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REVIEW ARTICLE **OPEN ACCESS**

Budesonide Nanocapsules for Crohn's Disease: Formulation and Evaluation

Nitin B. Kohale*[1], R.P. Singh[2], Manoj S. Charde[3]
1. Research Scholar, Department of Pharmaceutical Sciences, Institute of Pharmacy, NIMS University, Jaipur, Rajasthan, India
2. Institute of Pharmacy, NIMS University, Jaipur, Rajasthan, India
3. Govt. College of Pharmacy, Karad, Satara, Maharashtra, India
Correspondence Email: nitinkohale84@gmail.com

ABSTRACT
Nanocapsules are similar to vesicular systems in which the medicine is trapped in a polymeric membrane-enclosed chamber. Nanocapsules can release medications and their small size allows for better intracellular uptake than conventional particle systems. After intravenous and subcutaneous injections, the nanocapsule can target specific cells and locations. Due to its oily material and strong pressure-acting membrane, a nanocapsule resembles a polymeric nanocapsule and a liposome. Encapsulation protects, controls, and identifies items in the incorrect location. Budesonide is a corticoid used to treat bronchial diseases, Crohn's disease, and ulcerative colitis. Budesonide has strong receptor affinity but low systemic action due to hepatic metabolism. In steroid-responsive disorders. Budesonide is a strong glucocorticoid and a mild minralocorticosteroid. Asthma, Crohn's, and ulcerative colitis have unknown inflammation. Due of budesonide's first-phase elimination, both oral corrections are prolonged release tablets.
Keywords: *Budesonide, Nanocapsule, Crohn's disease, IBD, CDDR*

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INTRODUCTION

Nanocapsules are similar to vesicular systems in which the medicine is trapped in a polymeric membrane-enclosed chamber. Nano-vesicular systems reflect the typical spinal cord structure when the tree is confined in a water reservoir or under a polymer membrane or adhesive. 10 to 1000 nm nanocapsules are available. Nanocapsules can release medications and their small size allows for better intracellular uptake than conventional particle systems. After intravenous and subcutaneous injections, the nanocapsule can target specific cells and locations. Oily or watery cores are encased by polymer in nanocapsules. The nanocapsule core might be liquid or formed with oil. Due to its oily material and strong pressure-acting membrane, a nanocapsule resembles a polymeric nanocapsule and a liposome. Encapsulation protects, controls, and identifies items in the incorrect location [1,2].

COMPONENTS OF NANOCAPSULE:

- Lipids
- Oils
- Surfactant
- Water

METHOD OF PREPARATION OF NANOCAPSULE:

- Emulsification-diffusion
- Nano-precipitation
- Emulsification-conservation
- Layer by layer
- Phase inversion
- Solvent evaporation
- Double emulsification

CONTROL RELEASE DRUG DELIVERY

Controlled dose formulations provide continuous chemical release at a predetermined period. Any drug delivery system's purpose is to send the proper amount of medication to the body so you can receive the fastest and maintain the required drug dosage. The system must administer the drug at a price indicated by the body's needs. therapy time. Placement and transient medication delivery. Temporary delivery refers to adjusting the level of drug delivery to a certain organ. It immediately reaches the intended medical focus and maintains the same during therapy [3, 4].

ADVANTAGE OF CONTROL RELEASE:

- Optimal use of drug and improve the patient compliance.
- Controlled rate and site of release.
- Reduced dose frequency.
- Improved patient compliance.
- The maintenance of drug level within a desired range.
- Better drug utilization.
- Decrease toxicity.
- More consistent and prolonged therapeutic effect.

DISADVANTAGE OF CONTROL RELEASE:

- Stability problem.
- Undesirable by product of degradation.
- The chance of patient discomfort from the delivery device for instance if any surgery required to implant or remove the system.
- Higher cost of controlled release system compared with traditional pharmaceutical formulation.
- Toxicity due to dose dumping.
- More rapid development of tolerance.
- Increased Cost.

INFLAMMATORY BOWEL DISEASE (IBD)

IBD is a group of inflammatory conditions of the colon and small intestine. IBD is a stage of auto immune disease, in which the immune system attacks the elements of the digestive system.

The two main types of inflammatory bowel disease are ulcerative colitis and Crohn's disease.

