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Formulation and Evaluation of Transdermal Niosomal Patches of Doxorubicin for Breast Cancer

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ABSTRACT:
Here, we report the synthesis and Evaluation of Niosomes loaded transdermal patches it is effective means to deliver Doxorubicin to diagnosis cancer like breast cancer. Doxorubicin treats different type of cancer like, breast cancer, bladder cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia.
Niosomes are the non-ionic surfactant vesicles obtained on hydration of synthetic non-ionic surfactants.These are the promising vehicles for effective transdermal drug delivery.Niosomesdo not cause any cardiotoxicity Soliposomal encapsulation of the doxorubicin limits cardiotoxicity.
Pereparation of niosomesbased Doxorubicin Patches is gastroretentive drug delivery system.Reduce Side Effect with conventional formulations and increase penetration of drug and drug bioavaibility.
KEYWORDS: Lipocyte, macromolecules, bioavailability, Non-ionic Surfactants,

I. INTRODUCTION:

The skin is one of the largest organs and constitutes 16%[1] of the human body weight. It weighs around 5kgs and covers an area of about 2 square meters. It is one of the tissues in our body that duplicates the most and the fastest. The skin has three main functions: protection, regulation and sensation.

The integumentary system is formed by the skin and its derivative structures. The skin is composed of three layers: the epidermis, the dermis, and subcutaneous tissue. The outermost level, the epidermis, consists of a specific constellation of cells known as keratinocytes, which function to synthesize keratin, a long, threadlike protein with a protective role. The middle layer, the dermis, is fundamentally made up of the fibrillar structural protein known as collagen. The dermis lies on the subcutaneous tissue, or panniculus, which contains small lobes of fat cells known as lipocytes. The thickness of these layers varies considerably, depending on the geographic location on the anatomy of the body. The eyelid, for example, has the thinnest layer of the epidermis, measuring less than 0.1 mm, whereas the palms and soles of the feet have the thickest epidermal layer, measuring approximately 1.5 mm. The dermis is thickest on the back, where it is 30–40 times as thick as the overlying epidermis.

Introduction of gel:

The term "gel" refers to a physical condition that has qualities that are halfway between solids and liquids. [57] Gels are semi-rigid systems in which the dispersing medium's movement is constrained by an interlacing three-dimensional network of dispersed phase particles or solvated macromolecules. Gels (also known as jellies) are semisolid systems comprising either suspensions of minute inorganic particles or large organic molecules interpenetrated by a liquid, according to the USP. A two-phase system is one in which the gel mass comprises a network of small distinct particles. When the particle size of the dispersed phase is relatively big in a two-phase system, the gel mass is frequently referred to as a magma. Organic macromolecules (Carbomer) are uniformly transported throughout a liquid in single-phase gels, with no visible boundaries between the dispersed macromolecules and the liquid. The most popular treatments are water and hydroalcoholic solutions. Between the gel state and the sol, which is the fluid phase containing the dispersed or dissolved macromolecule, many polymer gels show reversibility. Because the constituents may not be totally molecularly dispersed (soluble or insoluble), or they may form aggregates that scatter light, some gel systems are as transparent as water, while others are murky. With a few exceptions, the concentration of the gelling agents is usually less than 10%, ranging from 0.5 percent to 2.0 percent. [58]

Introduction of Niosomalgel as a Topical Drug Delivery System[35-37]

Topical gels are semisolid dosage forms in which a liquid phase is restricted inside a three-dimensional polymeric matrix with high physical or chemical cross-linking produced from natural or semi-synthetic sources.[57]Niosomes are vesicles

International Journal of Pharmaceutical Research and Applications
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made from a mixture of cholesterol, non-ionic surfactant, and other biodegradable lipids that have been hydrated. In comparison to the traditional dose form of a medicine, niosomes improve pharmacological activity. Amphiphilic and lipophilic medicines can be carried by niosomes. Niosomes may be able to address drug instability, rapid disintegration, low bioavailability, and insolubility. Niosomes have a high drug delivery efficiency, making them ideal for site-specific delivery of anti-cancer, anti-infective, and other drugs. In comparison to other drug formulations, niosomes are a stable and cost-effective carrier. Parental drug delivery systems, topical drug delivery systems, oral drug delivery systems, and new drug delivery systems such as targeted drug delivery systems and controlled drug release systems all use niosomes.[63] Encapsulation of a drug in the vesicular system is expected to prolong its presence in the systemic circulation and improve penetration into target tissue, as well as potentially lower toxicity if selective uptake is achieved [64]. Niosomal gel administered topically can prolong the drug's effect on the skin (stratum corneum and epidermis) while lowering systemic absorption.[65] When compared to bulk drug formulations, all niosomal formulations showed faster in vitro drug release rates. [66]

Introduction of Vesicular Drug Delivery System [43-45]

Vesicles have become the choice in drug delivery system called Vesicular Drug Delivery System." E. g: Liposomes, Niosomes, Pharmacosomes etc. The vesicular system is highly ordered assembles of one are concentric lipid bilayer formed when certain amphiphilic building blocks are confronted with water. These biological vesicles origin was first reported in 1965 by Bingham.

Why Do We Use VDDS? [44-46]

Conventional chemotherapy for treatment of intracellular infections in not effective due to limitedpermeation of drugs into cells. To improve bioavailability at the site of diseases reduces harmful side effects ofconventional & controlled release drug delivery systems, overcome problem of degradation of drug &/ or drugdose.

Introduction of Niosomes[56-57]

The phenomenon of targeting drug delivery systems is to deliver the drug in the body in such a manner that it should show its action to the targeted desired site to achieve the therapeutic response, i.e., where its action should be needed by limiting undesirable interaction to non-targeted tissues. Paul Ehrlich introduced this idea in 1909, and he called this strategy "magic bullets". In the drug delivery system, although the oral administration route is beneficial but limited due to the hepatic first-pass metabolism that increases undesirable side effects, it reduces the therapeutic efficiency and bioavailability of many drugs in various treatments of diseases. Thereby, transdermal drug delivery system offers an attractive, a non-invasive, and better alternative method to reduce the number of doses, frequency of administration, systemic toxicity, hepatic first-pass metabolism, gastric irritation, unwanted side effects associated with oral, control drug level in plasma for a sustained period for locally and systematically that result enhancing bioavailability, and better patient compliance.

COMPOSITION OF NIOSOMES[58-59]

Two components use in niosome preparation are

- Cholesterol
- Non-ionic surfactants

A.Cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to niosome form.

