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"FORMULATION AND EVALUATION OF MICROSPONGE FOR TOPICAL DELIVERY OF OXAPROZIN"

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Abstract: Microsponge can be easily assimilated into the TDS which may retain dosage form on skin and has been used as oral delivery using bioerodible polymers particularly for colon precise delivery which may improve patient passivity due to its site specificity and extending dosage intermissions.

Key Word : Microsponge , Topical Delivery, Oxaprozin

I. Introduction

NOVEL DRUG DELIVERY SYSTEMS:

Drug delivery is the technique and expansion of controlling a API composite to get a therapeutic consequence which can alter release for the advantage of taming product efficiency and compliance. (Singh P et al., 2002) Most common routes of administration are:

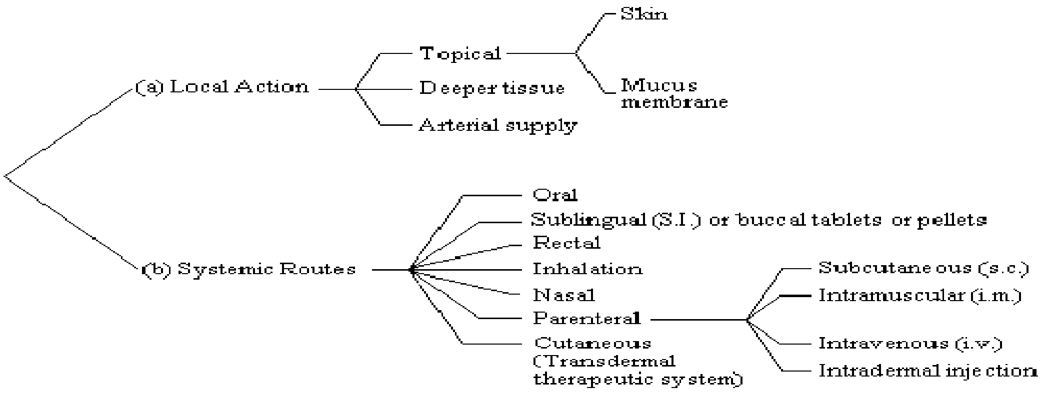


Figure 1.1: Various Routes of Drug Administration by Novel Drug Delivery System
(Kaparissides C et al., 2006)

Advantages of Novel Drug Delivery System: (Khachane K, et al., 2012)

- Modified Release
- Extended Release
- Sustained Release
- Controlled Release
- Targeted Release
- Drug Products Recurrence Action
- Persist Action

TOPICAL ROUTE: (Carter, S., 1987)

In topical drug delivery, there are many routes of the application such as skin, ophthalmic, rectal routes. It would be a great source of help in the applying the drug on the surface as the rate of absorption would be surpassed the first metabolic pathway and thereafter offer a great advantage. Cosmetic preparation could be used for the healthy purpose and simultaneously the dermatological preparation could be a helpful for the infected skin purpose there after a great choice of the dosage form. For the most of the purpose the drug applied on the skin is used for the local action, special preparation are made for the antifungal, antiseptic, emollient etc.

ADVANTAGES:

- Circumvent gastrointestinal drug absorption problems
- Substitute for oral administration of medication.
- Escape avoid drug deactivation by liver enzymes and first –pass metabolism.
- Non-invasive
- Useful for Drugs with a narrow therapeutic window.

DISADVANTAGES:

- ✓ Restricted to potential drug molecules.
- ✓ Skin irritation &/or contact dermatitis.

THE SKIN:

Topical formulations are intended to be applied to a certain area of skin for local action. They conveniently delivery drugs across the localize area of skin. Thus, they are product design to deliver drugs into the skin as a targeted organ for treating dermal disorders. For effective treatment of skin disorders the drug should penetrate and at the same time should depot in the skin for a required period of time. To elect such condition perfectly it requires drug diffusion outside the dosage form to the skin surface followed by its permeation to the barrier layer of skin (stratum corneum) both steps are highly prejudiced. Skin is a vital structure that shelters the entire surface of body, forming a protective barrier against pathogens and injuries from the environment. It is one of the largest organs, with a surface area of approximately 1.8 m^2. It shields the body against heat, light, injury and infection. The skin plays a vital role in the immune system and protects the body from disease. (Tortora G et al., 2000)

Functions of Skin: (Scanlon V. Et al., 2007)

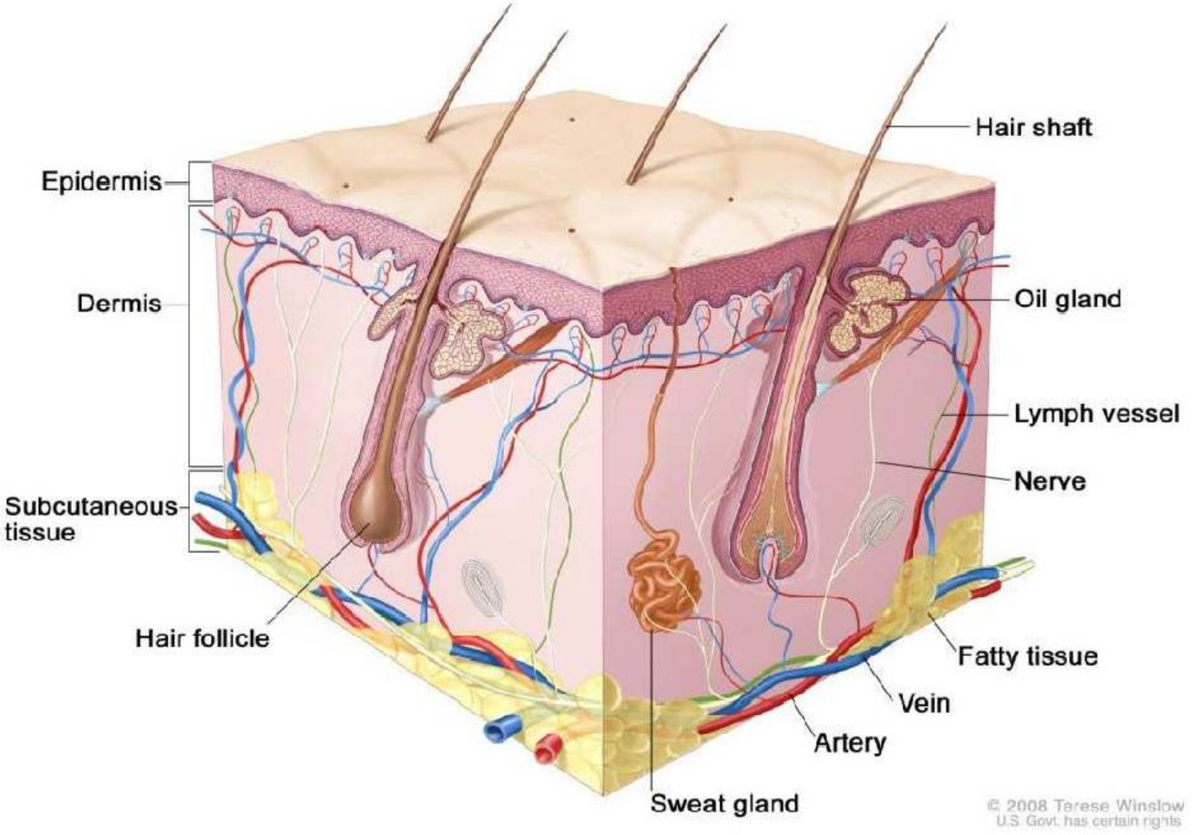
- ✓ Helps as a obstacle for physical, biological and chemical agents.
- ✓ Avert desiccation
- ✓ Photochemical creation of vitamin D
- ✓ Assists as a sensory organ
- ✓ Excretion via sweat

Skin is composed of three primary layers.

(a) EPIDEMIS: It is outer layer self-possessed of keratins stratified squamous epithelium.

(b) DERMIS: It is thick uneven collagenous connective tissue which underlies with the epidermis.

(c) HYPODERMIS: It is apparent fascia which shields the entire body.



Epidermis

It is composed of stratified keratinizing epithelial tissue and densest on the palms and soles. The cells which are maximum abundant are named keratinocytes without capillaries.

STRATUM GERMINATIVUM:

THE STRATUM GERMINATIVUM IS ALSO IDENTIFIED AS THE STRATUM BASALE.

STRATUM CORNEUM:

It is named as Horney layer holds 10 to 25 layers of dead, keratinized cells termed corneocytes which is 10mm thick.

TABLE 1.1: CONTENTS OF HUMAN STRATUM CORNEUM

Sr. No	**Components**	**Percentage**	**Gross Biochemical Composition**
1	Cell membrane	5	Lipid and non-fibrous protein
2	Cell contents	85	Lipid (20%) α- Protein (50%) β- Protein (20%) Non-fibrous Protein (10%)
3	Intercellular Protein	10	Lipid and non-fibrous Protein

Dermis

Hypodermis

Pathways and Mechanisms of Penetration (Goyal R, et al., 2007-08)

Skin is being known that numerous layers which are not similarly permeable i.e. dermis is less permeable than Epidermis. It has been prooved that stratum corneum significantly obstruct permeation with exclusion of sodium ions and water which are actively pulled into skin by passive diffusion.

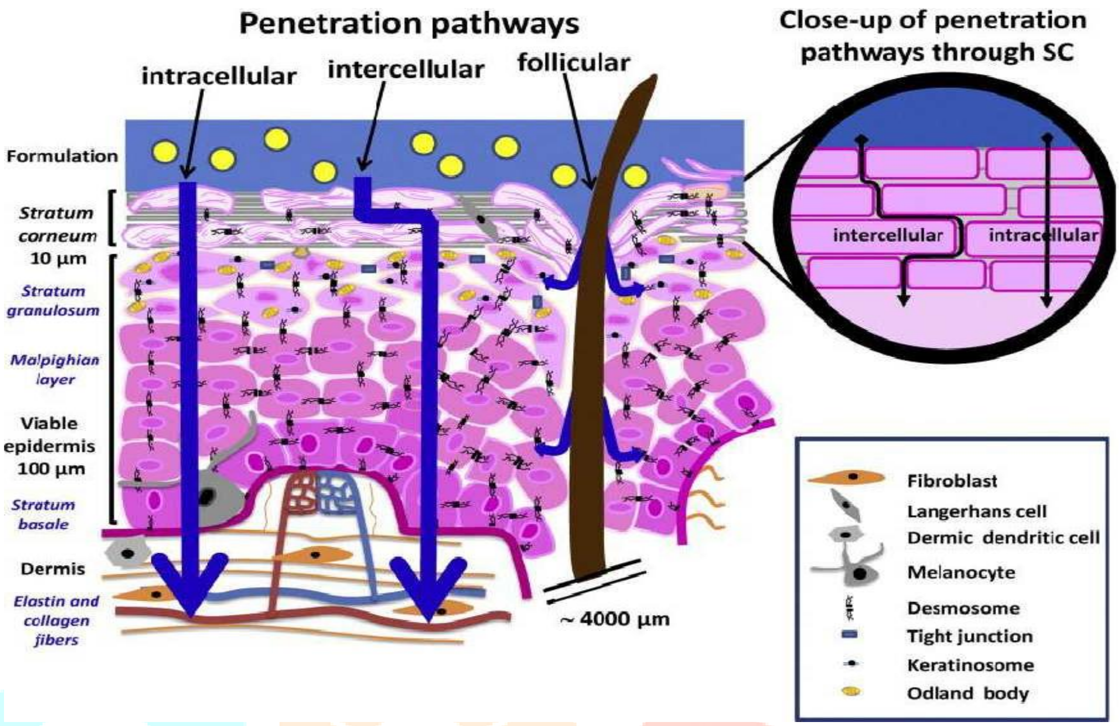


Figure1.3: Penetration Pathway of Skin (Barrett C., 1969)

The most substance penetrant by obeying Fick's law, expunged skin holds its impermeability and the stratum corneum that is serene of metabolically inactive cells and is considered as foremost obstacle to penetration.

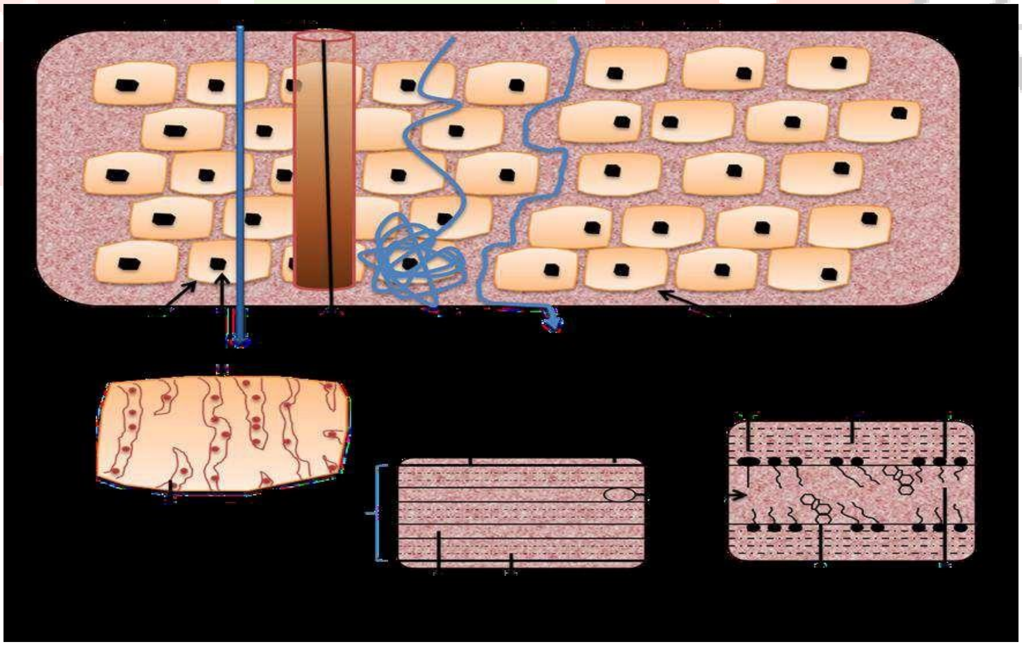


Figure1.4: penetration pathway of Stratum Corneum (Salmon N et al., 2006)

a) Stratum corneum as skin permeation barrier (Kumar D et al., 2011)

The skin allows to pass Water-soluble substances faster through ducts like 200-250 sweat ducts and hair follicles contains 40-70 per square centimeter but they do not back abundant for skin permeation. Therefore, stratum corneum allow permeation of most neutral molecules by passive diffusion.

b) Intracellular verses Transcellular diffusion (Kasper D et al., 2005)

The Intracellular constituencies of stratum corneum which are occupied with lipid rich unstructured material having intracellular volume of 5% dry and 1% in fully hydrated stratum corneum.

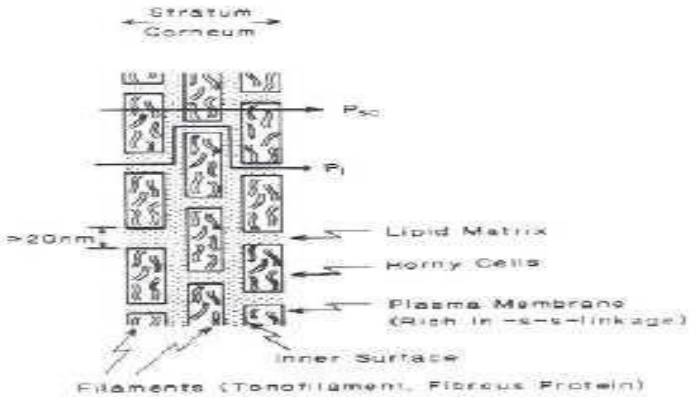


Figure 1.5: The microstructure of stratum corneum (Prasanthi D et al., (2011)

Factors Influencing Penetration: (Prasanthi D et al., 2011) There are various factors affecting the tropical drug delivery system

A) Biological Factors

- ✓ Skin
- ✓ Lipid Content
- ✓ Sweat glands
- ✓ Hair follicles
- ✓ Blood flow
- ✓ Inflammation

B) Physicochemical factors

- ✓ Skin hydration
- ✓ Temperature and pH change
- ✓ Drug Molecular size and shape

INTRODUCTION TO GEL:

Topical Gels:

The Topical Gels are defined as semisolid dosage form which is having a liquid phase controlled within a matrix of natural or synthetic polymer by physical or chemical cross linking. (Debjit B et al., 2012) The inorganic elements create a three-dimensional structure. Gel is having two phases in which inert particles are dispersed in dispersion phase and haphazardly coiled in the supple which look like as a single phase. Organic polymers such as Carbomers are used to prepare topical gel which imparts an aesthetically pleasing, clear form of gel and easily washable with water. The base type which are used to formulate a topical dermatological gel can greatly effects its efficacy. (Priya M et al., 2012 and Sudhir B et al., 2012)

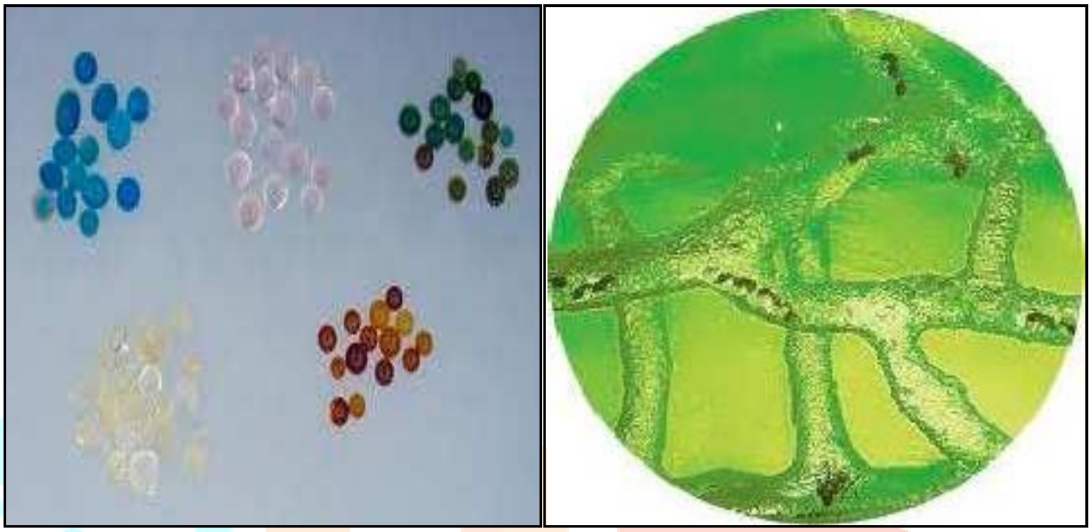


FIGURE 1.6: STRUCTURES OF GELS- (A) COLONIES AND (B) SILICA GEL

Classification of Gels: (Priya M et al., 2012 and Sudhir B et al., 2012) Topical Gels can be classified by two type based on their preparation method:

a. Nature of colloid phase used

i. Inorganic topical gels

ii. Organic topical gels

b. Based on nature of solvent

i. Aqueous topical gels

ii. Non aqueous topical gel

Steps involved in Topical Permeation of drug: (Chien Y., 2005 and Jain N et al., 2005) The permeation of a drug in the form of topical gel from skin comprises the following steps:

- Sorption of Drug by stratum Corneum
- Penetration into viable epidermis
- Drug Uptake from skin papillary layer by capillary system

Gel forming substances: (Jain N et al., 2005) Polymers used to prepare Topical Gel are as follows:

TABLE 1.2: GEL FORMING SUBSTANCES

A. **Natural polymer**	**B. Semi synthetic polymers**	**C. Synthetic polymers**
a. Proteins e.g. Collagen and Gelatine b. Polysaccharides e.g. Agar, Alginic acid, Pectin, Xanthin and Tragacanth	a. Cellulose derivatives e.g. CMC, MC, HPC, HPMC and HEC	a. Carbomers e.g. various grades of Carbopol -940, -934 and -941 c. Polyacrylamide d. PVA e. PEG **D. Inorganic substances** e.g. Aluminum hydroxide and Bentonite **E. Surfactants** e.g. Cetostearyl alcohol

INTRODUCTION TO MICROSPONGE DRUG DELIVERY SYSTEM:

Microsponge can be easily assimilated into the TDS which may retain dosage form on skin and has been used as oral delivery using bioerodible polymers particularly for colon precise delivery which may improve patient passivity due to its site specificity and extending dosage intermissions. (Won R., 1987, Newton D et al., 1991 and Kydonieus A et al., 1987)

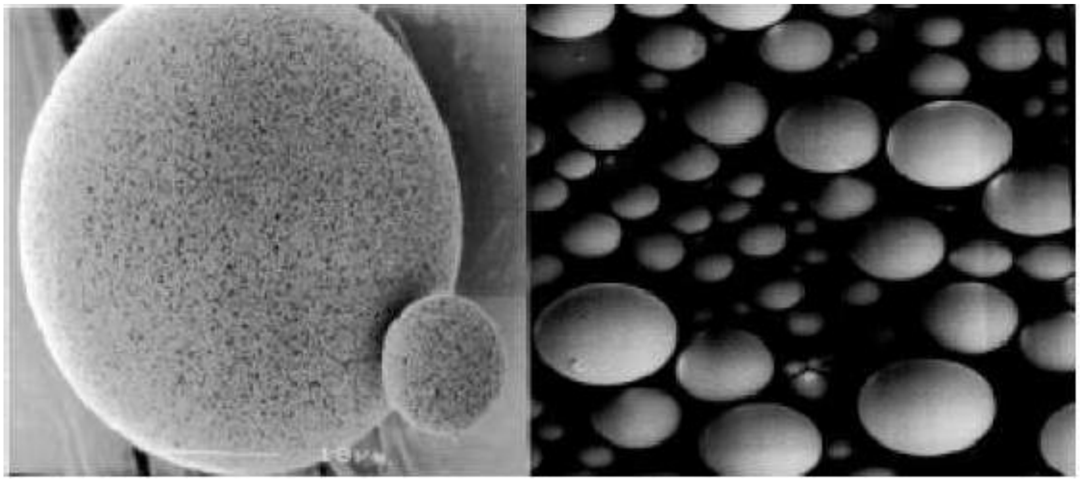
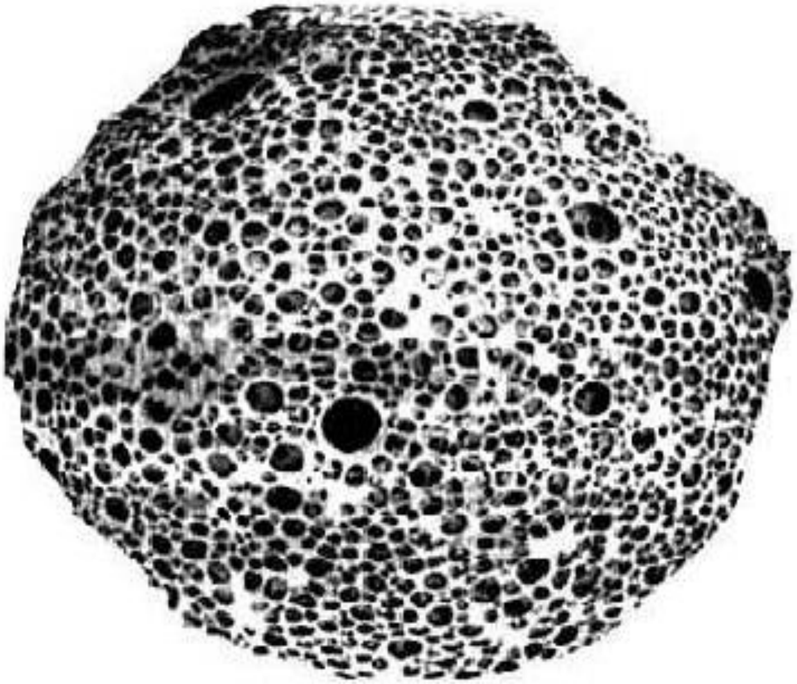


Figure 1.7: Photographs of highly porous nature of a microsponge Microsponge is defined as porous, inert units which is made up of synthetic polymers and act as a shield to the ensnared drug from degradation which can be easily entrapped in th form of creams, lotions, and powders. **(**Won R., 1987 and Delattre L et al., 1995) In case of Cosmetics and dermatological products, work only at outsided of skin. The active component in conventional marketed dosage form may extant in a moderately high concentration and absorbed rapidly on application upon skin. MDS may proposed to permit a modified rate of drug release of, thus posing prospective lessening in the side effects and maintain the therapeutic effect. (Cooke C., 1993 and Nacht S et al., 1992)

Formulation Aids: (Aritomi H et al., 1996)

The polymers which have been used to prepare microsponges are Ethyl cellulose, Eudragit RS 100, etc. which can form ‘cage’ like structure. Sometimes plasticizers may be used to stabilize structure of microsponges.



3.1POPULATION AND SAMPLE FIGURE 1.8: POROUS STRUCTURE OF MICROSPONGE

Ideal Characteristics of Materials: (Parthiban K et al., 2011 and Panwar A et al., 2011) Actives should exert following ideal requirement:

- ✓ It must be immiscible or little soluble in water.
- ✓ It must be either fully miscible or partially made miscible wth the help of third substance.
- ✓ It must be physically and chemically inert.
- ✓ The structure of MS should not collapse due to any physical or chemical change.
- ✓ It must be stable**.**

Advantages: (Parthiban K et al., 2011 and Panwar A et al., 2011)

- ✓ It can fascinate 6 times its weight water deprived of drying with advanced oil control.
- ✓ It may Improve grace and aesthetics, efficacy of product.
- ✓ It permits loading of immiscible drugs.
- ✓ It provides ER dosage and Countenances novel creation form which can decrease irritation, improved tolerance, hence extensive patients acceptance.
- ✓ It also increases physical and chemical stability.

Table 1.3: Comparisons between Conventional DDS and MDS (Panwar A et al., 2011) and Vyas S et al., 2002)

PARAMETERS	CONVENTIONAL DDS	MDS
Site	Outer layer of skin	Avoid unnecessary accumulation in epidermis and dermis
Absorption	Produce highly concentrated layer and Rapidly absorb	Modify the release of the drug
Irritation	Cause irritation	Reduce irritation

Table 1.4: Comparisons between Microcapsule and Microsponge (Delattre L et al., 1995)

PARAMETERS	MICROCAPSULE	MICROSPONGE
Concepts	Capsule	Sponge
Shell	Complete	Porous
Release mechanisms	Rupture or Burst of Cell	Pressure, Partition Coefficient, Temperature
Amount released	100%	Programmable

Table 1.5: Comparisons between Liposomes and Microsponge (Embil K et al., 1996 **and**

Viral S., 2012)

PARAMETERS	LIPOSOMES	MICROSPONGES
Concepts	Lipid bilayer	Sponge
Stability	Potential problems	Stable even change in pH and Temperature.
Microbiological stability	Preservation Needed	Preservation not needed
Programmable Properties	Chemical Composition and P.S.	Chemical Composition, Small P.S., resiliency in pore size and width
Entrapment efficiency	30%	50-60%
Cost	Expensive	Cost effective
Quality control	Require ultra pure raw material	Simply obtainable ingredients of satisfactory pureness

RELEASE MECHANISMS: (Kawashima Y et al., 1992 and Shah V., 1989)

They are intended to release API for prolong duration in retort to external elicits i.e. Change in temperature, pH, solubility and by apllying pressure.

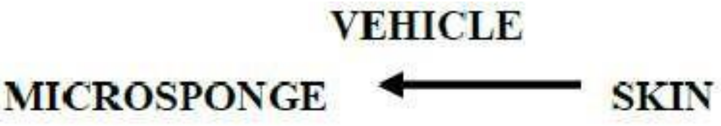


FIGURE 1.9: RELEASE MECHANISM OF ACTIVE INGREDIENT FROM MICROSPONGES

METHODS OF PREPARATION OF MICROSPONGES: (Tansel C et al., 2002 and Martin A et al., 1991)

Microsponges are suitably prepared by the following methods:

a) LIQUID-LIQUID SUSPENSION POLYMERIZATION:

In suspension polymerization process, the monomers dissolve with active components solvent solution which is before dispersed in aqueous part which contains of surfactants and dispersants by agitation in order to form suspension. After suspension is formation with separate globules of the chosen size and catalyst was added to initiate polymerization which leads to form a reservoir system.

b) Quasi-Emulsion Solvent Diffusion Method**:**

It is two-step process using an internal phase containing drug and polymer which are made dissolved in appropriate solvent. The internal phase is added into external phase comprising stabilizer and solvent with 2 hrs stirring. Then, mixture was filtered and collected microsponges were wash and dry in air oven at 40°C.

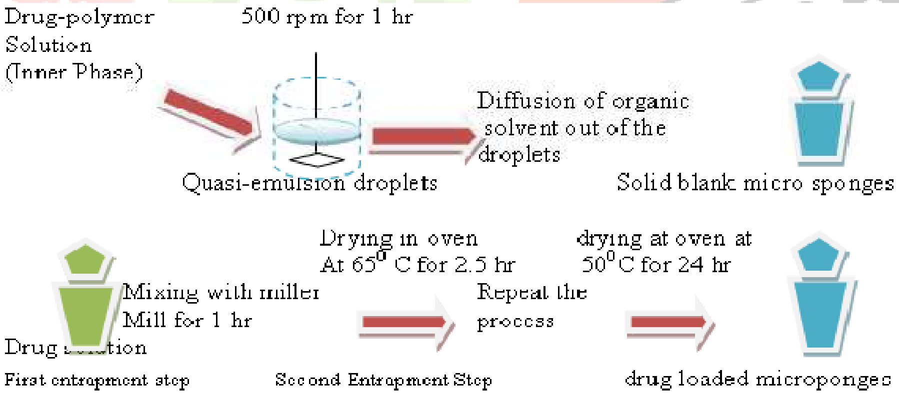


Figure 1.11: Preparation of microsponges by quasi emulsion solvent diffusion

METHOD EVALUATION PARAMETERS OF MICROSPONGES: (Netal A et al., 2009 and Vikas J et al., 2010)

Various methods are used for the evaluation of the MDS, they are following

- ✓ Particle size (Microscopy) Analysis
- ✓ Topography of microsponges

- ✓ Evaluation of pore structure
- ✓ % E.E. and % yield
- ✓ Compatibility studies by FT-IR and DSC
- ✓ % CDR study
- ✓ Kinetics of Drug release
- ✓ Other In-vitro studies

APPLICATIONS OF MICROSPONGES [Viral S. (2010)]

TABLE 1.6: APPLICATIONS OF MICROSPONGES

Sl. No.	Active agents	Application
1	Anti-acne (Benzyl peroxide)	Better efficacy with lower skin irritation.
2	Anti-inflammatory (hydrocortisone)	Prolong Action with minimum allergic reaction and dermatomes.
3	Anti-fungal	Sustained release action.
4	Rubefacients	Lower in skin irritancy with reduction in oiliness and odor.