Ulcerative colitis: covers only the colon that begins in the anus. It can remain limited to the rectum or expand approximately in an integrated manner to a flexible level up to the caecum. The study is mucosal and may disperse or merge. The first direct description of this condition was made in 1909 and in some respects resembles Crohn's disease [5].

Crohn's disease: in Crohn's disease the sores are spotted and flexible; it may involve any part of g.i.t from the mouth to the anus. Most patients have ileocaecal infections up to the ascending column, but in some may be limited to the small intestine. Because the lesions are transmuara, complex as piercing, abscess, fistula, lines, etc. Crohn's disease is less effective in medical treatment than ulcerative colitis. Crohn's disease, also known as Crohn's syndrome and regional enteritis. It may affect any part of the intestinal tract from the mouth to the anus. Crohn's disease is an incurable, or chronic, disease that causes inflammation, irritation, or inflammation of the gastrointestinal tract (GIT). Crohn's disease, also known as Crohn's syndrome and regional enteritis. It may affect any part of the intestinal tract from the mouth to the anus. Crohn's disease is an incurable, or chronic, disease that causes inflammation, irritation, or inflammation of the gastrointestinal tract (GIT).

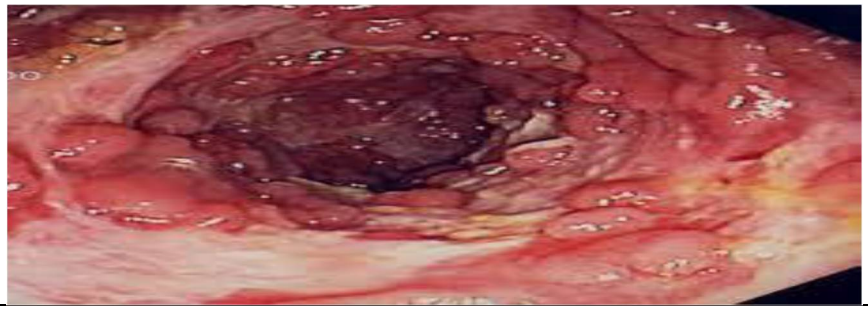


Fig 1 : Inflammation in colon

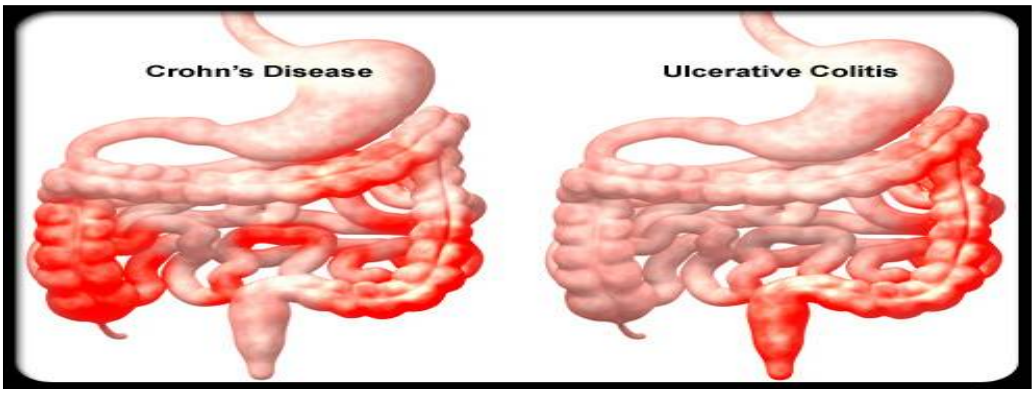


Fig 2 Different location of crohn's disease and ulcerative colitis

SYMPTOMS OF INFLAMMATORY BOWEL DISEASES:

Diarrhoea,
Abdominal pain and cramping
Mouth sores
Fever and fatigue
Blood in stool
Reduced appetite and weight loss

TREATMENT AND DRUG USE IN IBD:

Anti-inflammatory drug

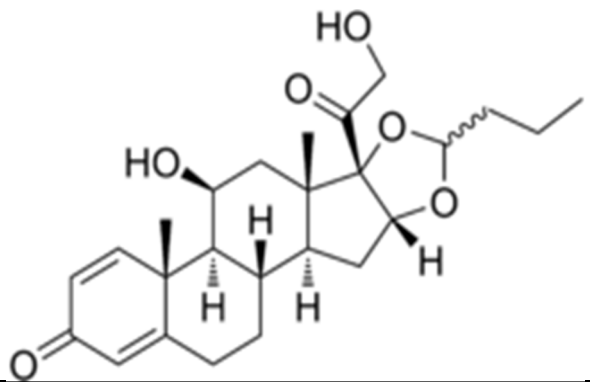
- 5-amino salicylic acid (5-ASA)compound
- Corticosteroid
- Immunosuppressant