B.Non-ionic Surfactants are generally used for the preparation of niosomes.

Examples: a. Tweens (20, 40, 60, 80)
b. Spans (Span 60, 40, 20, 85, 80)
c. Brijs (Brij 30, 35, 52, 58, 72, 76).

Mechanisms of action of niosomes as permeation enhancers [55]

There is no single mechanism that can sufficiently explain the ability of niosomes to increase drug transfer through the skin, and several mechanisms (Figure 3) have been proposed, including: alteration of the barrier function of the stratum corneum, as a result of reversible perturbation of lipid organization;28 reduction of transepidermal water loss, which increases hydration of the stratum corneum and loosens its closely-packed cellular structure;29 and adsorption and/or fusion of niosomes on the surface of the skin, as revealed by freeze fracture electron microscopy and small angle X-ray scattering, leading to a high thermodynamic activity gradient of drug at the interface, which is the driving force for permeation of a drug.

Adsorption of niosomes onto the cell surface occurs with little or no internalization of either aqueous or lipid components; it may take place either as a result of attracting physical forces

International Journal of Pharmaceutical Research and Applications
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or as a result of binding by specific receptors to ligands on the vesicle membrane and transfer of drug directly from vesicles to the skin. On the other hand, niosomes may fuse with the cell membrane, resulting in complete mixing of the niosomal contents with the cytoplasm. Finally, niosomes may be engulfed by the cell (endocytosis), with lysozymes present in the cytoplasm degrading or digesting the membranous structure of the niosome, thereby releasing the entrapped material into the medium.

Introduction of Transdermal Drug Delivery System [63-65]

The transdermal drug delivery is one most important of the novel drug delivery system. The transdermal drug delivery is one of the most effective methods of applications. Transdermal patches are flexible pharmaceutical preparations of varying sizes, containing one or more active substances. They are intended to be applied to the unbroken skin in order to deliver the active substance(s) to the systemic circulation after passing through the skin barrier. In this drug delivery system, across the skin to have an effect on the adjacent to the site of application or to have an effective distribution of the systemic circulation.
TDDS has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin as well as for systemic delivery of drug.

II. MATERIAL AND METHOD:

Material:

Doxorubicin (API), Span 80,Span 60,Tween 80, Cholesterol, Diethyl Ether, Methanol, Stearic acid, Stearyl amines, Carbopol 934p, Sodium Hydroxide, Triethanolamine.

Formulation of API Loaded Niosomes:

The API was first dissolve in an organic phase (diethyl ether and methanol), till entire drug was dissolve. In a 20 mL glass scintillation vial, Span 60, cholesterol, and lipid will be added to the solution and stirred using a magnetic spin bar. Purified water will be heated 60°C temperatures in a separate 50 mL glass beaker using a hot plate with magnetic stirring. The temperature of the water phase will be chosen to meet the design criteria. A 14G needle was used to fill the organic phase into a 10 mL syringe. Using predefined settings based on the experimental design, the organic phase mixture was injected into the preheated aqueous phase. The values discovered from the design of experiment will be used to mix the ingredients (DoE). The batch was cooled to room temperature in the final step of the process, and the formulation will be kept in a suitable glass storage container.

Method of Preparation API Niosomalgel

Niosomes aqueous dispersion were utilized for the formulation of topical gel. Gel polymer such as carbopol-934 were utilized to make niosome gel. 1g of carbopol-934 powder were dispersed into forcefully mixed and allowed to hydrate for 24 hrs. Following that, 10 mL of propylene glycol was added. The dispersion was neutralized with the drop wise addition of 10 percentTriethanolamine, mixing were continued until a translucent gel will be emerged.

Preparation of Transdermal Patch of Niosomal Gel

The prepared proniosomal gels were fabricate by encapsuling within a shallow compartment of drug impermeable backing membrane(laminatedaluminium foil). A micro porous tape of larger area was stuck onto the impermeable backing membrane to bring the transdermal patch in close contact with the skin. The device was closed by a release linear on the open side.

III. RESULT:

Preliminary Trial batches of Doxorubicin Niosome SelectionofConc.of Polymer

BATCH	Drug: Surfactant Ratio	Cholesterol Conc. (µM)	I.P.V(ml)	E.P.V(ml)	Speedof Stirring (R.P.M.)	Timeof Stirring (Min)
SELECTIONOFDRUG:SURFACTANTRATIO						
DRB1	1:1	60	15	10	600	30

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

DRB2	1:2	60	15	10	600	30
DRB3	1:3	60	15	10	600	30
DRB4	1:1	60	15	10	600	30
DRB5	1:2	60	15	10	600	30
DRB6	1:3	60	15	10	600	30
DRB7	1:1	60	15	10	600	30
DRB8	1:2	60	15	10	600	30
DRB9	1:3	60	15	10	600	30
SELECTIONOFCHOLESTEROL CONC.						
DRB10	1:3	30	15	10	600	30
DRB11	1:3	60	15	10	600	30
DRB12	1:3	90	15	10	600	30
SELECTIONOFI.P.V(ml)						
DRB13	1:3	60	5	10	600	30
DRB14	1:3	60	10	10	600	30
DRB15	1:3	60	15	10	600	30
SELECTIONOFE.P.V (ml)						
DRB16	1:3	60	15	10	600	30
DRB17	1:3	60	15	15	600	30
DRB18	1:3	60	15	20	600	30
SELECTIONOFSPEEDOFSTIRRING(R.P.M)						
DRB19	1:3	60	10	600	200	30
DRB20	1:3	60	10	600	400	30
DRB21	1:3	60	10	600	600	30
SELECTIONOFTIMEOFSTIRRING (Min)						
DRB22	1:3	60	10	600	600	30
DRB23	1:3	60	10	600	600	45
DRB24	1:3	60	10	600	600	60