MARKETED FORMULATIONS USING THE MDS:

Microsponge delivery systems can be used to improve the safety, efficiency and visual quality of topical prescription, over-the-counter (OTC) and personal care products.

TABLE 1.7: LIST OF MARKETED AND PATENTED PRODUCTS USING MICROSPONGE DDS

Product	Product Manufacturer
Carac Cream	Dermik Lab. Ltd.
Oil Control Lotion	Fountain Cosmetics
Retinol cream	Biomedic
Salicylic Peel 20 & 30	Biophora.

INTRODUCTION TO QUALITY BY DESIGN:

Quality by Design (QbD) is gradually evolving as a improvement of the quality of the product through its life succession. QbD is a considerable change compared to the traditional approach where formulation design and development typically consisted of univariate experiments which clues to incessant upgrading and revolution in products and processes and also offers increased regulatory flexibility within the design space. (Lourenço V et al., 2012)

History of QbD

The idea of QbD had initially charted in the 1960s by management counsellor Joseph Juran, who contended that quality should be intentional relatively than just attained in a chaotic way. (Lourenço V et al., 2012)

Previously, Quality was achieved final product testing and not by process design (QbD) with knowledge of process and formulation variables. The regulatory practice imposed pharmaceutical processes to be operated under pre-defined and fixed operating conditions irrespective of any sources of variability coming from raw materials or processing conditions. (Delasko J et al., 2005)

The FDA's document titled Pharmaceutical cGMPs defined Quality by Design as:

1. Developing product to meet predicted product quality.
2. Scheming manufacturing developments.

QbD Approach towards Development

According to ICH Q8 (R2), the first step in QbD is to aim the product profile. The TPP is distinct

be proficient to confirm that the anticipated quality, safety and effectiveness of a drug. It forms the basis of design for the development of the product. Separately labelling thought is based on Quality Target Product Profile (QTPP) which is the quality appearances that drug should preferably own in edict to reproducibly provide the therapeutic assistance assured in the label. Examples are purity, assay. QTPP is thus an extension of TPP, purity, strength and Ex. Identity. The next step after this is determining the Critical Quality Attributes (CQA). A CQA can be well-defined as "specificity of drug product that should be surrounded by proper boundary, range or dispersal to guarantee the preferred product quality". A risk assessment study is done to estimate these attributes. These studies help to design a safe and efficacious product with the desired CQAs. (Delasko, J et al., 2005)

A design space is interplanetary design to produce quality product. It can be created for separate unit operation or process as whole. Therefore, a design space is a convenient means of facilitating regulatory flexibility by allowing the manufacturers to work within an established range of inputs. A design space allows for easier post- approval marketing changes reducing the

regulatory hassles and planned by the aspirant which is subjected to regulatory assessment and consent. (Sandipan R et al., 2012 and Wu H et al., 2011)

MODELLING APPROACHES FOR DEVELOPING QbD: (Aksu B et al., 2012)

A number of modelling approaches can be proposed for initializing design spaces for pharmaceutical manufacturing mainly divided into three classes:

1. D.O.E.
2. Semi-empirical methods to advance operating regime plans and scaling guidelines.
3. First-principle models in which restricted number of experiments requisite to validate the model.

DESIGN SPACE METHOD USING DOE METHOD:

DoE can be used to know factors influencing end products according to the standards using design space methods. (Aksu B et al., 2012) A DoE is conducted to evaluate whether the variables in a process are feasible or not. The variables ranked as high risk are evaluated by conducting DoE studies to gain process understanding. DoE can competently screen and optimize formulation variables and recognize the desired combination of exicipients within the design space. (Awotwe D et al., 2012) DoE study can be performed to optimize the critical process parameters and their ranges in a design space.

These methods are incorporated in DoE includes:

1. Experimental design
2. Randomized trials
3. Statistical analysis
4. Multi- dimensional models for optimization or control

✓ Three different levels:

1. A laboratory scale screening to identify process parameters on the drug release and CPPs.
2. A laboratory scale optimization to optimize CPP ranges.
3. A pilot scale robustness to confirm the knowledge gained from lab scale.

ANOVA results should attend all DoE data analysis, particularly when the consequence of the model terms is concerned. After DoE studies and establishment of a design space, the next fundamental step towards QbD is to design a control strategy. (Awotwe D et al., 2012)

CONTROL STRATEGY

It is defined as “a strategic customary of controls, resulting from present product and process attentive that promises process concert and quality of product”. It may include the following:

- ✓ Rheostat of input substantial attributes
- ✓ Product Provisions
- ✓ Controls for unit operations

MONITORING PROGRAM:

There is a significant that the policy to validate control of exicipients properties created on the understanding of their effects and not relying solely on compendia standards. A control strategy can include different elements. (Wu H et al., 2009)

Process Analytical Technology (PAT)

PAT is a part of control strategy which ensure that process ruins within an established design space. PAT consents incessantly screen, check, investigate, tendency and adjust manufacturing processes. PAT is defined as a scheme for design, scrutiny and resistor on appropriate extents of quality constraints and recital characteristics of materials and inprocess constituents in mandate to confirm end product quality. (Gernaey K et al., 2010)

Real Time Release Testing (RTRT) :

It is modification of analytical control from an off-line, post- manufacturing approach to an approach where data is generated during manufacturing. i.e. The process of quality control is shifted upstream into the production process. RTR does not mean less testing, in fact, it often means more analytical data is generated. It provides for control closer to the source of variability in the process and allows for Real Time Release of the batch. RTRT allows leveraging of enhanced process understanding i.e. It facilitates the implementation of corrective actions in real time. (Brigitte G et al., 2012)

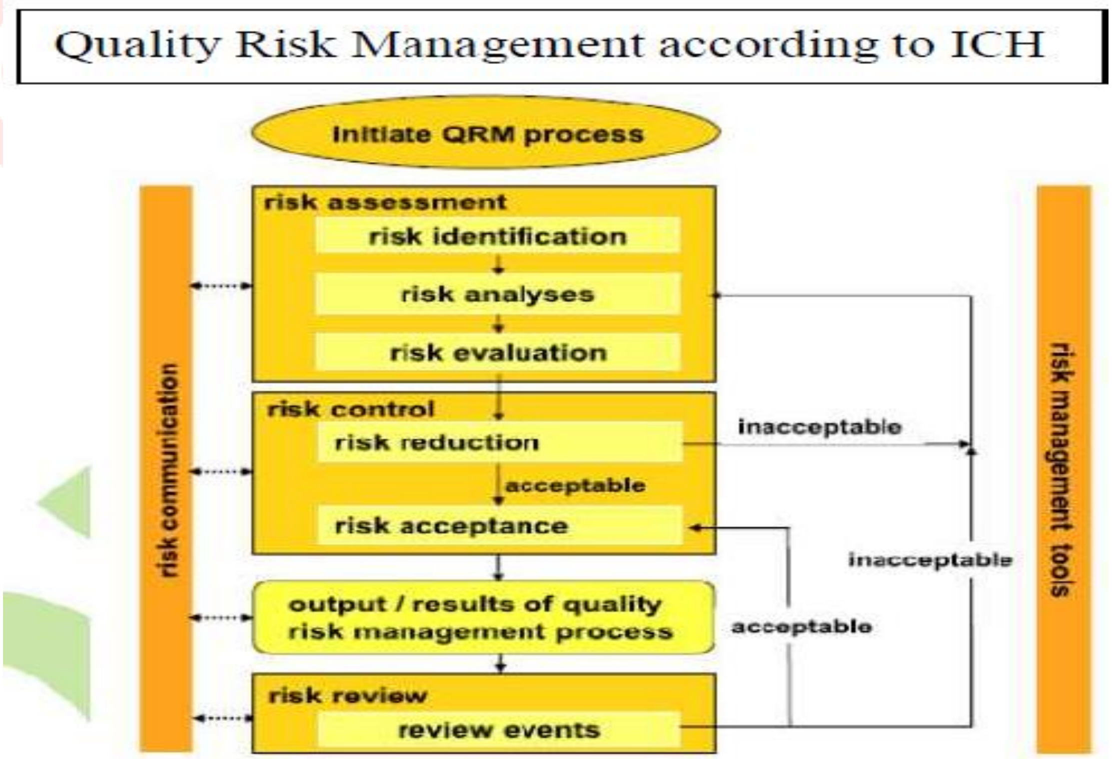


FIGURE 1.13: QUALITY RISK MANAGEMENT ACCORDING TO ICH

FACTORIAL DESIGN – AN OPTIMIZATION TECHNIQUE: (Lewis G et al., 1999)

It is used to formulate an satisfactory pharmaceutical formulation in the straight conceivable time in pharmaceutical Formulation & Development (F & D) center. The formula developed by the F & D center is then tried at the pilot plant scale and manufacturing scale. Ideally, minor changes are to be made during the scale-up. It is, therefore, very essential to study the formulation from all perspectives. In addition to the art of formulation, statistical analysis are helpful to pharmaceutical formulation to produce better quality product. The levels of factors can be varied independently at two or more levels. A factor is an consigned variable like concentration, temperature, pH etc. Predictions based on the results of an undersigned experiment will be more variable than those which would be obtained in a designed experiment, in particular, factorial design.

INTRODUCTION TO FUNGAL INFECTION AND TREATMENT:

The skin is subjected to various types of inflammatory dermatoses and attack by a variety of microorganisms, parasites and insects. In the most instances and there is successful resistance to invading organisms. (Hoffmann D., 1999) Depending on inflammatory potency, virulence of the infecting agent, the competence of the host's responses & infection result. Skin disorders are

classified as follows.

Fungal infections: (Kovacs S et al., 1995 and Livermore B et al., 1996)

Microorganism is minute alive beings such as bacteria and viruses and in spite of their irresistible plenty, comparatively rare of thousands of class of microorganisms conquer, grow, and source of infection in people.

FIGURE 1.14: FUNGAL INFECTION IMAGES

- ✓ Candidiasis:

- ✓ Athlete'sfoot(Tinea pedis):
- ✓ Jock itch (*Tineacruris*):
- ✓ Ringworm (*Tineacorporis*):
- ✓ Face fungus:
- ✓ Tinea versicolor:

1.8.2. Anti-fungal drugs: (Gandhi T et al., 2008-09)

TABLE 1.8: LIST OF ANTI-FUNGAL DRUGS

Drug	**Common Uses**
Amphotericin B	Wide variety of fungal infections
Anidulafungin Caspofungin Micafungin	*Aspergillus*, candidal, and possibly other infections
Oxaprozin and Clotrimazole	Candidal and other fungal infections, including cryptococcal
Flucytosine	Candidal and cryptococcal infections

INTRODUCTION TO PAIN AND ITS TREATMENT: (Donald G et al., 2000 and Richards A et al., 1995)

INTRODUCTION ON PAIN:

Pain is a hostile sensual and expressive experience concomitant with definite or possible tissue injury, or termed in terms of such damage.

PAIN PATHOPHYSIOLOGY:

The responsiveness of pain is a usual reaction to injury or disease which is a outcome of normal physiological processes in the nociceptive system. The few other indicators of pain associated to

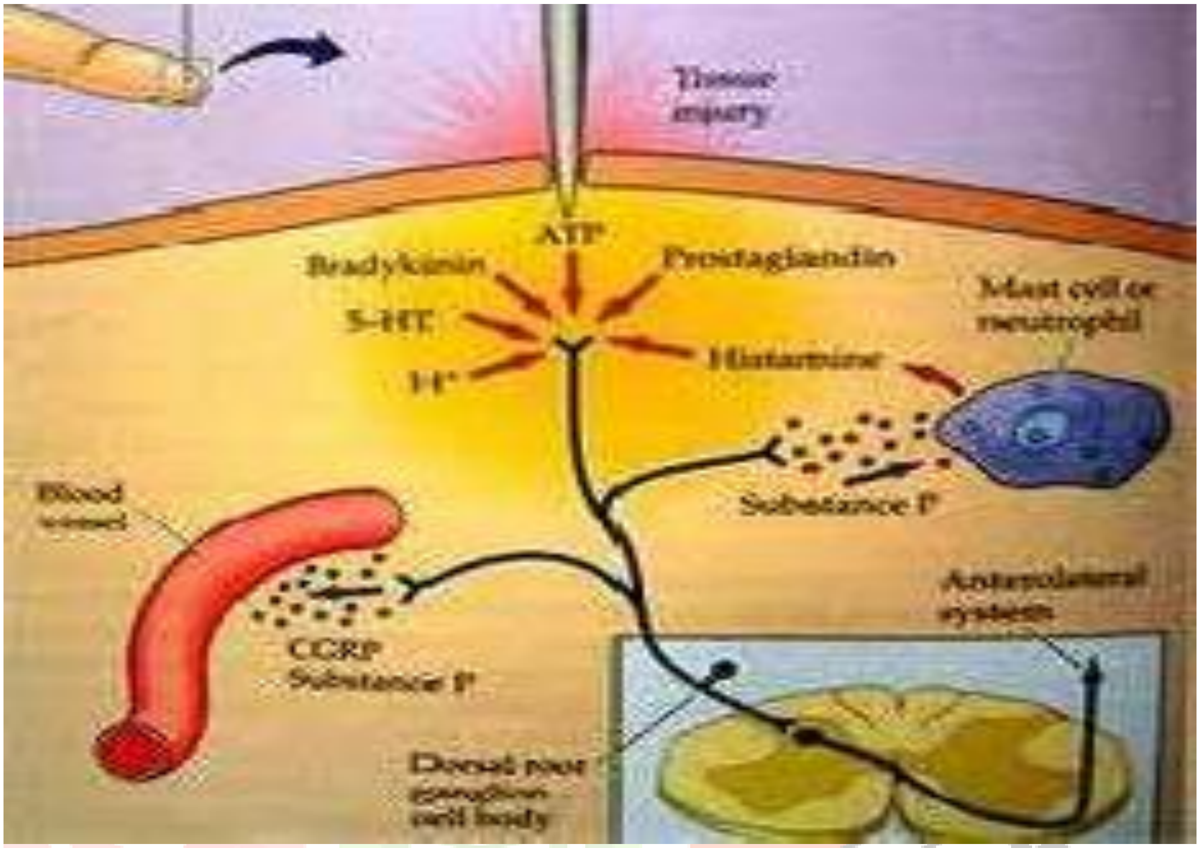


FIGURE 1.15: PAIN PATHWAY

CLASSIFICATION OF PAIN:

The pain may classify in three different classes which includes:

- ✓ Nociceptive
- ✓ Neuropathic
- ✓ Inflammatory

PAIN INTENSITY:

Pain intensity is classified into three types mainly as: mild, moderate and severe.

Mild: 0 to 4.

Moderate: 5 to 6

Severe: 7 to10

MANAGEMENT OF PAIN:

To the broad category of drugs in the management of pain and inflammation are:

1. Non-opioids

2. Non- opioids

1. OPIOIDS:

Opioids are the most potent pain relieving drug currently available. They produce analgesia by actions in the central nervous system. Examples: Codeine, Oxycodone, Morphine, Methadone, Meperidine, Tramadol, Fentanyl.

2. NON-OPIOIDS / NSAIDS:

NSAIDs are most extensively uses medication in clinical practice because of their well- established usefulness in minimizing pain and inflammation. They are the main choice in the pain management because of the integrated role of the COX pathway in the process of inflammation.

TABLE 1.9: CLASSIFICATION OF NSAIDS.

CLASS	DRUG
Salicylates	Aspirin, Methyl salicylate
Para-aminophenol derivatives	Acetaminophen
Acetic acid derivatives	Diclofenac, Aceclofenac, Sulindac
N-arylanthranilic acids	Mefenamic acid, Meclofenamic acid
Pyrazolidine acid derivatives	Phenylbutazone, Oxyphenbutazone
Propionic acid derivatives	Ibuprofen, Ketoprofen, Flubiprofen
Enolic acid derivatives	Celecoxib, Etoricoxib, Valdecoxib,

Drug Profile: (Bertram G., 1995 and Tripathi K et al., 2003)

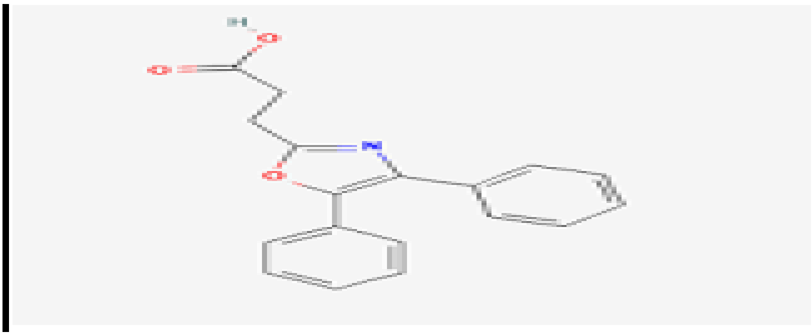
Oxaprozin

Drug Name : Oxaprozin

Functional category : Antifungal **Formula** : $C_{18}H_{15}NO_3$

Molecular weight : 293.3gm/mol

STRUCTURE :



INTRODUCTION OF POLYMER: (Rowe R et al., 2006)

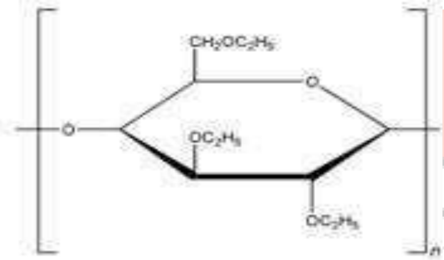
ETHYL CELLULOSE

1. **Nonproprietary Names**

   Ethylcellulose

   SynonymsEthocel and Surelease.

2. STRUCTURAL FORMULA



3. **Functional Category**

   Viscosity enhancer and Coating agent.

4. APPLICATIONS IN PHARMACEUTICAL FORMULATION:

- ✓ It can be used in drug microencapsulation
- ✓ It is used as viscosity modifier for topical DDS.
- ✓ It can be as a stabilizer for emulsions.

5. STABILITY AND STORAGE CONDITIONS

   It should be stored below 32 °C temperature in a dry and away from heat.

EUDRAGIT (POLYMETHACRYLATES)

1. **Nonproprietary Names**

   Ammonio methacrylate copolymer

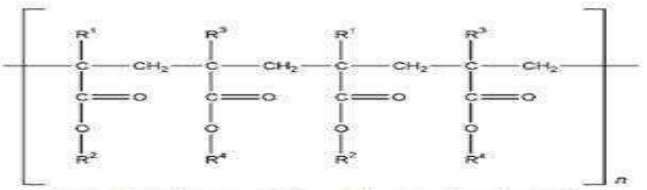
2. SYNONYMS

   Polymeric methacrylates

3. Molecular Weight

2,50,000 gm/mole

4. Structural Formula of Eudragit:



For *Eudragit RL* and *Eudragit RS:*
$R^1 = H, CH_3$
$R^2 = CH_3, C_2H_5$
$R^3 = CH_3$
$R^4 = CH_2CH_2N(CH_3)_3^+Cl^-$

5. **Applications:**

- ✓ They may form matrix layers of transdermal delivery systems
- ✓ It is used to prepare novel gel formulations.

6. **Solubility:** Acetone ,alcohols

7. **Stability and Storage Conditions**

The storage temperature should not exceed more than 30 ^{o}C and store in a tightly closed container

POLYVINYL ALCOHOL

1. Nonproprietary Name

Polyvinyl alcohol

2. Synonyms

Airvol, Alcotex.

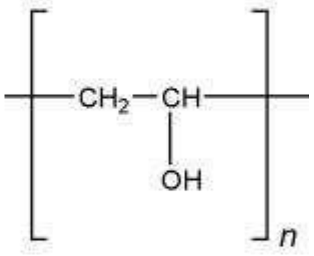
3. Chemical Name of PVA:

Ethanol homopolymer

4. Molecular Weight:

2, 00,000 gm/mole

5. Structural Formula of PVA:



6. Functional Category of PVA:

Stabilizing agent and viscosity-increasing agent.

7. APPLICATIONS IN PHARMACEUTICAL FORMULATION:

- ✓ As a stabilizer (0.25–3.0% w/v) and a viscosity modifier for viscous formulations.
- ✓ It may be used to prepare microspheres when mixed with a glutaraldehyde solution.

8. STABILITY AND STORAGE CONDITIONS

It is stable in compactly sealed packaging material in a cool and dry place.

CARBOMER

1. Nonproprietary Name:

Carbomers

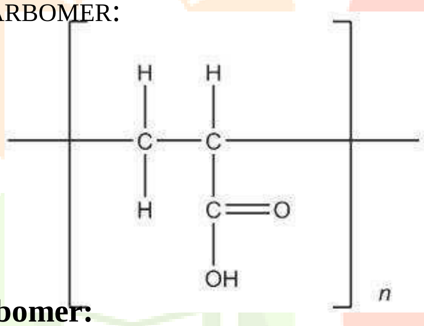
2. SYNONYMS:

Acrypol

3. MOLECULAR WEIGHT

Carbopol 940-104 400 g/mol

4. STRUCTURAL FORMULA OF CARBOMER:



5. Functional Category of Carbomer:

Bioadhesive materials, Emulsifying agent and Viscosity modifier;

6. APPLICATIONS OF CARBOMER:

- ✓ Viscosity modifiers in creams, gels, lotions and ointments.
- ✓ Controlling drug release

TABLE 1.10: USE OF CARBOPOL

Use	Concentration (%)
Emulgents	0.50
Gelling agent	0.50–2
Surfactant	0.50–1
SR agent	5–30

7. **Melting point**: 260°C.

10. STABILITY AND STORAGE CONDITIONS

It is stable and moisture sensitive substance which should not heat more than 104° C.

Propyl Paraben

1. Nonproprietary Name :

Propyl hydroxybenzoate

2.SYNONYMS:

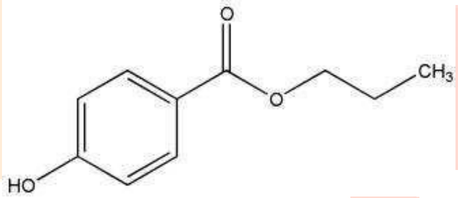
4-hydroxybenzoic acid propyl ester

3.Chemical Name: Propyl 4-hydroxybenzoate [94-13-3]

4. EMPIRICAL FORMULA WITH MOLECULAR WEIGHT OF PROPYL PARABEN:

$C_{10}H_{12}O_3$ and 180.20 gm/mole

5.STRUCTURAL FORMULA OF PROPYL PARABEN



6.Functional Category of Propyl Paraben

As Preservative.

7.APPLICATIONS IN PHARMACEUTICAL FORMULATION:

Propyl Paraben utmost often uses as preservatives.

TABLE 1.11: USE OF PROPYL PARABEN

Dosage form	Concentration (%)
Parenterals	0.005–0.20
Nasal Drops	0.0170
Ophthalmic	0.005–0.010
Topical	0.010–0.60

2. Typical Properties

Table 1.12: Solubility of Propyl paraben

Solvent	**Solubility in solvents**
Acetone	Freely soluble

Ethanol (95%)	Freely soluble
Ether	Very slightly soluble
PEG	Very slightly soluble
Water	Insoluble

2. RATIONAL, OBJECTIVES AND PLAN OF RESEARCH WORK

RATIONAL OF RESEARCH WORK

The Recent advancement of research is progressing at prodigious rates, which aims at idealizing DDS with maximizing efficacy of drug. The drug delivery technology landscape has turned out to be extremely modest and quickly embryonic which produces maximum effective and economical product. Preliminary studies and later Design of Experimentation (DoE) were carried out for high risk parameters using QbD approach based on the understanding of the effect of different process and formulation variables microsponges quality. Based on effect of CQAs of the target product profile, design space may be proposed to obtain robust formulation.

RATIONAL OF MICROSPONGES FOR TOPICAL DDS:

Many of marketed conventional dosage forms have quick drug absorption and more dosing frequency thorugh skin. Hence, necessity demands for delivery systems to enhance retention of drug either on skin surface or within the epidermis with reduction of transdermal penetration. The microsponge-based polymeric microspheres can be used frequently for topical which gives another possibility to advance drug products to provide a API effectively at least dose and to improve stability, diminish side effects and amend drug release. Conventional marketed gel proposed to act on outer layers of the skin which may release API on application and produce a very much concentrated layer which may be quickly absorbed. Hence the necessity subsists to exploit on quantity of period that drug which can present inside the epidermis, while lessening its transdermal penetration keen on the body.

Thus, it is essential to formulate Microspongic Topical gel to stream controlled release whose ultimate goal is the skin itself which may be employed to improve recital of topically applied drugs that may get the most out of thermodynamic action and decrease diffusion into stratum corneum.

RATIONAL OF OXAPROZIN LOADED MICROSPONGIC TOPICAL DDS:

Oxaprozin is a synthetic antifungal drug which is used to treat fungal infections for topical therapy. Oxaprozin oral DDS often produces gastric irritation, heartburn, vomiting and sometimes patients can develop ulceration and there is less patient compliance with long term therapy on high doses i.e. 100-200 mg/day for 2- 6 weeks. Topical therapy of OXAPROZIN can help to target infection site with modifying release rate and also minimizing systemic side effects, thus current investigation is to propose novel Microsponges as carriers for OXAPROZIN topical gel. Its accessibility and the opportunity it affords to maintain applied preparation intact for a prolonged time have resulted in its increasing use as a route of administration whether for local, regional or systemic effects. Hence, in the present investigation will be made to develop solid porous microsponge incorporated gels of Oxaprozin to overcome above mentioned problems of drug and enhanced its activity and thus it may increase the patient compliance.

2.1.4 OBJECTIVES OF RESEARCH WORK:

The prime objectives were to develop Microsponge loaded Topical drug delivery system that:

1. To localize drug into the systemic compartment devoid of being absorbed to avoid the systemic side effects.
2. To provide an increased residence time in epidermis by reducing transdermal penetration.
3. To control/ modify release of drug at a specific site and hence dose and dose frequency can be decreased thereby obtaining greater therapeutic efficacy.

PLAN OF RESEARCH WORK:

1. Literature survey and Patent Search related to Drug, Polymer, MDS Technology, Topical DDS and QbD.

2. Selection of Drug, Polymer and Methodology for the formulation & development of Microsponges and its subsequent topical delivery system

3. Preformulation study of Drug (Oxaprozin**)**

- ✓ Organoleptic characteristics of drug
- ✓ Melting Point.
- ✓ Solubility.
- ✓ Wavelength Maxima (λ_{max})
- ✓ Identification of drug by $\lambda_{max,}$ FT-IR and DSC study.
- ✓ Preparation of Calibration Curve of Drug
- ✓ Drug- polymer Compatibility study

4. Preparation of Drug loaded Microsponges.

5. Preliminary Trial Batches for selection of

- ✓ Effect of various Drug: polymer Concentration,
- ✓ Effect of Stabilizer type and concentration (%),
- ✓ Effect on Internal phase type and external phase type and concentration (mL),
- ✓ Effect of Speed (RPM) and Speed with Time (Min).

6. Risk assessment for Critical Quality Attribute to identify variables affecting drug product quality as per Preliminary trial batches to develop a Quality by Design Approach

7. Formulation of Drug loaded Microsponges Using Factorial Design approach

8. Characterization of Drug loaded microsponges

- ✓ Mean P.S.
- ✓ % Drug Content
- ✓ % Yield
- ✓ % Entrapment Efficiency
- ✓ % CDR
- ✓ Particle Morphology by SEM
- ✓ Porosity study
- ✓ Solvent Residual Analysis
- ✓ Kinetics of drug release

- ✓ Statical analysis
- ✓ Validation batches (Check Point Analysis) and its characterization of drug loaded microsponges in its subsequent topical drug delivery system

9. Preparation of Drug loaded Microspongic Topical Gel

10. Characterization of Drug loaded Microspongic Topical Gel

- ✓ Physical evaluation
- ✓ Measurement of pH
- ✓ Viscosity study
- ✓ Spreadability
- ✓ Homogeneity and grittiness
- ✓ Drug content
- ✓ *In vitro* diffusion studies
- ✓ Antifungal study of Cup Plate Method (Oxaprozin loaded microspongic topical gel)
- ✓ Primary skin irritancy studies
- ✓ Comparison with conventional topical gel
- ✓ Accelerated stability studies

LITERATURE REVIEW

LITERATURE REVIEW ON GEL:

Das et al (2013), had attempted study to prepare 4% lidocaine HCl topical gel and characterize for pH, viscosity, and in vitro skin permeation. The pH and viscosity of gels were found within the range of 5.98 to 6.06 and 4.58 × 106 to 4.88 × 106 cps respectively. The in vitro skin permeation was found flux of 851.34 ± 9.16 to 1568.15 ± 14.03g/cm2/hrs which was found best- fitted with Korsmeyer–Peppas model. No change was found in formulation after stability testing.