Sulfasalazine: This medicine may improve colon-based crohn's disease, but not small intestine. Sulfasalazine's positive effect is not related to antibacterial action. Sulfapyridine carries 5-ASA to the colon without absorption. Nausea, fever, joint discomfort, headache, malaise, anaemia, etc. Higher doses of mesalmine may produce remission in moderate Crohn's colitis, but efficacy is questionable. It doesn't maintain crohn's remission. Corticosteroid such as prednisolone can reduce inflammation everywhere in your body, but they have several negative effects, including puffy face, excessive facial hair, hyperactivity, diabetes, cataracts, and glaucoma. Deflazacort decreases colon inflammation. Doctors use them when other treatments fail. Long-term IBD treatment involves immunosuppressants. Example Azathioprine is the best immunosuppressant for IBD. Azathoprine can harm bone marrow.

Budesonide:

Budesonide is a corticoid used for bronchial diseases, Crohn's disease, and ulcerative colitis. Budesonide has strong receptor affinity but limited systemic action due to significant hepatic first-pass metabolism. In steroid-responsive disorders.

DRUG PROFILE:

Drug	**Budesonide**
State	**Solid**
Formula	$C_{25}H_{34}O_6$
Structure	
Category	Corticosteroid

Indication	The oral tablet is used for the treatment of mild to moderate active crohn's disease. The oral tablet is used for induction of remission in patients with active mild to moderate ulcerative colitis.
Molecular weight	430.53 gm/mole
IUPAC Name	16,17-(butylidenebis(oxy))-11,21-dihydroxy-(11-B,16-a)-pregna-1,4-dine 3,20-dine
Mechanism	Budesonide is an anti-inflammatory corticosteroid that exhibits potent gulcocorticoid activity & weak minralocorticosteroids. Inflammation in asthma, crohn's disease or ulcerative colitis is not known. Because budesonide undergoes significant first-pass elimination, the both oral preparation are formulated as an extended release tablet.
C_{max}	13.3 ± 5.9 hours
T_{max}	1.35 ± 0.96 ng/ml
Route of Administration	Intravenous, Oral
Bioavailability	10-20%
Protein binding	85-90%
Dose	Capsule oral-3mg, Tablets -9mg
Route of elimination	Excreted in urine & feces in form of metabolites.
Half life	2.0-3.6 hrs
Melting point	226^0C
Log P	1.9
PKa	Acidic -13.74, Basic- - 2.9
Water solubility	Insoluble

MATERIALS USED IN PRESENT WORK:

Materials used in Present Work		
Category	**Materials & reagents**	**Supplier**
Drug	Budesonide	Sun Pharma Pvt. Ltd.
Lipids	Cholesterol	SD fine, Ltd
	Lecithin 100	Sigma Aldrich Chemical. Pvt. Ltd
	Lipoid S 75	Lipoid, Germany
Surfactants	Tween 80	SRL
	PEG 600	SD fine. Ltd
	Cremophore RH 40	Sigma Aldrich Chemical. Pvt. Ltd
Oils	Olive oil	SD fine. Ltd
	Ethyl oleate	SD fine. Ltd
	Oleic acid	SRL
	Castor oil	SRL
Solvents	Ethanol	SD fine. Ltd
	Methanol	SD fine. Ltd
Non-solvent	Sodium chloride	Fisher
	Water	Water supply specialist Pvt .Ltd, , India

EQUIPMENT'S USED IN PRESENT WORK:

Equipments used in Present Work	
Equipments	**Manufacturer**
Digital weight balance	Scaletec Mechatronic Pvt.Ltd.
Magnetic stirrer	Remi Service Pvt. Ltd.
Mechanical stirrer	Remi Service Pvt. Ltd
Lyophillizer	Allied Frost, New Delhi
Malvern zeta seizer	Nano ZS-90 Malvern Instrument UK

U.V Visible spectroscopy	Shimadzu 1800, Japan
Scanning electron microscope	FEI SEM
Fourier Transform infrared spectrophotometer	Bruker Alpha,Germany
Dissolution test apparatus	LAMBINDIA DS 8000
Stability chamber	Remi Instrument Ltd,Mumbai

PRE-FORMULATION STUDY: IDENTIFICATION OF DRUG:

Organoleptic Property: As per Indian pharmacopeia 2014 drug was White color, Odorless

Solubility Study: 10 mg medication was placed in a test tube, and 10 ml of solvent was slowly added while shaking. In water, ethanol, methanol, and acetone, medication solubility was tested. Solubility was estimated using Indian Pharmacopeia 2010 terminology.