International Journal of Pharmaceutical Research and Applications
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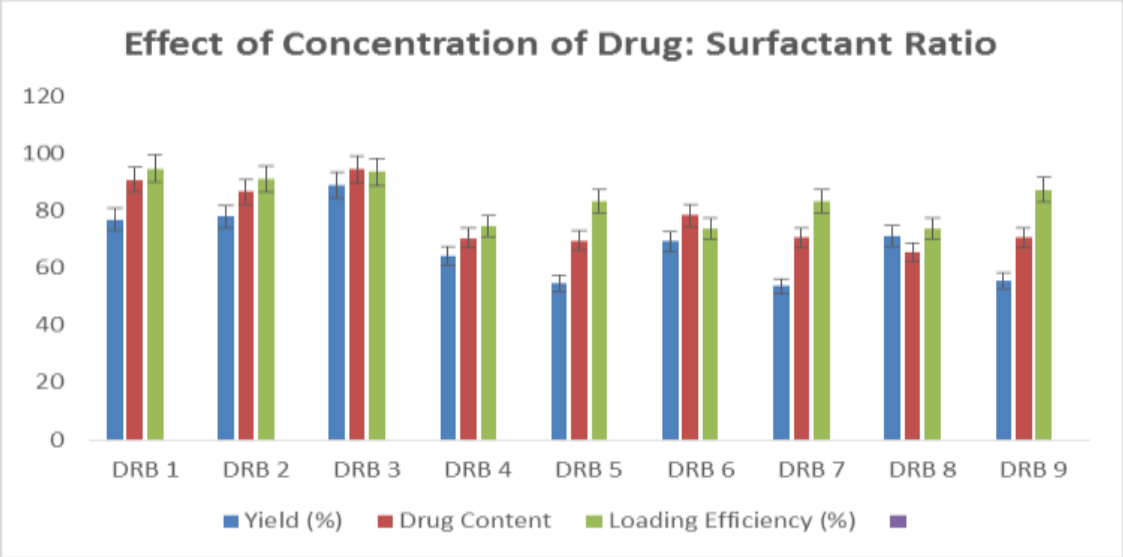
Effect of Conc. of Drug: Surfactant Ratio

Batch	Yield (%) (Mean±S.D.) (n = 3)	DrugContent (%) (Mean ±S.D.) (n = 3)	LoadingEfficiency (%) (Mean ±S.D.) (n = 3)
DRB1	76.93±0.74	90.84±1.52	94.63±1.18
DRB2	77.96±0.17	86.60±1.48	90.88±1.34
DRB3	**88.86±0.45**	**94.46±1.75**	**93.49±1.47**
DRB4	64.21±0.71	70.46±1.34	74.70±1.28
DRB5	54.61±0.73	69.55±1.74	83.28±1.49
DRB6	69.21±0.71	78.46±1.34	73.70±1.28
DRB7	53.61±0.73	70.55±1.74	83.28±1.49
DRB8	71.21±0.71	65.46±1.34	73.70±1.28
DRB9	55.61±0.73	70.55±1.74	87.28±1.49

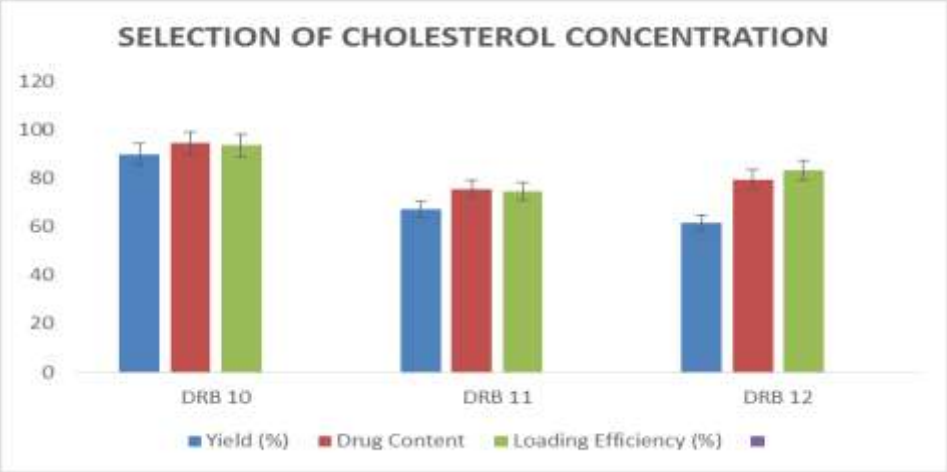


EffectofConc.ofDrug:SurfactantRatio

Effects of Drug to Polymer ratio

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

Batch	Yield(%) (Mean ± S.D.) (n = 3)	DrugContent (%) (Mean ±S.D.) (n = 3)	LoadingEfficiency (%) (Mean ±S.D.) (n = 3)
DRB10	**89.86±0.45**	**94.46±0.75**	**93.49±1.47**
DRB11	67.21±0.71	75.46±0.34	74.7±1.28
DRB12	61.61±0.73	79.55±0.74	83.28±1.49



EffectsofDrugtoPolymerration

Effects E.P.V

Batch	Yield(%) (Mean ± S.D.) (n = 3)	DrugContent (%) (Mean ±S.D.) (n = 3)	Loading Efficiency(%) (Mean ±S.D.) (n = 3)
DRB13	74.21±0.71	76.46±1.56	78.7±1.28
DRB14	67.61±1.73	78.55±1.96	86.28±1.49
DRB15	**91.86±0.45**	**93.46±0.97**	**96.49±1.47**