(Das et al., 2013)

Shelke et al (2013), had reviewed topical gel which is transparent or translucent semisolid formulation and used for localization in skin as topical drug delivery which facilitates a suitable delivery for drugs due to non-greasy and easy removal property. Comaped to ointment and gel, Topical Gel provides ease of application property and higher stability. Gel can be incorporated in NDDS to enhance its bioavailability and penetration. **(Shelke et al., 2013)**

Varun et al (2012), had prepared gels dosage forms which can control drug release and to defend drug from a unreceptive environment. Thus, it was preferred to formulate Oxaprozin into a gel using gelling agent like Carbopol 940-P, HPMC and Xanthan gum. Than they were characterized for drug content, pH, viscosity, in vitro diffusion and skin irritation. Competent delivery of drug to skin application was established to be highly beneficial in localizing the drug to desired site in the skin and reduced side effects associated with conventional treatment. **(Varun et al., 2012)**

Vinod et al (2012), had studied effect of polymer like Carbopol 934 and 940 on OXAPROZIN gel and its release which was developed for topical application. In present research, full factorial design had been designed to study the effect of type of Carbopol on OXAPROZIN gel formulation. OXAPROZIN topical gel formulation batches (F1 to F9) had been developed as per factorial design and further evaluated. Drug diffusion studies had shown time required for 90% of total drug release (t90%) from all formulations from 28.7 ± 2.3 to 208.4 ± 3.9 min. These results were in accordance with conception of inverse relationship between drug release and viscosity of formulation. It has been observed that drug release from all gel formulation batches obeyed korsmeyer-peppas model. (**Vinod et al., 2012)**

BakshAbrar et al (2012), had prepared Diclofenac sodium gel. using gel forming substances like Carbopol 934 and 940 and sodium carboxy methylcellulose (Na CMC) and evaluated for release characteristics through a standard cellophane membrane which was also compared with marketed gel formulations of Diclofenac sodium. *In-vitro* diffusion study Carbopol 934 and marketed gel were compared. The *in-vitro* diffusion study of Diclofenac sodium gel using Carbopol 940 gels was found better related to marketed gels. (**Bakshabrar et al., 2012)**

Niyaz et al (2011), had formulated gel and evaluated for % drug content, viscosity, in vitro diffusion study, antifungal activity and skin irritation study. The viscosity of the F1 formulation was within limits and F1 formulation did not confirm any skin irritation. Gel formulation F1 was found to be stable competent delivery of drug to skin application was found to be highly advantageous in localizing the drug to desired site in the skin and reduced side effects**. (Niyaz et al., 2011)**

Gaddam A. et al (2010), had prepared and evaluated gels incorporating Diclofenac SLN incorporated into carbopol gel for systemic delivery of the active after topical application. prepared Carbopol gel. Three different gel formulations (DSL1, DSL2 and DSL3) were formulated and evaluated for particle size, charge, viscosity, morphology, drug-lipid compatibility, *ex-vivo* permeation study and *in-vivo* absorption study. It was concluded that improvement in systemic delivery of Diclofenac sodium with gels incorporating SLN. (**Gaddam A et al., 2010)**

LITERATURE REVIEW ON MICROSPONGE DRUG DELIVERY:

Mandava et al (2012), had reviewed on microsponges technology which is a incomparable technology for precise release and having superior absorption in skin with reduction in skin diffusion of drug. Drug loaded microsponges may consist of microporous beads, typically 10-25 µm in diameter. MDS is non-irritating, non-allergenic and non-mutagenic which can increase effectiveness, better-quality safety, broad dosage stability, compacted side effects and better aesthetic properties as topical DDS. MDS technology is available as cosmetics, skin care OTC and sunscreen formulation at present available in market. **(Mandava et al., 2012)**

Ajay et al (2012), had compiled information's on MDS technology which has distinctive superiority for loading drug and tender a controlled release and economical produce. These features attract MDS technology sunscreens, anti-acne, anti-dandruff and skin depigmentation products to deliver an active agents in sophisticated advanced manner which is prooven useful as oral DDS, biopharmaceuticals and tissue engineering in recent times. (**Ajay et al., 2012)**

4. FORMULATION AND DEVELOPMENT OF OXAPROZIN LOADED MICROSPONGES FOR TOPICAL DELIVERY USING QUALITY BY DESIGN APPROACH

INTODUCTION

MDS is polymeric porous microspheres having small and sponge-like sphere-shaped particles which have a huge porous surface. **(**Newton D et al., 1991 and Kydonieus A et al., 1987) The incidence of Mycoses mainly superficial fungal infections is growing. Careful consideration has been paid to the triazole derivatives due to their broad spectrum antifungal activity and little toxicity. **(**Kovacs S et al., 1995 and Livermore B et al., 1996)

Oxaprozin is a antifungal drug which is used to treat fungal infections with probable disadvantage of itching in topical therapy which is capable to produce an elevated selective inhibition of the fungal cytochrome P450 system and also an inhibition of the C-14 α astral demodulation process. However, high doses (100-200 mg/day for 2- 6 weeks) may lead to potential side effects varying from headache, liver dysfunction and hepatic failure. With long term therapy of Oral administration of Oxaprozin often causes gastric irritation, heartburn, vomiting and in some patient can develop ulceration and having less patient compliance with long term therapy. (Bertram G., 1995 and Tripathi K et al., 2003)

Topical delivery like Lipogel, Microemulsion based Gel and Emulgel is desirable in order to minimize these adverse effects has been considered which in addition target infected site and also shrinks side effects, consequently the need generates to formulate and develop OXAPROZIN microsponges loaded topical gel which offers cosmetically acceptable product. (Bertram G., 1995 and Tripathi K et al., 2003)

MATERIALS AND METHODOLOGY

Materials and Equipments Required

The following materials, chemicals and instruments had used for Preparation and Characterization of Oxaprozin loaded Microsponges and its subsequent Topical Gel as per Table 4.1 and 4.2

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List of Materials

Table 4.1: List of Materials

MATERIALS	SOURCE
Oxaprozin	CAPTAB Pharma. Pvt. Ltd., Vadodara.
Ethyl cellulose	Astron Research Ltd., Ahmadabad.
Eudragit RS 100	Astron Research Ltd., Ahmadabad.
PVA	Astron Research Ltd., Ahmadabad.
Ethanol	Lobachemi Private Ltd., Mumbai.
Liquid Paraffin	Merck Specialties Pvt Ltd, Mumbai.
Petroleum Ether	Merck Specialties Pvt Ltd, Mumbai.
Carbopol 934 P	Ethicare Pharmaceutical Pvt. Ltd, Por.
Propylene Glycol	Astron Research Ltd. Ahmadabad.
Triethanolamine	Astron Research Ltd., Ahmadabad.

List of Equipments

Table 4.2: List of Instruments

EQUIPMENTS	MODEL AND SOURCE
UV – Visible Spectrometer	UV-1700, Shimadzu Corporation.
Mechanical Stirrer	Remi instrument division
Electronic Balance	Ohaus corporation NJ, USA
Humidity Cabinet	Analytical Technologies, Bangalore.
Scanning Electron Microscope	JEOL JSM-6380KVM Oxford Instruments, England
FT-IR Spectrophotometer	Shimadzu Corporation
Compound Microscope	Acculab
Dissolution Apparatus II, USP XXII	Macro scientific works private limited, Delhi.
Malvern	Malvern Instruments LTD.

Methodology

Preformulation of Drug (Nevine S et al., 2012, Saboji J et al., 2011 and Dash A et al., 2001)

The preformulation study is mostly generate data useful to develope stable dosage forms that can be mass-produced for manufacturer.

Organoleptic Characteristics of Oxaprozin

Physical examine was done to check Organoleptic Characteristics of Oxaprozin like color and odor.

Determination of Melting Point of Oxaprozin

Melting point of Oxaprozin had been evaluated by the capillary method.

Identification and Determination of Wavelength Max (λ_{max}) of Oxaprozin

Stock solution (1000µg/mL) of **Oxaprozin** in methanol was prepared. This solution was a diluted to obtain the 100µg / mL solution. 5 mL of solution of Oxaprozin was diluted to prepare 50µg/mL of Oxaprozin which was scanned between 200 - 400 nm against blank solution methanol.

Solubility study of Oxaprozin

Preformulation solubility analysis was done, which included to dissolve the drug with an excess quantity in glass vials containing 20mL suitable solvent system and supernatant solution was filtered using 0.45 µm pore size filter after 24 hrs at room temperature. The first 10 mL of the filtrate was discarded and last portion of the filtrate was suitably diluted with water and assayed spectroscopically at 260nm. The procedure was followed by using different solvents like water, acetone, ethanol, chloroform, ether and pH 6.8 Phosphate buffer.

Preparation of Calibration Curve for Oxaprozin

Sample Preparation of stock and standard solutions for Oxaprozin

Oxaprozin was weighed accurately 100 mg and dissolved in 100 mL of methanol to get a 1000µg / mL solution was used as a standard stock solution. From Standard Stock solution 10 mL was withdrawn and volume was made with methanol in order to get a standard stock solution containing 100µg/mL and was used to prepare further dilutions. From this Working standard solution, dilution with methanol was made to get 10, 20, 30, 40, 50 µg/mL and measured absorbance at 260 nm for Oxaprozin

Identification of Drug- Oxaprozin by FT-IR Spectroscopy

Potassium bromide IR disc was prepared using 1mg of Oxaprozin on Hydraulic Pellet press which was scanned of 4000-400 cm^{-1} re in FTIR and obtained IR Spectrum was compared with a reference spectrum of Oxaprozin.

Drug- Excipients Compatibility Studies by FT-IR

Potassium bromide IR disc was prepared using Oxaprozin, Ethyl cellulose, Eudragit RS100, PVA, Carbopol 934 and mixture on Hydraulic Pellet press was scanned 4000-400 cm^{-1} region in FTIR and obtained IR Spectrum was compared with a reference spectrum of Oxaprozin

Drug-Excipients Compatibility Studies by DSC

Thermal analysis of Drug Oxaprozin and polymers was studied employing differential scanning calorimetry which was done to ckeck compatability for Microsponges formulations

Formulation and Development of Oxaprozin Oxaprozin Microsponges by using QbD Approach

Method of Preparation of Oxaprozin Microsponges (Parikh B et al., 2010)

OXAPROZIN microsponges were prepared using Quasi- emulsion solvent diffusion methods. Two phases were prepared viz the inner phase and outer phase.The drug and polymer were dissolved in a Acetone. Later, inner phase was poured into outer phase which was containing PVA and Liquid paraffin as emulsifying agent and kept for 60 min with constant stirring. The obtained liquid had clarified to distinct the Microsponges and dried at 40 ° C in an oven.

Selection of Formulation and Process Variables of Preliminary Trial Batches of Oxaprozin Microsponges

Preliminary trials were undertaken to establish effect of various Drug: Polymer ratio, Surfactant Concentration, Stirring rate, stirring time, a type of internal phase, Internal phase volume, External phase volume and evaluated for % yield, Entrapment efficiency and size of particles for CQAs selection to develop QbD Approach as per Table 4.20.

Selection of Concentration of Retardant Material (Polymer) in Internal Phase The different ratio of drug: polymer (1:1, 1:2 and 1:3) were used to prepare microsponges to evaluate effect for their entrapped drug, loading efficiency and particle size.

Selection of Drug: Polymer Ratio

Blank microsponges were prepared using 20 mL internal phases (Acetone) and 50 mL of an external phase (Liquid Paraffin) with Polyvinyl alcohol with a ratio of Drug: polymer 7:1, 9:1, 11:1, 13:1 and 15:1 in the internal phase to check and select Drug: Polymer Concentration.

Selection of Internal Phase Type

For the selection of the internal and the external phases, various investigations were carried out using different internal phases viz. Acetone and Ethanol, with the constant external phases at 1500 RPM stirring speed. Various combinations of internal (Acetone and Ethanol) phase were investigated.

Selection of Internal Phase Volume

The varying volume of internal phase, i.e. Acetone was evaluated using 5mL, 10mL, 15mL and 20mL of the internal phase, with constant drug to polymer concentration at 9:1 in 50mL of Liquid paraffin as external phase, stirring speed of 1500 RPM with surfactant concentration of 0.75% w/v of the external phase to evaluate effect.

Selection of External Phase Volume

In order to evaluate the effect of external phase concentration i.e. Liquid paraffin, was evaluated using 40mL, 50mL and 60mL of the external phase. The formed particles were evaluated.

Selection of Surfactant Concentration

PVA as surfactant was used at diferent concentration ranging from 0.5 %, 0.75%, 1.0% and 1.25% w/v of the external phase and were observed for their physical characteristics to optimize and check the effect on microsponges.

Selection of Stirring Speed

The microsponge was formulated with varying speed of 1000, 1500, 2000 and 2500 RPM while all other variables continual and the formed microsponges were evaluated for free drug content and particle size to check stirring speed effect.

Selection of Stirring Time

The microsponges had produced at different time intervals i.e. 60 Min, 75 Min and 90 Min of stirring time while others are keeping all the other variables constant and the formed microsponges were evaluated.

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

Approach

Risk assesement has been done to select formulation and process variable which may affect product quality for CQAs by process characterization that define satisfactory changes in material and process parameters. Finally, This can result in quality assurance by Process Design Space to understand and develop control strategy. The critical quality attributes are categorized into high, medium and low risk parameters based on knowledge space. Usually high risk parameters are considered important for Design of Experiments as they are having more effect than others and need to be in accepting multivariate ranges. (Delasko J et al., 2005)

Formulation and Development of Oxaprozin Microsponges by DoE Using QbD Approach

A design space can signify formulation and process understanding viz. attributes which are related to drug substance, materials, equipment, IP and finished product quality. (Sandipan R et al., 2012) For this purpose, risk assessment had done based on the understanding process and formulation related parameters on microsponges quality. Preliminary studies and later Design of Experimentation (DoE) was carried out for high risk parameters. Based on effect of critical quality attributes of target product profile, we proposed design space for obtaining robust formulation. Characterization of microsponges was done for various parameters viz. Particle size analysis, shape, micromeritics properties, encapsulation efficiency, percentage yield, *in vitro* drug releases shape and surface topography (SEM).

Characterization of Oxaprozin Microsponges (Nokhodchi A et al., 2007, Maiti S et al., 2006, Costa P et al., 2009 and Lokhandwala H et al 2013)

Percentage Yield

It can be calculated by following formula.

$$\textbf{Percentage Yield} = \frac{\text{Weight of microspheres recovered}}{\text{Weight (drug + polymer)}} \textbf{X100}$$

Entrapment Efficiency

It can be calculated by following formula.

$$\textbf{Drug Encapsulation efficiency} = \frac{\textbf{Actual Drug Content}}{\textbf{Theoretical Drug Content}} \textbf{ X 100}$$

Drug Content:

Weight accurate amount of 25 mg of Microsponges and mix in 25 mL methanol with shaking filter this solution using whattman filter paper and withdraw 1 mL from this solution to volumetric flask with 10 ml dilution in volumetric flask.The quantitative determination of OXAPROZIN in microsponges had carried out using a linear model UV absorbance detector at 260 nm against blank (methanol).

Mean Particle Size Analysis:

Particle size analysis was done using Optical Microscope and Malvern Instrument.

Topography by SEM

Scanning electron microscopy (SEM) was used to illustrate ultra structure of prepared microsponges for morphology and surface topography.

Differential Scanning Calorimetry

Thermal analysis of Oxaprozin loaded microsponges formulations was studied employing differential scanning calorimetry to find out nature and probable interaction concerning drug and polymers used.

In Vitro Drug Release characterization of Microsponges

The dissolution test was performed using 900 mL of Phosphate buffer (pH 6.8) at the 37±.5 C and 150 RPM in USP-II apparatus dissolution apparatus. The samples were withdrawn at 1hr interval for 8 hrs with replacement of fresh medium and measured absorbance of the solution at λmax 260 nm using UV-Visible spectrophotometer to find out drug concentration.

Kinetics of Drug Release (Costa P et al., 2009 and Lokhandwala H et al., 2013)

The kinetic release study had performed to find drug release mechanism from dissolution parameter by using different various kinetic model equations.

Zero Order Release Kinetics

$$Qt = Q0 + K0t$$

Where,

Qt = amount of the drug dissolved in time t,

Q0 = initial amount of drug in the solution (most of the times, Q0 = 0) and K0 = zero order release constant expressed in units of concentration/time. **Plot:** Cumulative amount of drug remaining vs time.

First Order Kinetics

$$\text{Log } C = \text{Log } C0 - Kt / 2.303$$

Where,

C_0 = initial concentration of drug,

K = first order rate constant, and t = time.

Plot: log cumulative percentage of drug remaining vs. time.

Higuchi Model (Higuchi T., 1963)

$$Q = KH \times t^{1/2}$$

Where,

KH = Higuchi dissolution constant.

Plot: cumulative percentage drug release vs Square root of time.

Hixson-Crowell Model (Hixson A et al., 1931)

$$W_O^{1/3} - W_t^{1/3} = \kappa t$$

Where,

W_0 = initial amount of drug in the pharmaceutical dosage form, **Plot:** cube root of drug percentage remaining in matrix vs time. **4.2.2.2.5.8.5. Korsmeyer-PeppasModel (**Korsmer R et al., 1983)

$$Mt / M_\infty = k\ t^n$$

Where,

Mt / M∞ = fraction of drug released at time t, k = release rate constant and

n = release exponent.

Plot: log cumulative percentage drug release vs log time.

Table 4.3: Release Kinetic Mechanism

Release Exponent 'n'	**Drug Transport Mechanism**	**Rate as afunction of Time**
0.5	Higuchi Matrix	$t^{n-0.5}$
0.5<n<1.0	Non- Fickian Diffusion	t^{n-1}
1.0	Zero Order Release special Case–II Transport	Zero Order Release
Higher release (n>1)	Super Case–II Transport	t^{n-1}

Preparation and Characterization of Oxaprozin Microsponges loaded Topical gel

Method of Preparation Oxaprozin Microsponges loaded Topical Gel (Sanjay B et al., 2007)

The Carbopol 934-P was accurately weighed and liquefied in 100 mL of water for 2 hours soaking with 600 RPM agitation then penetration enhancer was added to the formulated gel which may prevent drying of gel. To this aqueous solution of Triethanolamine was added with

slow agitation with continuous stirring. The Oxaprozin Loaded Microsponges were added in the gel.

Preliminary Trial batches of Topical Gel

Preliminary trials were undertaken to develop Oxaprozin loaded Microsponges gel. The various concentrations of Carbopol 934 were taken as shown in Table no.4.64.

Characterization of Topical Gel: (Rohit S et al., 2009, Lalit K et al., 2010, Sung-su K et al., 2007, Bhalaria M et al., 2009 and Wester R., 1980)

Physical evaluation:

It was done to evaluate Organoleptic property, Occlusiveness and wash ability of gel.

Measurement of pH of gel:

The pH had checked by a digital pH meter of formulated gel.

Viscosity study of gel:

50 gm of prepared gel was kept in 50 mL suitable beaker and spindle Groove was dipped at specific RPM in Brookfield Viscometer. This was done three times and recorded observation were considered as mean of viscosity.

Spreadability of gel:

An accurately weighed quantity of 1 g of gel was pushed among two slides and left as such for about 5 minutes. Diameters of speed circles were measured in cm and were taken as comparative values for spreadability when no further spreading. The readings attained are mean of three determinations.

Homogeneity and grittiness

The consistency of prepaed gel was determined by pressing between the thumb and the index finger. Minor quantity gel is wiped on skin of back of hand to check the homogeneity and grittiness.

Drug content:

1 gm of each gel formulation had dissolved in 20 mL of alcohol in volumetric flask with 30 min stirring. Fnally, it was diluted and filtered. Further dilution was made up to 10 mL alcohol and again 1 mL was withdrawn from above and diluted to 10 mL alcohol. The absorbance had measured at 260 nm in uv.

In vitro diffusion studies

Weighed 1 gm of gel was transferred in 20 mL alcohol in 250 mL volumetric flask with stirring for 30 mins. The volume was made up to 100 mL and filtered. 1 mL of above solution was diluted to 10 mL with alcohol and further 1 mL of the above solution was diluted to 10 mL with alcohol. The absorbance of the solution was measured spectrophotometrically at 260 nm.

Kinetics of Drug Release

As per Chapter-4.2.2.2.5.8.

Anti fungal activity of Microspongic Gel

In conical flask, Sabouraud's dextrose agar dissolved in 100 ml water and pH adjusted to 5.6. The medium had been kept aside at R.T. after sterilization completed. Then Culture (*Candida albicans*) suspension (0.5 mL) in 0.9% w/v NaCl was introduced to above of medium. This 20 mL medium (20 mL) was decanted into a sterilized Petri dish by obtaining uniform in thickness. After 0.1 mL solidifying sample solutions was fed into the cup by sterile pipette This petri dish had placed for incubation at 37 ºC for 24 hours and zone of inhibition was found out.

Accelerated stability studies of Microspongic Gel

The drug or dosage form quality may affect under impact of by varying temperature, humidity and light with time which can be found out by stability testing. It can be carried out at 25°C ± 2°C/ 60% RH ± 5% RH and 40°C ± 2°C/ 75% RH ± 5% RH for the selected formulation for three months. Samples were withdrawn on 0th, 30th, 60th and 90th day and were analyzed for physical appearance and drug content.

Table 4.4: ICH Specification for Stability Study

STUDY TYPE WITH DURATION	STORAGE CONDITION
Long Period (12 Months**)**	25°C ± 2°C/ 60% RH ± 5% RH and 30°C ± 2°C/ 65% RH ± 5% RH
Intermediate Period (12 Months**)**	30°C ± 2°C/ 65% RH ± 5% RH
Accelerated Period (12 Months)	40°C ± 2°C/ 75% RH ± 5% RH

RESUTS AND DISSCUSSION

Preformulation Study for Oxaprozin

Oxaprozin is a synthetic triazole antifungal drug. It is a completely synthetic compound. It is BCS class-2 drug. The pure drug Oxaprozin and various other excipients such as Eudragit RS 100, Ethyl cellulose, PVA, Carbopol 934, etc. were subjected to various Preformulation parameters such as Organoleptic characteristic study, Melting Point Determination, solubility study Wavelength$_{max}$ (λ_{max}) Determination, Calibration curve, Identification of Drug by Oxaprozin, DSC study and FT-IR study. This includes the various Preformulation studies for the present research work and the result discusses below every parameter.

Organoleptic Characteristics of Oxaprozin

Table 4.7:Organoleptic Characteristics

PARAMETER	OBSERVED RESULT
Color	White powder
Odor	Odorless or with a faint characteristic odor
Appearance	White crystalline powder

The color of the Oxaprozin was visualized white with odorless or with a faint characteristic odor having a white crystalline powder appearance as shown in table 4.7.

Determination of Melting Point of Oxaprozin

The melting point results is shown in table 4.8.

Table 4.8: Melting point of Oxaprozin

Drug Name	Standard Value	Observed Value (Mean ± S.D.) (n = 3)
Oxaprozin	140℃	139 ± 1.38℃

Identification and Determination of Wavelength $_{Max}$ (λ_{max}) of Oxaprozin

Stock solution (1000µg/mL) of Oxaprozin in methanol was prepared. This solution was a diluted to obtain 100µg/mL solution. 5 mL of solution of Oxaprozin and volume was diluted to prepare 50µg/mL of Oxaprozin. This solution was scanned 200 - 400 nm against methanol.

The U.V spectrum of Oxaprozin was shown in figure 4.1. The resultant solution was scanned in the range of 200 to 400nm. The maximum absorbance was occurring at the 260 nm which

indicate the $\lambda_{max}$of Oxaprozin as shown in Table 4.9, which is partially similar to Oxaprozin λ_{max}as per I.P (260 nm).

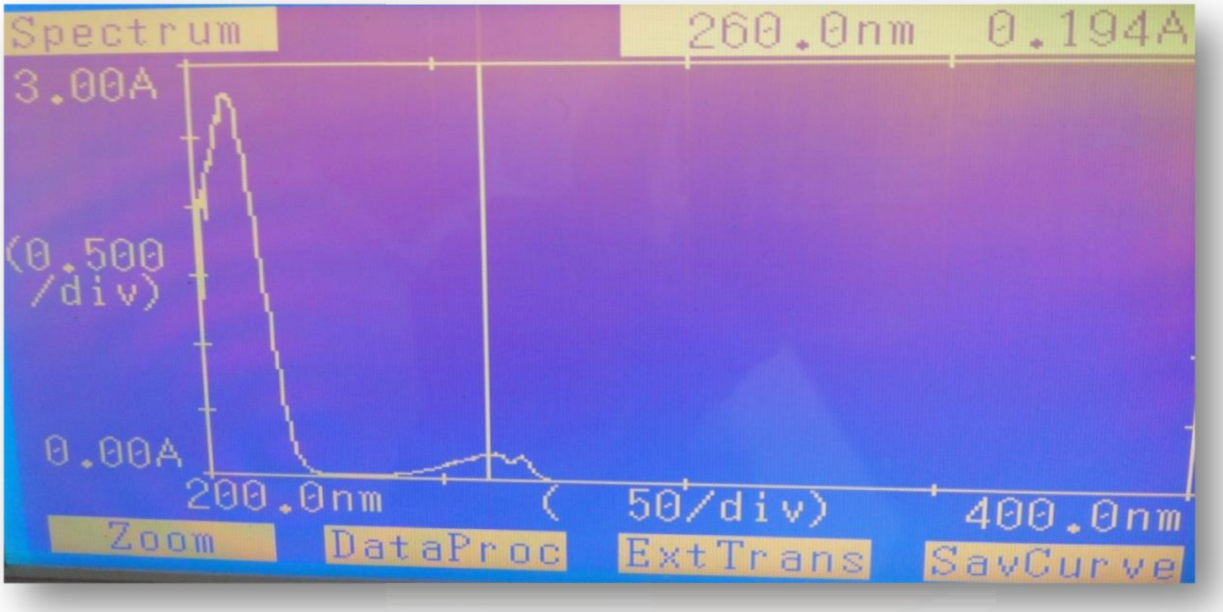


Figure 4.1: λmax Spectrum for Oxaprozin

Table 4.9: Wavelength$_{max}$ (λ$_{max}$) of Oxaprozin

Drug Name	Actual λ max	Observed λ max
Oxaprozin	260nm	261nm

Solubility study of Oxaprozin

Table 4.10: Solubility of Oxaprozin

Solvent	Solubility
Water	Very Slightly soluble
Acetone	Freely Soluble
Methanol	Freely Soluble
Ethanol (95 %)	Freely Soluble
Chloroform	Slightly Soluble
MeOH (15%) + Phosphate buffer pH 7	Freely Soluble
0.1N HCl	Slightly soluble

Preparation of Calibration Curve for Oxaprozin

Table 4.11: Calibration curve of Oxaprozin

Sl. No.	Concentration (mcg/mL)	Absorbance(nm) (Mean ± S.D.) (n = 3)
1	0	0
2	10	0.142±0.48
3	20	0.355±0.82
4	30	0.519±0.55
5	40	0.646±0.73
6	50	0.792±0.69

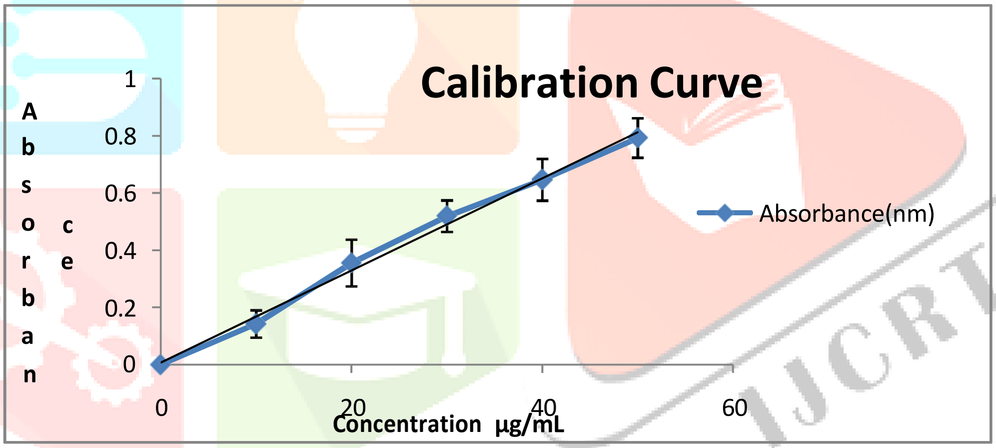


Figure 4.2: Oxaprozin Calibration curve

Table 4.12: Summery Report of calibration curve for Oxaprozin

Sl. No.	Parameters	Oxaprozin
1	**Wavelength (λmax)**	260
2	**Beer's limit (µg/mL)**	0-50
3	**Corrélation coefficient (R^2)**	0.994
4	**Slope**	0.016

The calibration curve for Oxaprozin was obtained by using the 0-50 µg/mL solution of Oxaprozin in methanol. The absorbance was measured at 260 nm. The calibration curve for Oxaprozin was shown in figure 4.2. The absorbance obtained for the given concentrations was shown in table 4.11. The calibration curve (Table 4.12) shows a regression equation Y= 0.0163x and R^2value 0.9940. The result revealed that the drug concentration between 0 – 50 µg/ml follows Beer Lambert’s law as the regression coefficient was 0.9940.

Identification of Drug- Oxaprozin by FT-IR Spectroscopy

Potassium bromide IR disc was prepared using 1mg of Oxaprozin on Hydraulic Pellet press and scanned in region of 4000-400 cm^{-1} and obtained IR Spectrum was compared with a reference spectrum of Oxaprozin.