MELTING POINT DETERMINATION:

Open-capillary melting point determination. By tapping, Budesonide powder was placed in the open end of a 5-cm-long, 1-mm-diameter capillary. The melting point apparatus orifice was then capillarized (Veego Model: VMP-D). The digital display shows the drug's melting point range as the temperature at which the solid turned liquid.

IDENTIFICATION BY FTIR:

Pure drug, Lipids, Surfactant, Oils (Lipoid S 75, Tween 80, Olive oil), and drug with each constituent were FTIR'd (Bruker, ALPHA-T). The physical mixture's ingredient amounts matched the optimised batch. IR and KBr were added to the pure drug and physical mixture. This mixture was scanned from 4000 to 400 cm-1.

ESTIMATION OF BUDESONIDE BY UV-VISIBLE SPECTROSCOPY:

Budesonide was estimated by UV-Visible spectroscopic method using phosphate buffer pH 6.8 and 0.1 N HCl.

PREPARATION OF PHOSPHATE BUFFER PH 6.8:

The ingredient mentioned in Table were weighed accurately and dissolved in 1000 ml of distilled water and pH was adjusted to 6.8.

Formula for phosphate buffer pH 6.8	
Ingredient	**Quantity**
Di sodium hydrogen phosphate	28.8 g
Potassium hydrogen phosphate	11.45 g
Distilled water	1000 ml

DETERMINATION OF ƛMAX BY UV ABSORBANCE:

25 mg Budesonide was dissolved in 25 ml of methanol and made up to 100 /ml with phosphate buffer pH 6.8. 5ml of stock solution was diluted to 100 ml with Phosphate Buffer pH 6.8 to make 5g/ml. UV-Visible spectrophotometer scans final solution for 200-400 nm absorption.

Preparation of calibration curve of Budesonide in phosphate buffer pH 6.8

25 mg medication was dissolved in 25 ml methanol water (1000 g/ml). 2.5 ml of the solution was diluted with distil water to 25 ml (100 g/ml), then 20 ml was diluted with 100 ml 6.8 buffer. 2,4,6,8, and 10 ml of the aforementioned solution (20g/ml) were removed and diluted with distil water to make 4, 8, 12, 16, and 20 g/ml solutions. Each solution's absorbance at 246 nm was measured against Phosphate buffer pH 6.8 as a blank.

PREPARATION OF 0 .1 N HCL:

The ingredient mentioned in Table 4.5 was accurately dissolved in 1000 ml distilled water.

Formula for 0.1 N HCL	
Ingredient	**Quantity**
HCL	8.5 ml
Distilled water	1000 ml

Preparation of calibration curve of Budesonide in 0.1N HCL

Dissolve 25 mg medication in 25 ml methanol water (1000 g/ml). Withdraw 5 ml and dilute with 0.1 N HCl water to 50 ml (100 g/ml). 25 ml was removed and diluted with 100 ml 0.1N HCl. 2, 4, 6, 8, and 10 ml of the aforementioned solution (25g/ml) were removed and diluted with 0.1 N HCl to make 4, 8, 12, 16, and 20 g/ml solutions. Each solution's absorbance at 246 nm was measured against 0.1 N HCl as a blank.

SELECTION OF EXCIPIENTS

SCREENING OF LIPIDS

Formulation is prepared by taking different lipids, Surfactant and Oil their different concentration. Then making a trial batch of this and evaluate it. Then optimize the formulation by particle size and PDI. This is obtained desired particle size and entrapment efficiency.

- **SCREENING OF OILS**

Formulation is prepared by solubility of drug in Oils. take 10 mg drug and dissolve in 10 ml oil and put in the orbital shaker for 24 hrs after that take absorbance by UV method highly soluble oil is optimized.

- **SCREENING OF SURFACTANT**

Formulation is prepared by taking different surfactant and their different concentration .Then making a trial batch of this and evaluates it. Then optimize the surfactant. This is obtained desired particle size and entrapment efficiency.