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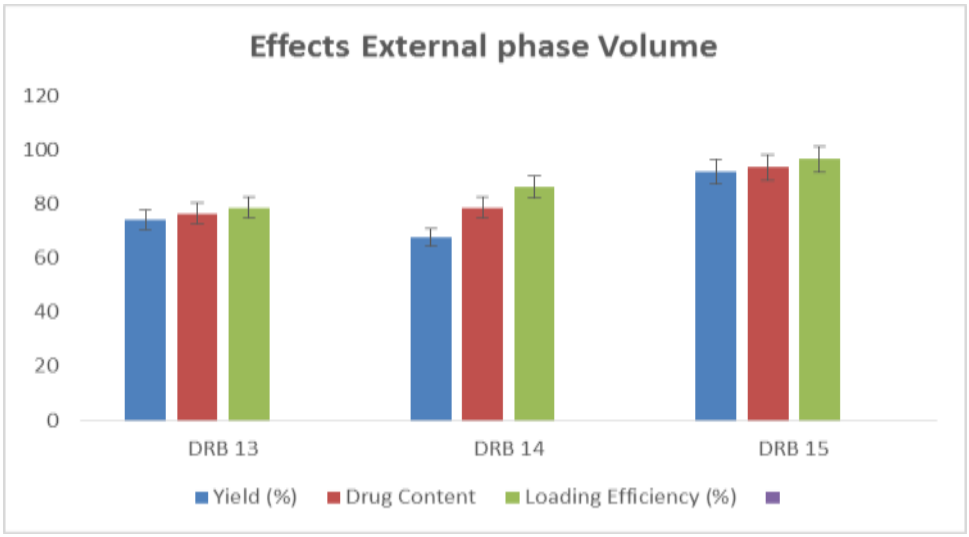
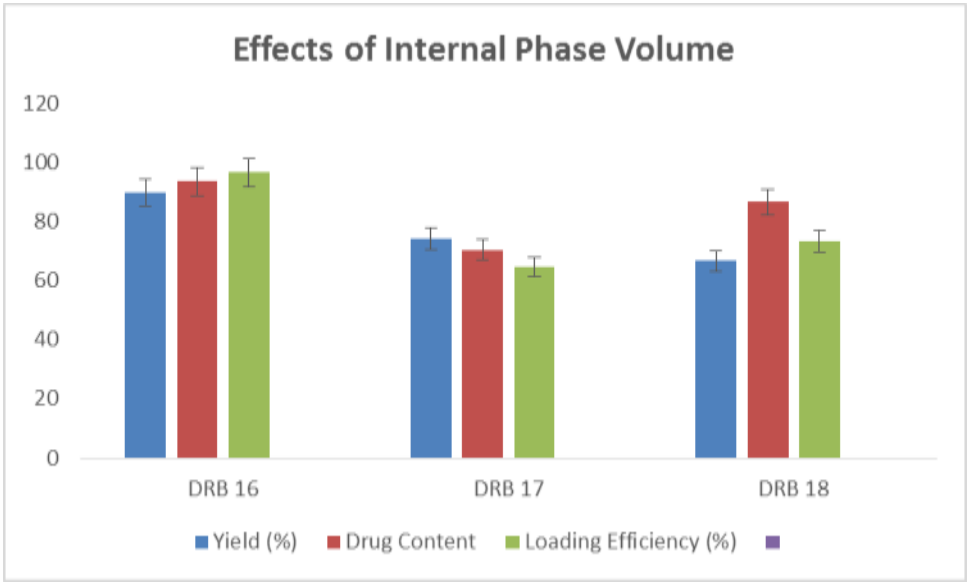
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494



EffectsE.P.V

Effects of I.P.V

Batch	**Yield(%) (Mean ± S.D.) (n = 3)**	**DrugContent (%) (Mean ±S.D.) (n = 3)**	**Loading Efficiency(%) (Mean ±S.D.) (n = 3)**
DRB16	**89.86±1.45**	**93.46±1.75**	**96.49±1.47**
DRB17	74.21±1.71	70.46±1.34	64.7±1.28
DRB18	66.61±1.73	86.55±1.74	73.28±1.49

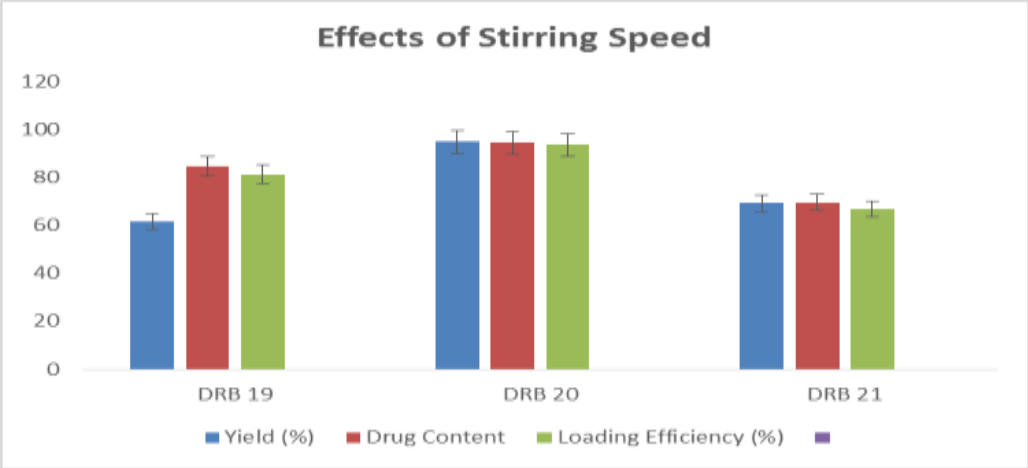


Effects of I.P.V

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

Effects of Stirring

Batch	Yield(%) (Mean ± S.D.) (n = 3)	DrugContent (%) (Mean ±S.D.) (n = 3)	Loading Efficiency(%) (Mean ±S.D.) (n = 3)
DRB19	61.61±0.73	84.55±0.74	81.28±0.49
DRB20	**94.86±0.45**	**94.46±0.75**	**93.49±0.47**
DRB21	69.21±0.71	69.46±0.34	66.7±0.28

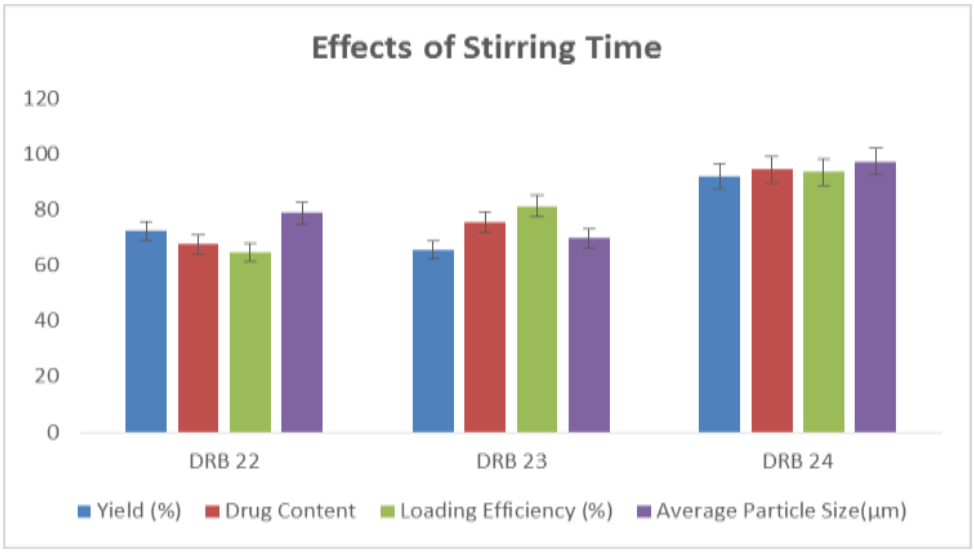


Effects ofSpeed of Stirring

Effects of Time of Stirring

Batch	Yield(%) (Mean ± S.D.) (n = 3)	DrugContent (%) (Mean ±S.D.) (n = 3)	Loading Efficiency(%) (Mean ±S.D.) (n = 3)
DRB22	72.21±0.73	67.46±0.34	64.7±2.4
DRB23	65.61±0.95	75.55±0.74	81.28±2.6
DRB24	**91.86±0.67**	**94.46±0.75**	**93.49±2.69**

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494



Effects of Time of Stirring

Risk Assessment ofCQAs

In order to thoroughly examine effects of itemising and collaboration constraints, fundamental quality credits are sought in high, medium, and generally safe limits thattakedataspaceintoaccount. Highbet limitsaretypicallyseenasbeingcrucialfor Design of Experiments since they have a greater impact than others and should be included in well-known multivariate compasses. Table lists risk assessment and CQAs for ensuring perfect definition.