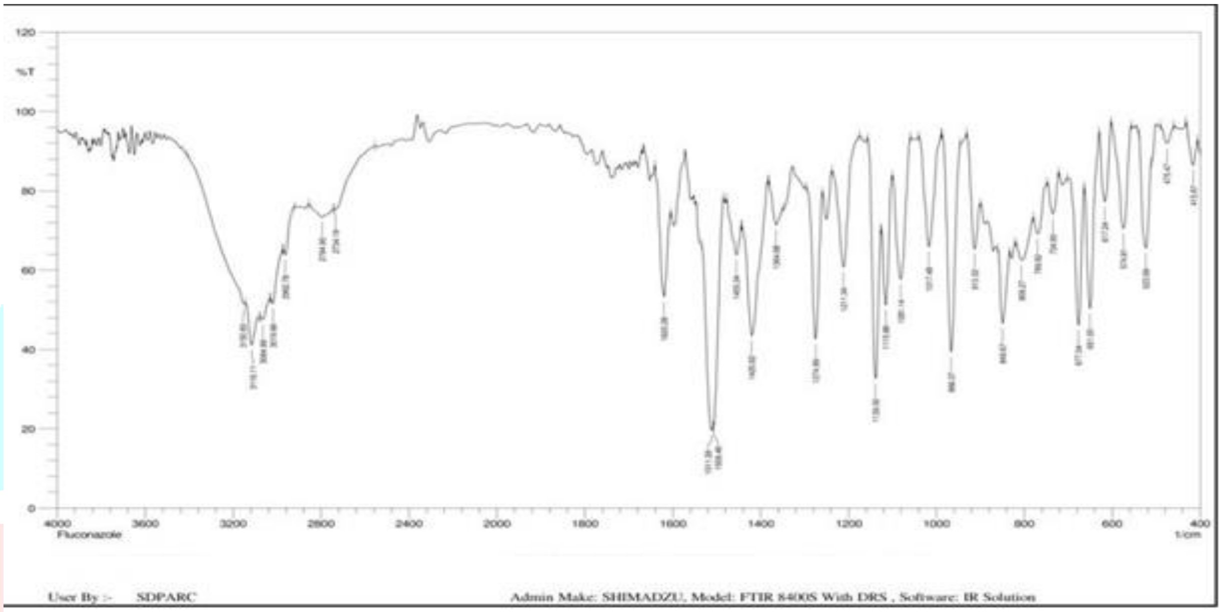


Figure 4.3:Identification of Oxaprozin by IR Spectrum Table 4.13: Identification IR

Oxaprozin

Type of Vibration	Standard Wave number (cm^{-1})	Observed Wave number (cm^{-1})
C=N Stretching	1600-1700	1620.26
C-F Stretching	1000-1400	1139.00
C-H Stretching	3000-3100	3116.11

Drug- Excipients Compatibility Studies by FT-IR

Drug- Oxaprozin IR Spectrum:

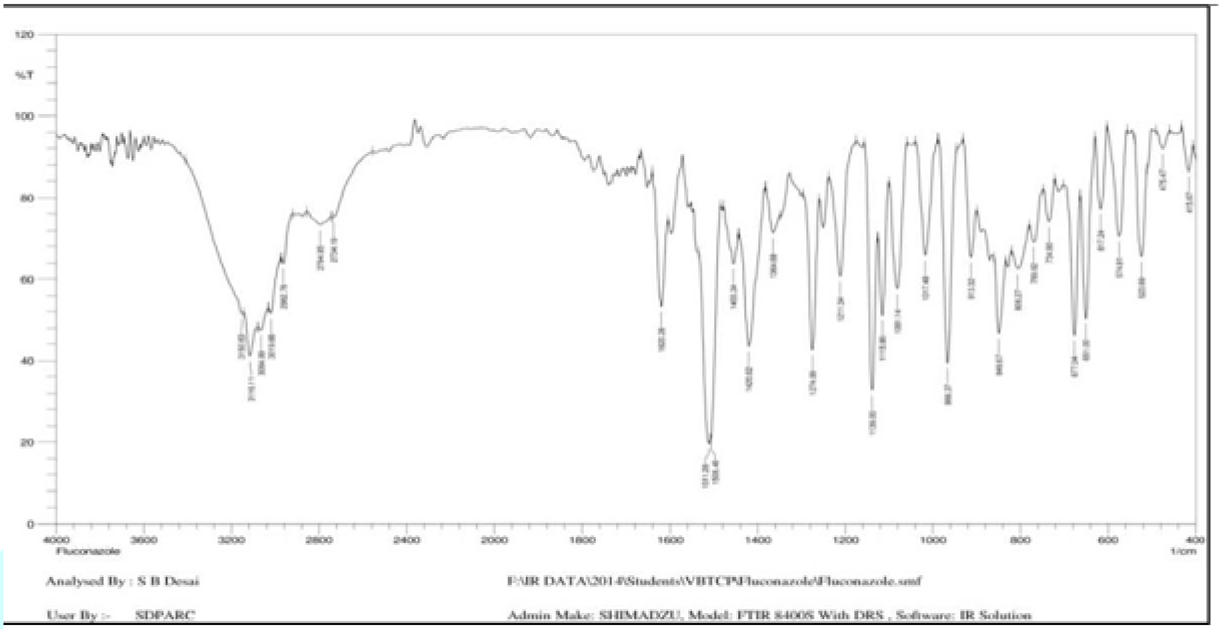


Figure 4.4: sample Drug Oxaprozin IR Spectrum

Table 4.14: Oxaprozin observed IR peaks

Type of Vibration	Standard Wave number (cm^{-1})	Observed Wave number (cm^{-1})
C=N Stretching	1600-1700	1620.26
C-F Stretching	1000-1400	1139.00
C-H Stretching	3000-3100	3116.11

Oxaprozin + Eudragit RS 100 IR Spectrum

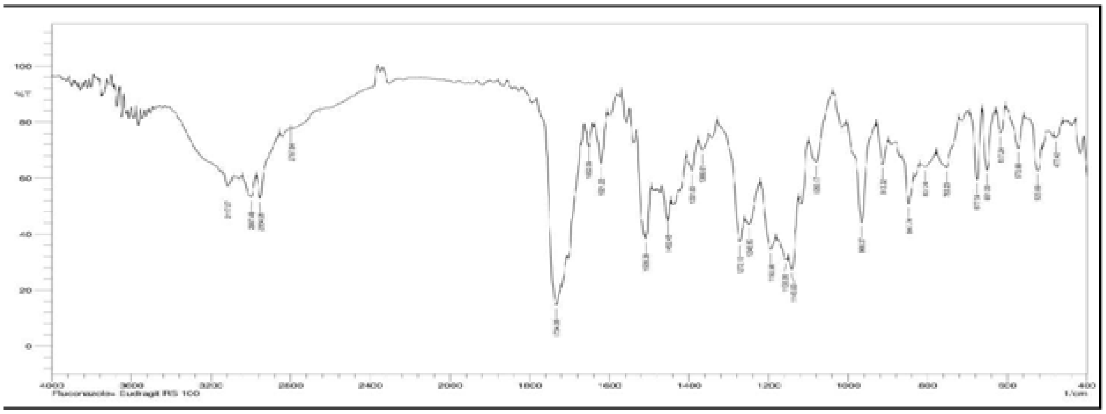


Figure 4.5: Oxaprozin and Eudragit RS 100 IR Spectrum

Table 4.15: FT-IR peaks of Oxaprozin and Eudragit RS 100 (mixture)

Type of Vibration	Observed Wave number (cm^{-1})	Peak obtained in mixture (cm^{-1})
C=N Stretching	1600-1700	1621.22
C-F Stretching	1000-1400	1140.93
C-H Stretching	3000-3100	3117.07
C=O Stretching	1690-1760	1734

Oxaprozin + Ethyl Cellulose IR Spectrum

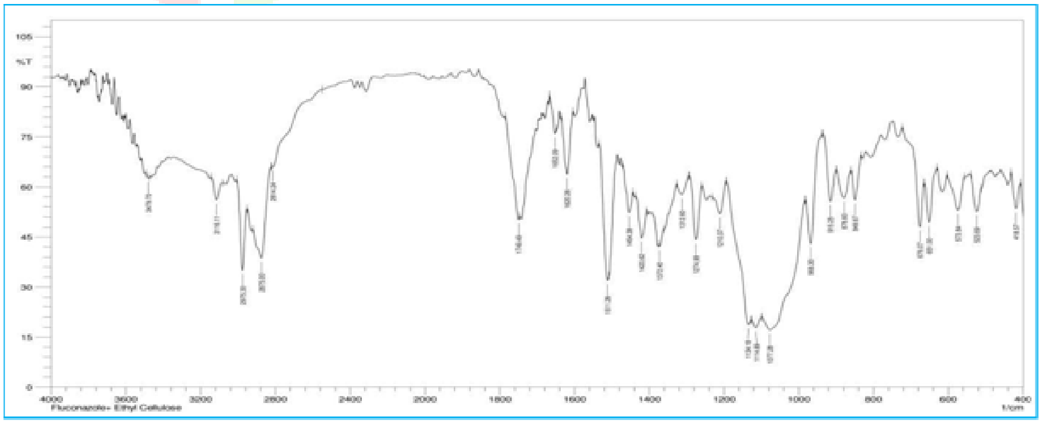
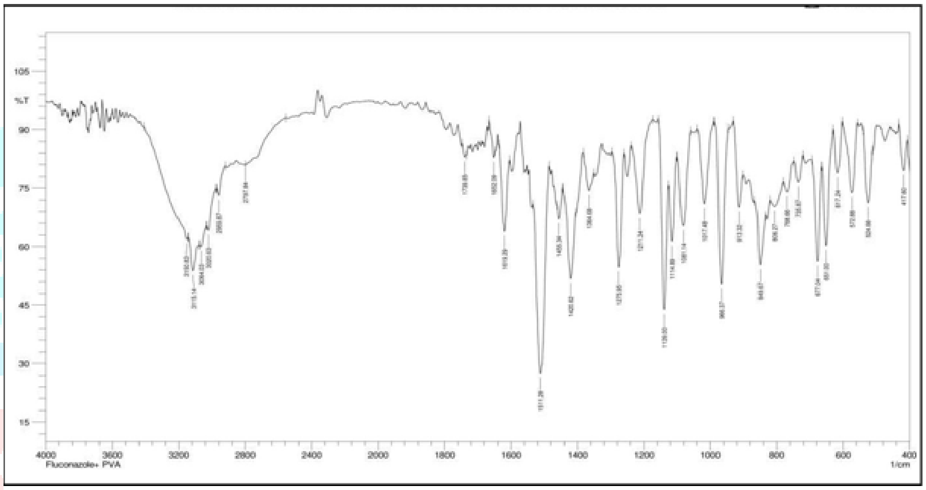


Figure 4.6: FT-IR Spectrum of Oxaprozin +Ethyl cellulose

Table 4.16: FT-IR peaks of Oxaprozin +Ethyl cellulose

Type of Vibration	Observed Wave number (cm^{-1})	Peak obtained in mixture (cm^{-1})
C=N Stretching	1600-1700	1620.26
C-F Stretching	1000-1400	1114.89
C-H Stretching	3000-3100	3116.11
C=O Stretching	1690-1760	1749.49

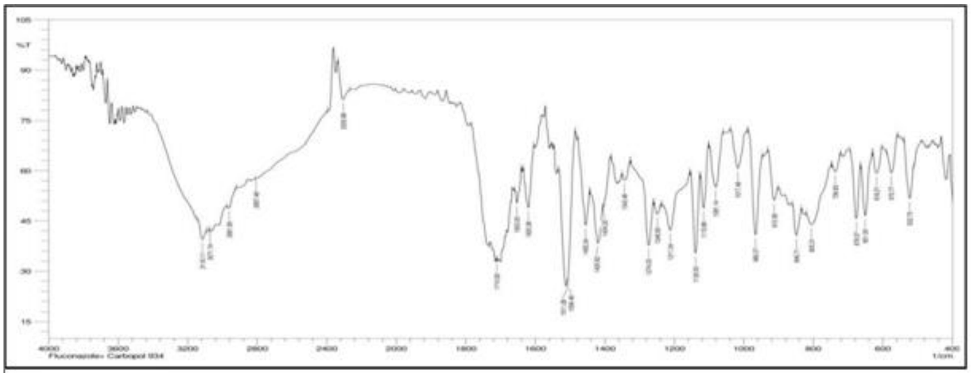


Oxaprozin + PVA IR Spectrum

Figure 4.7: FT-IR Spectrum of Oxaprozin +PVA

Table 4.17: FT-IR peaks of Oxaprozin +PVA

Type of Vibration	Observed Wave number (cm^{-1})	Peak obtained in mixture(cm^{-1})
C=N Stretching	1600-1700	1619.29
C-F Stretching	1000-1400	1139.00
C-H Stretching	3000-3100	3115.14
C=O Stretching	1690-1760	1739.85



Oxaprozin + Carbopol 934 IR Spectrum

Figure 4.8: FT-IR Spectrum Oxaprozin +Carbopol 934

Table 4.18: FT-IR peaks of Oxaprozin +Carbopol 934

Type of Vibration	Observed Wave number (cm^{-1})	Peak obtained in mixture(cm^{-1})
C=N Stretching	1600-1700	1620.26
C-F Stretching	1000-1400	1139.00
C-H Stretching	3000-3100	3116.11
C=O Stretching	1690-1760	1710.92

Formulation (Oxaprozin + Eudragit RS 100 + Ethyl Cellulose + PVA + Carbopol 934) IR Spectrum

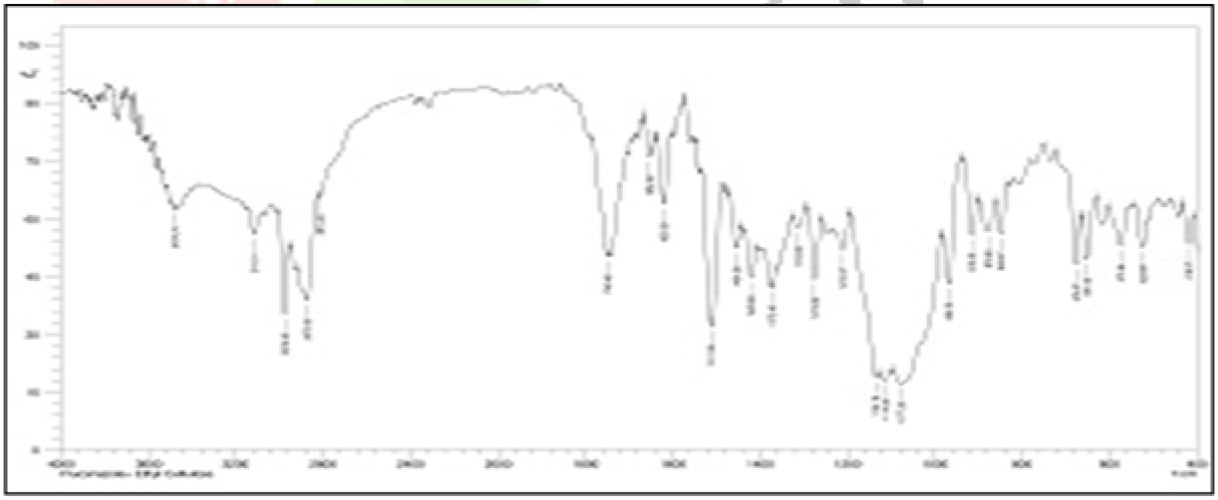


Figure 4.9: FT-IR Spectrum Formulation

Table 4.19: FT-IR peaks of Formulation

Type of Vibration	Observed Wave number(cm^{-1})	Peak obtained in mixture (cm^{-1})
C=N Stretching	1600-1700	1630.86
C-F Stretching	1000-1400	1178.39
C-H Stretching	3000-3100	3106.83
C=O Stretching	1690-1760	1736.09

The IR spectrum of standard drug Oxaprozin and Eudragit RS 100, Ethyl cellulose, PVA and Carbopol 934P shows same peak, functional group at the difference frequency shown in figure – 4.9 and table 4.14.- 4.19. The results revealed no changes seen in the IR peaks of Oxaprozin, when mixed with polymers. These observations indicate the compatibility of polymers with Oxaprozin.

Drug-Excipients Compatibility Studies by DSC

DSC graph of Oxaprozin

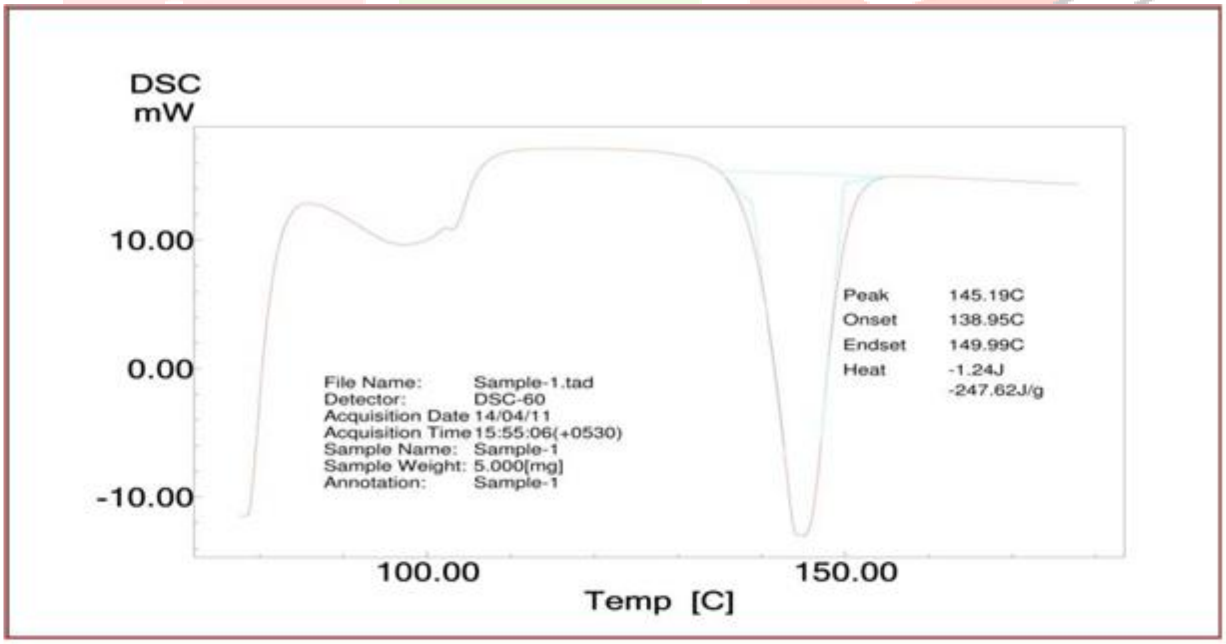


Figure 4.10: DSC graph of Oxaprozin

DSC graph of Oxaprozin and Eudragit RS 100

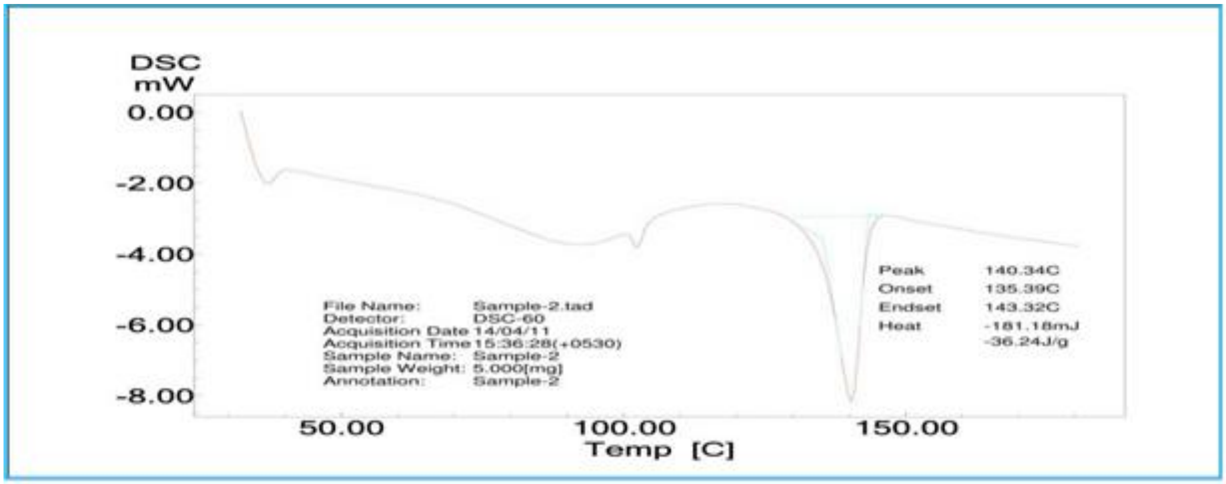


Figure 4.11: DSC graph of Oxaprozin and Eudragit RS 100

DSC graph of Oxaprozin and Ethyl Cellulose

Figure 4.12: DSC graph of Oxaprozin and Ethyl Cellulose

The compatibility study of drug, exicipients and the formulation was obtained and found no interaction using DSC study. The thermogram of pure Drug (Fig.4.10) exhibits a sharp melting endotherm at 145.19 ^{o}C, DSC thermogram of Oxaprozin and Eudragit RS 100 (Fig. 4.12) shows melting endotherm peaks at 140.34 ^{o}C, DSC thermogram of Oxaprozin and Ethyl Cellulose (C) shows melting endotherm peak at 138.13 ^{o}C, which was indicating that there was no modification in thermal features of Drug and Polymer.

Selection of Formulation and Process Variables of Preliminary Trial Batches of Oxaprozin Microsponges

Table 4.20: Formulation Design of Trial batches for Oxaprozin Microsponges

Batch	Drug: Polymer Ratio	Type of Internal phase	Volume of Internal Phase (mL)	Volume of Liquid Paraffin (mL)	Surfactant Conc. (%)	Stirring Speed (R.P.M.)	Stirring Time (Mins)
PRELIMINARY SELECTION OF CONCENTRATION OF RETARDENT MATERIALS							
TFM1	**1:1**	Ethanol	10	50	0.75	1500	60
TFM2	**1:2**	Ethanol	10	50	0.75	1500	60
TFM3	**1:3**	Ethanol	10	50	0.75	1500	60
PRELIMINARY SELECTION OF DRUG:POLYMER RATIO							
TFM4	**7:1**	Ethanol	10	50	0.75	1500	60
TFM5	**9:1**	Ethanol	10	50	0.75	1500	60
TFM6	**11:1**	Ethanol	10	50	0.75	1500	60
TFM7	**13:1**	Ethanol	10	50	0.75	1500	60
TFM8	**15:1**	Ethanol	10	50	0.75	1500	60
PRELIMINARY SELECTION OF INTERNAL PHASE							
TFM9	11:1	**Acetone**	10	50	0.75	1500	60
TFM10	11:1	**Ethanol**	10	50	0.75	1500	60
PRELIMINARY SELECTION OF INTERNAL PHASE VOLUME							
TFM11	11:1	Ethanol	**5**	50	0.75	1500	60
TFM12	11:1	Ethanol	**10**	50	0.75	1500	60
TFM13	11:1	Ethanol	**15**	50	0.75	1500	60
TFM14	11:1	Ethanol	**20**	50	0.75	1500	60
PRELIMINARY SELECTION OF EXTERNAL PHASE VOLUME							
TFM15	11:1	Ethanol	10	**40**	0.75	1500	60
TFM16	11:1	Ethanol	10	**50**	0.75	1500	60
TFM17	11:1	Ethanol	10	**60**	0.75	1500	60
PRELIMINARY SELECTION OF SURFACTANT CONCENTRATION							
TFM18	11:1	Ethanol	10	50	**0.5**	1500	60
TFM19	11:1	Ethanol	10	50	**0.75**	1500	60
TFM2	11:1	Ethanol	10	50	**1**	1500	60

0							
TFM21	11:1	Ethanol	10	50	**1.25**	1500	60
PRELIMINARY SELECTION OF STIRRING SPEED							
TFM22	11:1	Ethanol	10	50	0.75	**1000**	60
TFM23	11:1	Ethanol	10	50	0.75	**1500**	60
TFM24	11:1	Ethanol	10	50	0.75	**2000**	60
TFM25	11:1	Ethanol	10	50	0.75	**2500**	60
PRELIMINARY SELECTION OF STIRRING TIME							
TFM26	11:1	Ethanol	10	50	0.75	2000	**60**
TFM27	11:1	Ethanol	10	50	0.75	2000	**75**
TFM28	11:1	Ethanol	10	50	0.75	2000	**90**

Selection of Concentration of Retardant Material (Polymer) in Internal Phase

Table 4.21: Effect of Concentration of Retardant Materials on Batches TFM1 – TFM3

Batch	Yield (%) (Mean ± S.D.) (n = 3)	Loading Efficiency (%) (Mean ± S.D.) (n = 3)	Average Particle Size(µm) (Mean ± S.D.) (n = 3)
TFM1	**62.01±2.28**	**86.44±1.73**	**47.38±3.46**
TFM2	66.31±1.33	91.16±1.19	62.43±2.33
TFM3	71.84±1.89	97.55±2.45	93.37±6.32

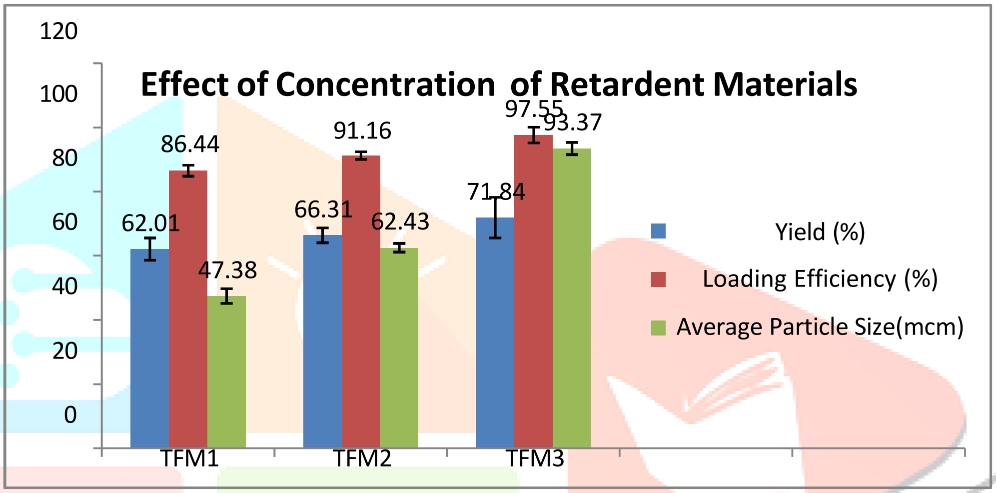


Figure 4.13: Effect of Concentration of Retardant Materials on Batches TFM1 – TFM3

Retardant Material concentration i.e. 1:1 was to be required in internal phase because at this concentration, the microsponges showed good physical characteristic like proper shape, size, porosity, particle size distribution and did not collapse even after removal from the solvent and subsequent drying.

Selection of Drug: Polymer Ratio

The drug to polymer ratio was having some effect on the particle size observed by results obtained which are presented in Table No. 4.22. As increasing Drug: Polymer ratio till 15:1 ratio,

% E.E was gradually increased, but no further increase. Hence, the preparation of microsponges was stopped at the ratio 15: 1 and 11:1 and 13:1 have been taken into consideration for further study.

Table 4.22: Effect of Drug: Polymer Ratio on Batches TFM4 - TFM8

Batch	Yield (%) (Mean ± S.D.) (n = 3)	Loading Efficiency (%) (Mean ± S.D.) (n = 3)	Average Particle Size(µm) (Mean ± S.D.) (n = 3)
TFM4	63.08±3.46	85.71±1.73	89.38±2.28
TFM5	67.31±2.33	96.56±1.19	61.43±1.33
TFM6	**68.54±6.32**	**93.83±2.45**	**50.17±1.89**
TFM7	**72.32±1.46**	**95.77±1.73**	**46.23±2.28**
TFM8	0	0	0

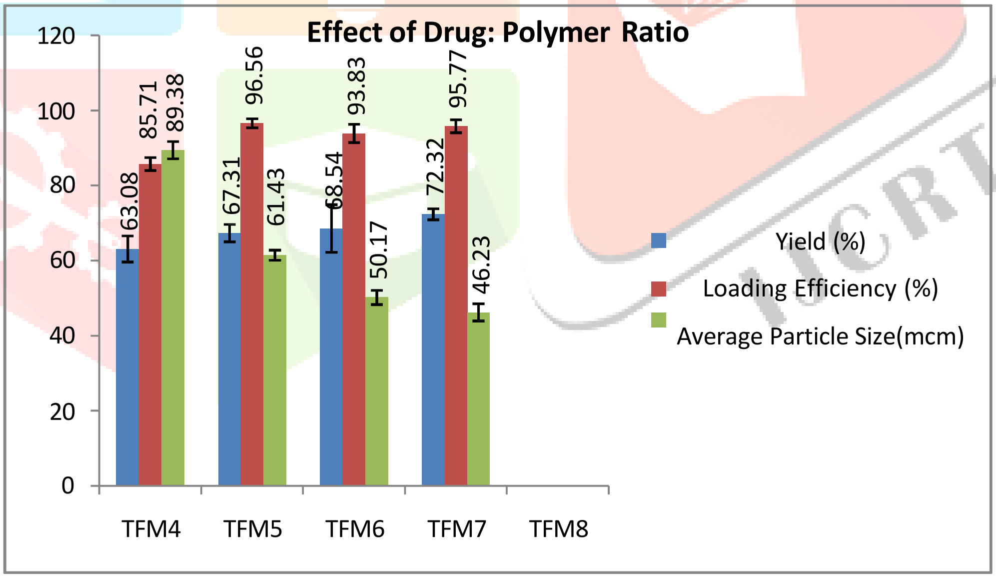


Figure 4.14: Effect of Drug: Polymer Ratio on Batches TFM4 - TFM8

Selection of Internal Phase Type

Table 4.23: Effect of Internal Phase on Batches TFM9 – TFM10

Batch	Yield (%) (Mean ± S.D.) (n = 3)	Loading Efficiency (%) (Mean ± S.D.) (n = 3)	Average Particle Size(µm) (Mean ± S.D.) (n = 3)

TFM9	**66.82±2.46**	**87.16±2.73**	**49.12±2.28**
TFM10	59.51±3.33	78.37±1.19	74.63±1.33

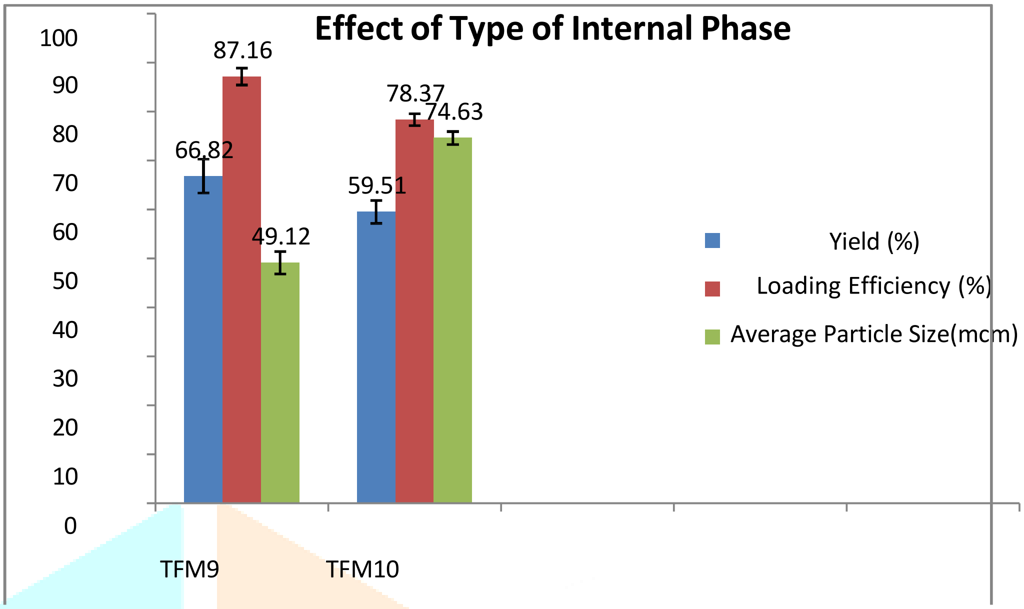


Figure 4.15: Effect of Internal Phase on Batches TFM9 – TFM10

Acetone was selected as the internal phase as it showed the highest drug entrapment of about 87.16%. The rate of diffusion of this solvent mixture was high when compared to other solvent, thus decreasing the time required for preparation. The drug was found to be freely soluble in acetone providing better entrapment of the drug and imparting good microsponges characteristics.