- **DRUG - EXCIPIENTS COMPATIBILITY STUDY**

The FTIR of drug, Lipid with drug, Surfactant with drug, Oil with drug, and physical mixture of drug with Lipid, Surfactant, Oil were performed using Fourier Transform Infrared Spectrophotometer (Bruker, ALPHA-T). The drug and physical mixture were separately mixed with IR grade KBr. Then these mixture were scanned at transmission mode in region of 4000 – 400 cm^{-1}.

METHOD OF PREPARATION OF LIPID NANOCAPSULE

PHASE INVERSION METHOD:

The lipid nanocapsules were created by phase inversion. They had a liquid oily core surrounded by a cohesive interface and were distributed in water. Oil- and lipid-based oil phase. The aqueous phase contains NaCl and surfactant. Mixing oil with medication creates the emulsion. (1)Drug dissolved in organic solvent. Magnetic stirrer evaporating solvent. Then add lipids and heat to 85oC. The oil phase was then mixed with NaCl and surfactant. Inversion required three temperature cycles. (85-60-85-60-85oC cycles) (Step 2) By dilution with cold deionized water (2oC), stable nanocapsules are formed. Lyophilize it.

CHECK POINT BATCH PREPARATION:

After optimising the model, a check point batch was prepared and evaluated. Formulation preparation followed the optimization procedure.

EVALUATION OF LIPID NANOCAPSULES:

PARTICLE SIZE, POLYDISPERSITY INDEX:

The mean size and Polydispersity index of size distribution of lipid nanocapsule was determined by photon correlation spectroscopy using Zetasizer NanoZS90 (Malvern Instrument).Each sample was diluted with distilled water. The result shown in Figure.

ZETA POTENTIAL:

Zeta potential was determined by using Zetasizer. Clear disposable zeta cell cuvette was used for determining zeta potential. The cuvette was filled with using micro pipette. 20 zeta runs made for each sample and temperature was maintained at 25^{o}C. The results are shown in Figure 5.24.

% ENTRAPMENT EFFICIENCY:

% EE was calculated by determined the amount of nanoencapsulated Budesonide in the aqueous surfactant solution. The aqueous medium was separated by using the centrifuge. Volume of 1.5 ml of the Lipid nanocapsule of Budesonide was placed in tube and speed of centrifuge was kept 15,000 rpm for 1 hr. The concentration of Budesonide in the aqueous phase was determined using UV-visible spectrophotometer at max 246nm.

% EE was calculated using following equation:

$$\% EE = \frac{\text{Drug content in nanocapsule}}{\text{Total content of used drug}} \times 100$$

DRUG CONTENT:

The formulation containing 100 mg equivalent quantity of drug was taken in 100 ml volumetric flask, dissolved in PBS pH 6.8 and volume was made up to 100 ml with PBS pH 6.8 and then it was filtered. The absorbance values were measured with suitable dilutions at 246 nm using UV – Visible spectrophotometer in triplicate. The concentrations of drug were calculated from standard calibration curve prepared in PBS pH 6.8.

SCANNING ELECTRON MICROSCOPY:

The morphological characteristics of lipid nanocapsules were determined by using a scanning electron Microscopy (SEM). The surface morphology and appearance of the particles were observed at X2700 magnification and an accelerating voltage of 15kV.

IN-VITRO RELEASE STUDY:

Budesonide was released from lipid nanocapsules using 0.1 N HCL and pH 6.8 phosphate buffer. Dialysis membrane 150 (Hi Media, Mumbai, India) had 2.4 nm pores and 14000 molecular weight. The dialysis bag holds lipid nanocapsules and permits medication dissolution. Before usage, the bag was soaked in buffer solution. USP type II dialysis bag method was used for in vitro diffusion. The dialysis bag was sealed with 2 cc of lipid nanocapsules. 900 ml 0.1 N HCL for 2 hours and phosphate buffer 6.8 for 8 hours at 37+2^{o}C. The

sink condition was maintained by replacing fresh dissolving medium at predetermined intervals. UV spectrophotometer at 246nm measured Budesonide in the sample. (1800, Japan).

