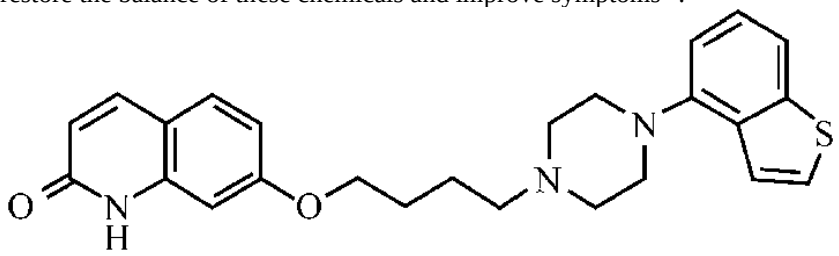

Fig-4: Structure of Brexpiprazole

Non-proprietary Name: Brexpiprazole
Proprietary Name: Rexulti
Empirical Formula: C25H27N3O2
Molecular Weight: 401.504 g/mol
Bioavailability: Approximately 95%
Description: White to off-white crystalline powder. It is practically insoluble in water.
Solubility: Brexpiprazole is sparingly soluble in water.
Partition Coefficient (Log P): The calculated Log P value for brexpiprazole is approximately 4.4.
Storage Conditions: Brexpiprazole should be stored at room temperature between 68°F to 77°F (20°C to 25°C). It should be kept in a tightly closed container, protected from light and moisture.

Overview of the ADME characteristics of Brexpiprazole[17]

1. Absorption: Brexpiprazole is well absorbed after oral administration, with an estimated bioavailability of approximately 95%.
2. Distribution: Brexpiprazole has a moderate to high volume of distribution, indicating that it is distributed widely throughout the body. The drug binds moderately to plasma proteins (about 95%).
3. Metabolism: Brexpiprazole undergoes extensive hepatic metabolism primarily via the CYP3A4 and CYP2D6 enzymes. The main metabolites of Brexpiprazole are hydroxylated derivatives.
4. Excretion: Brexpiprazole and its metabolites are primarily excreted in the feces and urine. The elimination half-life of Brexpiprazole is approximately 91 hours, indicating a relatively long duration of action.

Mechanism of action of Brexpiprazole[18,19]

Brexpiprazole is an atypical antipsychotic medication that acts as a partial agonist at serotonin 5-HT1A and dopamine D2 receptors and as an antagonist at serotonin 5-HT2A and noradrenaline alpha1B/2C receptors. This

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unique combination of pharmacological actions results in a complex mechanism of action that contributes to its therapeutic effects in conditions such as schizophrenia and major depressive disorder.

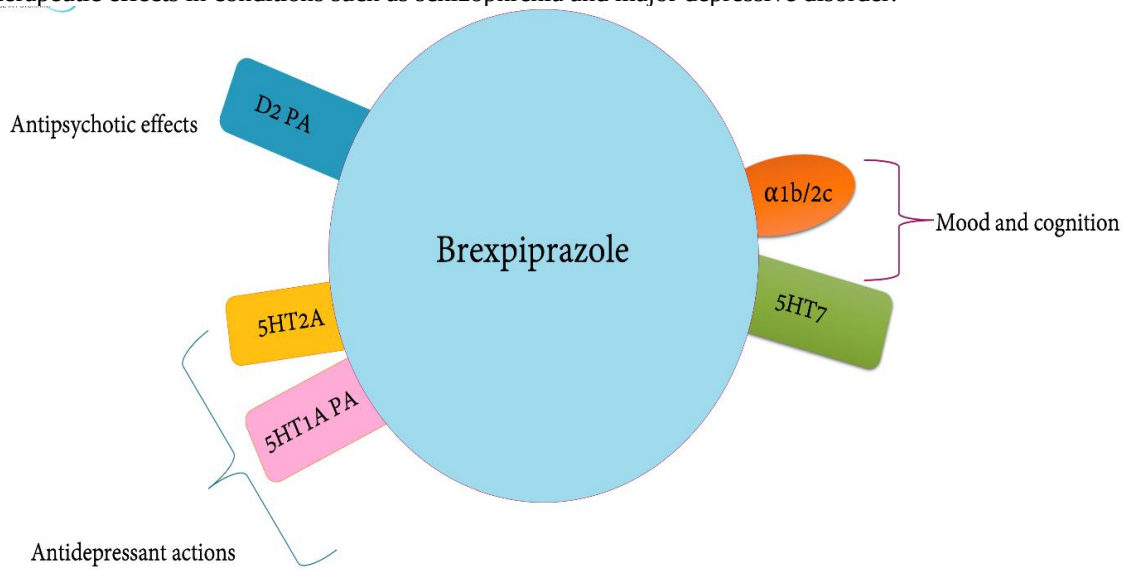

Fig-5: Mechanism of Brexpiprazole

5.2 METHODOLOGY

5.2.1 Determination of Lambda max and Construction of Standard Graph of Brexpiprazole by UV-Visible spectrophotometer[20]

5.2.1.1 Preparation of Stock Solution

In this step, 100 mg of Brexpiprazole was accurately weighed and transferred into a 100 mL volumetric flask. To dissolve the drug, 20 mL of methanol was added, and the volume was made up to 100 mL using distilled water. This resulted in a stock solution with a concentration of 1 mg/mL.

5.2.1.2 Preparation of Diluted Solutions

From the stock solution, 10 mL was taken and diluted to 100 mL using methanol, resulting in a diluted solution with a concentration of 100 µg/mL. Various dilutions of Brexpiprazole were prepared by further diluting this solution to concentrations ranging from 2 to 10 µg/mL.

5.2.1.3 Analysis Using UV Spectrophotometer

The prepared solutions were then analyzed using a UV spectrophotometer. A blank solution was used as a reference, and the absorbance of the Brexpiprazole solutions was measured over a wavelength range of 200-800 nm. This allowed for the determination of the absorbance spectra of the different dilutions of Brexpiprazole. A calibration curve was constructed by using 1-5ppm standard solutions.

5.2.1.4 Calculation of Brexpiprazole Concentration

By analyzing the absorbance spectra of the Brexpiprazole solutions, the concentration of Brexpiprazole in each dilution could be calculated using Beer-Lambert's Law. This method is commonly used in pharmaceutical analysis to determine the concentration of drugs in solution based on their absorbance at specific wavelengths.

Solubility Study of Brexpiprazole

To determine the solubility of the selected drugs in different excipients, the following detailed procedure can be followed:

- **Sample Preparation:**

Add an excess amount of selected drug to 1 gram of each excipient in separate glass vials. Cap the vials containing the excipient and selected drug formulation.

- **Mixing and Solubilization:**

Use a cyclo-mixer to mix the excipient and drug for 2 minutes. This step facilitates the solubilization of the drug in the excipient.

- **Heating and Equilibration:**

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Place the capped vials in a water bath set at a temperature range of 40-50°C for 5 minutes. This helps in enhancing the solubilization process. Subsequently, allow the vials to cool down to room temperature and place them on an isothermal rotary shaker set at a speed of 100 rpm for 72 hours. This ensures that the drug reaches equilibrium and is uniformly dispersed in the excipient.

- **Centrifugation and Extraction:**

After the equilibration period, centrifuge each vial at a speed of 3,000 rpm for 15 minutes using a centrifuge. The centrifugation step helps in separating the undissolved drug from the supernatant liquid. Carefully remove the vials from the centrifuge and extract the supernatant liquid using a micropipette. This supernatant contains the dissolved drug in the excipient.

- **Dilution and Analysis:**

Aliquot samples of the supernatant fluid are drawn using the micropipette and diluted with methanol. Analyze the diluted samples using a suitable analytical technique (e.g., UV-Visible spectrophotometer) to quantify the concentration of drug in each excipient. By following this detailed procedure, the solubility of drug in various excipients can be effectively determined.

5.2.2 Drug excipients compatibility studies

5.2.2.1 Importance of Drug-Excipient Compatibility Studies

The study of drug-excipient compatibility is a crucial phase in the early stages of drug development. It helps to understand the potential interactions between the active pharmaceutical ingredient (API) and the excipients used in the formulation. These compatibility studies are essential for selecting suitable excipients, determining the stability of the drug, and identifying any potential interactions or degradation products that may occur during the formulation process[21].

5.2.2.2 FTIR Analysis

In this study, Fourier Transform Infrared (FTIR) spectroscopy was used to analyze the samples. The samples were screened in the spectral range of 400-4000 cm-1. FTIR spectroscopy is a powerful analytical technique that can provide information about the functional groups present in a sample based on their characteristic absorption bands[22].

5.2.2.3 Comparison of Absorption Peaks

The absorption peaks observed in the FTIR spectra of the pure drug were compared with those of the optimized formulation and excipients. By comparing the spectra, researchers can identify any shifts or changes in the absorption peaks, which may indicate potential interactions between the drug and excipients[23].

The characteristic absorption peaks of the drug were observed in the combination spectrum, indicating that the drug and excipients are compatible with each other. This suggests that the excipients selected for the formulation do not adversely affect the stability or integrity of the drug.

5.2.3 Preparation of Niosomes by Thin Film Hydration method

The thin-layer hydration method is a commonly used technique for the preparation of niosomes, which are non-ionic surfactant-based vesicles similar to liposomes[24-27]. Here is a general method for the preparation of niosomes using the thin-layer hydration method:

5.2.3.1 Materials:

- Non-ionic surfactant (e.g., Span or Tween series)
- Cholesterol (optional, for stabilization)
- Phospholipids (optional, for additional stability)
- Organic solvent (e.g., chloroform or ether)
- Buffer solution (e.g., phosphate buffer)

5.2.3.2 Procedure:

1. Preparation of Film:

Dissolve the non-ionic surfactant and any optional components (e.g., cholesterol, phospholipids) in an organic solvent to form a thin film. The concentration of surfactant and other components should be based on the desired niosome composition. Evaporate the solvent under reduced pressure to form a thin film on the wall of a round-bottom flask.

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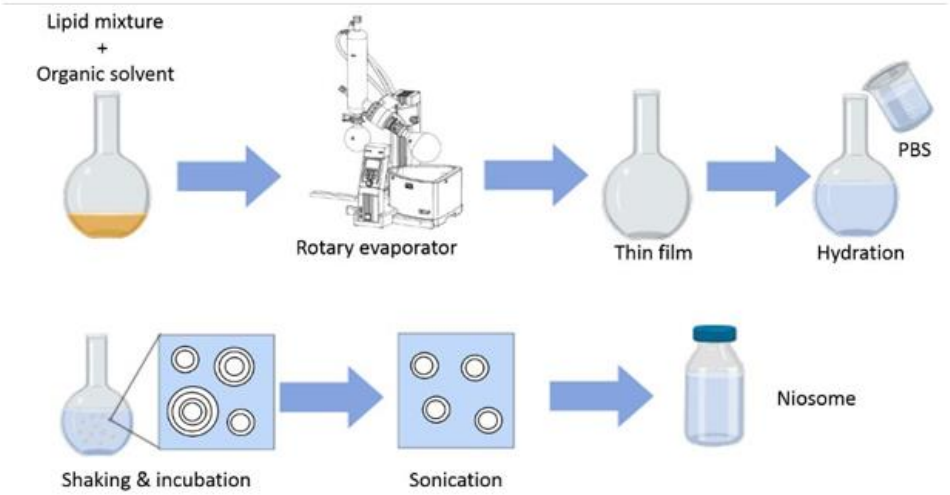

Fig-6: Preparation of Niosomes by Thin Film Hydration method

2. Hydration:
Add the desired aqueous phase (e.g., buffer solution) to the flask containing the thin film. The aqueous phase should be added slowly to ensure complete hydration of the film. Swirl the flask gently to aid in the hydration process.
3. Vesicle Formation:
Allow the hydration process to continue for a specific period to allow the formation of niosomes. The hydration time may vary depending on the composition and size of niosomes desired.
4. Processing:
After hydration, the niosome suspension can be further processed by sonication or extrusion to obtain a more uniform size distribution.
Optionally, the niosome suspension can be purified by methods such as ultracentrifugation or dialysis to remove unincorporated components.