Selection of Internal Phase Volume

It was observed that particle size increases by decreasing the solvent volume. When acetone volume increased from 5.0 to 20.0mL, % E.E. and drug content decreased as presented in Table No.18. It might be probably because of lowering amount of drug in the high volume of acetone.

Table 4.24: Effect of Internal Phase Volume Batches TFM11 – TFM14

Batch	Yield (%) (Mean ± S.D.) (n = 3)	Loading Efficiency (%) (Mean ± S.D.) (n = 3)	Average Particle Size(µm) (Mean ± S.D.) (n = 3)
TFM11	57±1.73	91.2±2.28	59.48±3.46
TFM12	**61.26±1.19**	**89.69±1.33**	**26.14±2.33**
TFM13	**64.78±2.45**	**91.41±1.89**	**17.27±6.32**
TFM14	52±1.19	84.2±1.33	55.23±2.33

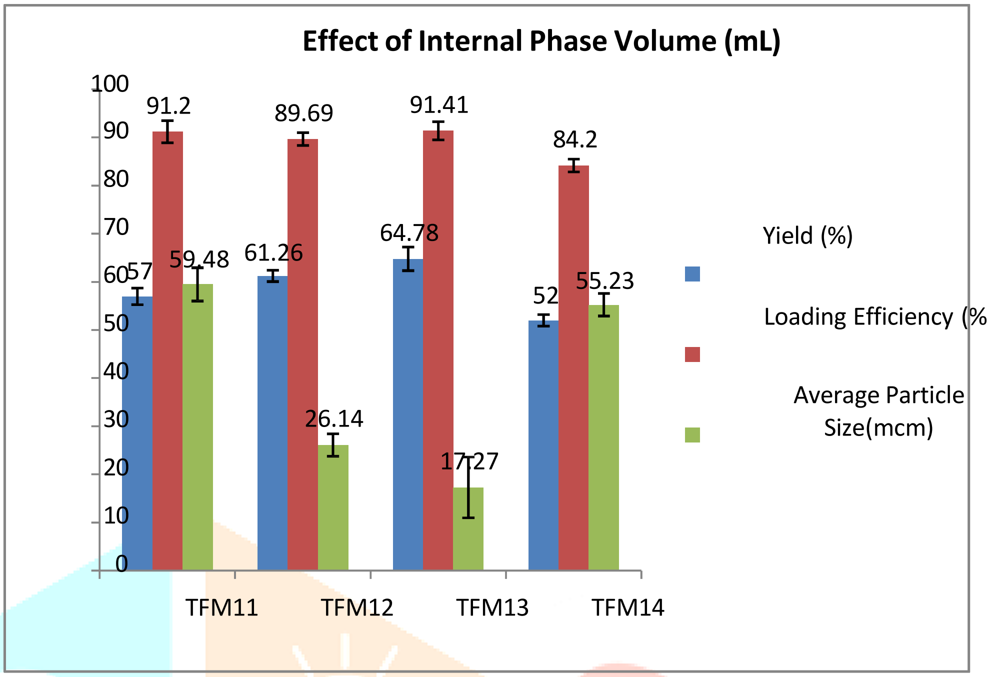


Figure 4.16: Effect of Internal Phase Volume Batches TFM11 – TFM14

Selection of External Phase Volume

The volume of external phase was having crucial effect in the formation of microsponges with reduction in free drug concentration and particle size. The results show that particle size ranged from 17.27µm to 59.48µm. It was found that 50 mL was the optimum volume necessary.

Table 4.25: Effect of External Phase Volume on Batches TFM15 - TFM16

Batch	Yield (%) (Mean ± S.D.) (n = 3)	Loading Efficiency (%) (Mean ± S.D.) (n = 3)	Average Particle Size(µm) (Mean ± S.D.) (n = 3)
TFM15	58.26±1.33	86.41±1.19	29.12±2.33
TFM16	**62.22±2.28**	**88.58±1.73**	**19.53±3.46**
TFM17	49.37±1.89	81.39±2.45	58.23±6.32

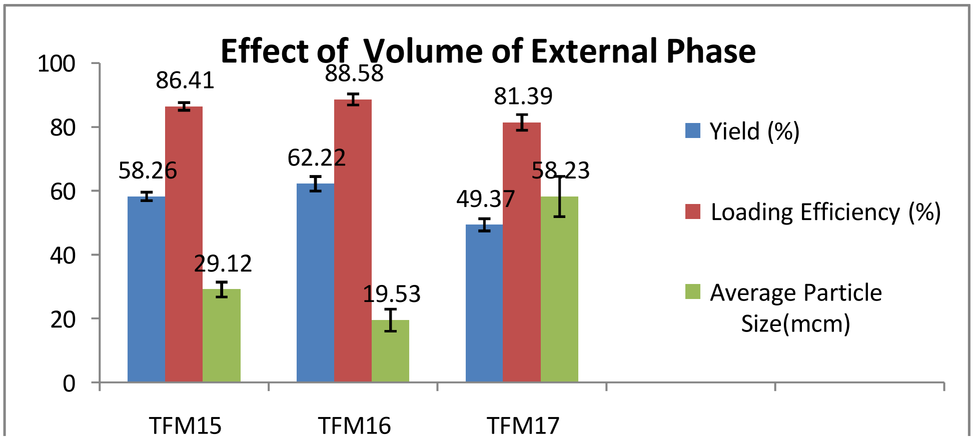


Figure 4.17: Effect of External Phase Volume on Batches TFM15 - TFM16

Selection of Surfactant Concentration

Table 4.26: Effect of Surfactant Concentration on Batches TFM18 – TFM21

Batch	Yield (%) (Mean ± S.D.) (n = 3)	Loading Efficiency (%) (Mean ± S.D.) (n = 3)	Average Particle Size(µm) (Mean ± S.D.) (n = 3)
TFM18	53.27±1.89	79.58±2.45	57.18±6.32
TFM19	**66.23±2.28**	**92.12±1.73**	**51.28±3.46**
TFM20	**67.23±1.33**	**88.34±1.19**	**55.43±2.33**
TFM21	0	0	0

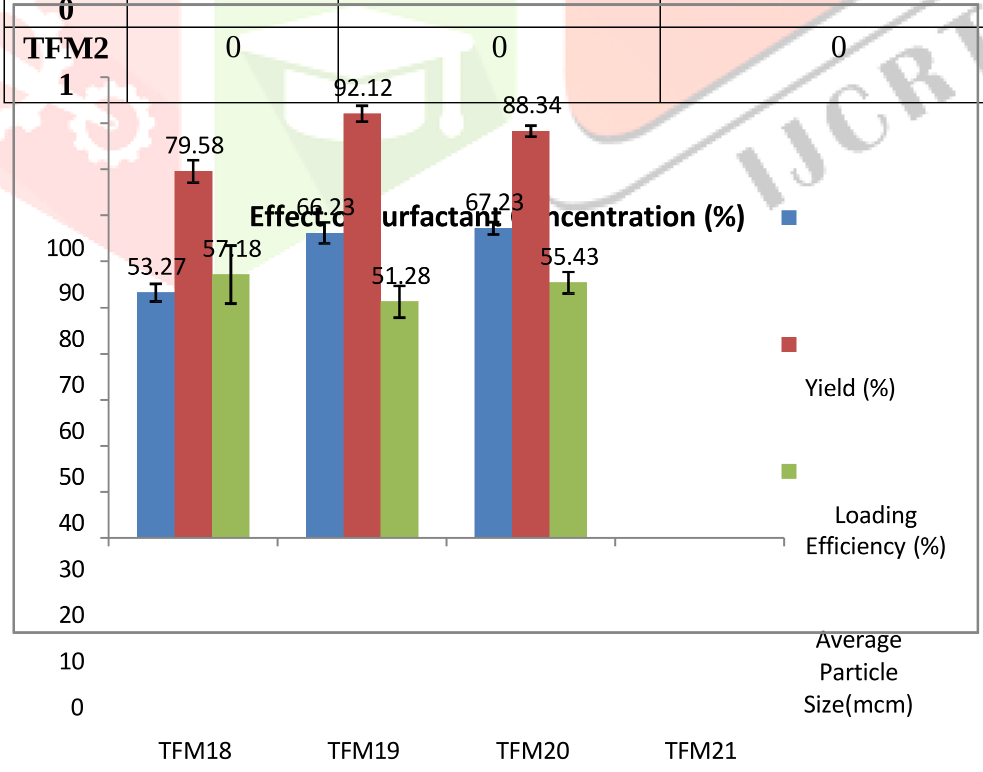


Figure 4.18: Effect of Surfactant Concentration on Batches TFM18 – TFM21

Microsponges did not form in absence of surfactant. By varying the concentration of surfactant from 0.5%, 0.75%, 1% and 1.25% w/v of external phase, the P.S. also varied from 51.28µm to 57.18µm.

Selection of Stirring Speed

Table 4.27: Effect of Stirring Speed on Batches TFM22 – TFM25

Batch	Yield (%) (Mean ± S.D.) (n = 3)	Loading Efficiency (%) (Mean ± S.D.) (n = 3)	Average Particle Size(µm) (Mean ± S.D.) (n = 3)
TFM22	0	0	0
TFM23	**52.87±2.28**	**79.34±1.73**	**33.13±3.46**
TFM24	**24.27±1.33**	**77.67±1.19**	**20.81±2.33**
TFM25	0	0	0

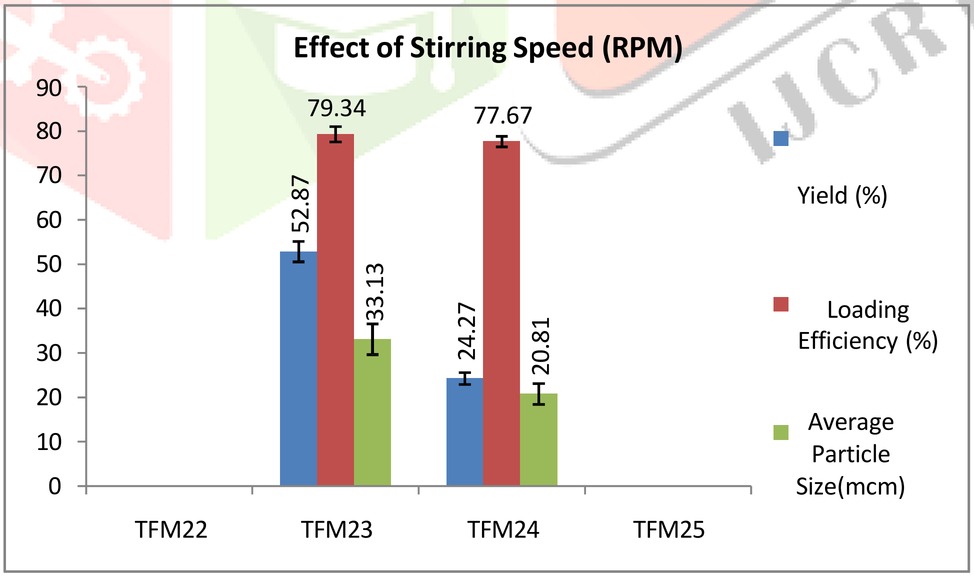


Figure 4.19: Effect of Stirring Speed on Batches TFM22 – TFM25

It was marked that E.E. decrease with increasing the stirring speed. From results shown Table No.4.27, Stirring speed had marked effect on particle diameter due to the turbulence effect due to higher speed.

Selection of Stirring Time

Table 4.28: Effect of Stirring Time on Batches TFM26 – TFM28

Batch	**Yield (%) (Mean ±** S.D.) (n = 3)	**Loading Efficiency (%) (Mean ±** S.D.) (n = 3)	**Average Particle Size(µm) (Mean ±** S.D.) (n = 3)
TFM26	0	0	0
TFM27	**77.28±2.28**	**73.53±1.73**	**40.14±3.46**
TFM28	72.13±1.33	71.12±1.19	61.43±2.33

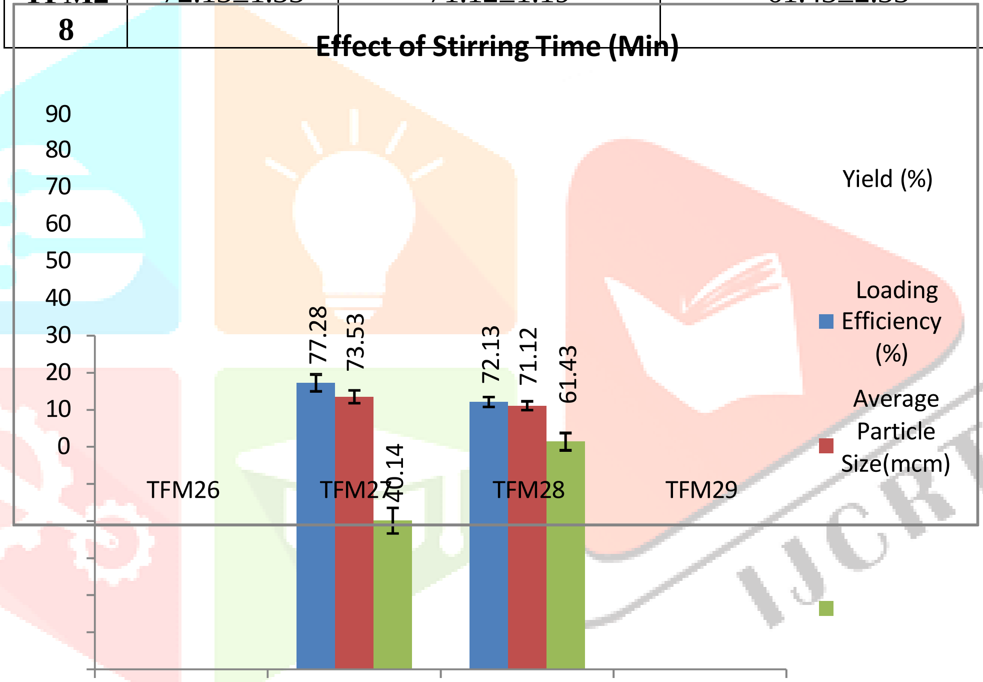


Figure 4.20: Effect of Stirring Time on TFM26 – TFM28

The results of the study showed that the particle size ranged from 4.14µm to 61.43µm.

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

The critical quality attributes are categorized into high, medium and low risk parameters based on knowledge space. Usually high risk parameters are considered important for Design of Experiments as they are having more effect than others and need to be in accepting multivariate ranges. Different critical quality attributes are categorized as shown in Table 4.29. The Critical parameters and critical quality attributes (CQAs) for selection of optimum formulation are shown in table no 4.29. (Lourenço V et al., 2012)

Table 4.29: Risk assessment to identify variables affecting drug product quality

Drug Product CQAs	Drug: Polymer Ratio	Volume Of Internal Phase	% Stabilizer Concentration	Agitation Speed
Drug Content	High	Low	Medium	Medium
Entrapment Efficiency	High	Low	High	Medium
Particle Size	High	Medium	High	High
Drug Release	High	Low	Medium	Medium

Formulation and Development of Oxaprozin Microsponges by DoE Using QbD Approach

Various batches of Oxaprozin microsponges by DoE Using QbD approach were prepared according to 2^4 factorial designs which are as follow:

Formulation and Development of Oxaprozin - Ethyl Cellulose Microsponges by using QbD Approach

2^4 Factorial Design for Oxaprozin Microsponges

Various batches of Oxaprozin Microsponges with Ethyl Cellulose were prepared according to 2^4 factorial design which are as Table 4.30.

Table 4.30: 2^4 Factorial Batches

Independent Variables of Formulations		
Independent Variables	Low(-)	High(+)
Drug Concentration (X_1)	11:1	13:1
PVA (X_2)	0.75%	1%
Internal Phase volume (X_3)	10	15
Speed (RPM) (X_4)	1500	2000
Dependent Variables		
Y1 = % Drug Content		
Y2 = % Entrapment efficiency		
Y3 = Particle Size		

Y4 =% CDR

Compositions of Factorial Batches in Coded Form

Table 4.31: Compositions of Factorial Batches in Coded Form

OZ- EC MS 2^4 =16 Batches				
Batch No	**Variable level in coded form**			
	Drug Con.-mg (X1)	**Int. Phase Vol.- mL (X2)**	**PVA Con.- mg (X3)**	**Speed- RPM (X4)**
OZCM1	+1	-1	+1	-1
OZCM2	+1	-1	-1	+1
OZCM3	-1	-1	-1	+1
OZCM4	-1	+1	-1	-1
OZCM5	-1	+1	+1	+1
OZCM6	+1	+1	+1	+1
OZCM7	+1	+1	-1	-1
OZCM8	+1	+1	-1	+1
OZCM9	+1	+1	+1	-1
OZCM10	-1	-1	-1	-1
OZCM11	+1	-1	+1	+1
OZCM12	-1	+1	-1	+1
OZCM13	+1	-1	-1	-1
OZCM14	-1	-1	+1	+1
OZCM15	-1	+1	+1	-1
OZCM16	-1	-1	+1	-1

Formulation Design by 2^4 Factorial Designs

Table 4.32: Formulation Design by 2^4 Factorial Design

Batch	Drug	Drug: Polymer Ratio	Int. Phase Vol.-mL (X2)	Liquid Paraffin (mL)	PVA Con.-mg (X3)	Speed-RPM (X4)	Time of stirring (Min)
OZCM1	OZ	91.66	10	50	1	1500	60
OZCM2	OZ	91.66	10	50	0.75	2000	60
OZCM3	OZ	90	10	50	0.75	2000	60
OZCM4	OZ	90	15	50	0.75	1500	60
OZCM5	OZ	90	15	50	1	2000	60
OZCM6	OZ	91.66	15	50	1	2000	60
OZCM7	OZ	91.66	15	50	0.75	1500	60
OZCM8	OZ	91.66	15	50	0.75	2000	60
OZCM9	OZ	91.66	15	50	1	1500	60
OZCM10	OZ	90	10	50	0.75	1500	60
OZCM11	OZ	91.66	10	50	1	2000	60
OZCM12	OZ	90	15	50	0.75	2000	60
OZCM13	OZ	91.66	10	50	0.75	1500	60
OZCM14	OZ	90	10	50	1	2000	60
OZCM15	OZ	90	15	50	1	1500	60

OZCM16	OZ	90	10	50	1	1500	60

Characterization of of Batches OZCM1-OZCM16

Table 4.33: Characterization of Batches OZCM1-OZCM16

Batch No	Yield-% (Y1) (Mean ± S.D.) (n = 3)	E.E.-% (Y2) (Mean ± S.D.) (n = 3)	P.Size-μm (Y3) (Mean ± S.D.) (n = 3)	Drug Content (Mean ± S.D.) (n = 3)
OZCM1	75.12±1.23	90.27±2.34	24.12±3.46	91.27±1.24
OZCM2	86.91±2.23	94.49±1.38	8.48±2.59	95.19±1.45
OZCM3	74.32±1.79	87.32±2.33	20.72±3.79	88.32±1.57
OZCM4	75.57±1.79	88.15±2.33	28.23±3.79	83.53±1.24
OZCM5	65.34±1.23	75.87±2.34	14.19±3.46	79.72±1.75
OZCM6	71.25±2.23	76.42±1.38	15.65±2.59	81.22±1.24
OZCM7	71.61±2.09	85.68±2.45	26.53±4.03	87.85±1.67
OZCM8	73.28±1.79	80.33±2.33	11.72±3.79	80.33±1.82
OZCM9	75.22±1.23	73.81±2.34	24.38±3.46	76.13±1.37
OZCM10	73.55±2.23	86.74±1.38	23.68±2.59	84.41±1.41
OZCM11	83.11±2.09	92.14±2.45	18.82±4.03	91.34±2.27
OZCM12	67.29±1.79	78.26±2.33	16.25±3.79	74.66±1.46
OZCM13	74.38±2.09	88.39±2.45	13.87±4.03	88.39±2.33
OZCM14	69.76±1.23	88.56±2.34	20.78±3.46	86.64±1.15
OZCM15	61.35±2.09	76.21±2.45	35.26±4.03	78.59±2.08
OZCM16	72.83±2.23	87.45±1.38	29.81±2.59	87.38±1.51

% Cumulative Drug Release profile

Table 4.34: % Cumulative Drug Release profile of Batches OZCM1 - OZCM5

Time (Hr)	OZCM1 (Mean ± S.D.) (n = 3)	OZCM2 (Mean ± S.D.) (n = 3)	OZCM3 (Mean ± S.D.) (n = 3)	OZCM4 (Mean ± S.D.) (n = 3)	OZCM5 (Mean ± S.D.) (n = 3)
0	0	0	0	0	0
1	26.12 ± 1.58	27.25 ± 1.92	26.13 ± 1.98	25.13 ± 1.24	23.53 ± 1.11
2	36.62 ± 2.09	37.44 ± 1.62	38.62 ± 1.38	36.52 ± 2.66	32.71 ± 1.55
3	46.31 ± 1.27	46.68 ± 1.10	47.31 ± 1.76	44.31 ± 1.24	43.33 ± 1.26
4	53.81 ± 1.72	53.21 ± 2.17	55.82 ± 2.13	51.82 ± 1.29	52.47 ± 1.67
5	60.47 ± 1.92	60.61 ± 1.22	61.47 ± 1.88	59.97 ± 1.43	58.39 ± 1.83
6	73.59 ± 1.29	72.24 ± 2.1	74.53 ± 1.79	72.53 ± 1.46	65.35 ± 1.33
7	81.16 ± 1.28	85.37 ± 1.91	82.16 ± 2.01	81.06 ± 1.08	71.88 ± 1.31
8	89.21 ± 1.83	96.56 ± 2.23	89.78 ± 1.02	88.78 ± 1.98	83.35 ± 1.82

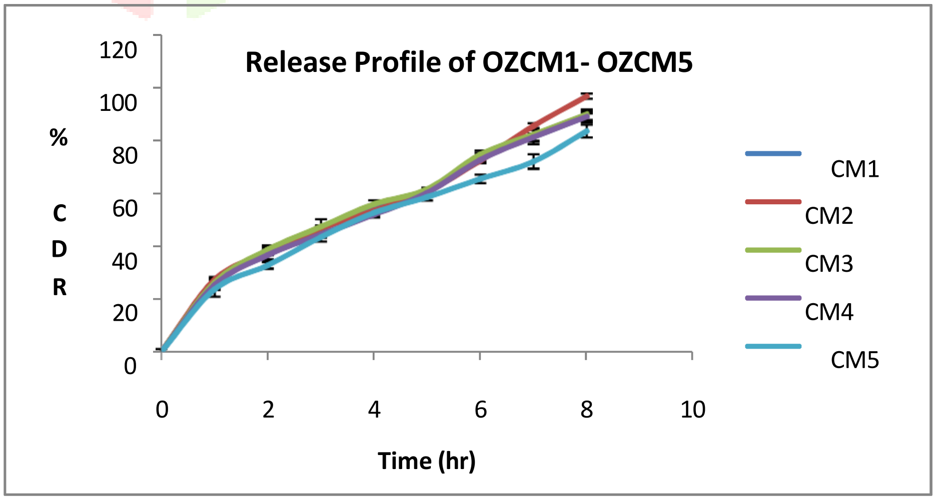


Figure 4.22: % Cumulative Drug Release profile of Batches OZCM1 - OZCM5

Table 4.35*:* % Cumulative Drug Release profile of Batches OZCM6– OZCM11

Time	**OZCM6 (Mean ± S.D.) (n = 3)**	**OZCM7 (Mean ± S.D.) (n = 3)**	**OZCM8 (Mean ± S.D.) (n = 3)**	**OZCM9 (Mean ± S.D.) (n = 3)**	**OZCM10 (Mean ± S.D.) (n = 3)**	**OZCM11 (Mean ± S.D.) (n = 3)**
0	0	0	0	0	0	0
1	27.15±1.29	24.68±1.26	26.12±1.63	24.12±1.44	24.28±1.35	26.25±1.25
2	33.44±1.81	38.14±1.82	36.62±1.19	35.42±1.32	37.94±1.58	32.34±1.42
3	42.68±1.15	46.37±1.51	46.31±1.36	43.31±1.11	45.27±1.15	41.78±1.74
4	52.21±2.39	55.78±1.38	53.81±1.68	50.72±1.83	54.78±1.27	53.31±2.29
5	62.61±1.56	59.89±1.72	60.47±1.59	58.87±1.42	58.87±1.73	61.41±2.63
6	71.24±1.41	68.54±2.47	73.59±1.35	71.43±1.29	67.77±1.49	72.54±1.17
7	84.37±2.62	80.49±1.34	81.16±1.84	80.16±2.43	81.29±2.15	85.46±1.53
8	91.42±1.34	87.26±1.64	89.21±2.59	88.86±1.14	87.62±1.16	91.24±1.37

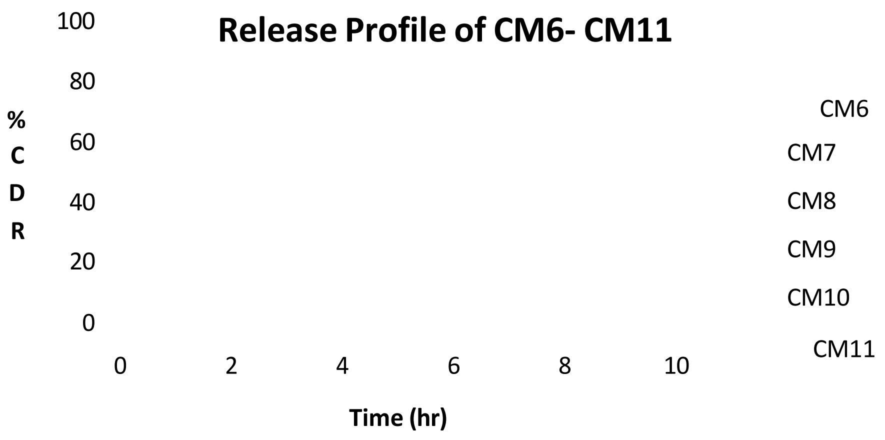


Figure 4.23: % Cumulative Drug Release profile of Batches OZCM6 – OZCM11

Table 4.36*:* % Cumulative Drug Release profile of Batches OZCM12– OZCM16

Time	OZCM12 (Mean ± S.D.) (n = 3)	OZCM13 (Mean ± S.D.) (n = 3)	OZCM14 (Mean ± S.D.) (n = 3)	OZCM15 (Mean ± S.D.) (n = 3)	OZCM16 (Mean ± S.D.) (n = 3)
0	0	0	0	0	0
1	25.96±1.26	25.13±1.24	23.98±1.64	22.58±1.35	24.23±1.27
2	33.36±1.67	36.52±2.56	35.04±1.47	39.32±2.16	33.21±1.46
3	41.96±1.88	44.31±1.72	46.37±1.17	47.54±1.34	44.23±1.62
4	53.21±1.51	51.82±1.25	53.98±1.26	56.23±1.62	51.97±1.81
5	61.52±1.38	59.97±1.53	59.01±1.32	61.29±1.83	59.32±1.52
6	71.99±2.75	72.53±1.69	66.17±1.62	66.58±1.42	66.15±1.36
7	84.86±1.67	81.06±1.28	81.38±1.87	75.81±1.31	73.02±1.11
8	91.20±1.19	88.56±1.46	87.82±1.53	81.18±1.18	84.52±2.33

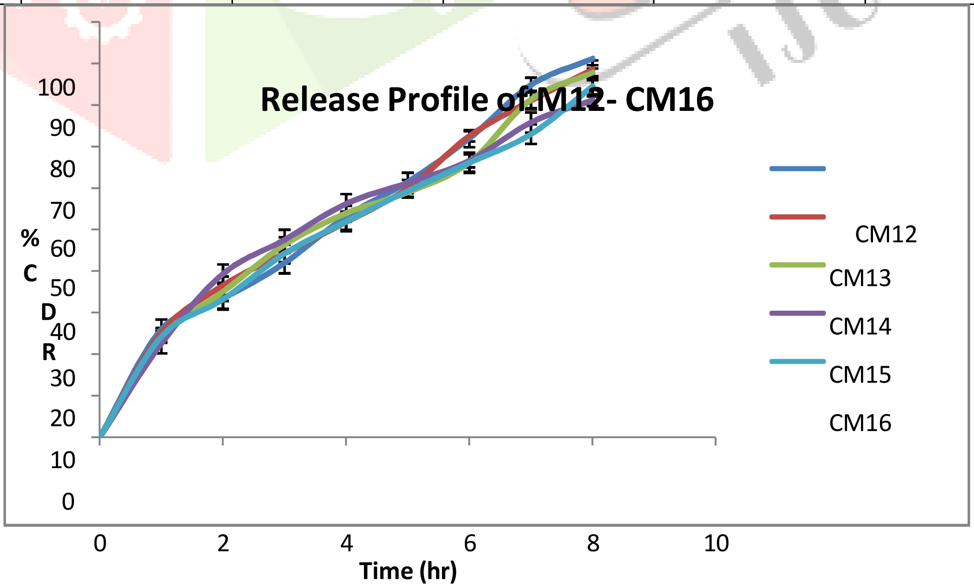


Figure 4.24: % Cumulative Drug Release profile of OZCM12 – OZCM16

The % CDR was experimental to range from 83% to 92%, signifying the capability of the OZ microsponges for complete drug release. In case of OZCM12 – OZCM16**,** a eminent early rate of release in 2 to 3 hr had been detected. This might be bacuase of drug absorbed at surface that go through rapid release.