RELEASE KINETIC OF LIPID NANOCAPSULES:

To study the release kinetics of Budesonide from lipid nanocapsules, the releasedata were fitted to following equation:

Zero order kinetics:

$f_t = K_0 t$

Where, f_1 = fraction of dose released at time t,

K_0 = zero order release rate constant

First order kinetics:

$\ln Q_t = \ln Q_0 + K_t$

Where, Q_t = amount of drug remaining to be released at time t,

Q_0 = amount of drug remaining to be released at zero hour,

K_t = first order release rate constant

Higuchi's model:

$Q_t = K_H t^{1/2}$

Where K_H = Higuchi release rate constant.

Hixson – Crowell model:

$W_0^{1/3} - W_t^{1/3} = K_S t$

Where, W_0 = initial amount of drug present in matrix ,

W_1 = amount of drug released at time t

K_S = Hixon – Crowell release rate constant

KorsmeyerPeppas model:

$M_t / M_\infty = Kt^n$

Where, M_t = amount of drug release at time t,

M_∞ = amount of drug released at infinite time

K = Korsmeyer- Peppas' release rate constant

n = release exponents

The type of drug transport mechanism		
Diffusional Exponent, n	**Type of transport (release)**	**Time dependent**
n = 0.5	Fickian diffusion	$t^{½}$
n = > 0.5 - < 0. 1	Anomalous transport	t^{n-1}
n = >1.0	Case II transport	time dependent
n >>1.0	Super case II transport	t^{n-1}

EX-VIVO PERMEATION STUDY:

Chick intestine was studied ex-vivo. 10 cm of intestine was cut, cleaned, and emptied. Thread intestine end. Drug and 0.1 N HCl from other open end. Another intestine was filled with 0.1 N HCl. Both were placed in 50 ml beakers with 50 ml SGF and 100 rpm. 2 ml samples were taken at 2-hour intervals to measure drug diffusion.

STABILITY STUDY:

Optimized Budesonide Lipid nanocapsule formulation was tested for one month. Optimized Budesonide Lipid nanocapsule formulation was stored in sealed glass vials for 1 month. Lipid nanocapsule stability was studied at 40°C/75% RH, 25°C/60% RH, and 4° following ICH guidelines.

RESULT AND DISCUSSION:

Budesonide is a glucocorticoid used to treat Crohn's disease and ulcerative colitis. This study aimed to formulate and evaluate Budesonide nanocapsules for Crohn's disease. Lipid nanocapsule selection criteria included medication solubility in diverse solvents, lipids, and oils. UV spectroscopy for drug spectrum analysis and calibration curve linearity. Melting point was determined with equipment [6, 7]. 5 ml olive oil in a test tube with 5 mg medication yields the highest solubility. After 24 hours in orbital shaker, UV spectroscopy measured the concentration. Olive oil provides the maximum medication solubility. Lipoid S 75 (70% Phosphotidylcholin) was chosen based on particle size and PDI. Tween 80 has the highest entrapment efficiency and nanoscale size range. Phase-Inversion nanocapsules were made from selected components [8, 9]. IR spectra was recorded and functional group was evaluated to find drug structure. IR spectra of medication and Lipid, Oil, Surfactant were collected and compared. 17 batches were created utilising Box-Behnken design with Lipid, Oil, and Surfactant. Particle size, % Entrapment efficiency, Zeta potential, drug content, and in-vitro release were assessed for the optimised batch. All Lipid nanocapsules

exhibit an optimal particle size between 20 and 150. Zeta potential reveals stable formulation and 78.62+ 0.43 entrapment efficiency. SEM photos show nanometer-sized spherical particles with smooth surfaces. In vitro release profile and kinetic studies were done. In-vitro zero-order release enables sustained release. Ex-vivo permeation study compared pure medication to improved formulation. Optimized formulation releases more medicine than pure drug. The batch's stability was studied at 4^{o}C, 25^{o}C, 40^{o}C for 1 month [10].

CONCLUSION

Screening Lipids, Oils, and Surfactants helped identify Excipients. Lyophillizer converts the Phase-inversion-prepared lipid nanocapsule into dry powder. Box-Behnken design enhanced nanocapsule formulation. Optimized batch F3 has 83.1 nm and 0.231 PDI. Entrapment efficiency is 78.62%. F3 has tiny particles and good entrapment effectiveness. Stable Lipid nanocapsules had good particle size, PDI, Zeta potential, and %Entrapment efficiency. Comparing lipid nanocapsules with pure medication in Ex-Vivo. It increases penetration and drug release over pure drug. Lipid nanocapsules are better for oral medication delivery.

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