Fig-7: Rotary Evaporator

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Table-4: Formulation of Brexpiprazole Niosomal Dispersion

Formulation code	Surfactant	Brexpiprazole (mg)	Surfactant (mg)	Cholesterol (mg)	Solvent (Chloroform: Methanol) (ml)	Buffer Solution (ml)
BN1	Span 40	200	100	100	2:1	4ml
BN2	Span 40	200	200	100	2:1	4ml
BN3	Tween 60	200	100	100	2:1	4ml
BN4	Tween 60	200	200	100	2:1	4ml
BN5	Tween 80	200	100	100	2:1	4ml
BN6	Tween 80	200	200	100	2:1	4ml

5.2.4 Characterization of Niosomes:

The evaluation of niosomes is essential to assess their performance, stability, and suitability for drug delivery applications. Several methods are commonly used to characterize niosomes and evaluate their properties[28-31]. Here are some key methods for evaluating the performance of niosomes:

5.2.4.1 Size and Morphology Analysis:

Particle size and morphology of niosomes are crucial parameters that influence their stability, drug encapsulation efficiency, and skin penetration properties. Techniques such as dynamic light scattering (DLS) can be used to determine the size distribution, surface morphology, and shape of niosomes. The size of niosomal dispersion is a critical parameter that influences the stability, drug encapsulation efficiency, and drug delivery properties of niosomes[28-31]. The measurement of particle size distribution can be determined using dynamic light scattering (DLS) technique with the Malvern Zetasizer instrument. Here is an overview of how the size of niosomal dispersion is determined by the Malvern Zetasizer:

Sample Preparation: A niosomal dispersion sample is prepared in a suitable solvent or buffer solution at a specified concentration. The sample should be well-dispersed to ensure accurate size measurement and to avoid the presence of aggregates that may affect the results.

Loading Sample: The prepared niosomal sample is loaded into the sample cell of the Malvern Zetasizer. It is important to properly clean the sample cell and ensure that there is no air bubbles or contaminants that may impact the measurement.

Size Measurement: The Malvern Zetasizer uses the principle of dynamic light scattering (DLS) to measure the size distribution of particles in the niosomal dispersion. In this technique, a laser beam is directed through the sample, and the scattered light is detected and analyzed. The Brownian motion of particles results in fluctuations in the scattered light intensity, which is used to calculate the size distribution of particles in the sample.

Data Analysis: The Malvern Zetasizer software processes the data collected from the light scattering experiments and generates a size distribution plot. The instrument provides parameters such as the mean particle size, polydispersity index (PDI), and size distribution profile of the niosomal dispersion[28-31]. The mean particle size represents the average size of particles in the sample, while the PDI indicates the uniformity of particle sizes (a lower PDI value suggests a more homogeneous size distribution).

Interpretation of Results: The size distribution data obtained from the Malvern Zetasizer can offer insights into the uniformity, stability, and physical characteristics of the niosomal dispersion. The analysis of particle size is crucial for optimizing niosomal formulations, determining drug encapsulation efficiency, and predicting the drug release behavior and skin penetration properties of niosomal transdermal patches.

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By utilizing the Malvern Zetasizer for measuring the size of niosomal dispersion, researchers can obtain valuable information on the particle size distribution, homogeneity, and stability of niosomes, which are essential for designing and evaluating niosomal formulations for effective drug delivery applications.

5.2.4.2 Polydispersity index (PDI):

In addition to the methods mentioned for evaluating niosomes' performance, it is essential to consider the polydispersity index (PDI) as a parameter for characterizing vesicle size distribution[28-31]. PDI is a dimensionless value that reflects the homogeneity or heterogeneity of particle sizes within a sample and can be Techniques such as dynamic light scattering (DLS). A low PDI value indicates a narrow size distribution with uniform vesicle sizes, while a high PDI value suggests a broad range of sizes or a more heterogeneous population of niosomes. Measurement of PDI provides insights into the uniformity and stability of niosomal formulations, which are crucial factors affecting their performance in drug delivery applications. A low PDI value signifies a more consistent size distribution, which can enhance the reproducibility and efficiency of drug encapsulation, drug release kinetics, and skin penetration capabilities of niosomes.

5.2.4.3 Zeta Potential:

Zeta potential is a key parameter in characterizing colloidal systems, such as niosomes, and it provides information about the surface charge and stability of particles in a dispersion. It is defined as the electric potential at the slipping plane of a particle or vesicle in a dispersion and is influenced by the charge distribution on the particle surface. Zeta potential plays a crucial role in determining the stability, aggregation behavior, and interaction with biological membranes of colloidal systems[28-31].

The Malvern Zetasizer is a widely used instrument for measuring zeta potential and particle size distribution in colloidal dispersions. Here is a brief overview of how zeta potential is determined by the Malvern Zetasizer:

1. Sample Preparation: A niosomal dispersion sample is prepared in an appropriate solvent or buffer solution at a specified concentration. The sample should be well-dispersed and free of any aggregates that may affect the zeta potential measurement.
2. Loading Sample: The prepared niosomal sample is loaded into the sample cell of the Malvern Zetasizer instrument. Care should be taken to ensure that the sample cell is clean and free from contamination.
3. Zeta Potential Measurement: The Malvern Zetasizer utilizes the technique of electrophoretic light scattering to measure the zeta potential of the niosomes. In this technique, a laser beam is passed through the sample, and the scattered light from the particles is analyzed to determine their electrophoretic mobility. The instrument applies an electric field to the sample, causing the niosomes to migrate according to their surface charge. The velocity of particle movement is then correlated to the zeta potential value using the Henry equation.
4. Data Analysis: The Malvern Zetasizer software calculates the zeta potential value based on the measured electrophoretic mobility of the niosomes. The zeta potential measurement can provide valuable information on the stability and interaction propensity of the niosomal dispersion. A high absolute zeta potential value (positive or negative) indicates strong repulsive forces between particles, leading to enhanced stability and reduced aggregation tendency.

5.2.4.4. Entrapment Efficiency Determination Method for Niosomes:

Entrapment efficiency is a measure of the amount of drug that is effectively encapsulated within the niosomes compared to the total amount of drug added during the formulation process. Entrapment efficiency is calculated by comparing the drug content in the niosomes with the total drug content added[28-31].

Procedure:

1. Preparation of Niosome Formulation:

The niosome formulation containing the drug is prepared using the method appropriate for the specific formulation. The drug is typically added during the formation of the niosomes to allow encapsulation within the vesicles.

2. Centrifugation and Separation:

The niosome suspension is subjected to centrifugation at a high speed (e.g., 14,000 rpm) for a specified duration (e.g., 30 minutes). This centrifugation step helps to separate the drug-loaded niosomes from any untrapped or free drug molecules in the suspension. As a result of centrifugation, the drug-loaded niosomes pellet at the bottom of the centrifuge tube, forming a pellet, while the untrapped drug remains in the supernatant.

3. Separation of Supernatant:

After centrifugation, the supernatant containing the untrapped drug is carefully decanted or aspirated from the pelleted niosome fraction. The supernatant may then be filtered using a suitable filter to remove any residual niosomes or particulate matter before analysis.

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4. Assay of Untrapped Drug:
The concentration of the untrapped drug in the filtered supernatant is determined using a suitable analytical method such as high-performance liquid chromatography (HPLC), UV-visible spectrophotometry, or another validated technique. The drug concentration in the supernatant directly reflects the amount of drug that was not encapsulated within the niosomes.
5. Calculating Entrapment Efficiency:
The total drug input refers to the initial amount of drug added during niosome formulation, while untrapped drug concentration is determined from the supernatant assay. Entrapment efficiency is calculated using the following formula:

Entrapment Efficiency (%) = [(Total drug input - Untrapped drug)/Total drug input] x 100%

Entrapment efficiency determination is crucial for assessing the ability of niosomes to encapsulate and retain the drug. A high entrapment efficiency indicates effective drug encapsulation within the vesicles, which is essential for drug delivery applications. By accurately quantifying the entrapment efficiency, researchers can optimize niosome formulations for enhanced drug delivery efficacy.
5.2.4.5 Drug Content Determination Method in Niosomal suspension:
Drug content determination is a critical parameter that quantifies the amount of active pharmaceutical ingredient (API) present in the niosomal formulation. It provides valuable information about the actual drug concentration in the final product, which is essential for ensuring dosage accuracy and efficacy[28-31].
Procedure:
1. Sample Preparation:
A known weight of the niosomal formulation (e.g., 100 mg) is taken and added to a suitable solvent, such as methanol, to dissolve the niosomes and release the entrapped drug molecules. The choice of solvent should be based on the solubility of the drug and niosome components.
2. Dissolution of Formulation:
The niosomal gel sample is dissolved in the solvent by gentle agitation or sonication to ensure proper dispersion of the drug molecules into the solution. The dissolution process facilitates the release and solubilization of the drug from the niosomes into the solvent.
3. Analysis:
The dissolved sample is then analyzed using a suitable analytical method to quantify the drug content. Common analytical techniques for drug content determination include UV-Visible spectrophotometry, high-performance liquid chromatography (HPLC), or other validated methods depending on the characteristics of the drug.
4. Quantification:
The concentration of the drug in the solution is determined based on the absorbance or peak area obtained from the analytical analysis. This concentration corresponds to the amount of drug present in the niosomal formulation.
5. Calculations:
The drug content in the niosomal formulation is calculated by converting the measured drug concentration from the analysis into the total amount of drug present in the initial sample (100 mg niosomal). The calculation may involve simple unit conversions based on the analytical results.
Determining the drug content in the niosomal formulation is essential for quality control and dosage accuracy. By accurately quantifying the drug content, researchers and manufacturers can ensure that the formulated product meets the specified drug concentration requirements for effective and consistent drug delivery. This information is crucial for evaluating the performance and efficacy of the niosomal as a drug delivery system.

5.2.5 Central Composite Design (CCD) in Optimization of Niosomes:

Central Composite Design (CCD) is a powerful experimental design technique that allows researchers to study the relationship between multiple factors and a response variable of interest in a systematic and efficient manner. In the context of optimizing niosomes, CCD can be employed to investigate the influence of various formulation factors on the entrapment efficiency of the vesicles[32-35].
Factors:
1. Surfactant Concentration: The concentration of the non-ionic surfactant plays a crucial role in the formation and stability of niosomes. Higher surfactant concentrations may lead to increased encapsulation of the drug within the vesicles.
2. Temperature of Hydration: The temperature at which the niosome formulation is hydrated can affect the size, structure, and stability of the vesicles. Optimal hydration temperature can promote efficient drug encapsulation and vesicle formation.

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3. Time of Hydration: The duration of hydration represents the time allowed for the surfactants and other components to form niosomes. Longer hydration times may enhance entrapment efficiency by allowing for better encapsulation of the drug within the vesicles.

Response Variable:

Entrapment Efficiency: Entrapment efficiency is a critical parameter that indicates the ability of niosomes to encapsulate the drug effectively. It reflects the proportion of drug retained within the vesicles compared to the total amount of drug added during formulation. Higher entrapment efficiency signifies better drug loading and potential for enhanced drug delivery efficacy.

Quadratic Model and 15 Runs:

A quadratic model is commonly used in CCD to capture both linear and quadratic effects of the independent variables on the response variable. This model allows for the exploration of curvature in the response surface, enabling a more accurate representation of the relationship between factors and the response.

With 15 experimental runs planned in the CCD, researchers can systematically vary the levels of surfactant concentration, hydration temperature, and hydration time to assess their individual and interactive effects on the entrapment efficiency of niosomes. The experimental results obtained from these runs can be used to fit the quadratic model and generate response surfaces to visualize the optimal conditions for maximizing entrapment efficiency.

By leveraging CCD and the quadratic model, researchers can efficiently explore the complex interactions among formulation factors and optimize the entrapment efficiency of niosomes for targeted drug delivery applications. This systematic approach enhances the understanding of the formulation process and facilitates the development of robust niosome formulations with superior drug encapsulation capabilities

Table-5: Formulation of Brexpiprazole Loaded Niosomal Patches

Formulation Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Brexpiprazole Niosomal Dispersion (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Polymers (mg)									
HPMC E5	75	100	125	-	-	-	50	75	100
HPMC 15 CPS	-	-	-	75	100	125	100	75	50
PEG 200	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Glycerine	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Chloroform	3	3	3	3	3	3	3	3	3
Methanol	2	2	2	2	2	2	2	2	2

5.2.6 Incorporation of Niosomal suspension into Transdermal Patches by Solvent Casting Method

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Transdermal patches are pharmaceutical delivery systems that deliver therapeutic agents through the skin and into the systemic circulation. Niosome formulations, with their potential for enhanced drug encapsulation and controlled release, are often incorporated into transdermal patches to improve drug delivery efficiency[36-38]. The solvent casting method is a common technique used to prepare transdermal patches containing niosome formulations.