Release Kinetic

Table 4.37: Release Kinetic of Batches OZCM1 - OZCM8

Model	Parameter	**OZCM1**	**OZCM2**	**OZCM3**	**OZCM4**	**OZCM5**	**OZCM6**	**OZCM7**	**OZCM8**
Zero Order	R^2	0.9293	0.9274	0.931	0.9315	0.9808	0.9155	0.931	0.9279
	Slope	8.496	8.421	8.943	8.825	-8.35	9.22	8.943	8.883
	Intercept	13.27	12.89	13.69	14.14	15.54	15.67	13.69	14.45
First Order	R^2	0.9904	0.9747	0.9909	0.9907	0.9937	0.9743	0.9114	0.9798
	Slope	-0.162	0.158	-0.1845	-0.182	-0.1645	-0.2035	-0.162	-0.1878
	Intercept	4.51	4.5	4.54	4.53	4.49	4.53	4.51	4.52
Higuchi Model	R^2	0.9974	0.9913	0.9968	0.9928	0.9978	0.9954	0.9944	0.9992
	Slope	26.82	26.61	28.17	27.85	26.79	29.33	27.04	28.25
	Intercept	1.34	1.63	1.57	1.01	0.41	0.52	0.17	0.2
Hixon Crowell	R^2	0.8729	0.8647	0.8842	0.8729	0.8702	0.878	0.8589	0.86
	Slope	0.88	0.85	0.92	0.88	0.9	0.94	0.86	0.88
	Intercept	2.96	2.97	2.96	2.96	3.07	3.12	3.11	3.18
CorsmeyerPeppas	R^2	0.4298	0.4114	0.4795	0.4828	0.4641	0.5073	0.4795	0.4499
	Slope	0.57	0.55	0.59	0.56	0.56	0.57	0.53	0.53

	Intercept	-0.67	-0.62	-0.6	-0.59	-0.58	-0.56	-0.6	-0.56

Table 4.38: Release Kinetic of Batches OZCM9 – OZCM16

Model	Parameter	**OZCM9**	**OZCM10**	**OZCM11**	**OZCM12**	**OZCM13**	**OZCM14**	**OZCM15**	**OZCM16**
Zero Order	R2	0.9273	0.9374	0.891	0.9315	0.9169	0.9155	0.819	0.9208
	Slope	8.496	8.421	8.39	8.825	8.883	9.22	8.39	-8.35
	Intercept	13.27	12.89	15.61	14.14	14.45	15.67	15.61	15.54
First Order	R^2	0.9883	0.9717	0.9809	0.9743	0.9927	0.9917	0.9883	0.9698
	Slope	-0.1638	0.158	-0.1845	-0.2035	-0.1645	-0.182	-0.1638	-0.1878
	Intercept	4.48	4.5	4.54	4.53	4.49	4.53	4.48	4.52
Higuchi Model	R^2	0.9974	0.9913	0.9968	0.9928	0.9978	0.9954	0.9944	0.9992
	Slope	26.82	26.61	28.17	27.85	26.79	29.33	27.04	28.25
	Intercept	1.34	1.63	1.57	1.01	0.41	0.52	0.17	0.2
Hixon Crowell	R^2	0.8886	0.8647	0.8242	0.8786	0.8712	0.868	0.8689	0.86
	Slope	0.94	0.85	0.92	0.94	0.9	0.94	0.86	0.88
	Intercept	2.97	2.97	2.96	2.97	3.07	3.12	3.11	3.18
CorsmeyerPeppas	R^2	0.4298	0.4114	0.4444	0.4828	0.4641	0.5073	0.4444	0.4499
	Slope	0.56	0.57	0.54	0.56	0.54	0.56	0.54	0.53
	Intercept	-0.67	-0.62	-0.59	-0.59	-0.58	-0.56	-0.59	-0.56

The mechanism was analyzed with the support of PCP V2.08 dissolution software using as shown Table 4.37 and 4.38. According to the results the best fit model for the Microsponge was Higuchi (matrix) model. By plotting the values of Higuchi model, near straight lines with parallel positive slopes were obtained representing that, the best fit model for the formulations was Higuchi model.

Statistical Analysis

Statistical analysis had done by Design expert software version 9.0.2.0. and generated the first order polynomial equations. From preliminary results, a 2^4 full factorial design was utilized in which four factors were evaluated, separately at two levels and possible sixteen combinations were formulated. Two level factorial study was carried out using four different variable. In first factorial design, the amount of drug (OZ) : polymer (EC) ratio (X1), amount of PVA Concentration (X2), Internal Phase Concentration (X3) and Speed (X4) were taken as independent variables while % Yield (Y1), % E. E (Y2). Particle sizes (Y3), % CDR (Y4) were selected as dependent variables for both factorial designs. The full model was found insignificant so reduced model was apllied for all four independent variables and detailed ANOVA, Response Surface Counter Plot and 3 D plot are as follows:

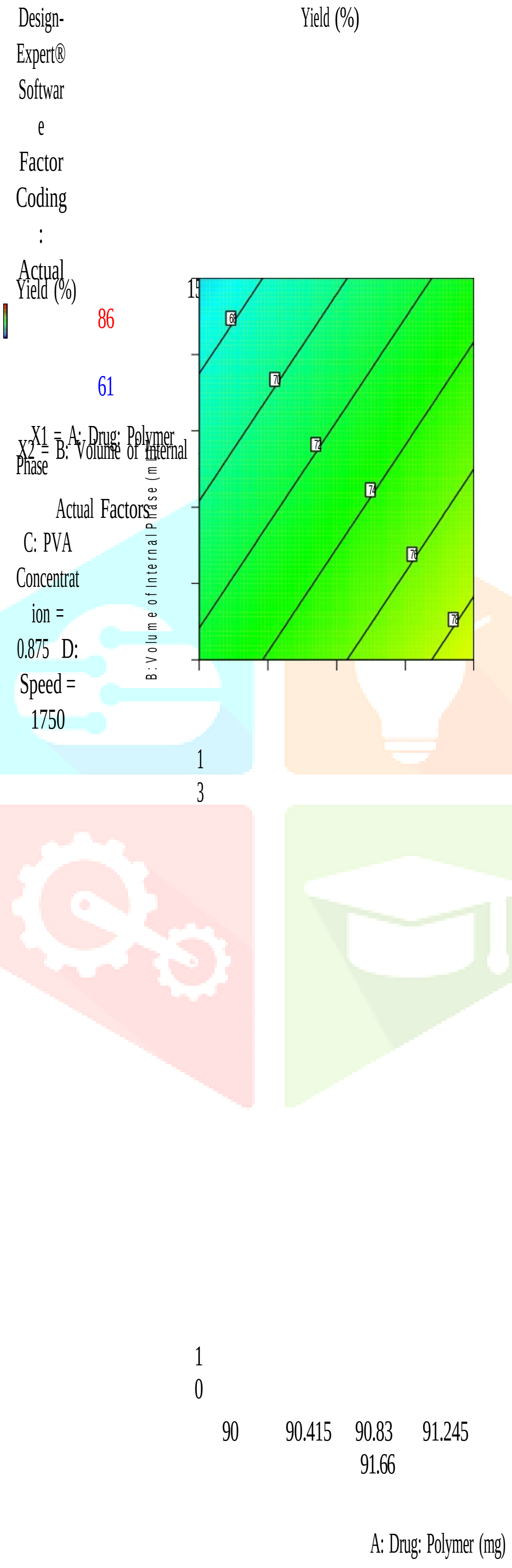
Effect on % Yield (Y1) - Surface Response Study

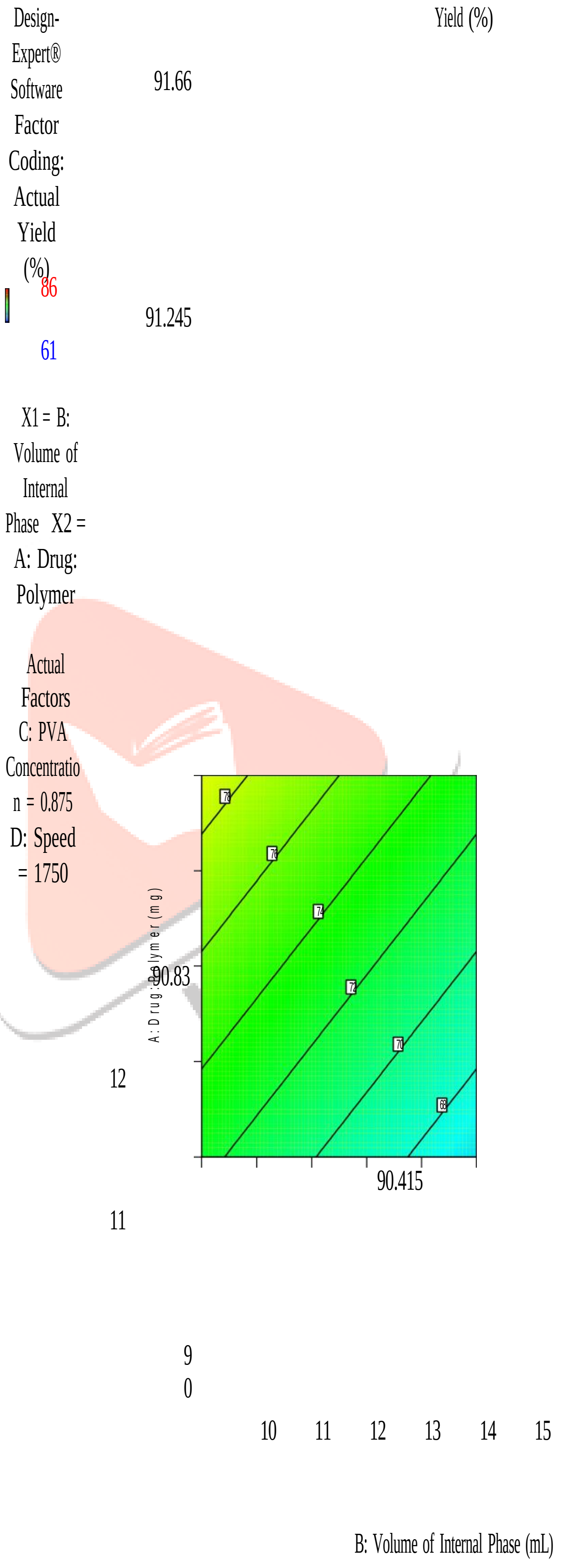
The positive value of the coefficient of X1 in the equation indicates decrease in the yield with Drug Concentration. The negative value of coefficient of X2 PVA concentration indicates decrease in the response of Y1 i.e. % yield. The negative value of coefficient X3, time indicates decrease in yield. It indicates the linearity of the surface response and contour plot as shown in figure 4.25 and 4.26.

Y1 (%Yield) = 74.625 + 3.25 * A - 2.875 * B - 1.5 * C + 0.75 * D

Table 4.39: ANOVA Table for Response Y1

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob> F	
Model	346.25	4	86.5625	4.545047733	0.020689632	Significant
A-Drug: Polymer Ratio	169	1	169	8.873508353	0.012545423	
B-Volume of Internal Phase	132.25	1	132.25	6.943914081	0.023193888	
C-PVA concentration	36	1	36	1.890214797	0.019653474	
D-Speed	9	1	9	0.472553699	0.006050235	
Residual	209.5	11	19.04545455			
Cor Total	555.75	15				


Design-Expert® Software
Factor Coding: Actual
Yield (%)
Yield (%)
86
61
X1 = A: Drug: Polymer
X2 = B: Volume of Internal Phase
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
15
13
10
B: Volume of Internal Phase (m
68
70
72
74
76
78
90
90.415
90.83
91.245
91.66
A: Drug: Polymer (mg)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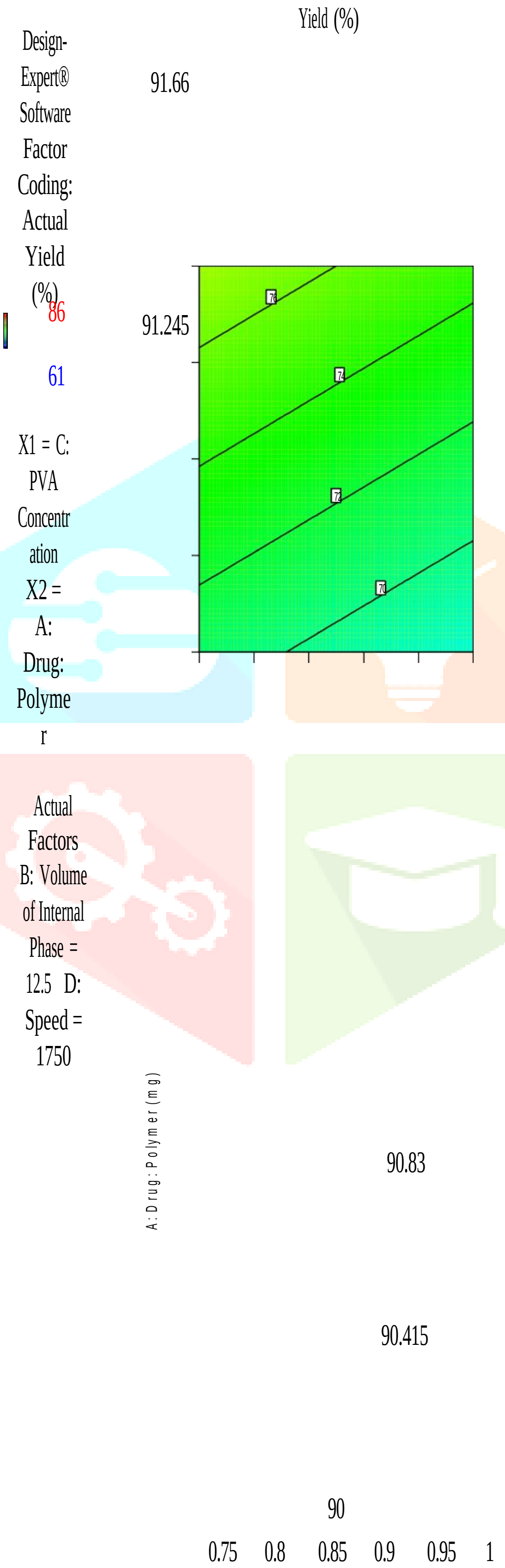
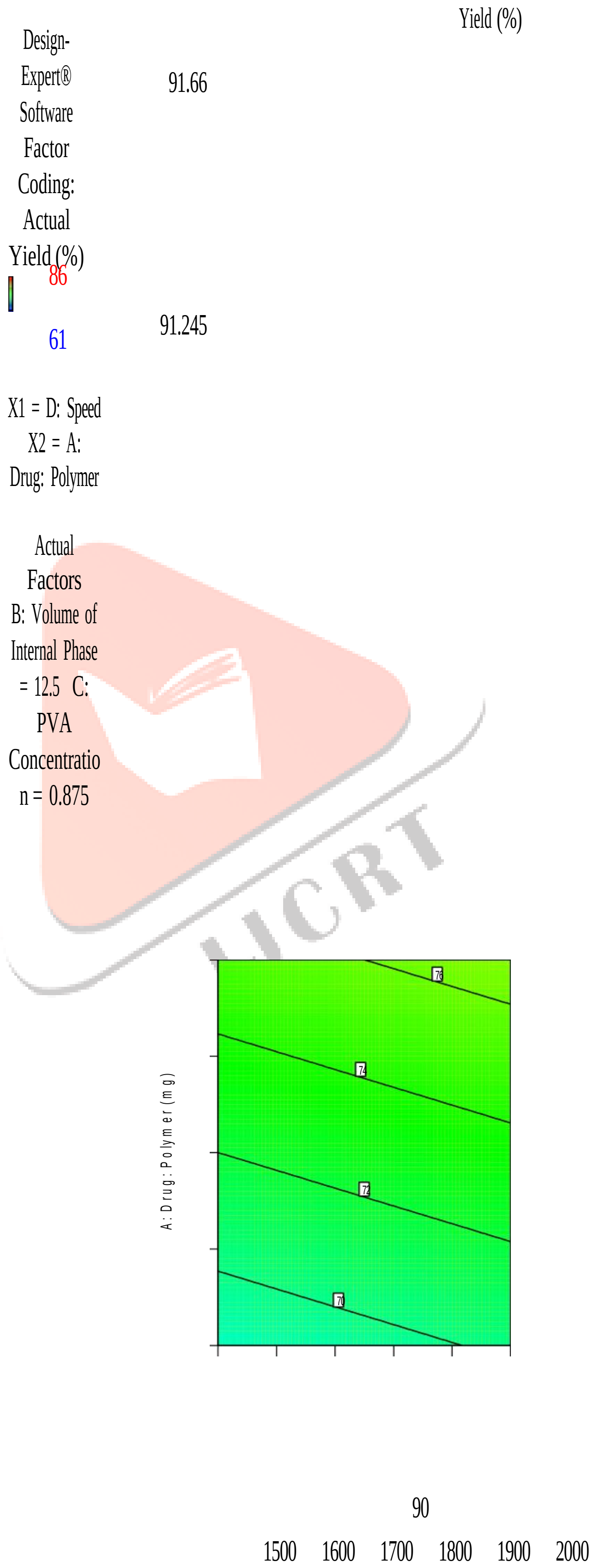
Factor Coding: Actual
Yield (%)
Yield (%)
86
61
X1 = B: Volume of Internal Phase
X2 = A: Drug: Polymer
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
91.66
91.245
90.83
90.415
90
A: Drug: Polymer (mg)
78
76
74
72
70
68
10
11
12
13
14
15
B: Volume of Internal Phase (mL)

(a)


Yield (%)
Design-Expert® Software
Factor Coding: Actual
Yield (%)
86
61
X1 = C: PVA Concentration
X2 = A: Drug: Polymer
Actual Factors
B: Volume of Internal Phase = 12.5
D: Speed = 1750
91.66
91.245
90.83
90.415
90
A: Drug: Polymer (mg)
76
74
72
70
0.75
0.8
0.85
0.9
0.95
1

(b)


Yield (%)
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Factor Coding: Actual
Yield (%)
86
61
X1 = D: Speed
X2 = A: Drug: Polymer
Actual Factors
B: Volume of Internal Phase = 12.5
C: PVA Concentration = 0.875
91.66
91.245
90
A: Drug: Polymer (mg)
76
74
72
70
1500
1600
1700
1800
1900
2000

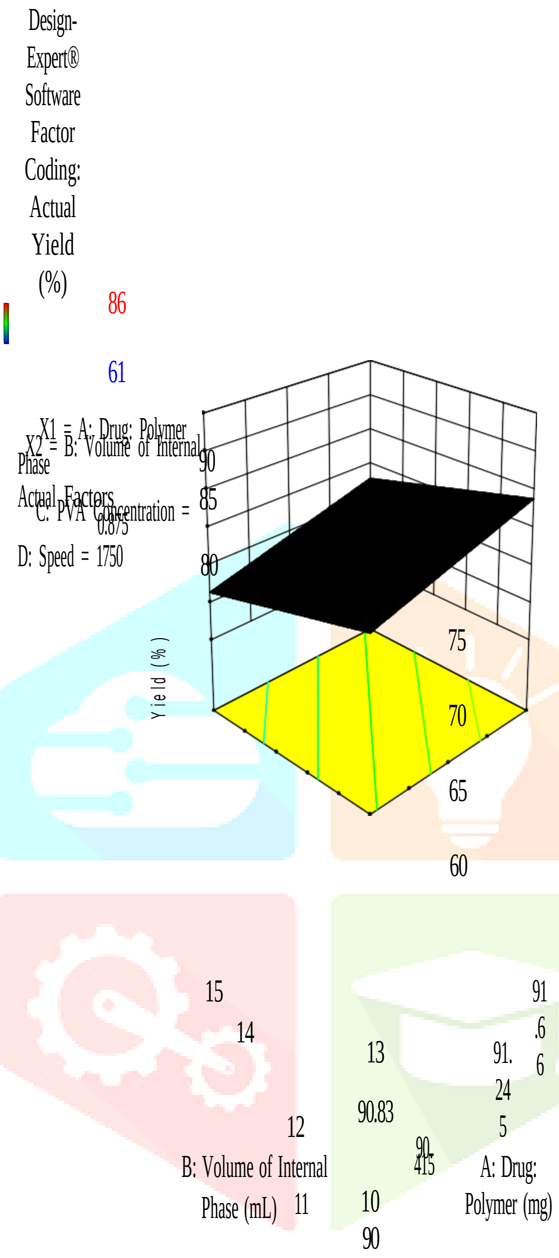
C: PVA Concentration (mg) D: Speed (RPM)

(c) (d)

Figure 4.25: Response Surface Plot:

(a) Drug Polymer Ratio and Internal Phase Concentration, (b) Internal Phase Concentration and Drug Polymer Ratio, (c) PVA concentration and Drug Polymer

Ratio and (d) Speed and Drug: Polymer Ratio on % yield (Y1)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Factor Coding: Actual
Yield (%)
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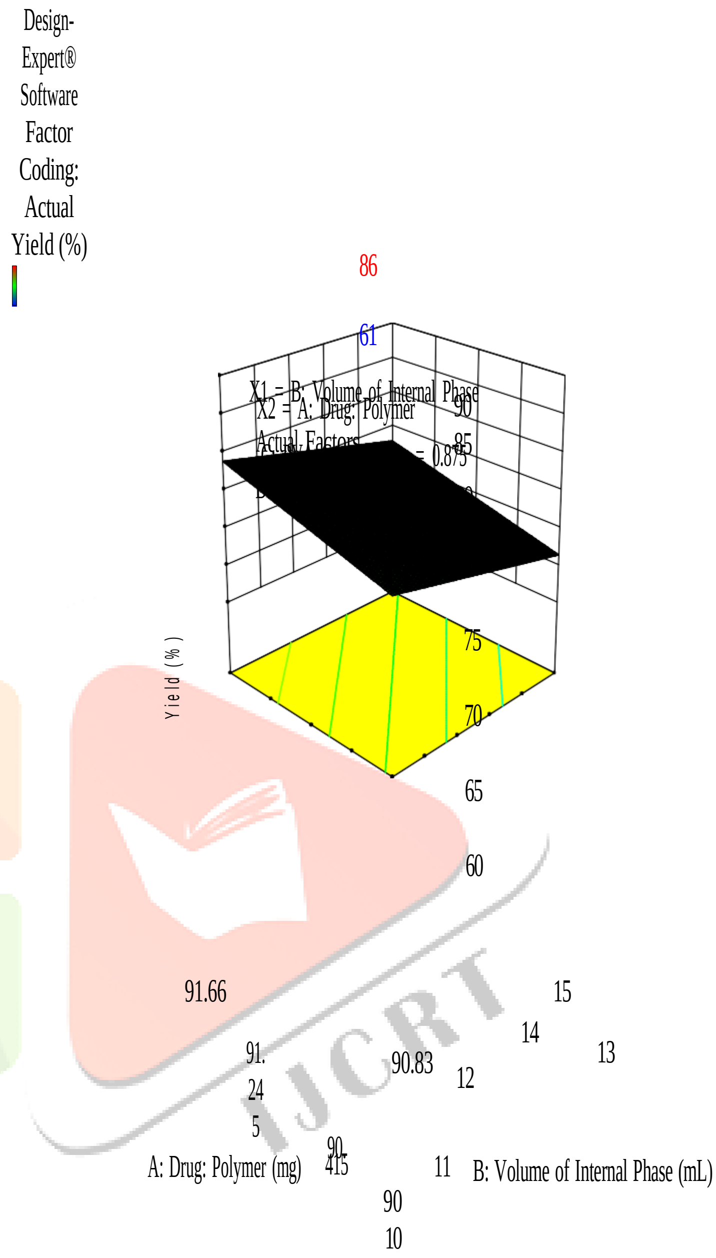
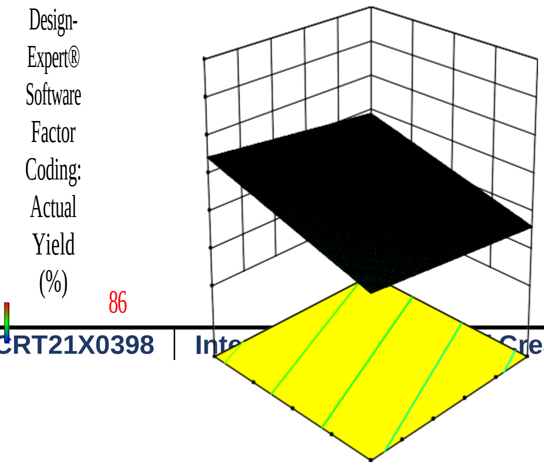
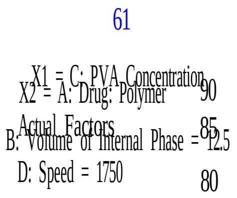
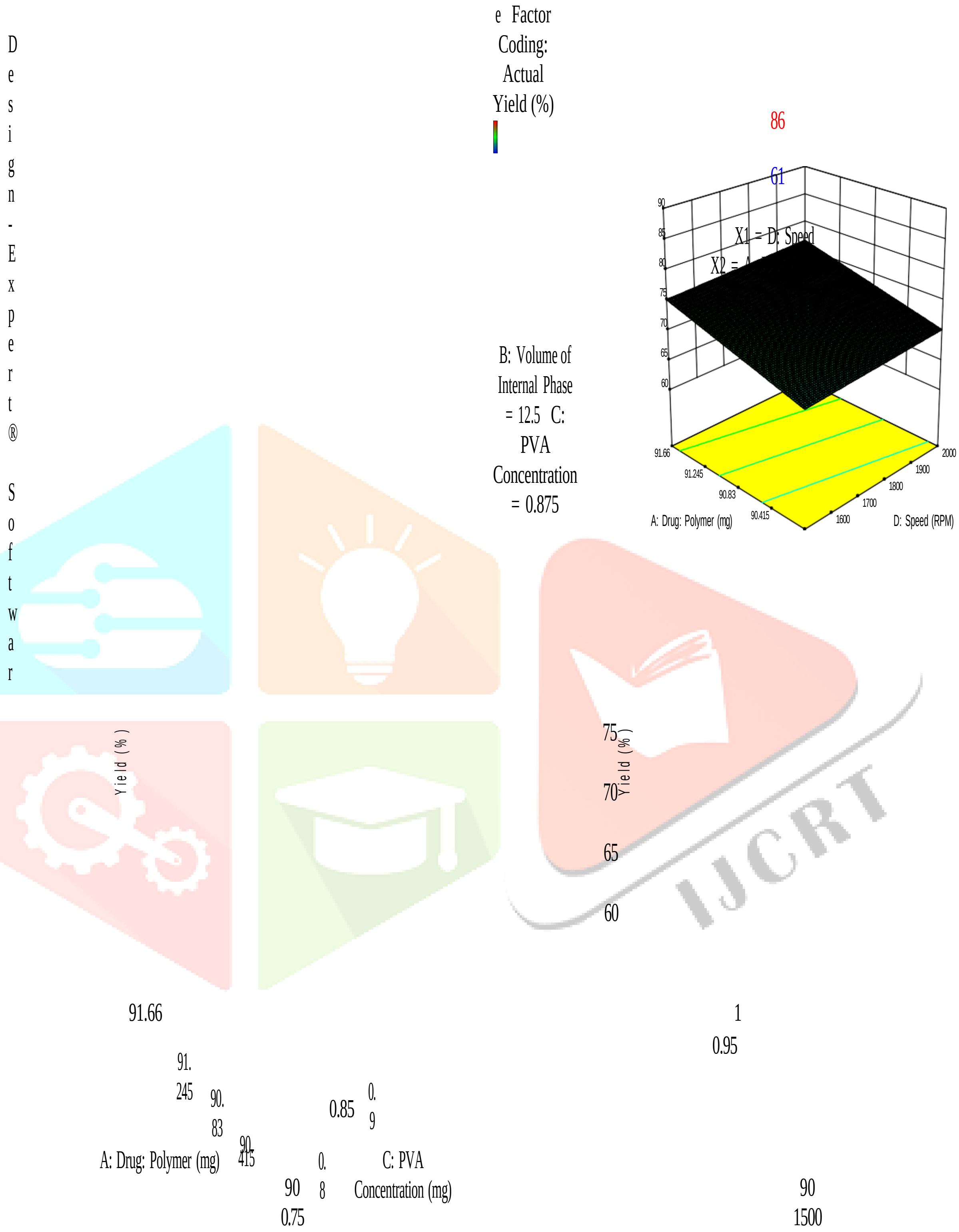
61
X1 = A: Drug: Polymer
X2 = B: Volume of Internal Phase
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
90
85
80
75
70
65
60
Yield (%)
15
14
13
12
11
10
90
91.6
91.245
90.83
90.415
B: Volume of Internal Phase (mL)
A: Drug: Polymer (mg)


Design-Expert® Software
Factor Coding: Actual
Yield (%)
86
61
X1 = B: Volume of Internal Phase
X2 = A: Drug: Polymer
Actual Factors
= 0.875
90
85
75
70
65
60
Yield (%)
91.66
91.245
90.83
90.415
90
A: Drug: Polymer (mg)
15
14
13
12
11
10
B: Volume of Internal Phase (mL)

(a) **(b)**


Design-Expert® Software
Factor Coding: Actual
Yield (%)
86


61
X1 = C: PVA Concentration
X2 = A: Drug: Polymer
Actual Factors
B: Volume of Internal Phase = 12.5
D: Speed = 1750
90
85
80


Design-Expert® Softwar
e Factor Coding: Actual
Yield (%)
86
61
X1 = D: Speed
X2 = A
B: Volume of Internal Phase = 12.5 C: PVA Concentration = 0.875
90
85
80
75
70
65
60
91.66
91.245
90.83
90.415
A: Drug: Polymer (mg)
1600
1700
1800
1900
2000
D: Speed (RPM)
Yield (%)
75
70
65
60
91.66
91.245
90.83
90.415
90
A: Drug: Polymer (mg)
0.75
0.8
0.85
0.9
C: PVA Concentration (mg)
1
0.95
90
1500

(c) **(d)**

Figure 4.26: 3D Surface Plot: (a) Drug Polymer Ratio and Internal Phase Concentration, (b) Internal Phase Concentration and Drug Polymer Ratio, (c) PVA concentration and Drug Polymer Ratio and (d) Speed and Drug: Polymer Ratio on % yield (Y1)

Effect on % Entrapment Efficiency (Y2)- Surface Response Study

The positive value of the coefficient of X1 in the equation indicates decrease in the yield with Drug Concentration. The negative value of coefficient of X2 PVA concentration indicates decrease in the response of Y2 i.e. % E.E. The negative value of coefficient X3, time indicates decrease in yield. It indicates the linearity of the surface response and contour plot as shown in figure 4.27 and 4.28.