RiskAssessment ofCQAs

DrugProduct CQAs	Surfactant Conc.	Cholesterol Conc.	Speed of Stirring	Timeof Stirring
%Yield	Higher	Higher	Higher	Medium
Entrapment Efficiency	Higher	Higher	Higher	Medium
VesicleSize	Higher	Higher	Higher	Lower
DrugRelease	Higher	Higher	Higher	Lower

Formulation and Development of Dox Niosome by Design of Experiment (DoE) Using QbD Approach
3^2 FactorialDesignApproach
3^2FactorialBatches

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

Independentvariables			
Independent variables(X)	**Lower(-1)**	**Medium(0)**	**Higher(+1)**
Cholesterol(mg)	5	10	15
Span60(mg)	10	15	20
Dependentvariables(Y)			
Y1=ParticleSize			
Y2=Entrapment Efficiency			

Compositions of Factorial Batches

Factorial Batches in Coded Form

DRBN3^2= batches		
Batches	**Codedform**	
	Vol.of cholesterol (mg) (X1)	**Vol. of Cholesterol(mg) (X2)**
DRBN1	-1	-1
DRBN2	0	-1
DRBN3	+1	-1
DRBN4	-1	0
DRBN5	0	0
DRBN6	+1	0
DRBN7	-1	+1
DRBN8	0	+1
DRBN9	+1	+1

Compositions of Factorial Batches

Factorial Batches in Decoded Form

DRBN3^2= batches		
Batches	**Decodedform**	
	Vol.ofCholesterol (mg) (X1)	**Vol.ofCholesterol (mg)(X2)**
DRBN1	05	10

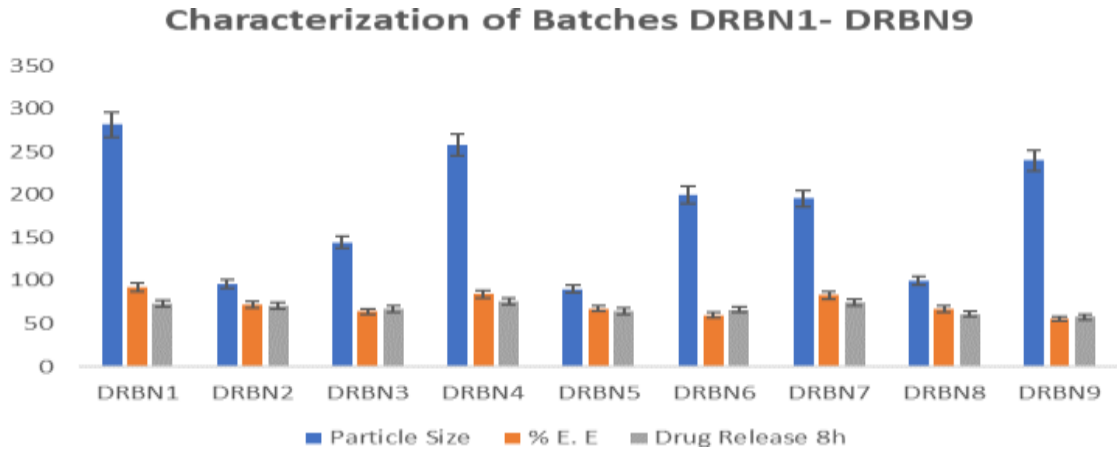
International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

DRBN2	10	10
DRBN3	15	10
DRBN4	05	15
DRBN5	10	15
DRBN6	15	15
DRBN7	05	20
DRBN8	10	20
DRBN9	15	20

Evaluation of Batches

Evaluation of Batches

Batch No	**Particle Size (nm)**	**%E.E**	**Drug Release 8h (%)**
DRBN1	281.49±1.28	92.41±1.28	73.9±1.29
DRBN2	96.29±1.26	72.4±1.67	70.59±0.37
DRBN3	144.59±0.27	64.19±1.78	66.9±1.67
DRBN4	257.91±1.67	84.3±2.37	75.99±1.42
DRBN5	90.31±1.74	67.59±0.97	64.56±1.72
DRBN6	199.49±1.37	60.04±1.69	65.99±1.26
DRBN7	195.49±1.67	82.89±1.89	74.61±1.72
DRBN8	99.41±0.29	66.98±0.38	60.89±1.32
DRBN9	239.91±1.39	55.89±1.67	57.89±2.78



Evaluation of Batches

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

Statistical Analysis:

Experiment 10.0.1's design, Statistical evaluation was done using this data, and initial polynomial conditions were created. In order to sort out potential nine mixtures, a 32 complete factorialdesign withtwo components that were surveyed, freelyat three levels, was used. Utilising two innovative elements, three level factorial assessments were completed. Cholesterol percentage (X1) and Span 60 percentage (X2) were chosen as independent components in first factorial arrangement, whereas particle size (Y1) and % entrapment efficiency (%) (Y2) were chosen to serve as dependent components for both factorial plans.