Procedure:

1. Selection of Materials:

Niosome formulation: The niosome formulation prepared using the desired surfactants, drug, and other components is selected for incorporation into the transdermal patch.

Polymers: Biocompatible polymers such as HPMC E5 and HPMC 15cps were used in the formulation of transdermal patches.

Plasticizers: Glycerine and PEG-200 are used for flexibility of the patch.

Solvents: Chloroform and Methanol are used as solvent systems for the patch.

2. Preparation of Patch Formulation:

The niosome formulation is combined with the polymer(s) in a suitable Chloroform-methanol solevent system to form a homogenous mixture. Glycerine and PEG-200 were used as plasticizers for flexibility of the patch. The polymer helps to stabilize the niosomes, provide structural integrity to the patch and control drug release.

3. Solvent Casting:

The solvent casting method involves the following steps:

The niosome-polymer mixture is cast onto a flat, non-stick surface such as a glass plate or a Teflon sheet. The solvent is allowed to evaporate slowly, leaving behind a thin film of the niosome-polymer mixture. This process ensures the formation of a uniform patch.

4. Drying and Solidification:

After the solvent evaporation, the cast film is dried further to remove any residual solvent and ensure solidification of the patch.

5. Cutting and Packaging:

The solidified film is cut into individual patches (2×2 cm^2) of the desired size and shape. The patches are packaged in airtight and light-resistant packaging to protect the formulation from external factors that may affect its stability.

Optimization: The solvent casting method provides a straightforward and reproducible approach to prepare transdermal patches containing niosome formulations, enabling researchers to optimize drug delivery systems for specific therapeutic applications.

By incorporating niosome formulations into transdermal patches using the solvent casting method, researchers can develop innovative drug delivery systems with improved efficacy, patient convenience and targeted delivery capabilities.

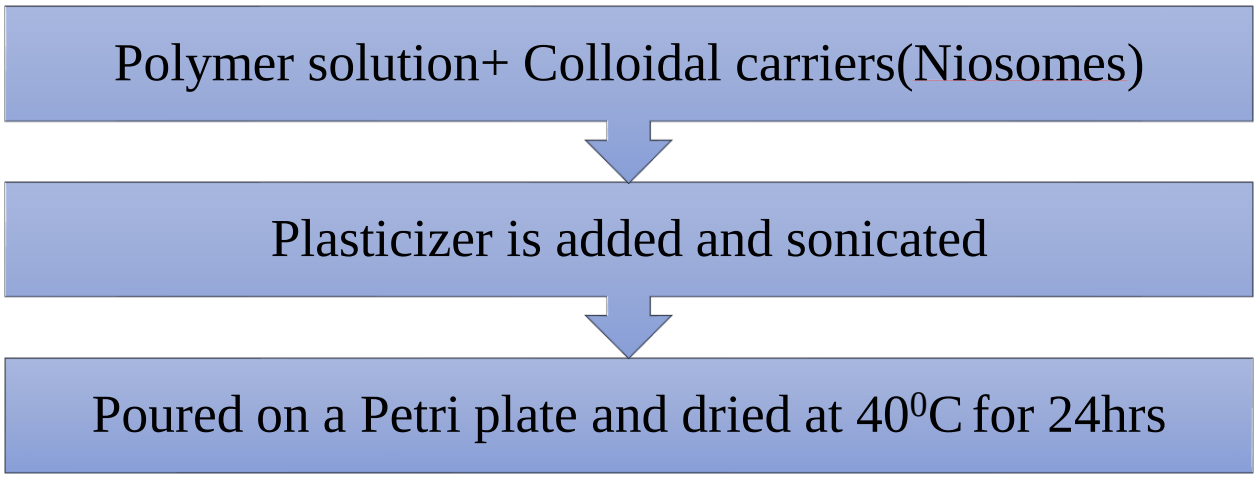

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Fig-8: Optimized Brexpiprazole Niosomal Patch

5.2.7 Characterization of Niosomal patch

All the transdermal patches were visually inspected for colour, clarity, flexibility and smoothness.

5.2.8.1 Uniformity of weight

Five different patches of the individual batch were weighed and the average weight was calculated. The individual weight should not deviate significantly from the average weight of five. Weight uniformity testing is a critical quality control measure used to ensure that individual transdermal patches within a batch have consistent weights. Discrepancies in patch weight can impact drug delivery efficacy, dosage accuracy, and patient safety. To assess weight uniformity, multiple patches from the same batch are weighed individually, and the average weight is calculated to determine if the individual weights deviate significantly from the average[39-41].

Procedure:

1. Sampling:

Select five transdermal patches from the same batch for weight uniformity testing. The patches should be representative of the entire batch and randomly chosen to provide an accurate assessment.

2. Weighing Process:

Each selected patch is removed from its packaging and placed on a calibrated analytical balance. The weight of each individual patch is recorded to the nearest milligram or as per the specified measurement precision. Repeat the weighing process for all five patches, ensuring consistent handling and measurement techniques.

3. Calculation of Average Weight:

Calculate the average weight of the five patches by adding the individual weights and dividing by the total number of patches weighed (in this case, five).

The average weight provides a reference value to compare against the individual weights to assess uniformity.

4. Assessment of Weight Deviation:

Compare the individual weights of the patches with the average weight calculated. If the individual weights of the patches deviate by a predefined acceptable limit (e.g., ±5% of the average weight), it indicates potential weight variation within the batch. Any patch whose weight significantly deviates from the average weight may warrant further investigation, including retesting or rejection of the patch. Record the individual weights, average weight, and any deviations observed during the weight uniformity testing.

5.2.8.2. Moisture content

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Fig-9: Desiccator

After the preparation of the transdermal patches containing niosome formulations using the solvent casting method, the next step involves assessing the moisture content of the film to ensure its stability and quality. This procedure involves weighing the film, drying it in a desiccator containing calcium chloride to eliminate moisture, and determining the moisture content as a percentage of the initial weight[39-41].

Procedure:

1. Weighing the Film:

The transdermal patch film, obtained after cutting the solid matrix into individual patches, is carefully weighed using a precise analytical balance to record the initial weight.

2. Drying in a Desiccator:

The film is then placed in a desiccator containing an efficient desiccant, such as calcium chloride, which helps to absorb moisture from the film. The desiccator is sealed, creating a dry environment that facilitates the removal of moisture from the film.

3. Drying Process:

The desiccator with the film is left undisturbed for at least 24 hours to allow for effective drying of the film. During this period, the calcium chloride absorbs moisture from the film, aiding in the drying process.

4. Weighing for Constant Weight:

After the drying period, the film is removed from the desiccator, and its weight is measured at regular intervals until a constant weight is obtained. The constant weight indicates that the film has reached an equilibrium state with respect to moisture content, signifying that the drying process is complete.

5. Calculation of Moisture Content:

The moisture content of the film is calculated as the difference between the constant weight obtained after drying and the initial weight of the film. The moisture content is expressed as a percentage by weight, representing the moisture content relative to the original weight of the film. The moisture content value is recorded and reported as part of the quality control data for the transdermal patch batch. Any deviations from the acceptable moisture content range may trigger further investigations or corrective actions to ensure product stability.

5.2.8.3. Thickness:

Measuring the Thickness of Transdermal Patches Using a Screw Gauge:

The thickness of transdermal patches is a critical parameter that directly affects drug release kinetics, permeation through the skin, and the accuracy of the dose delivered to the patient. Measuring the thickness of patches using a screw gauge is a common quality control practice to ensure uniformity and consistency in patch thickness across a batch. This procedure involves measuring the thickness at multiple positions on the patch and calculating an average value to assess the uniformity of thickness distribution[39-41].

Procedure:

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1. Screw Gauge Setup:
Prepare a screw gauge, a precision measuring instrument with a calibrated spindle and anvil, suitable for measuring small thicknesses with high accuracy. Zero the screw gauge by ensuring that the spindle is in contact with the anvil and the reading is set to zero.
2. Sample Preparation:
Select a transdermal patch from the batch for thickness measurement. Ensure that the patch is representative of the entire batch and free from any defects that may affect measurement accuracy. Lay the patch flat on a smooth surface, ensuring that it is positioned evenly for consistent measurements.
3. Thickness Measurement:
With the screw gauge in hand, gently place the spindle on the surface of the transdermal patch at the desired position. Carefully rotate the thimble of the screw gauge to lower the spindle until it lightly touches the patch surface without causing deformation. Record the thickness measurement displayed on the screw gauge. Repeat this process at least three times at different positions on the patch to capture variations in thickness.
4. Calculation of Average Thickness:
Calculate the average thickness of the transdermal patch by summing the individual measurements taken at different positions and dividing by the total number of measurements (in this case, three). The average thickness value provides a representative measurement that reflects the overall uniformity of the patch thickness. Compare the individual thickness measurements with the average thickness value to evaluate the uniformity of the patch. Any significant deviations from the average thickness may indicate variations in patch quality and dose accuracy, warranting further investigation and potential adjustments in manufacturing processes.

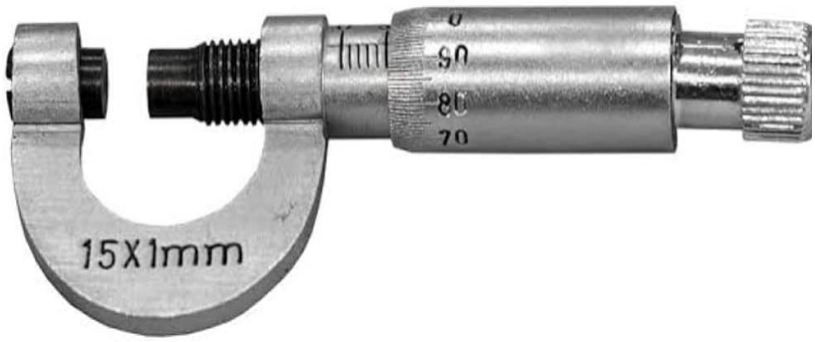

Fig-10: Screw Gauge

5.2.8.4. Measuring Surface pH of Transdermal Patches Using a pH Meter[39-41]:
The surface pH of transdermal patches is an important parameter to consider as it can influence skin irritation, compatibility with the skin's pH, and the effectiveness of drug delivery. Measuring the surface pH provides valuable information about the patch formulation and its potential impact on skin health. This procedure involves soaking the patch in water and using a pH meter to determine the pH of the solution, reflecting the surface pH of the patch material.
Procedure:
1. Sample Preparation:
Select a transdermal patch from the batch for surface pH measurement. Ensure that the patch is intact and free from any contaminants that may affect the pH reading.
Place the patch in a clean petri dish, ensuring that it lies flat and covers the base of the dish.
2. Soaking the Patch:
Add 0.5 mL of distilled water to the surface of the patch in the petri dish to soak it. Ensure that the water covers the entire surface of the patch evenly. Allow the patch to soak in the water for a specified period to allow for the extraction of any potentially pH-altering substances from the patch material.
3. pH Measurement:
Calibrate the pH meter according to the manufacturer's instructions using standard buffer solutions of known pH values. Submerge the pH meter probe into the water covering the patch surface to measure the pH of the solution.

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Allow the pH meter to stabilize and record the pH reading displayed on the meter. Repeat the measurement to ensure accuracy.

4. Data Interpretation:

The pH value obtained from the measurement reflects the surface pH of the transdermal patch material after being soaked in water. Compare the measured pH value with acceptable pH ranges established for transdermal patches to assess skin compatibility and potential irritant effects.

Fig-11: pH meter

5.8.2.5. Determination of Folding Endurance of Formulated Transdermal Patches:

Folding endurance is a critical parameter used to evaluate the mechanical durability and flexibility of transdermal patches. It provides valuable information about the patch's ability to withstand repeated bending stresses without breaking or cracking, which is essential for maintaining the integrity of the patch during handling, storage, and application. This procedure involves manually folding a strip of the patch at the same place until it reaches its breaking point, with the number of folds indicating the patch's resistance to brittleness[39-41].

Procedure:

1. Sample Preparation:

Select a representative transdermal patch from the batch for folding endurance testing. Ensure that the patch is free from any defects or irregularities that may affect the test results. Cut a strip of the patch measuring 2 x 2 cm^2 using a sharp blade or scissors. The strip should be uniform in size and shape for consistent testing.