Entrapment Efficiency(Y2) = 84.8125 + 0.8125 * A - 4.937 * B - 1.9375 * C - 0.1875 * D

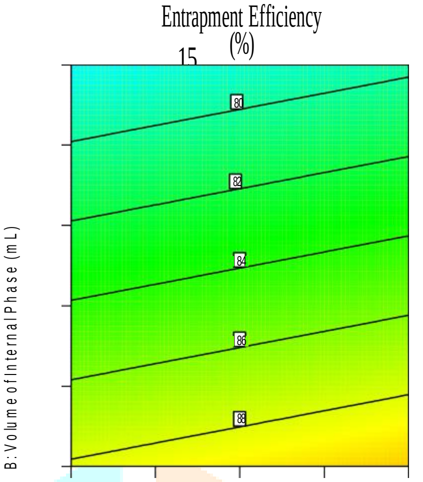
Table 4.40: ANOVA Table for Response Y2

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob> F	
Model	461.25	4	115.3125	7.324070733	0.003958699	Significant
A-Drug: Polymer Ratio	10.5625	1	10.5625	0.67087694	0.043013442	
B-Volume of Internal Phase	390.0625	1	390.0625	24.77481054	0.00041713	
C-PVA concentration	60.0625	1	60.0625	3.814868279	0.03670241	
D-Speed	0.5625	1	0.5625	0.035727174	0.00853522	
Residual	173.1875	11	15.74431818			
Cor Total	634.4375	15				

Design-Expert® Software
Factor Coding: Actual
Entrapment Efficiency (%)
94
73

X1 = A: Drug: Polymer
X2 = B: Volume of Internal Phase

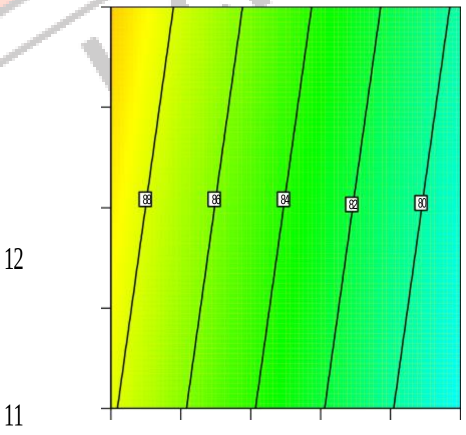
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750



Design-Expert® Software
Factor Coding: Actual
Entrapment Efficiency (%)
94
73

X1 = B: Volume of Internal Phase
X2 = A: Drug: Polymer

Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750

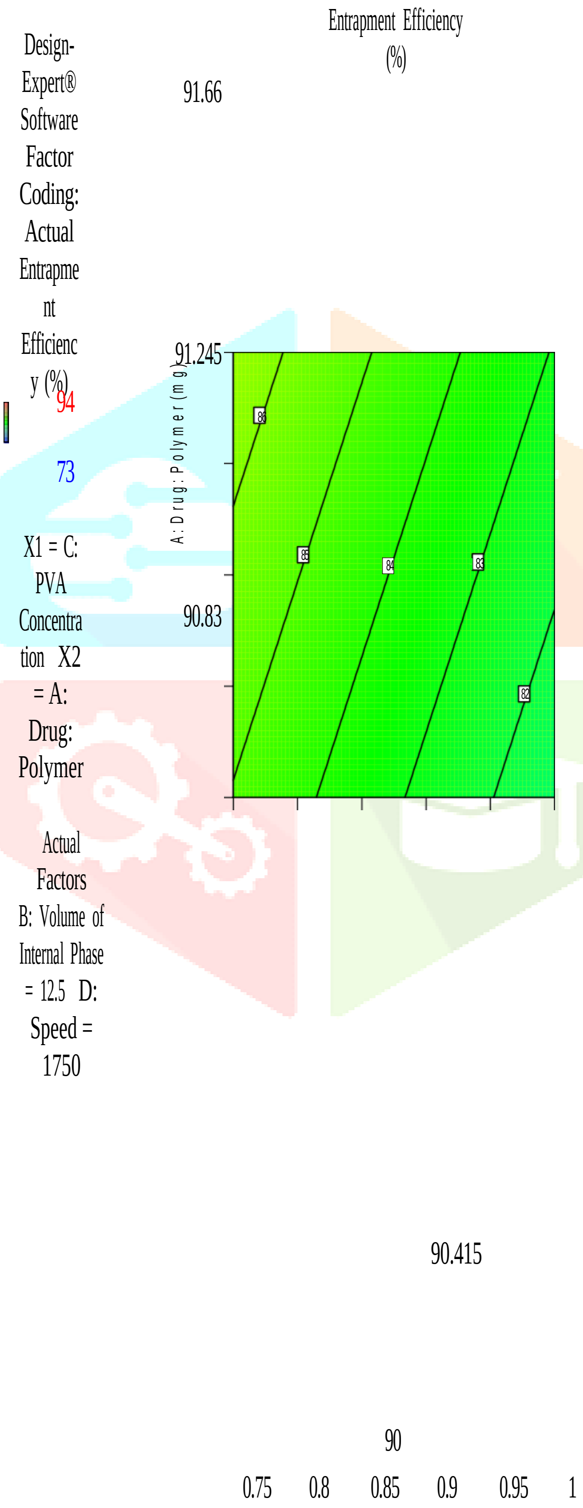


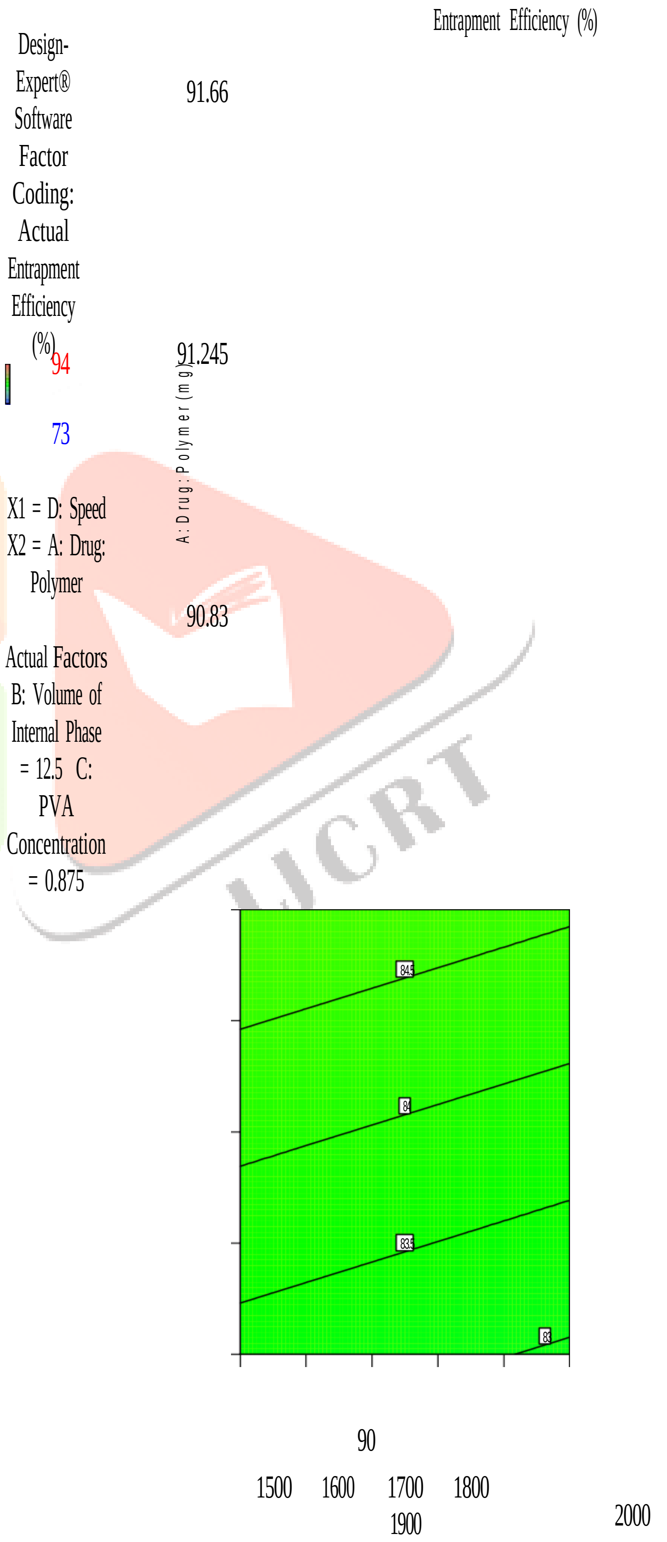
A: Drug: Polymer (mg)

B: Volume of Internal Phase (mL)

(a)

(b)





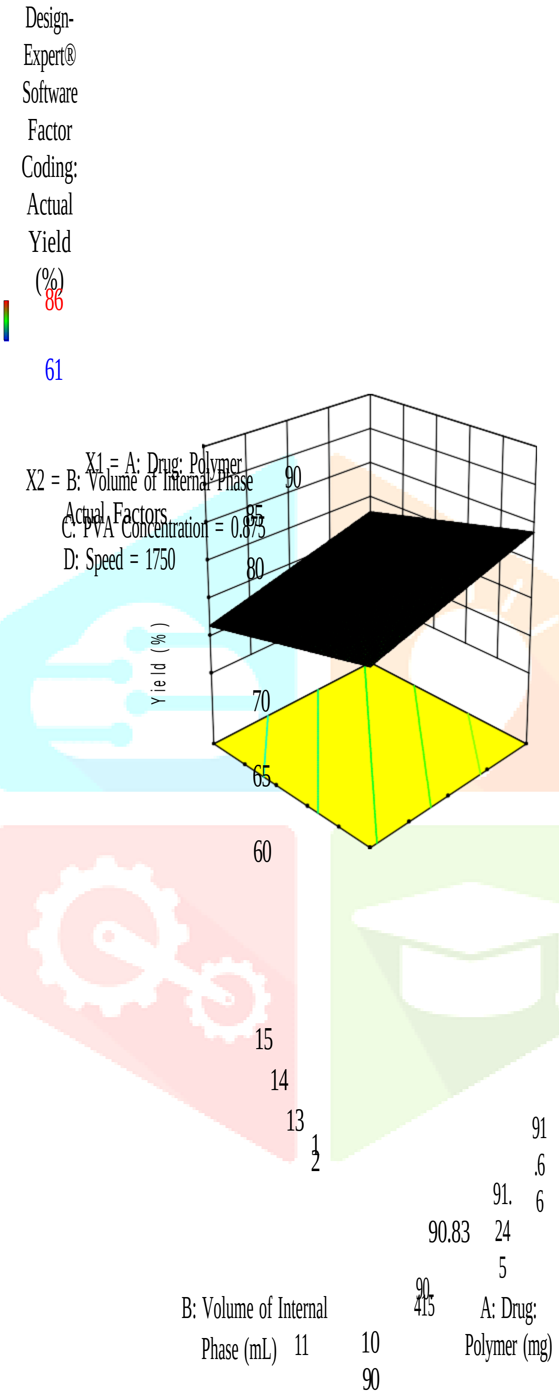
C: PVA Concentration (mg)

D: Speed (RPM)

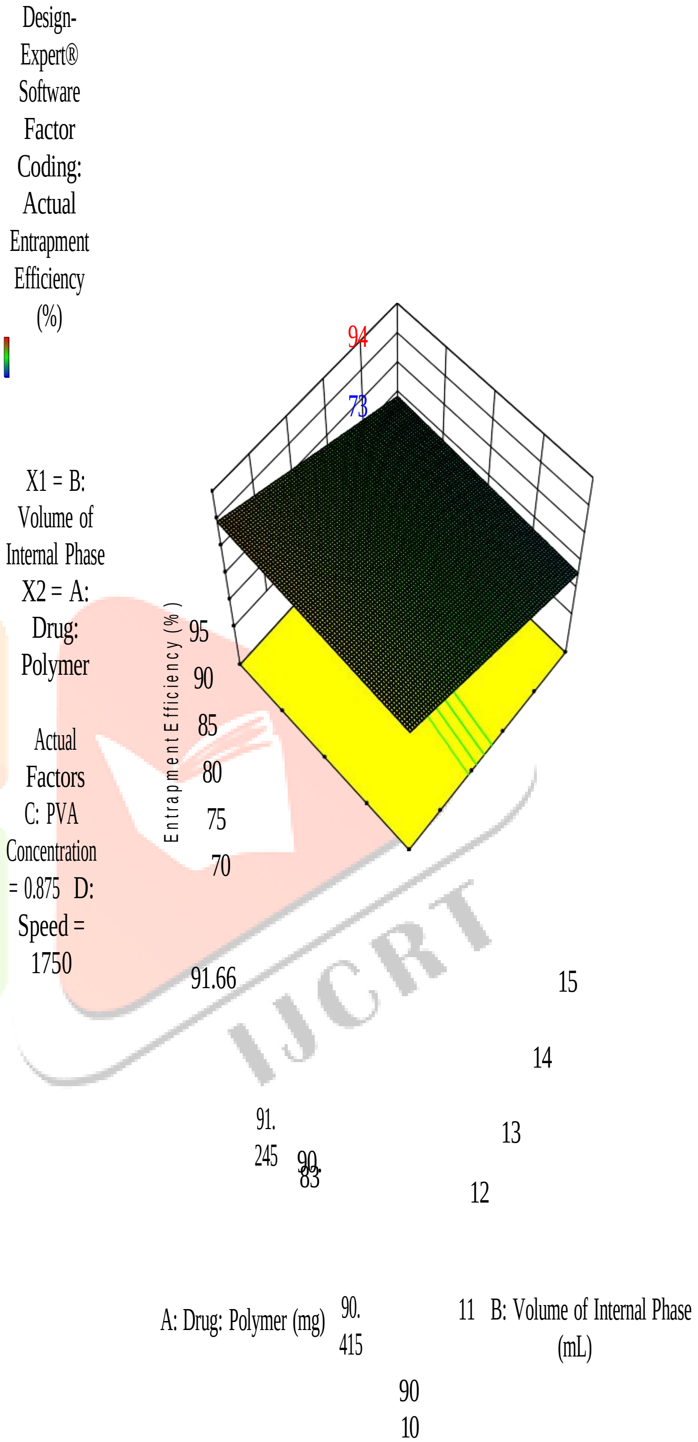
(c) **(d)**

Figure 4.27: Response Surface Plot:

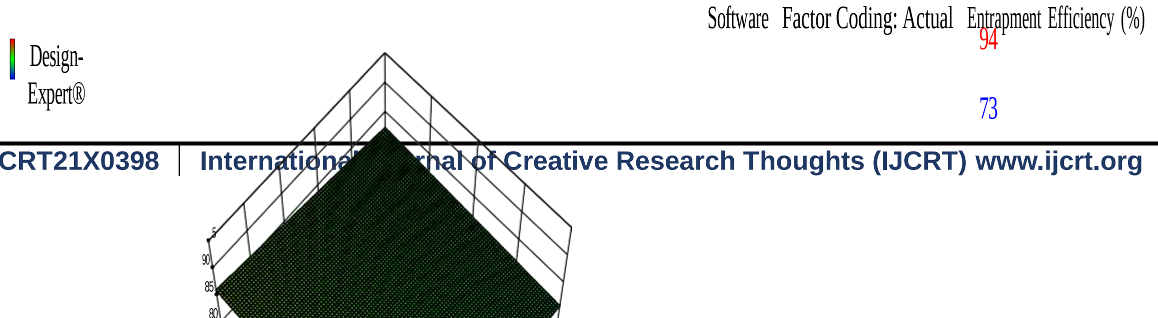
(a) Drug Polymer Ratio and Internal Phase Concentration, (b) Internal Phase Concentration and Drug Polymer Ratio, (c) PVA concentration and Drug Polymer Ratio and (d) Speed and Drug: Polymer Ratio on % E.E. (Y2)

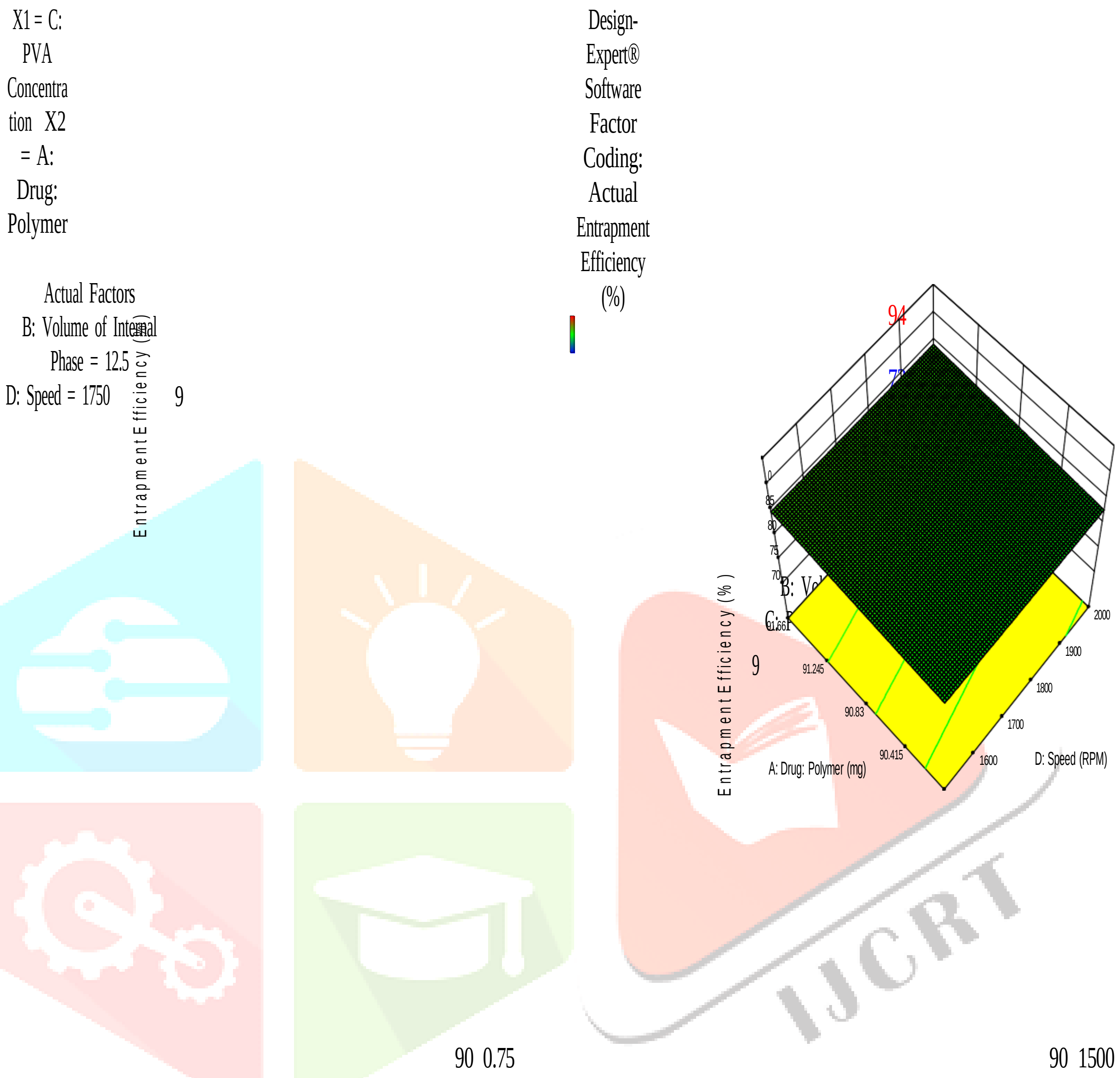

Design-Expert® Software
Factor Coding: Actual
Yield (%)
86
61
X1 = A: Drug: Polymer
X2 = B: Volume of Internal Phase
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
Y i e l d (%)
90
85
80
70
65
60
15
14
13
12
11
10
90
90.415
90.83
91.245
91.66
B: Volume of Internal Phase (mL)
A: Drug: Polymer (mg)

(a)


Design-Expert® Software
Factor Coding: Actual
Entrapment Efficiency (%)
94
73
X1 = B: Volume of Internal Phase
X2 = A: Drug: Polymer
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
E n t r a p m e n t E f f i c i e n c y (%)
95
90
85
80
75
70
91.66
91.245
90.83
90.415
90
15
14
13
12
11
10
A: Drug: Polymer (mg)
B: Volume of Internal Phase (mL)

(b)


Design-Expert®
Software Factor Coding: Actual Entrapment Efficiency (%)
94
73
5
90
85
80



(c) (d)

Figure 4.28: 3D Surface Plot: (a) Drug Polymer Ratio and Internal Phase Concentration, (b) Internal Phase Concentration and Drug Polymer Ratio, (c) PVA concentration and Drug Polymer Ratio and (d) Speed and Drug: Polymer Ratio

on % E.E. (Y2)

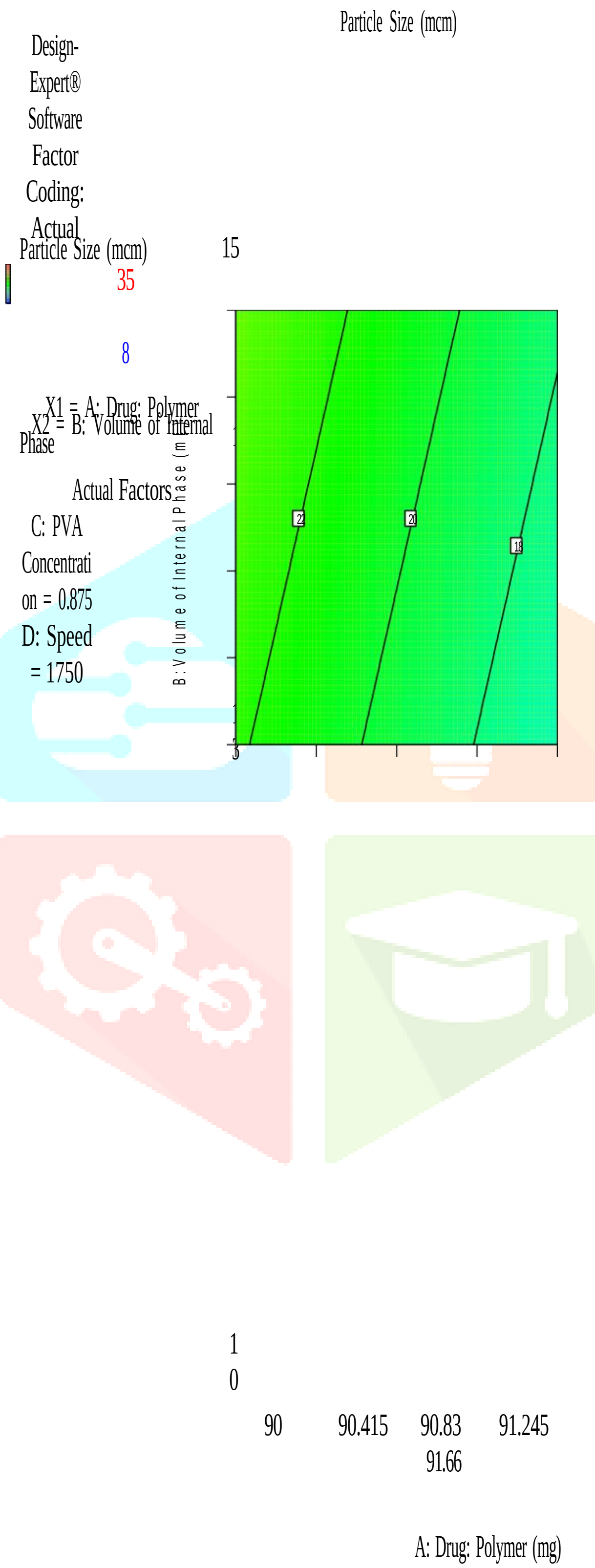
Effect on Particle Size (Y3)- Surface Response Study

The positive value of the coefficient of X1 in the equation indicates decrease in the yield with Drug Concentration. The negative value of coefficient of X2 PVA concentration indicates decrease in the response of Y3 i.e. % P.S. The negative value of coefficient X3, time indicates decrease in yield. It indicates the linearity of the surface response and contour plot as shown in figure 4.29 and 4.30.