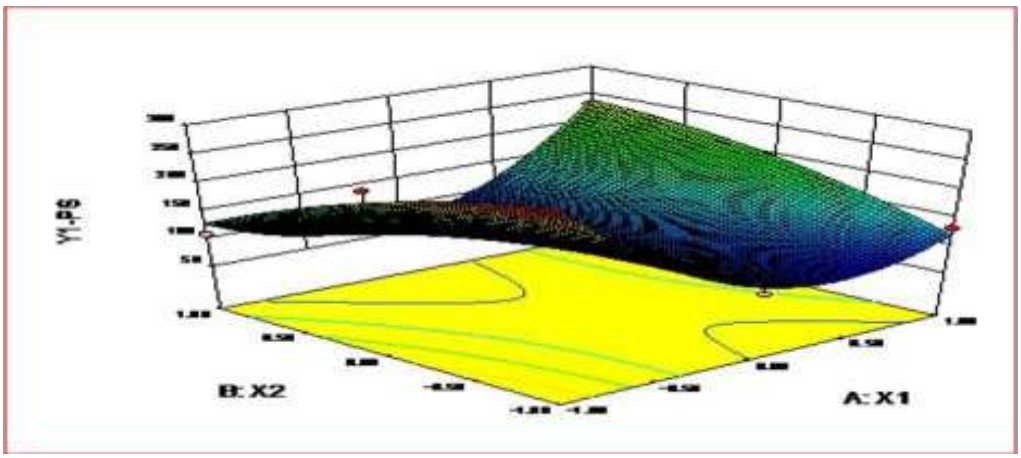
Effecton Particle Size(Y1)-Surface Response Study:

Negative value indicated that as Cholesterol and Span 60 value increases Particle Sizeand % EE decreases.

Y1(PS) =+109.89-19.66X1-15.00X2+9.07X1X2+114.80X15-25.46X35

ANOVA Table for Y1 Particle Size

Source	Sumof Squares	Df	Mean Square	FValue	p-value Prob>F	
Model	48410.69	5	9787.9	15.59	0.0375	Significant
A-X1	1510.80	1	16610.8	4.56	0.2353	
B-X2	752.00	1	732.00	1.59	0.3547	
AB	20842.57	1	206032.58	32.89	0.0229	
A2	24506.11	1	24586.92	39.22	0.0091	
B2	988.89	1	984.69	1.64	0.3255	
Residual	2210.86	3	652.41			
CorTotal	50067.12	8				



Response surface plot

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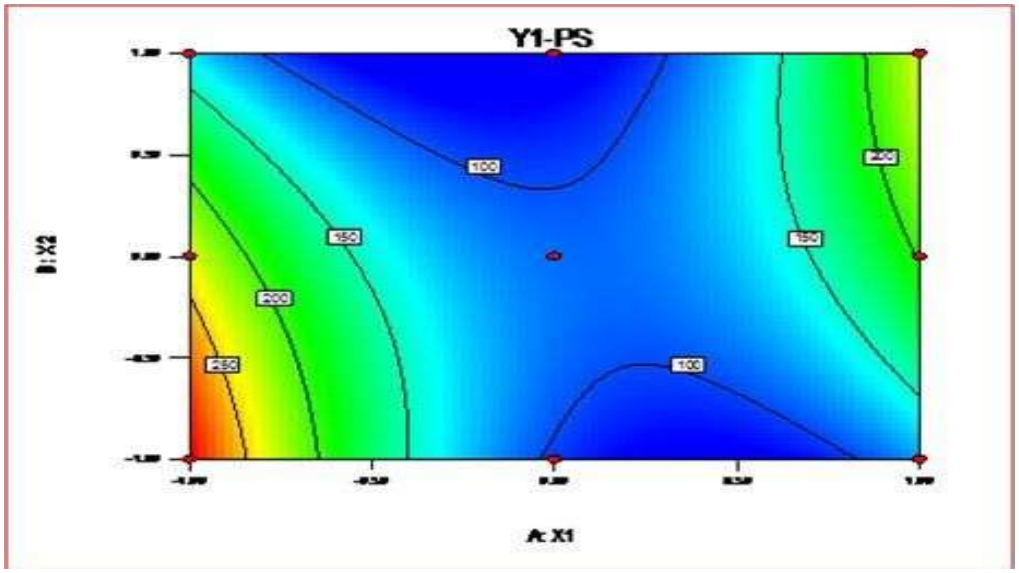
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494



Con tour plot

Effect on Entrapment Efficiency(Y2)-Surface Response Study:
Negativevalueindicated thatasCholesterol andSpan 60 valueincreasesParticleSize and % EE decreases.
Y2(EE)=+68.57-16.00X1-7.00X2-8.32783E-024X1X2+7.66X23+1.66X

ANOVA Table for Entrapment Efficiency

Source	**Sumof Squares**	**Df**	**Mean Square**	**FValue**	**p-value Prob>F**	
Model	1124.44	5	206.55	109.84	0.0017	Significant
A-X1	1054.00	1	1054.00	430.43	0.0005	
B-X2	97.00	1	95.00	44.09	0.0081	
AB	2.260E-016	1	2.260E-015	1.098E-044	1.0000	
A2	39.78	1	38.78	19.99	0.0252	
B2	4.78	1	4.78	2.69	0.2898	
Residual	7.37	3	4.18			
CorTotal	1188.58	8				

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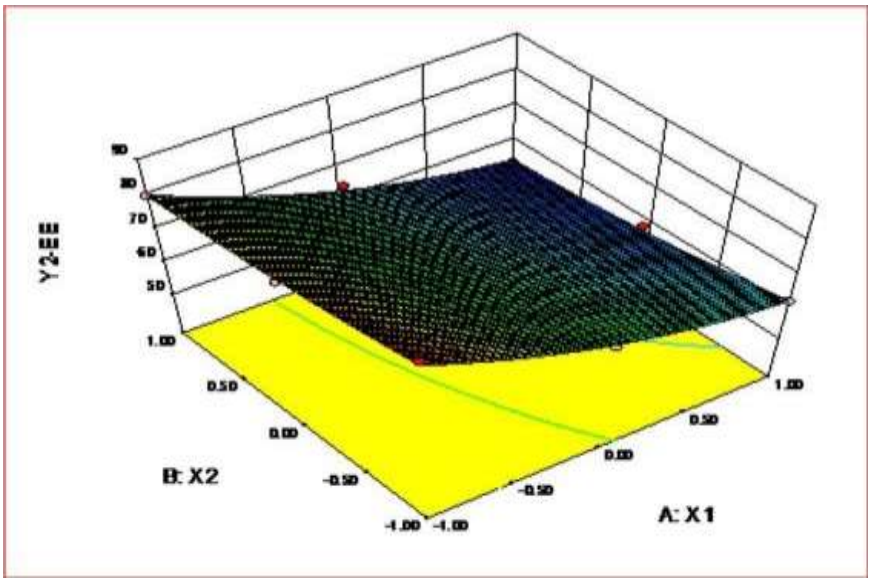
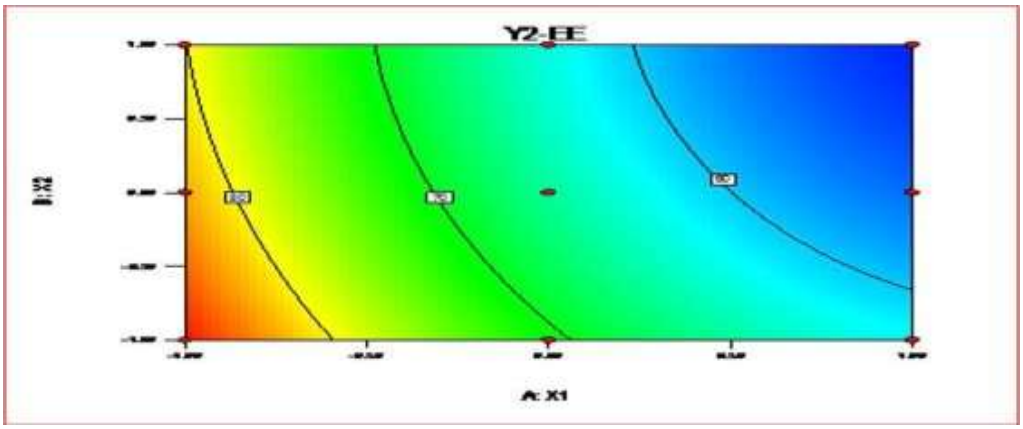