2. Folding Endurance Testing:

Hold one end of the patch strip securely and begin folding it at the same place repeatedly, always in the same direction, until the patch reaches its breaking point. Ensure that each fold is made with consistent force and precision to simulate real-world handling conditions and assess the patch's mechanical strength. Count the number of times the patch strip can be folded at the same place without breaking or showing signs of cracking. Record the observed number of folds as the folding endurance value for the transdermal patch, reflecting its resistance to brittleness and ability to withstand mechanical stress.

A higher number of folds before breaking indicates good folding endurance, suggesting that the patch has excellent flexibility and mechanical resilience. Conversely, a lower number of folds may indicate brittleness, poor adhesion strength, or inadequate flexibility, which could compromise the patch's integrity and usability.

5.2.8.6. In Vitro Diffusion Studies Using Franz Diffusion Cell:

In vitro diffusion studies conducted with a Franz diffusion cell play a pivotal role in pharmaceutical research to assess the permeation characteristics of drug formulations. This experimental approach allows for the evaluation of drug release patterns, diffusion rates, and permeability through a synthetic membrane, mimicking transdermal drug delivery conditions[39-41].

Procedure:

1. Design and Validation of Franz Diffusion Cell:

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Develop a vertical Franz diffusion cell tailored to the specific research requirements, ensuring precision and reproducibility in drug permeation experiments. Prior to initiating the permeation study, validate the Franz diffusion cell to verify its functionality and reliability for simulating transdermal drug delivery conditions.

2. Preparation of Diffusion Cell Assembly:

Mount a cellophane membrane on the diffusion cell assembly, providing an effective diffusion area of 2.303 cm^2, which serves as the permeation barrier. The cellophane membrane emulates the skin's barrier properties, allowing for the assessment of drug permeability and diffusion across the membrane interface.

3. Receptor Compartment Setup:

Set up the receptor compartment of the Franz diffusion cell with 22.5 ml of phosphate buffer solution at pH 6.8, serving as the receptor fluid. Maintain the receptor fluid at a controlled temperature of 37 ± 0.5°C throughout the study to replicate physiological conditions conducive to drug permeation. Agitate the receptor fluid at a constant speed of 100 rpm to ensure uniform mixing and enhance drug diffusion across the membrane.

Apply the drug formulation or transdermal patch onto the cellophane membrane in the donor compartment of the diffusion cell. Monitor and collect samples from the receptor compartment at regular intervals to quantify the cumulative amount of drug that has permeated through the cellophane membrane.

5. Data Analysis and Plotting:

Calculate the cumulative amount of drug that permeated across the cellophane membrane over time during the permeation study. Plot the permeation data against time to generate a drug release profile, allowing for the visualization of drug permeation kinetics and diffusion trends.

Fig-12: Franz Diffusion cell

5.2.8 Mathematical models

Drug release kinetics models are used to describe and predict the release behavior of drugs from pharmaceutical dosage forms such as transdermal patches. Each model makes certain assumptions about the release process and can be used to analyze experimental release data[42,43]. Here is an overview of the five commonly used drug release kinetics models:

5.2.9.1. Zero-Order Kinetics:

In zero-order kinetics, the drug is released at a constant rate over time, regardless of the drug concentration in the dosage form. The release rate is independent of the drug concentration and follows a linear profile. The equation for zero-order release can be expressed as:

$$Q = k0 * t$$

Where,

Q is the amount of drug released at time t

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k0 is the zero-order release rate constant

5.2.9.2. First-Order Kinetics Model:

In first-order kinetics, the drug is released at a rate proportional to the remaining drug concentration in the dosage form. The release rate decreases exponentially over time. The equation for first-order release can be expressed as:

$$\ln(Q0 - Qt) = -kt$$

Where,

Q0 is the initial amount of drug in the dosage form
Qt is the amount of drug released at time t
k is the first-order release rate constant

5.2.9.3. Higuchi Kinetic Model:

The Higuchi model describes drug release from a matrix system where the rate of drug release is proportional to the square root of time. This model is commonly applied to semi-solid and solid dosage forms like transdermal patches. The equation for Higuchi release can be expressed as:

$$Q = kH * \text{sqrt}(t)$$

Where,

Q is the amount of drug released at time t
kH is the Higuchi release rate constant

5.2.9.4. Hixson-Crowell Kinetic Model:

The Hixson-Crowell model is based on the assumption that the drug release is due to changes in the surface area and diameter of the dosage form over time. It describes drug release from systems where the dissolution or erosion of the dosage form affects the release rate. The equation for Hixson-Crowell release can be expressed as:

$$Q1/3 - Q0\ 1/3 = kHC * t$$

Where,

Q0 is the initial amount of drug in the dosage form
Q1/3 is the amount of drug released at time t
kHC is the Hixson-Crowell release rate constant

5.9.2.5. Korsmeyer-Peppas Kinetic Model:

The Korsmeyer-Peppas model is often used to describe drug release from polymeric matrices, including transdermal patches. It is based on Fickian diffusion and can also account for anomalous (non-Fickian) transport mechanisms. The equation for Korsmeyer-Peppas release can be expressed as:

$$M(t) = kKP * t^n$$

Where,

M(t) is the fraction of drug released at time t
kKP is the Korsmeyer-Peppas release rate constant
n is the release exponent that indicates the release mechanism (Fickian diffusion for n = 0.5, case II transport for n = 1, anomalous transport for 0.5 < n < 1)

5.2.9 Accelerated Stability Studies

Accelerated stability studies for transdermal patches are typically performed following a systematic approach to simulate accelerated aging conditions and assess the stability and performance of the patches over a shorter period compared to real-time stability testing[44-46]. Here is a general overview of how these studies are conducted:

1. Selection of Stress Conditions: The first step in performing accelerated stability studies for transdermal patches is to select appropriate stress conditions that are known to accelerate degradation processes. Common stress factors include elevated temperature, high humidity, and exposure to light. These stress conditions should be chosen based on the potential degradation pathways of the patch components and the expected impact on stability.
2. Sample Preparation: Transdermal patches are prepared according to the intended formulation and manufacturing process. Multiple patches from the same batch are typically used to ensure representativeness in the study. The patches are labeled, stored in appropriate packaging, and subjected to the selected stress conditions.
3. Accelerated Aging Chamber: The prepared transdermal patches are placed in an accelerated aging chamber that allows for controlled exposure to the selected stress conditions. The chamber is set to the desired temperature, humidity levels, and may include light exposure as specified for the study.
4. Sampling and Analysis: Samples of the transdermal patches are collected at predefined time points during the accelerated stability study. The samples are analyzed for various stability-indicating parameters, such as drug

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content, adhesive strength, physical appearance, moisture content, drug release kinetics, and other critical quality attributes. Analytical techniques such as high-performance liquid chromatography (HPLC), UV-Visible spectroscopy, texture analysis and visual inspection may be used for analysis.

Storage Condition	Testing Condition
Controlled room temperature 20-25°C	40°C and 75% RH for 6 months
Refrigerated	25°C and 60% RH for 6 months

Conditions for Accelerated Stability Studies
International Council for Harmonisation (ICH) Guidelines
The ICH guidelines, specifically Q1A(R2), provide a framework for stability testing, including accelerated conditions. The standard conditions for accelerated stability testing are:
Temperature: 40°C (±2°C)
Relative Humidity: 75% RH (±5% RH)

6. RESULTS AND DISCUSSION:

6.1. ANALYTICAL METHOD OF BREXPIPRAZOLE BY UV SPECTROPHOTOMETRY

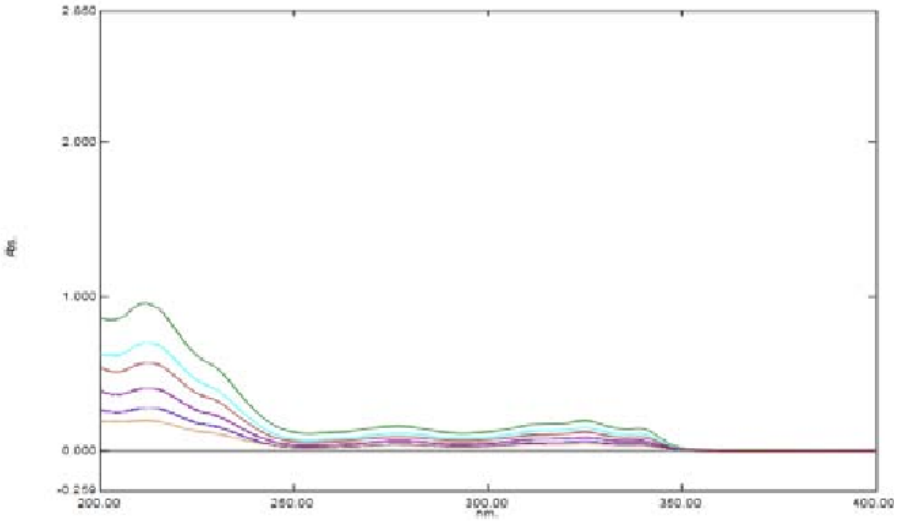

Fig-13: Scan Spectrum of Brexpiprazole by UV-Spectrophotometry

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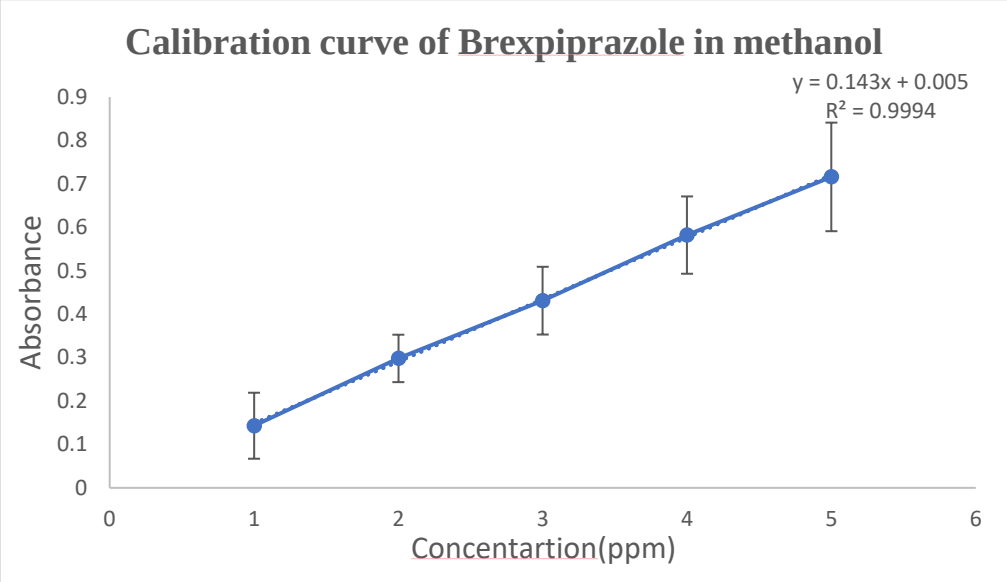

Fig-14: Calibration Curve of Brexipiprazole

Table-6: Calibration Curve of Brexipiprazole

Concentration (ppm)	Absorbance
.31	0.143±0.078
2	0.298±0.055
3	0.431±0.099
4	0.582±0.121
5	0.716±0.213

Where n = 3, Mean ± SD

The lambda max of drug was found to be at 216nm. The calibration curve for Brexpiprazole was developed at 216nm wavelength Fig-13, demonstrates an extremely strong positive correlation between concentration and absorbance within the concentration range of 1-5 ppm with a correlation coefficient value of 0.9994 shown in Fig-14, the Table-6 indicates absorbance values with corresponding standard deviations based on three replicates. The calibration curve can be used for determination of unknown concentration of Brexpiprazole in further analyses.

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Solubility Studies of Brexpiprazole in various excipients

Table-7: Solubility studies of Brexpiprazole in Various excipients

Excipient	Solubility(mg/ml)
Span 20	29.86 ± 3.30
Span 40	108.10 ± 4.37
Span 60	100.93 ± 8.36
Span 80	93.88 ± 5.35
Tween 20	106.00 ± 5.39
Tween 40	18.34 ± 13.35
Tween 60	169.95 ± 3.40
Tween 80	113.38 ± 4.45
Chloroform	269.44 ± 3.34
Methanol	297.30 ± 3.88

Where n = 3, Mean ± SD

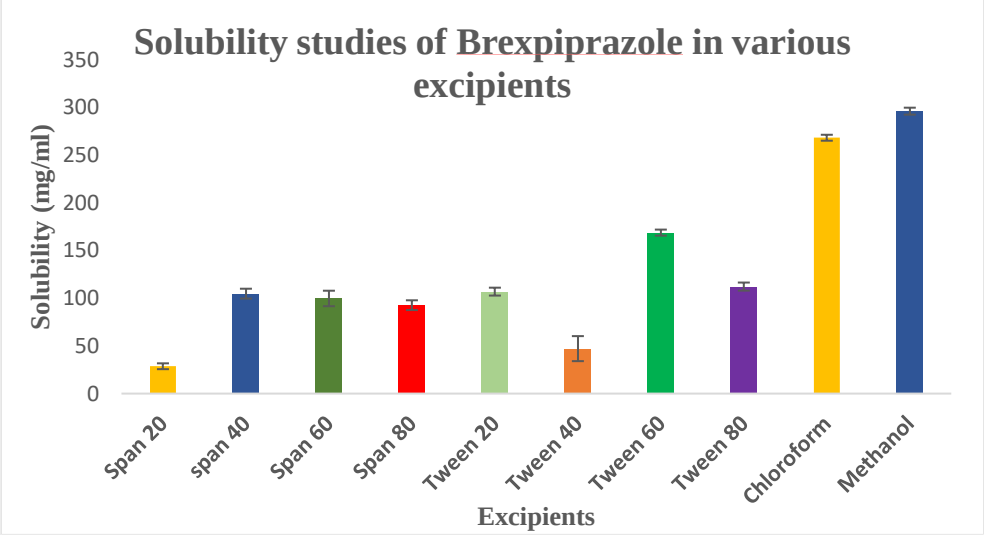

Fig-15: Solubility studies of Brexpiprazole in various excipients

The results obtained by performing solubility studies of Brexpiprazole were furnished in table-7, the data represents Brexpiprazole has maximum solubility in Methanol & chloroform solvents and exhibited optimum solubility in Span 40, Tween 60 & Tween 80. Hence, these excipients were chosen for the further studies.

6.2 Drug Excipient Compatibility Studies by FTIR

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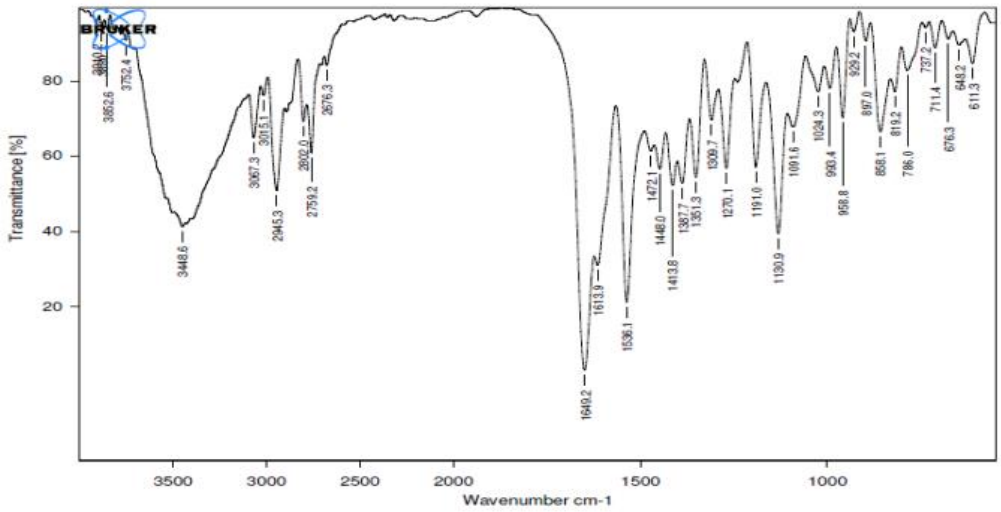

Fig-16: FTIR spectra of Brexpiprazole

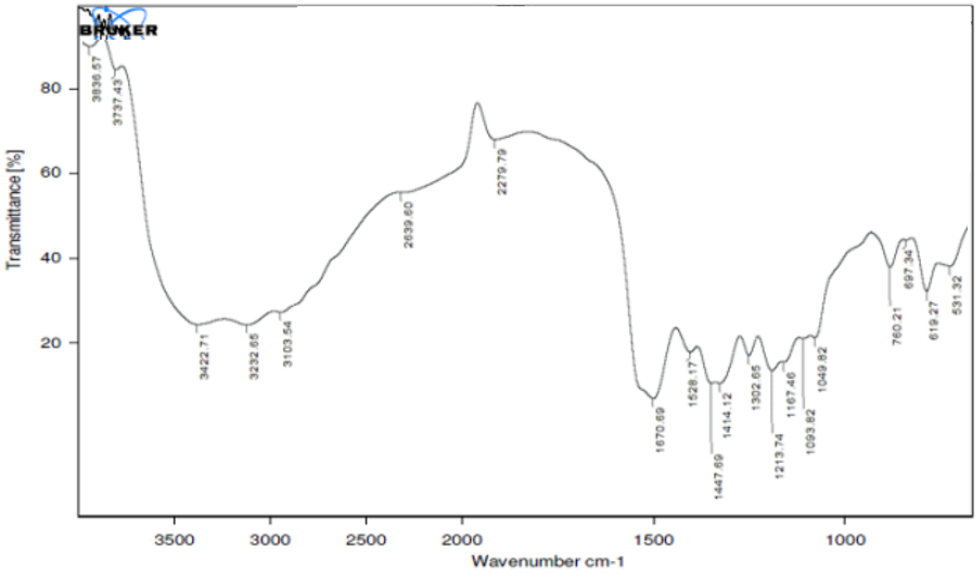

Fig-17: FTIR spectra of Brexpiprazole + Excipients used in Niosomal Patch.

Table-8: FTIR spectra compatibility

Functional group	Wavenumber(cm^{-1})	
	Brexpiprazole	Niosomal Patch BRX
N-H	3448	3422
C–N	1270	1213
C=O	1650	1670

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C-H	3067	3103

In the drug-excipient compatibility studies of brexpiprazole utilizing FTIR spectroscopy, the spectral analysis revealed notable outcomes. The FTIR spectra of physical mixtures containing brexpiprazole and various excipients exhibited no significant shifts or new peaks compared to the pure drug spectrum, indicating overall compatibility with the selected excipients. This suggests that the proposed formulation, incorporating the identified excipients, maintains the chemical integrity of Brexpiprazole. Moreover, the absence of prominent spectral changes implies minimal risk of chemical interactions or degradation during formulation development. These findings support the feasibility of the optimized formulation's stability and efficacy. Based on the provided FTIR spectral data comparing Brexpiprazole and a niosomal patch containing Brexpiprazole (BRX), several functional groups and their corresponding wavenumbers were analyzed to assess compatibility:

N-H Stretching: Brexpiprazole exhibits a peak at approximately 3448 cm^{-1}, indicating N-H stretching. In the niosomal patch BRX, this peak slightly shifts to 3422 cm^{-1}. The observed shift suggests a minor alteration in hydrogen bonding interactions within the N-H group, potentially due to interactions with the formulation components. However, the shift is relatively small, suggesting that these interactions are likely minimal and not indicative of significant incompatibility.

C-N Stretching: Brexpiprazole shows a characteristic peak around 1270 cm^{-1}, corresponding to C-N stretching vibrations. In the niosomal patch BRX, this peak shifts to 1213 cm^{-1}. This shift indicates a change in the environment surrounding the C-N bond, possibly due to interactions with the excipients present in the niosomal patch formulation. Despite the shift, the presence of the peak suggests that the C-N bond remains intact, indicating overall compatibility between Brexpiprazole and the niosomal patch formulation.

C=O Stretching: The peak associated with C=O stretching in Brexpiprazole appears around 1650 cm^{-1}. In the niosomal patch BRX, this peak shifts slightly to 1670 cm^{-1}. This shift suggests a change in the carbonyl group environment, potentially due to interactions with formulation components. However, the presence of the peak in both spectra indicates that the C=O bond remains largely unaffected, implying compatibility between Brexpiprazole and the niosomal patch formulation.

C-H Stretching: Brexpiprazole exhibits a peak around 3067 cm^{-1}, attributed to C-H stretching vibrations. In the niosomal patch BRX, this peak shifts to 3103 cm^{-1}. The observed shift indicates a change in the C-H bond environment, possibly due to interactions with the formulation components. However, the presence of the peak in both spectra suggests that the C-H bonds remain intact, indicating overall compatibility between Brexpiprazole and the niosomal patch formulation shown in Table-8 & Fig-16, 17.

6.3 Evaluation of Brexpiprazole Niosomal Dispersion

Table-9: Evaluation of Brexpiprazole Niosomal Dispersion

Formulation code	**Vesicle Size(nm)**	**Zeta Potential (mv)**	**PDI**	**% Entrapment efficiency**
BN1	684.1	-12.8	0.754	90.17±2.27
BN2	297.0	-11.1	0.772	65.33±3.14
BN3	**281.4**	**-25.7**	**0.436**	**89.16±5.36**
BN4	**225.0**	**-30.5**	**0.299**	**90.95±.054**
BN5	749.0	-6.07	0.325	86.40±4.25
BN6	411.3	-18.9	0.256	78.84±2.35

Where n = 3, Mean ± SD

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Results

			Size (d.n..	% Intensity:	St Dev (d.n..
Z-Average (d.nm):	281.4	Peak 1:	250.4	98.2	222.6
PdI:	0.436	Peak 2:	4586	1.8	836.1
Intercept:	0.854	Peak 3:	0.000	0.0	0.000
Result quality	Good				

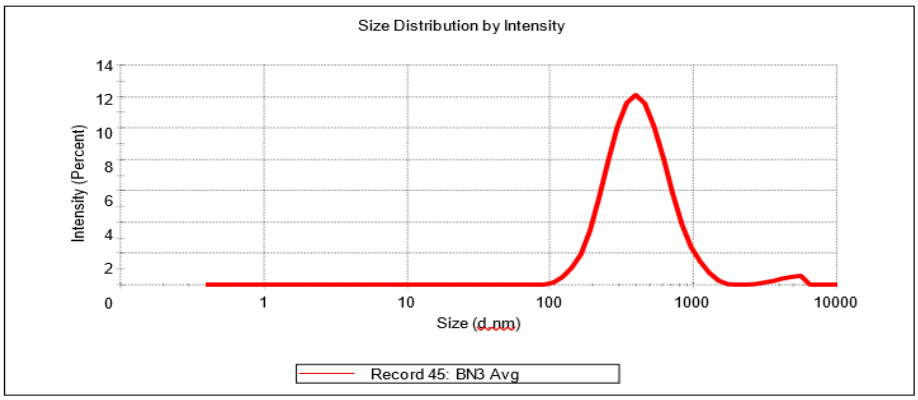

Fig-18: Size and PDI of BN3

Results

			Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-25.7	Peak 1:	-22.6	100.0	8.14
Zeta Deviation (mV):	5.63	Peak 2:	-3.80	2.0	1.80
Conductivity (mS/cm):	0.0817	Peak 3:	0.00	0.0	0.00
Result quality	Good				