Responsesurface



Contourplot

Validation:

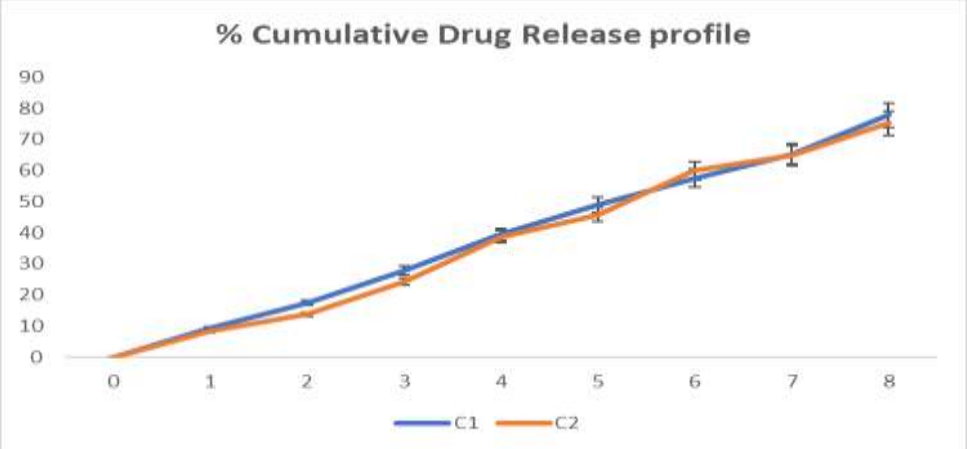
Check point batches	Independent Variables		Response variables	Predicted value	Observed value
	X1	X2			
C1		1	Y1(nm)	95.82	96.27
			Y2(%)	77.22	76.82
C2	-0.75	1	Y1(nm)	117.6	118

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

			Y2(%)	80.37	78.7

%CumulativeDrugRelease profile
%CDRofoptimized Batch

Time(hr)	Batch 1	Batch2
0	0	0
1	9.15±1.96	8.18±1.54
2	17.38±1.68	13.73±1.75
3	27.73±1.15	24.2±1.5
4	39.47±1.16	38.65±1.17
5	48.91±1.57	45.73±1.58
6	57.49±1.91	59.89±1.69
7	65.25±1.16	64.87±1.71
8	77.84±1.21	75.13±1.08



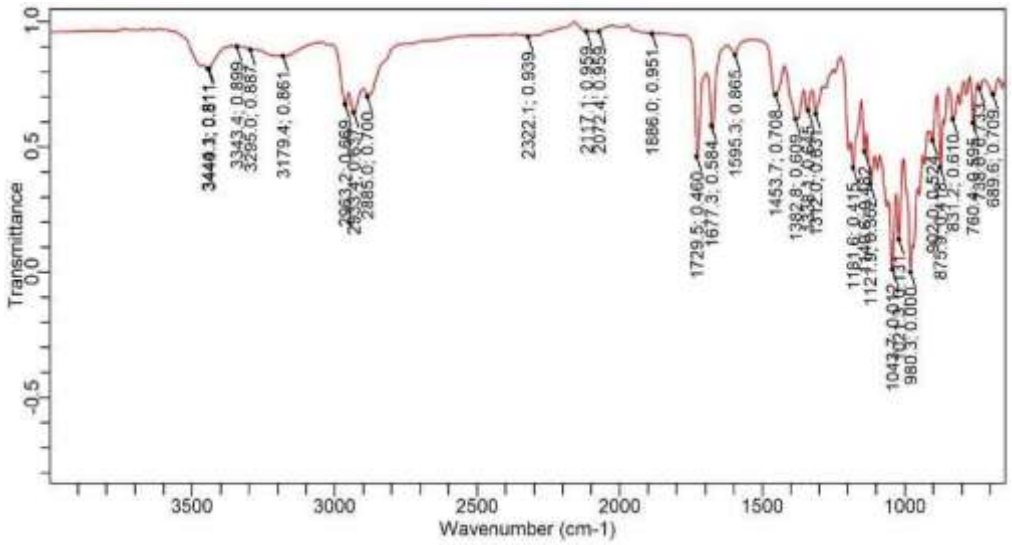
%CumulativeDrugRelease profile

Selection of Optimized Formulation

TheBatch2 withsmallest particlesizeof118 nm, % E.E.of78.7%, and CDRof75.13 in 8 hours was chosen as recommended smoothed out batch and subsequently taken into consideration for stacking into gel.