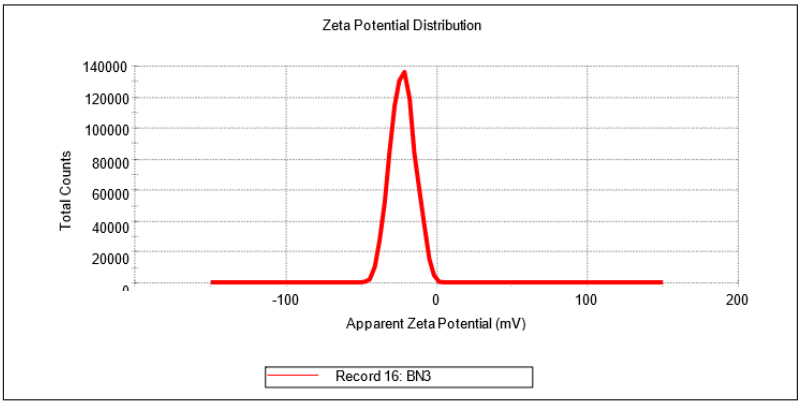

Fig-19: Zeta potential of BN3

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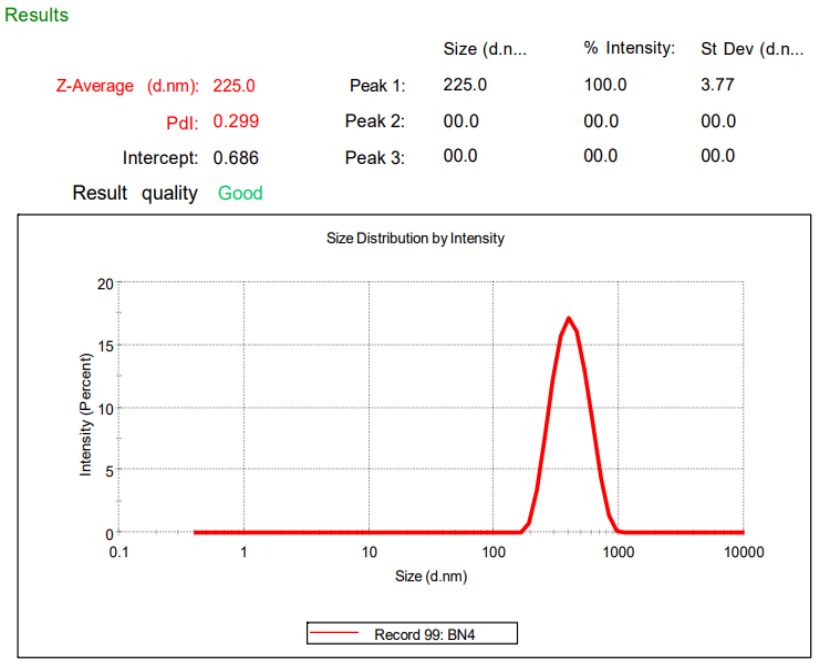

Fig-20: Size and PDI of BN4

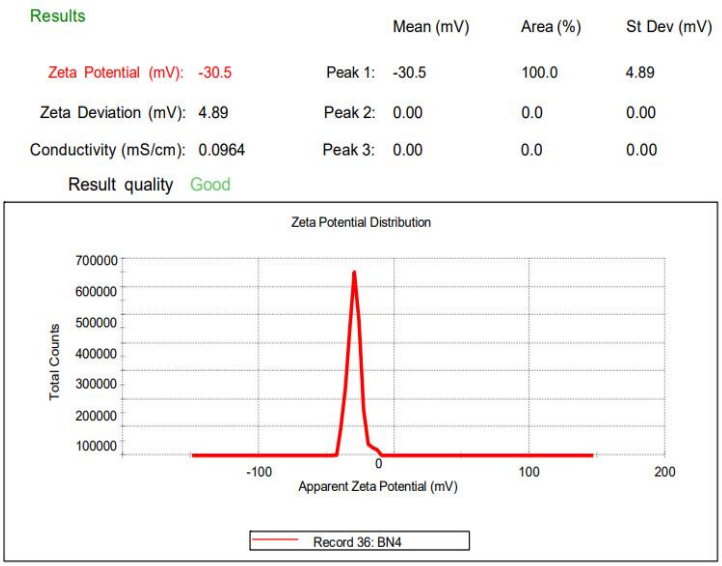

Fig-21: Zeta potential of BN4

The table-9 provides information on six different niosomal formulations (BN1 to BN6) of Brexpiprazole, including vesicle size, zeta potential, polydispersity index (PDI), and % entrapment efficiency.

From the data, it can be observed that BN4 has the smallest vesicle size of 225.0 nm, which is the lowest among all formulations. A smaller vesicle size is typically considered favorable as it can lead to improved drug delivery and uptake. Additionally, BN4 also has the lowest PDI value of 0.299, indicating a narrow size distribution and uniformity of vesicles within the formulation (Figure-20).

Moreover, both BN3 and BN4 show high % entrapment efficiency values of 89.16% and 90.95% respectively. High entrapment efficiency is crucial for ensuring that a significant amount of the drug is effectively encapsulated within the vesicles, enhancing the drug delivery system's efficacy.

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Furthermore, both BN3 and BN4 (Figure-19 & 21) exhibit more negative zeta potential values compared to the other formulations. A higher negative zeta potential can promote stability by preventing vesicle aggregation through electrostatic repulsion.
Based on the data provided, BN3 and BN4 stand out as promising niosomal formulations of Brexpiprazole due to their small vesicle size, low PDI, high % entrapment efficiency, and negative zeta potential values. These characteristics collectively suggest that BN3 and BN4 could potentially offer enhanced drug delivery and stability, making them the best candidates among the six formulations.

6.4 Design of Experiments (DoE)

Table -10: Optimization of Brexpiprazole Niosomal Dispersion with DoE

	Factor 1	**Factor 2**	**Factor 3**	**Response 1**
Run	A: Surfactant concentration (Tween-60)	B:Temperature of hydration	C: Stirring Time	Entrapment efficiency
	mg	Celsius	Min	%
BNR1	100	75	20	66.75
BNR2	150	65	30	73.59
BNR3	100	55	25	64.27
BNR4	100	75	20	69.83
BNR5	250	70	20	80.35
BNR6	200	60	20	84.27
BNR7	250	55	30	87.22
BNR8	200	70	30	90.35
BNR9	100	75	25	67.29
BNR10	150	70	30	67.92
BNR11	150	65	25	77.95
BNR12	150	60	25	72.22
BNR13	150	55	20	64.38
BNR14	200	65	25	81.29
BNR15	150	65	30	77.94

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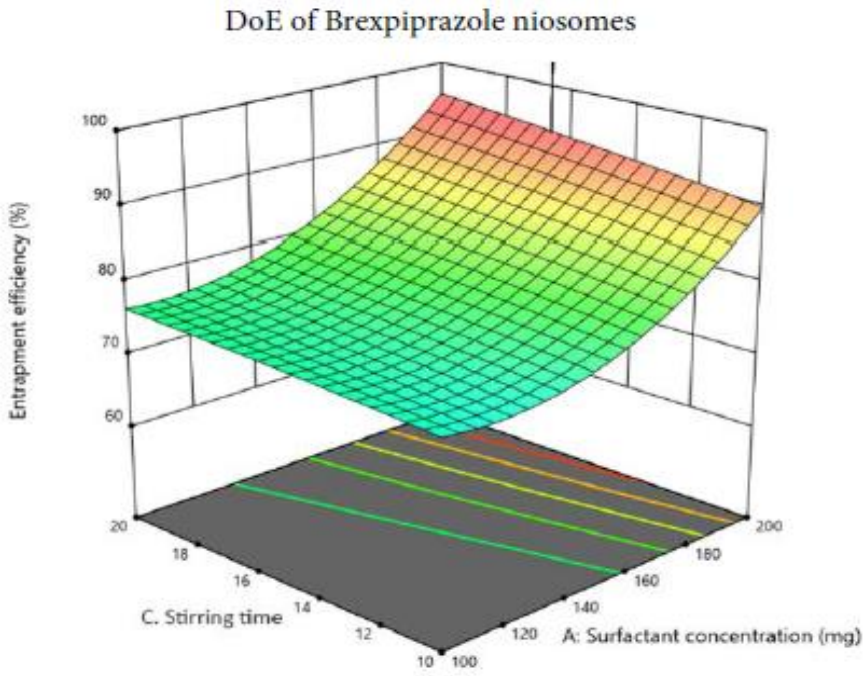

Fig-22: DoE of Brexpiprazole Niosomes-Surfactant concentration & Stirring time

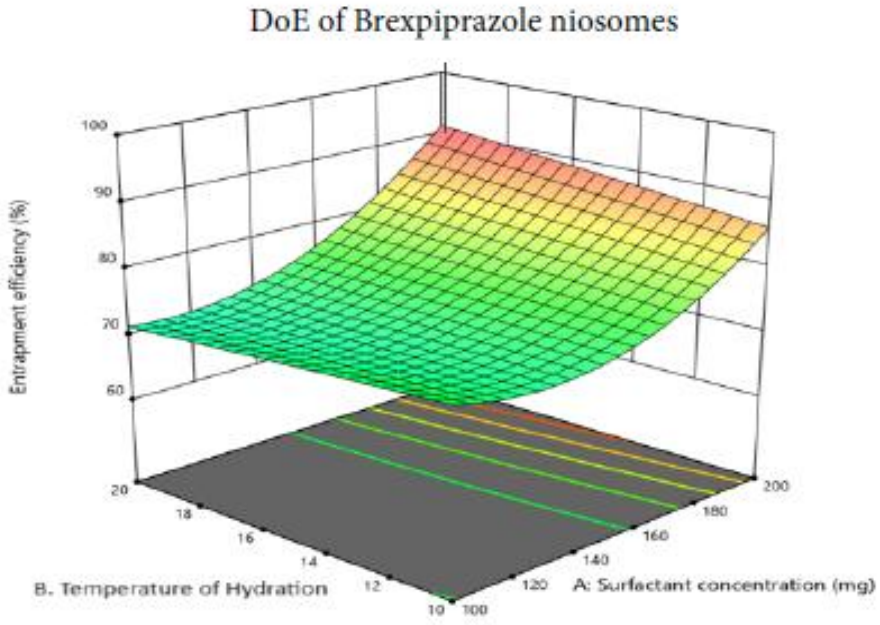

Fig-23: DoE of Brexpiprazole Niosomes-Surfactant concentration & Temperature of hydration

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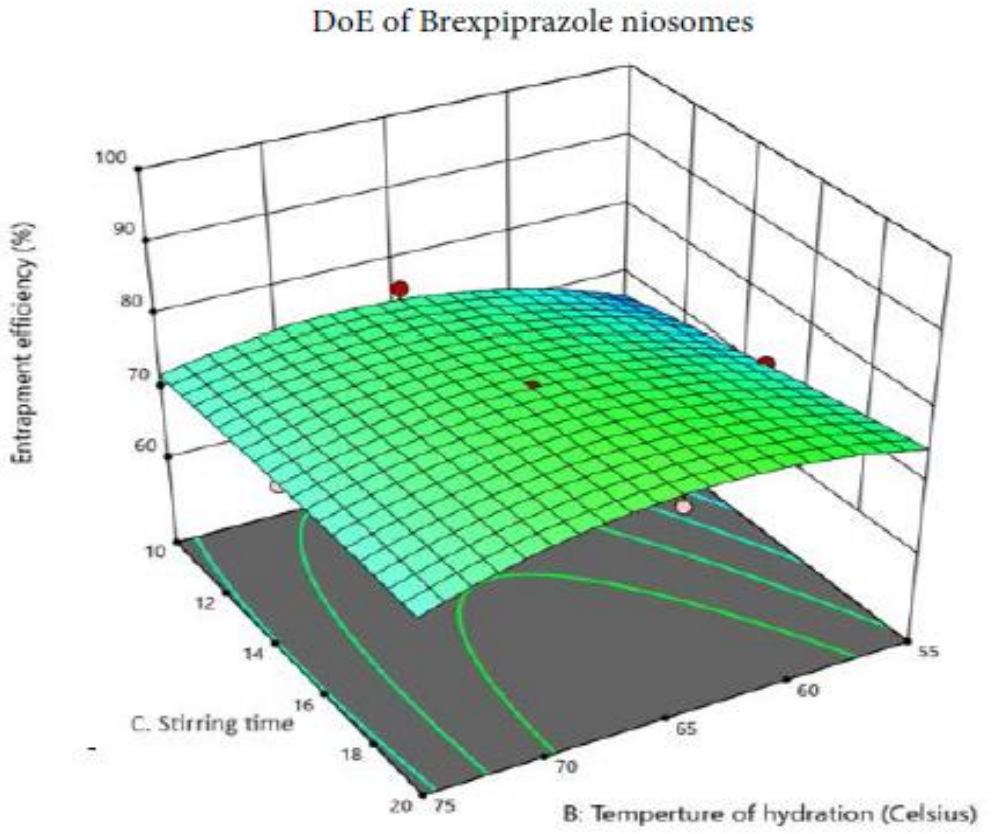

Fig-24: DoE of Brexpiprazole Niosomes-Stirring time & Temperature of hydration

The responses obtained from DoE are plotted against factors by central composite design (Table-10) and displayed by response surface curves in Figures-22-24.

6.5 Evaluation of Brexpiprazole Transdermal patches

Table-11: Evaluation of Brexpiprazole Transdermal patches

Formulation Code	Weight Variation (mg)	Thickness (mm)	% Moisture Content	Folding Endurance	Drug Content	Surface pH
BT1	308±9	0.295±0.01	0.36±0.15	<250	98.56±2.85	6.51±0.10
BT2	303±20	0.305±0.12	0.20±0.02	>250	98.34±3.51	6.45±0.20
BT3	305±12	0.279±0.23	0.36±0.03	<250	95.46±4.55	6.82±0.01
BT4	295±05	0.346±0.14	0.89±0.08	<250	97.66±5.66	6.92±0.17
BT5	298±14	0.333±0.11	0.47±0.03	>250	94.61±6.33	6.34±0.18

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BT6	307±19	0.295±0.13	0.69±0.06	>250	98.61±8.73	6.49±0.29
BT7	313±06	0.307±0.01	0.54±0.03	>250	99.03±3.85	6.71±0.04
BT8	306±08	0.313±0.07	0.80±0.02	>250	95.61±8.11	6.75±0.07
BT9	300±12	0.319±0.04	0.45±0.06	>250	98.52±5.40	6.26±0.29

Where n = 3, Mean ± SD

Based on the data values obtained in Table-11, Formulations BT6 and BT7 stand out in terms of having high drug content, good folding endurance (>250), and surface pH values within an acceptable range (Table-11). These formulations exhibit promising characteristics for further development and potential use.

Table-12: Invitro Drug Diffusion Studies of Optimised Brexpiprazole Niosomal Patch

TIME (Hours)	**% CDR of BT6**	**% CDR of BT7**
0	0	0
0.25	3.91±0.14	3.25 ± 0.83
0.5	8.05±0.21	3.89 ± 0.76
1	21.67±2.14	7.03 ± 1.17
2	35.74±4.32	14.65 ± 3.35
4	47.69±4.11	26.72 ± 3.14
6	58.33±3.24.	38.67 ± 2.27
8	73.74±5.18	49.31 ± 4.21
10	84.6±5.52	54.72 ± 4.55
12	97.16±6.54	75.58 ± 5.57
24	99.82±6.17	98.14 ± 5.20

Where n = 3, Mean ± SD

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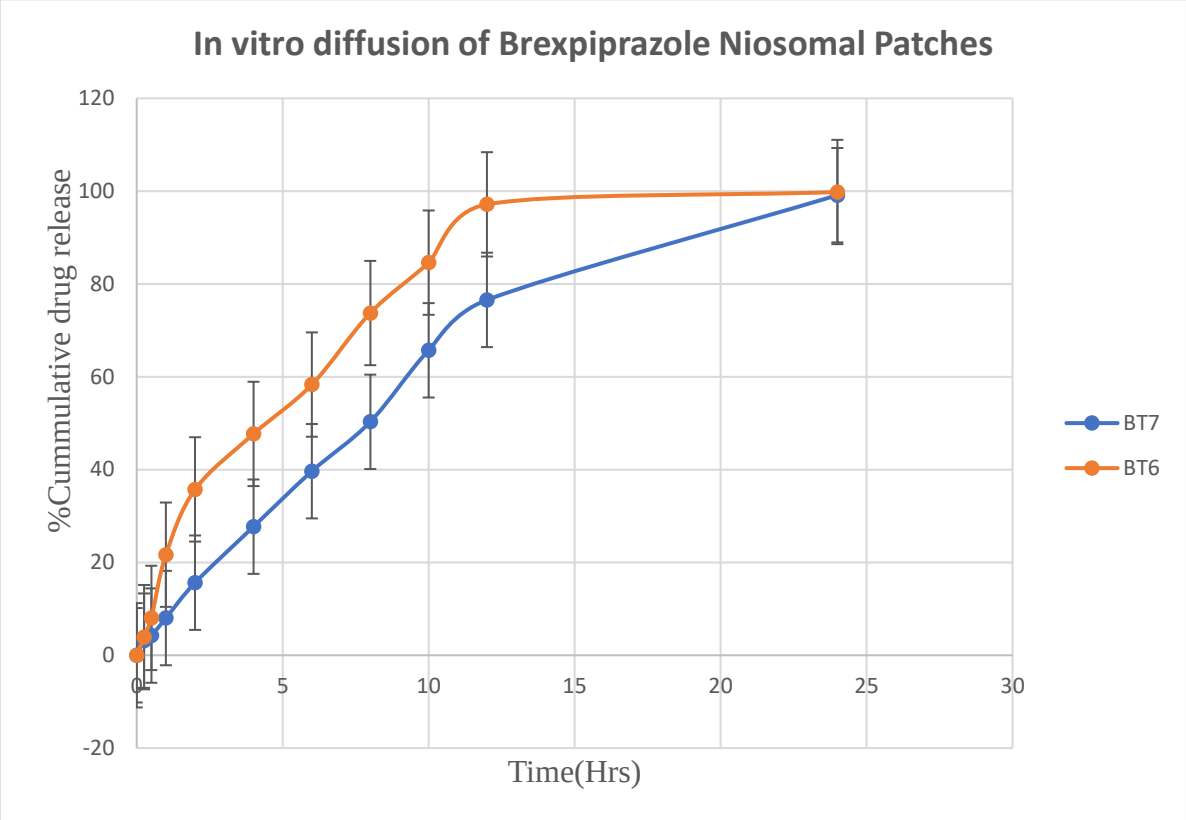

Fig-25: Invitro Drug Diffusion Studies of Brexpiprazole Niosomal Patches

Where n = 3, Mean ± SD

The sustained release characteristics are needed for the formulation, BT7 would be the preferred option. Despite BT6 reaching above 95% CDR at 12th hour, the sustained release of BT7 upto 24 hours (Table-12 & Figure-25). The study suggests BT7 exhibits more prolonged release profile compared to BT6. Therefore, BT7 is considered for further studies.

5.6 Drug release kinetics of Optimised Brexpiprazole Niosomal Patch (BT7)

Table-13: Drug release kinetics of Optimised Brexpiprazole Niosomal Patch (BT7)

Time (Hours)	%CDR	Log % CDR	√T	Log T	$Wo^{1/3}$-$Wt^{1/3}$	% DR	Log % DR
0	0	0	0	0	0	100	2
0.25	3.15	0.4983	0.5000	-0.6021	1.4659	96.85	1.9861
0.5	4.24	0.6274	0.7071	-0.3010	1.6185	95.76	1.98118
1	8.02	0.9042	1.0000	0.0000	2.0017	91.98	1.96369

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2	15.64	1.1942	1.4142	0.3010	2.5008	84.36	1.92614
4	27.71	1.4426	2.0000	0.6021	3.0261	72.29	1.85908
6	39.66	1.5984	2.4495	0.7782	3.4102	60.34	1.78061
8	50.3	1.7016	2.8284	0.9031	3.6914	49.7	1.69636
10	65.71	1.8176	3.1623	1.0000	4.0353	34.29	1.53517
12	76.57	1.8841	3.4641	1.0792	4.2464	23.43	1.36977
24	99.13	1.9962	11.1355	1.3802	4.5327	0.87	-0.06

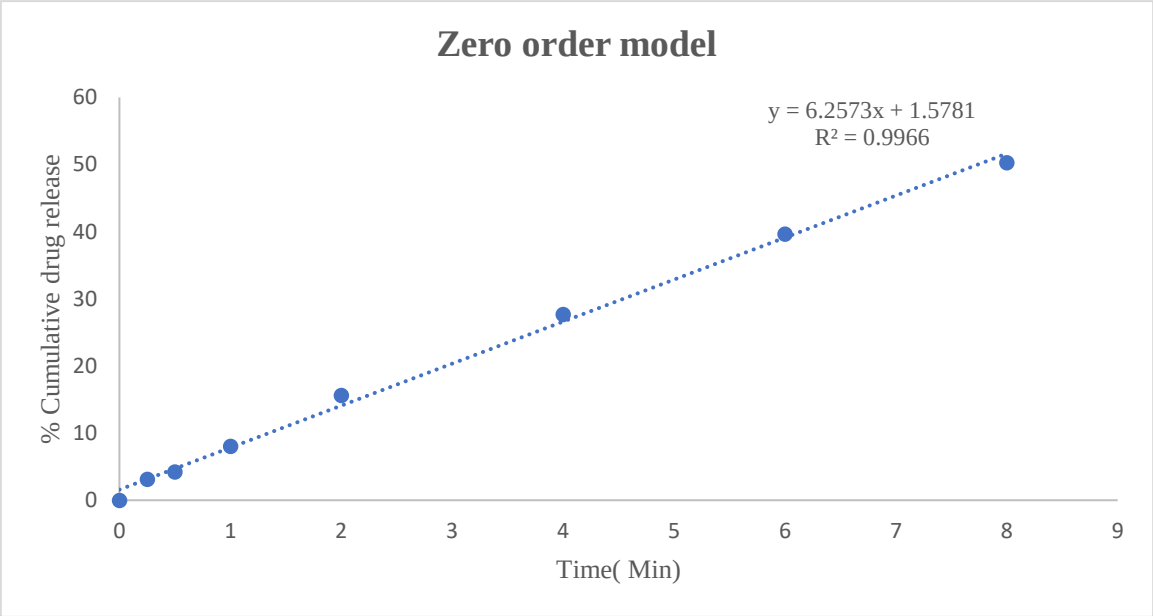

Fig-26: Zero order release kinetics of Optimised Brexpiprazole Niosomal Patch (BT7)

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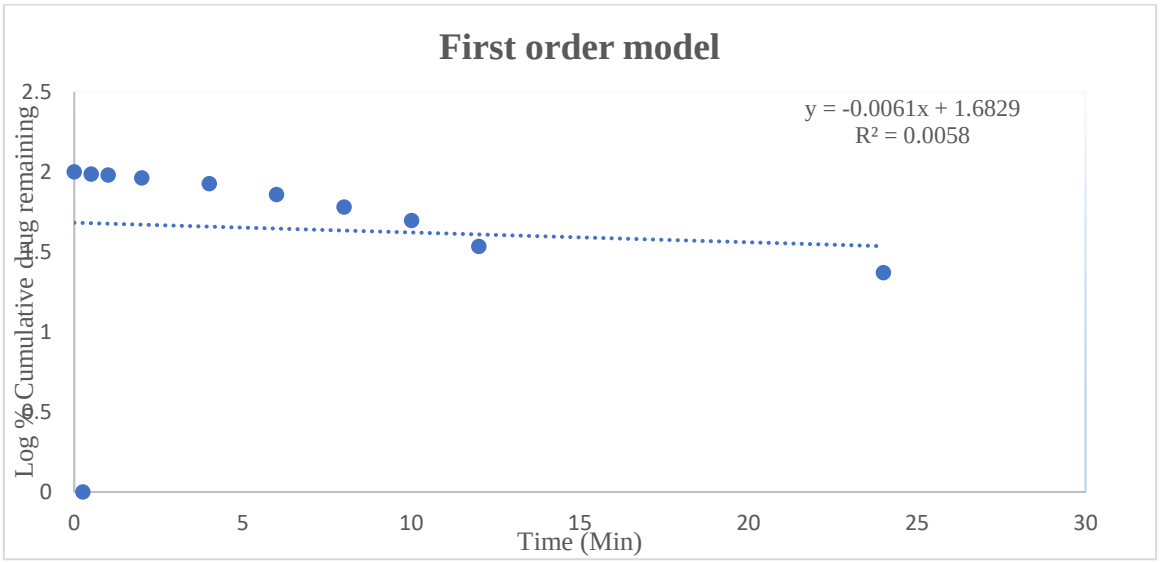

Fig-27: First order release kinetics of Optimised Brexpiprazole Niosomal Patch (BT7)