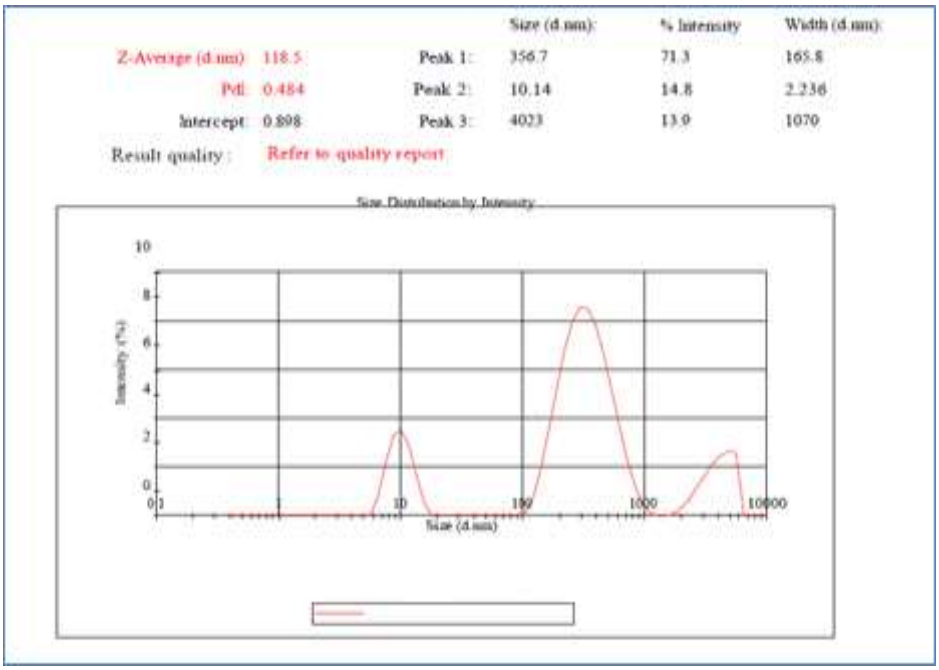
International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

AnalysisofOptimized Form
FTIR Spectrum of Batch 2



FTIRSpectrumofBatch 2

Characteristic peaks of Dox



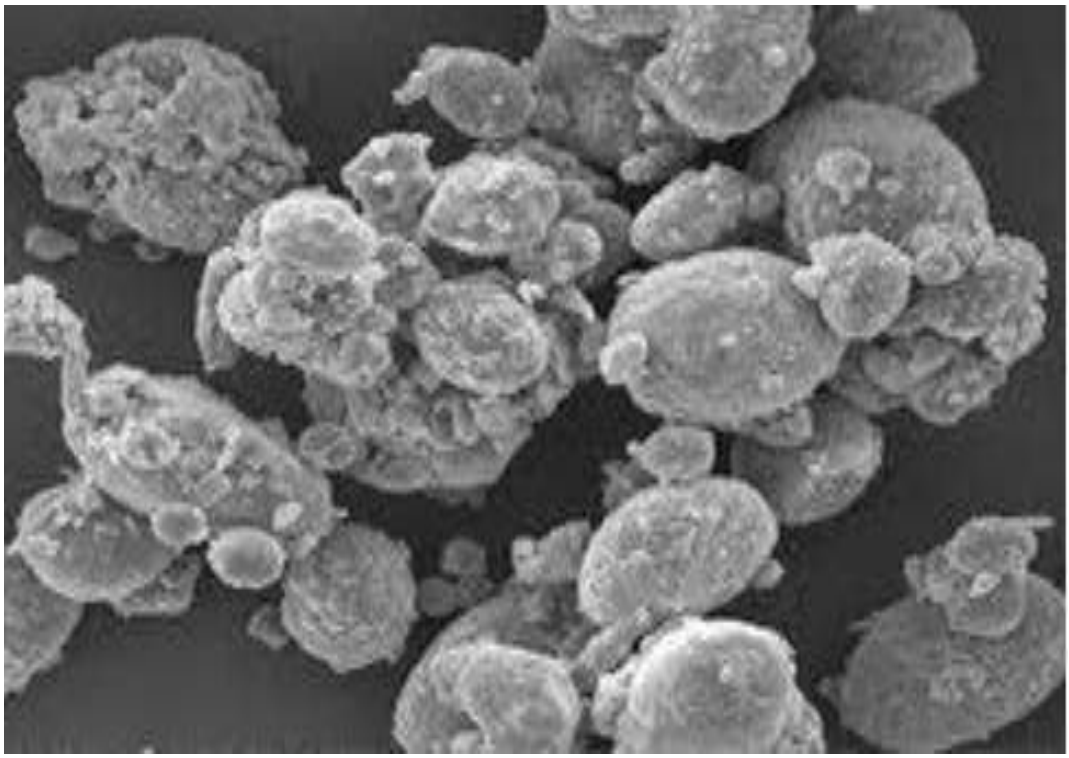
Particle Size Analysis of Batch 2

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

Characterization of Transdermal Patch
Transdermal Patch Evaluation

Parameter	**Result (Mean±S.D.)(n=3)**
pH	6.5±0.06
Viscosity(cps)	9360±1.24
Drugcontent(%)	98.7±2.34
Entrapmentefficiency(%)	92.57±1.34

Scanningelectronmicroscopy



SEM

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

Invitro diffusion study of Transdermal Patch

Time(hr)	OptimizedTransdermal Patch (Mean±S.D.) (n=3)
0	0
1	5.13±0.25
2	13.14±0.42
3	23.59±0.67
4	35.23±0.74
6	44.67±0.34
8	53.25±0.95
10	61.01±0.75
12	69.60±0.15

Kinetics of Drug Release

Model	Parameter	Optimized Gel
ZeroOrder	R^2	0.9322
	Slop	8.232
	Intercept	11.16
FirstOrder	R^2	0.9524
	Slop	0.126
	Intercept	4.27
Higuchi Model	R^2	0.9543
	Slop	25.19
	Intercept	1.64

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 429-450 www.ijprajournal.com ISSN: 2456-4494

Hixon Crowell	**R^2**	0.8358
	Slop	0.75
	Intercept	2.29
Corsmeyer Peppas	**R^2**	0.4247
	Slop	0.24
	Intercept	-0.46

Accelerated stability studies of Transdermal Patch

Parameter	**OptimizedTransdermalPatch**		
	0days	**15Days**	**30Days**
pH	6.5±0.06	6.4±0.04	6.5±0.03
Viscosity(cps)	9360±1.24	9362±1.04	9350±1.01
Drugcontent(%)	98.7±2.34	97.4±1.40	97.7±2.47
Entrapment efficiency(%)	92.57±1.34	91.42±1.31	91.57±1.17

IV. DISCUSSION

Since dawn of man, topical delivery systems have been applied to treat a variety of conditions and as cosmetics. defining of appropriate drug candidates for transdermal delivery and ensuing development of passive and active technologies have improved delivery, increased drug dosing accuracy, and better met individual needs over time. search for sufficiently powerful pharmaceuticals that can enter skin with acceptable transdermal technology remains a focus in future development of medications in transdermal patches and related delivery forms. Meeting therapeutic and cosmetic demands that cannot be adequately supplied in a cost-effective manner through other delivery channels is a major challenge.

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