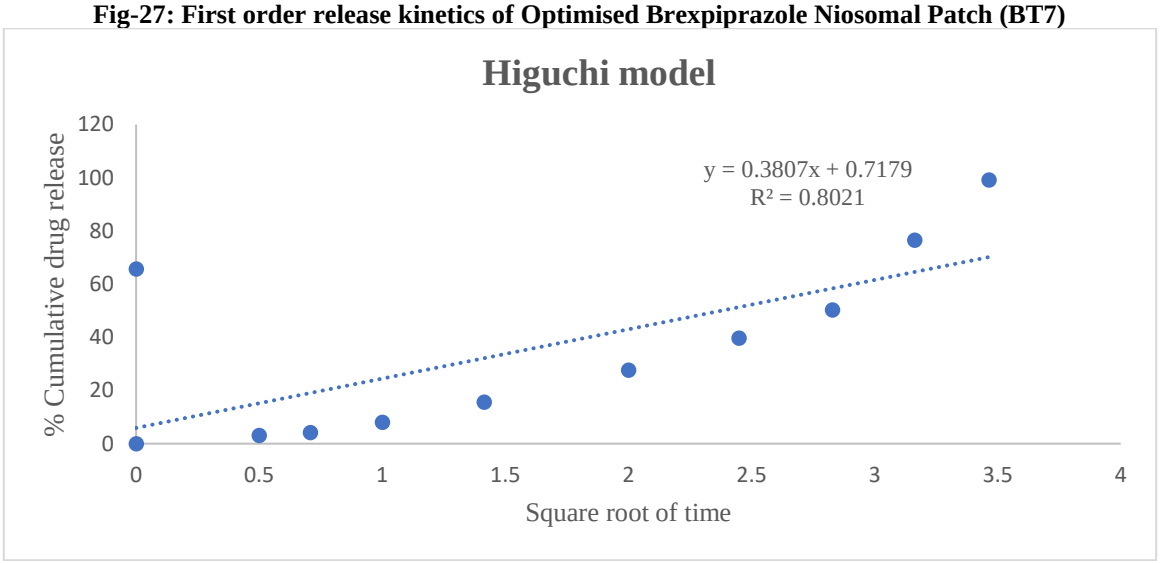

Fig-28: Higuchi Model for Optimised Brexpiprazole Niosomal Patch (BT7)

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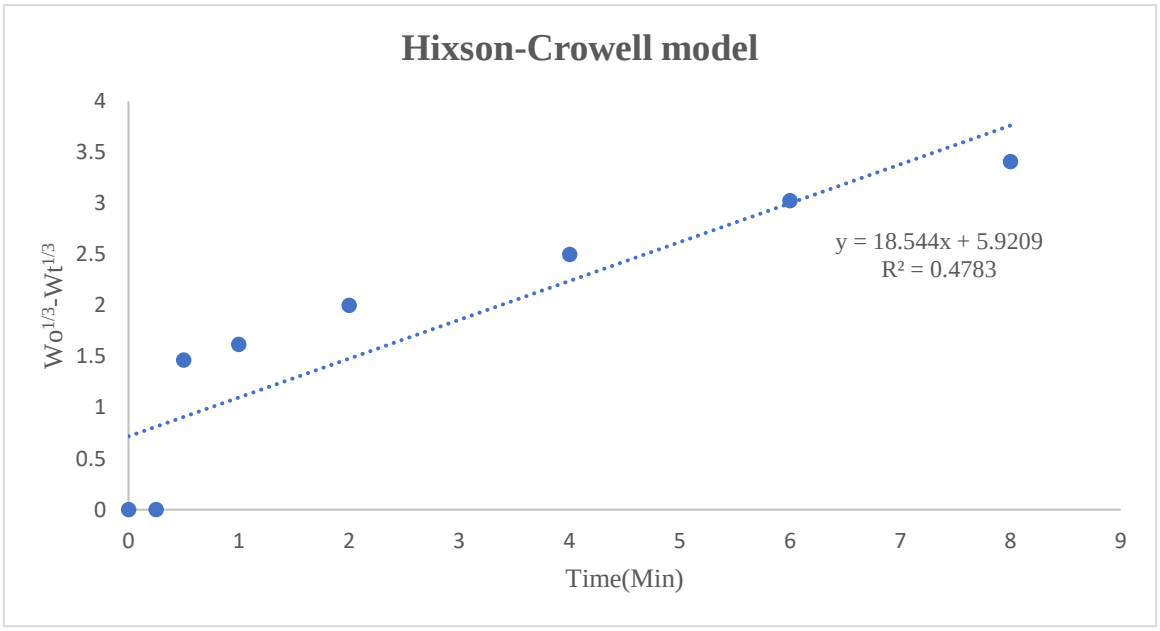

Fig-29: Hixson-crowell model for Optimised Brexpiprazole Niosomal Patch (BT7)

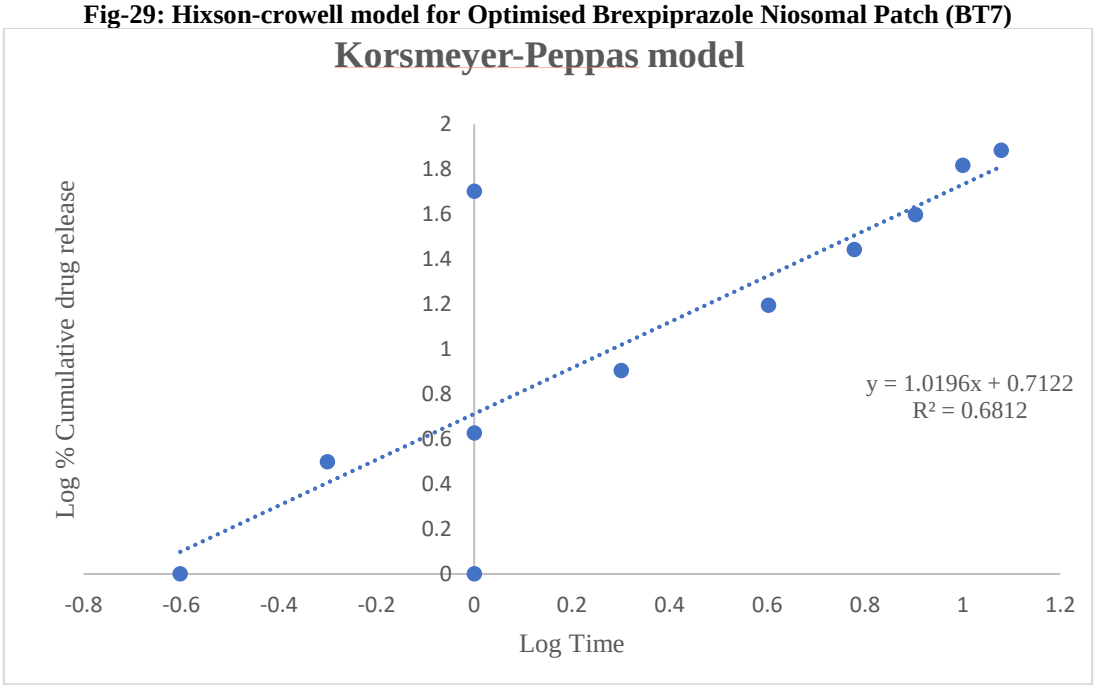

Fig-30: Korsemeyer-peppas model of Optimised Brexpiprazole Niosomal Patch (BT7)

Mathematical models were used to analyze the drug release pattern of BT7 formulation. The correlation coefficient (R^2 value) was calculated for zero and first-order kinetics. BT7 showed a strong fit With an R^2 value close to 1 for zero-order release, indicating a consistent release rate over time (Table-13 & Figures-26,27). Additionally, the comparison of Higuchi and Hixons and Crowell models revealed that the r2 value was higher for Higuchi (Figures-28,29), suggesting a diffusion-based drug release mechanism. Further analysis using the Korsmeyer-Peppas model indicated a super case-II type of diffusion (Figure-30). In conclusion, BT7 follows zero-order kinetics with a super case-II diffusion.

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6.7 Accelerated Stability studies

Table-14: Accelerated Stability studies of Optimised Brexpiprazole Niosomal Patch (BT7)

Evaluation Parameters	1st Month	2nd Month	3rd Month
Weight Variation (mg)	301±21	307±15	295±08
Thickness (mm)	0.35±0.11	0.327±0.18	0.331±0.21
Folding Endurance	>250	>250	>250
% Moisture Content	0.34±0.14	0.25±0.11	0.31±0.23
% Drug Content	98.66±1.85	98.34±2.45	98.01±2.11

Where n = 3, Mean ± SD

Table-15: Invitro Diffusion studies of Optimised Brexpiprazole Niosomal Patch (BT7) After 3months of Stability Studies

TIME (Hours)	% CDR BT7
0	0
0.25	2.02 ± 1.69
0.5	3.29 ± 1.62
1	6.99 ± 2.03
2	13.61 ± 4.21
4	26.68 ± 4.00
6	39.63 ± 3.13
8	49.07 ± 5.07
10	63.68 ± 5.41

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12	74.54 ± 6.43
24	98.1 ± 6.06

Where n = 3, Mean ± SD

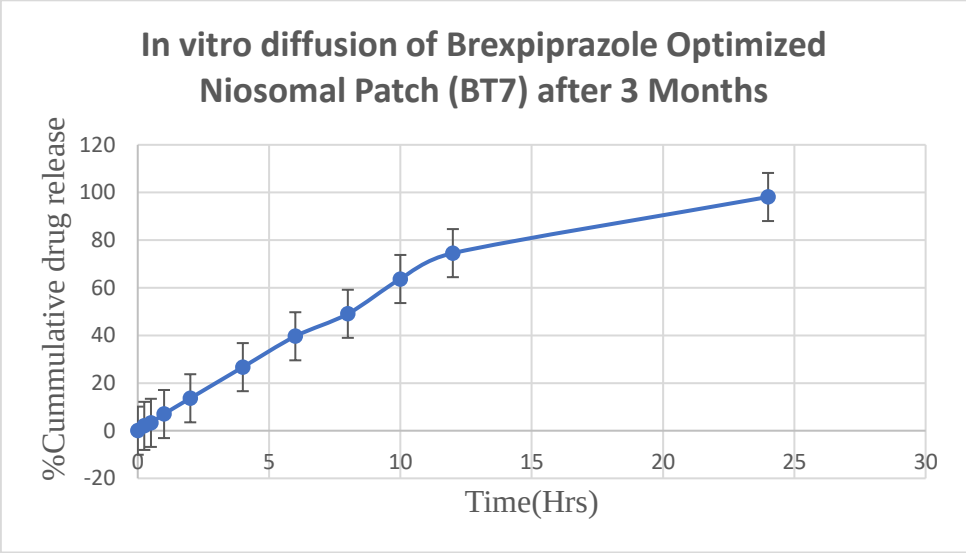

Fig-31: Invitro Diffusion studies of Optimised Brexpiprazole Niosomal Patch (BT7) After 3months of Stability Studies

After conducting accelerated studies over three months with sampling intervals at the end of each month, several evaluation parameters were monitored. Over the course of a three-month accelerated study, the formulation exhibited minor variations in weight, ranging from 295 mg to 307 mg, and fluctuations in thickness, measured between 0.35 mm and 0.331 mm. Despite these slight changes, the folding endurance consistently exceeded 250, indicating robust mechanical stability. Moisture content showed marginal variance, fluctuating from 0.25% to 0.34%, remaining within acceptable limits throughout the study. Moreover, the drug content remained consistently high, exceeding 98% in each sampling interval (Table-14). In vitro drug release studies conducted at the end of each month revealed no significant differences in the evaluated parameters, suggesting the formulations have integrity and consistent drug release characteristics over time (Table-15 & Figure-31). These findings support its stability and suitability for further development.

7. Conclusion:

The incorporation of niosomal formulations into transdermal patches enhanced drug delivery through the skin by utilizing the unique properties of niosomes, such as improved drug encapsulation and sustained release. Transdermal patches offer a convenient and non-invasive drug delivery method, promoting patient compliance and comfort compared to traditional oral formulations. Targeted Delivery: Transdermal patches allow for targeted delivery of drugs, avoiding first-pass metabolism and offering sustained release kinetics.

Niosomal dispersions using various surfactants identified BN3 and BN4 as having the least particle size with favorable zeta potential and polydispersity index. These formulations were further optimized using a central composite design, resulting in the formulation of 15 variants (BNR1 to BNR15) with Tween 60 as the surfactant. Among these, BNR8 exhibited the highest entrapment efficiency and was selected for incorporation into the patch. Subsequent evaluation of niosomal patches (BT1 to BT9) revealed that BT7 demonstrated the best performance. Overall, these findings indicate the potential of niosomal patches of Brexpiprazole for sustained drug release, highlighting their stability and suitability for future development and potential therapeutic applications.

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