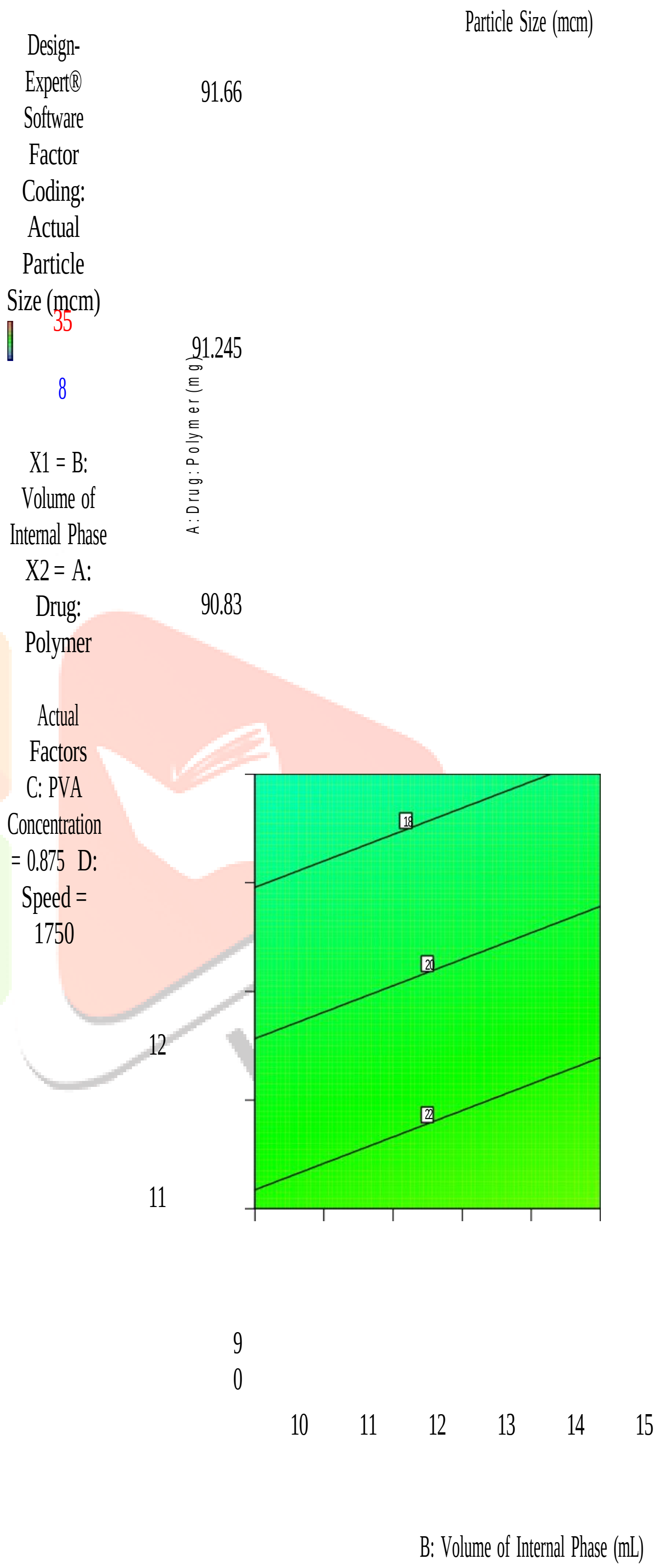
Particle Size(Y3) = 20.25 - 2.875 * A + 0.875 * B + 2.125 * C – 5 * D

Table 4.41: ANOVA Table for Response Y3

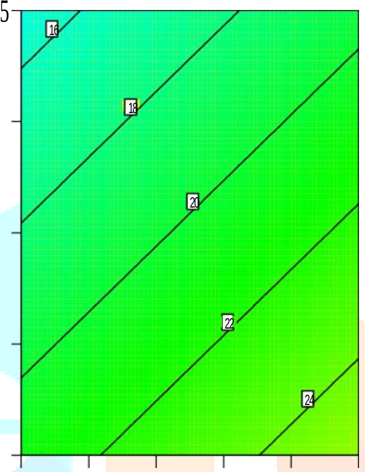
Source	**Sum of Squares**	**Df**	**Mean Square**	**F Value**	**p-value Prob> F**	
Model	516.75	4	129.1875	6.825878115	0.005150598	Significant
A-Drug: Polymer Ratio	85.5625	1	85.5625	4.520864605	0.003950814	
B-Volume of Internal Phase	0.5625	1	0.5625	0.029720805	0.044625621	
C-PVA concentration	115.5625	1	115.5625	6.105974182	0.031064758	
D-Speed	315.0625	1	315.0625	16.64695287	0.001819993	
Residual	208.1875	11	18.92613636			
Cor Total	724.9375	15				

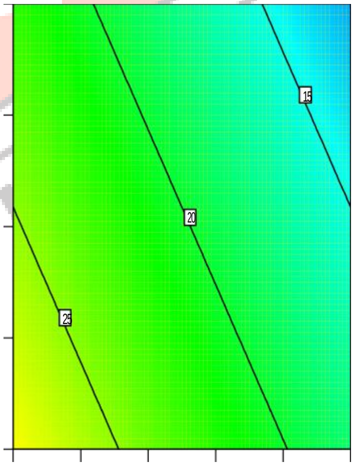

Particle Size (mcm)
Design-Expert® Software
Factor Coding: Actual
Particle Size (mcm)
35
8
X1 = A: Drug: Polymer
X2 = B: Volume of Internal Phase
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
15
10
B: Volume of Internal Phase (mL)
22
20
18
90
90.415
90.83
91.245
91.66
A: Drug: Polymer (mg)

(a)


Particle Size (mcm)
Design-Expert® Software
Factor Coding: Actual
Particle Size (mcm)
35
8
X1 = B: Volume of Internal Phase
X2 = A: Drug: Polymer
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
91.66
91.245
90.83
A: Drug: Polymer (mg)
12
11
90
18
20
22
10
11
12
13
14
15
B: Volume of Internal Phase (mL)

(b)


Design-Expert® Software
Factor Coding: Actual
Particle Size (mcm)
35
8
X1 = C: PVA Concentration
X2 = A: Drug: Polymer
Actual Factors
B: Volume of Internal Phase = 12.5
D: Speed = 1750
Particle Size (mcm)
91.66
91.245
90.83
90.415
90
A: Drug: Polymer (mg)
16
18
20
22
24
0.75
0.8
0.85
0.9
0.95
1
C: PVA Concentration (mg)

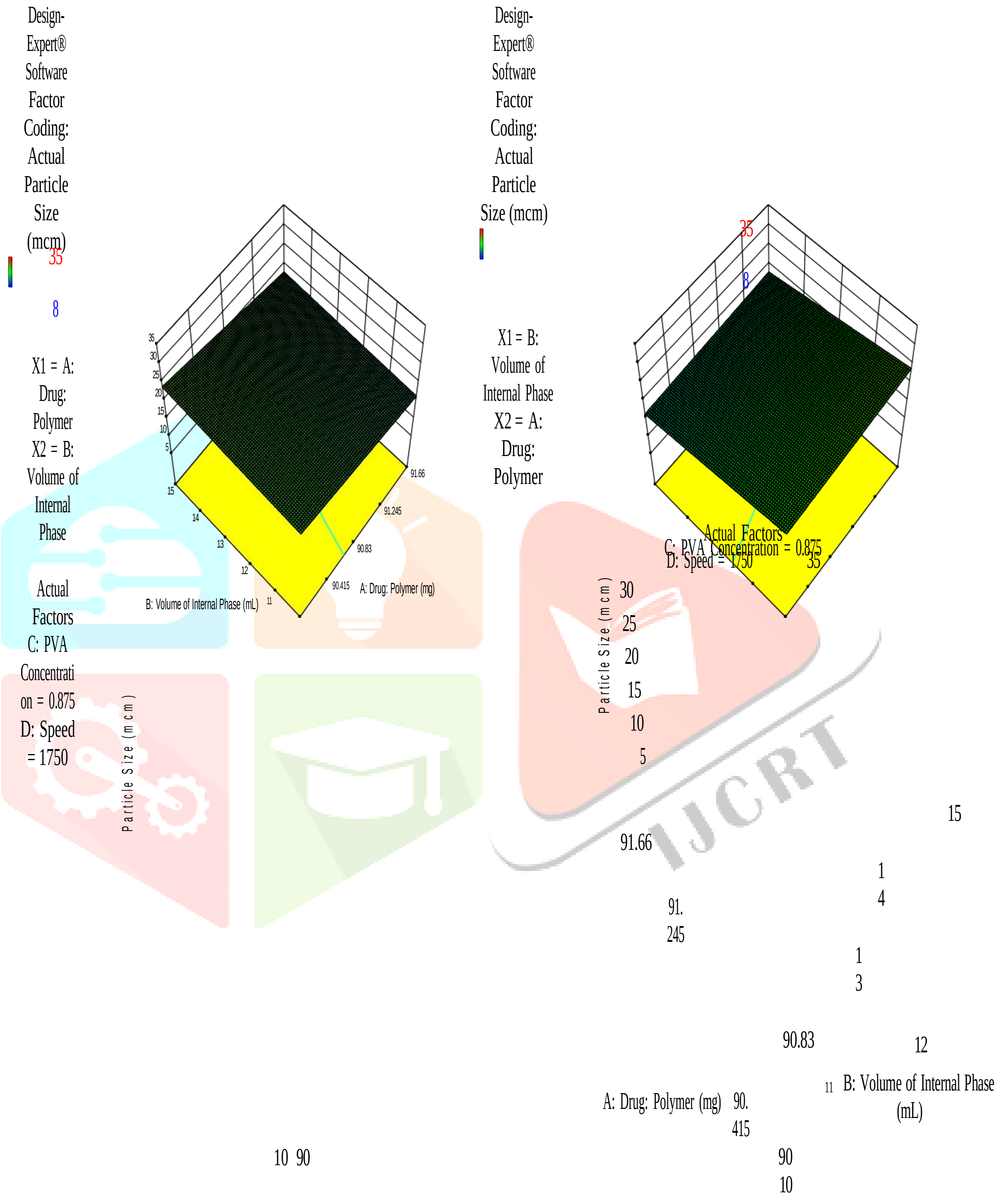

Design-Expert® Software
Factor Coding: Actual
Particle Size (mcm)
35
8
X1 = D: Speed
X2 = A: Drug: Polymer
Actual Factors
B: Volume of Internal Phase = 12.5
C: PVA Concentration = 0.875
Particle Size (mcm)
91.66
91.245
90
A: Drug: Polymer (mg)
15
20
25
1500
1600
1700
1800
1900
2000
D: Speed (RPM)

(c) **(d)**

Figure 4.29: Response Surface Plot:

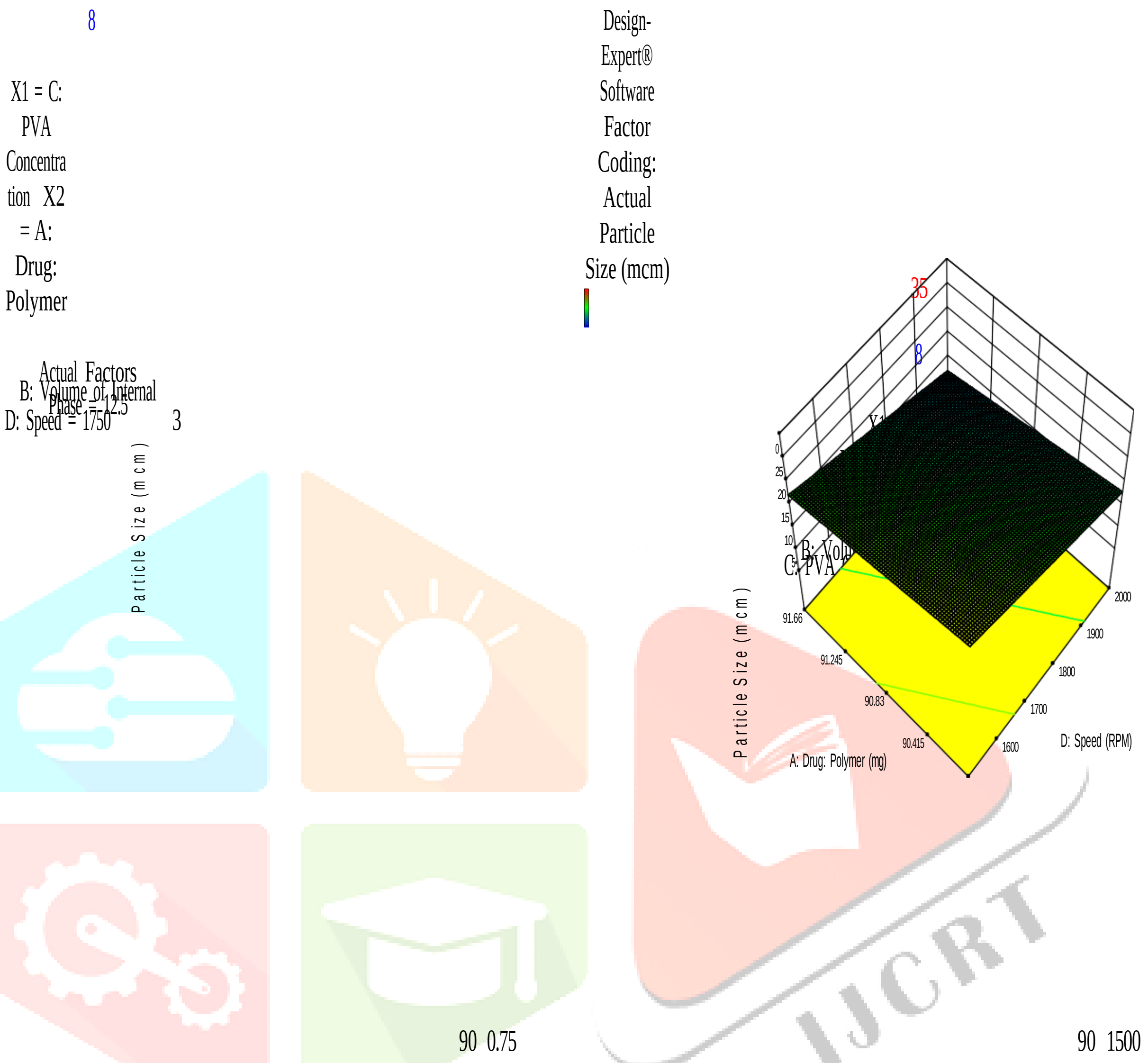
(a) Drug Polymer Ratio and Internal Phase Concentration, (b) Internal Phase Concentration and Drug Polymer Ratio, (c) PVA concentration and Drug Polymer

Ratio and (d) Speed and Drug: Polymer Ratio on P.S. (Y3)


Design-Expert® Software
Factor Coding: Actual
Particle Size (mcm)
35
8
X1 = A: Drug: Polymer
X2 = B: Volume of Internal Phase
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
Particle Size (mcm)
35
30
25
20
15
10
5
15
14
13
12
11
10
B: Volume of Internal Phase (mL)
91.66
91.245
90.83
90.415
90
A: Drug: Polymer (mg)
Design-Expert® Software
Factor Coding: Actual
Particle Size (mcm)
35
8
X1 = B: Volume of Internal Phase
X2 = A: Drug: Polymer
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
Particle Size (mcm)
35
30
25
20
15
10
5
91.66
91.245
90.83
90.415
90
A: Drug: Polymer (mg)
15
14
13
12
11
10
B: Volume of Internal Phase (mL)

(a) **(b)**


Design-Expert® Software Factor Coding: Actual Particle Size (mcm)
35
5
30
25



(c) **(d)**

Figure 4.30: 3D Surface Plot: (a) Drug Polymer Ratio and Internal Phase Concentration, (b) Internal Phase Concentration and Drug Polymer Ratio, (c) PVA concentration and Drug Polymer Ratio and (d) Speed and Drug: Polymer Ratio on % P.S.. (Y3)

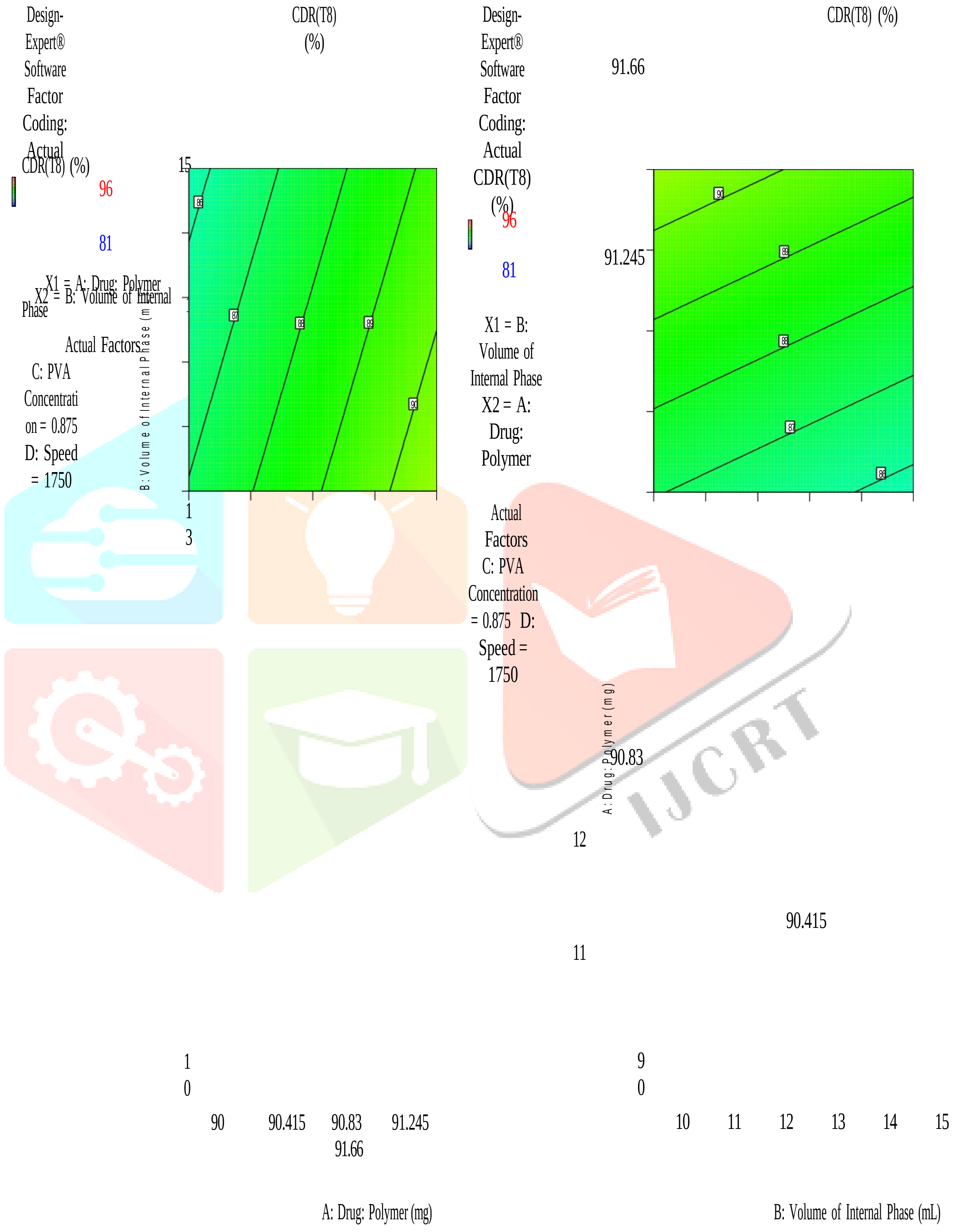
Effect on % CDR (Y4)- Surface Response Study

The positive value of the coefficient of X1 in the equation indicates decrease in the yield with Drug Concentration. The negative value of coefficient of X2 PVA concentration indicates decrease in the response of Y4 i.e. % CDR. The negative value of coefficient X3, time indicates decrease in yield. It indicates the linearity of the surface response and contour plot as shown in figure 4.31 and 4.32.

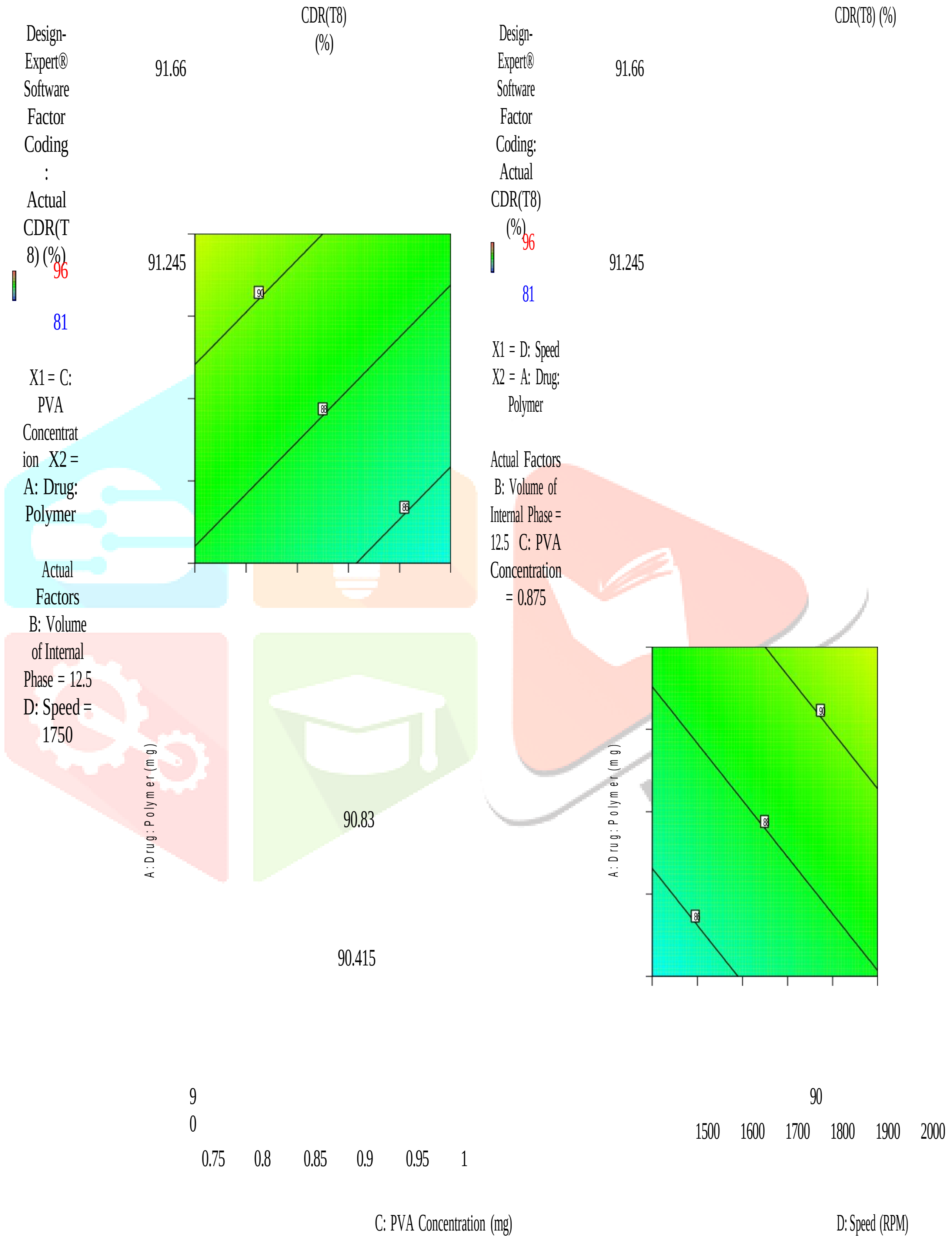
$$\% \ \mathrm{CDR}\ (Y4) = 86 + 1.875 * A - 0.625 * B - 1.375 * C + 1.625 * D$$

Table 4.42: ANOVA Table for Response Y4

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob> F	
Model	135	4	33.75	8.25	0.002502441	Significant
A-Drug: Polymer Ratio	56.25	1	56.25	13.75	0.003452561	
B-Volume of ,kInternal Phase	6.25	1	6.25	1.527777778	0.0242190276	
C-PVA concentration	30.25	1	30.25	7.394444444	0.019957378	
D-Speed	42.25	1	42.25	10.32777778	0.008251239	
Residual	45	11	4.090909091			
Cor Total	180	15				

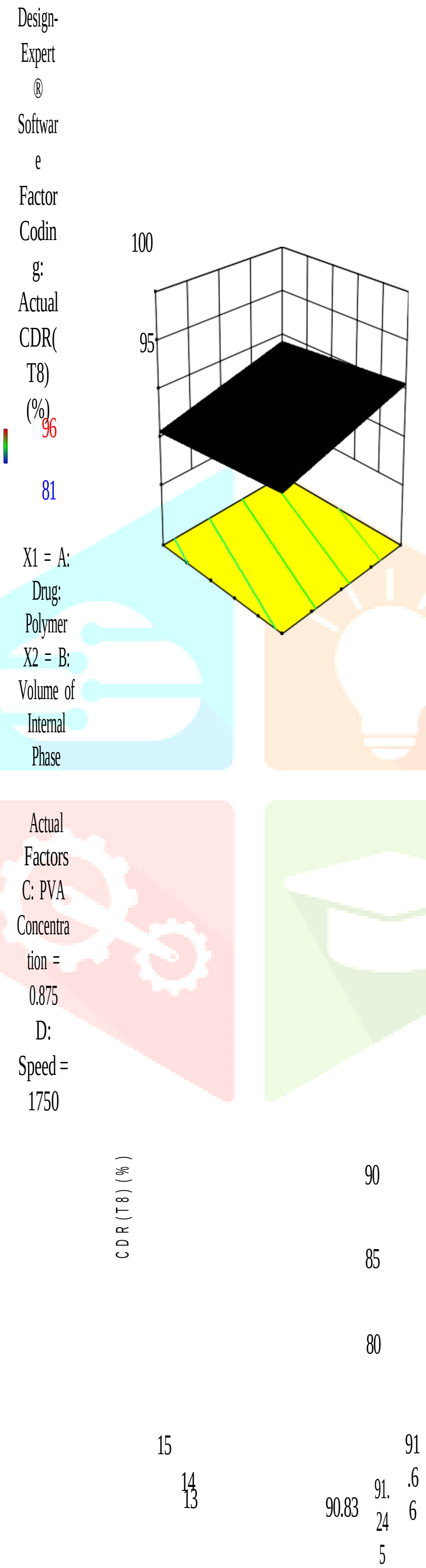

Design-Expert® Software
Factor Coding: Actual
CDR(T8) (%)
96
81
X1 = A: Drug: Polymer
X2 = B: Volume of Internal Phase
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
CDR(T8) (%)
15
13
10
B: Volume of Internal Phase (mL)
88
87
88
89
90
90
90.415
90.83
91.245
91.66
A: Drug: Polymer (mg)
Design-Expert® Software
Factor Coding: Actual
CDR(T8) (%)
96
81
X1 = B: Volume of Internal Phase
X2 = A: Drug: Polymer
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
CDR(T8) (%)
91.66
91.245
90.83
90.415
90
A: Drug: Polymer (mg)
12
11
90
89
88
87
86
10
11
12
13
14
15
B: Volume of Internal Phase (mL)

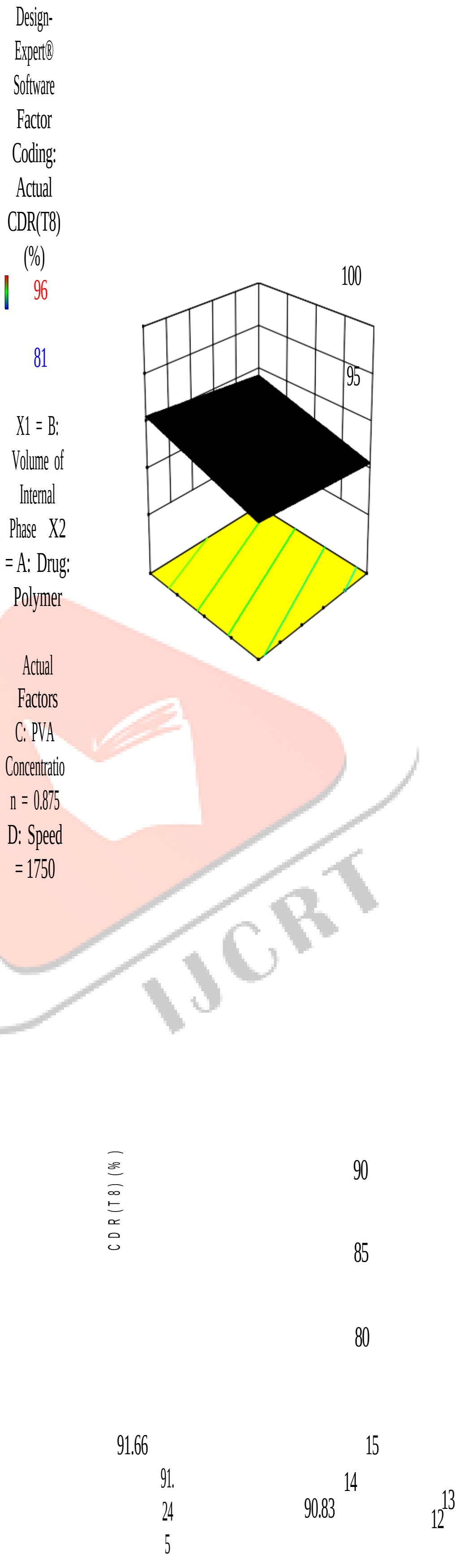
(a) (b)


Design-Expert® Software
Factor Coding: Actual
CDR(T8) (%)
96
81
X1 = C: PVA Concentration
X2 = A: Drug: Polymer
Actual Factors
B: Volume of Internal Phase = 12.5
D: Speed = 1750
CDR(T8) (%)
91.66
91.245
90.83
90.415
90
90
88
86
A: Drug: Polymer (mg)
0.75
0.8
0.85
0.9
0.95
1
C: PVA Concentration (mg)
Design-Expert® Software
Factor Coding: Actual
CDR(T8) (%)
96
81
X1 = D: Speed
X2 = A: Drug: Polymer
Actual Factors
B: Volume of Internal Phase = 12.5
C: PVA Concentration = 0.875
CDR(T8) (%)
91.66
91.245
90
90
88
86
A: Drug: Polymer (mg)
1500
1600
1700
1800
1900
2000
D: Speed (RPM)

(c) **(d)**

Figure 4.31: Response Surface Plot: (a) Drug Polymer Ratio and Internal Phase Concentration, (b) Internal Phase Concentration and Drug Polymer Ratio, (c) PVA concentration and Drug Polymer Ratio and (d) Speed and Drug: Polymer Ratio on % CDR (Y4)


Design-Expert® Software
Factor Coding: Actual
CDR(T8) (%)
96
81
X1 = A: Drug: Polymer
X2 = B: Volume of Internal Phase
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
100
95
CDR(T8)(%)
90
85
80
15
14
13
90.83
91.245
91.66


Design-Expert® Software
Factor Coding: Actual
CDR(T8) (%)
96
81
X1 = B: Volume of Internal Phase
X2 = A: Drug: Polymer
Actual Factors
C: PVA Concentration = 0.875
D: Speed = 1750
100
95
CDR(T8)(%)
90
85
80
91.66
91.245
15
14
90.83
13
12

12
B: Volume of Internal
Phase (mL) 11 10 90.
90 41
5

A: Drug:
Polymer (mg)

(a)

A: Drug: Polymer (mg) 90.
41
5
90
10

11 B: Volume of Internal Phase (mL)

(b)

Design-
Expert
®
Softwar
e
Factor
Codin
g:
Actual
CDR(
T8)
(%)
96

81

X1 =
C:
PVA
Concen
tration
X2 =
A:
Drug:
Poly
mer

Actual
Factors
B:
Volume
of Internal
Phase =
12.5 D:

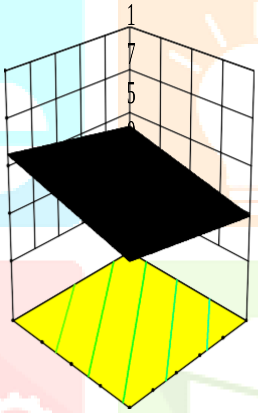
S
p
e
e
d

=

1
7
5

100

95



Design-Expert® Software

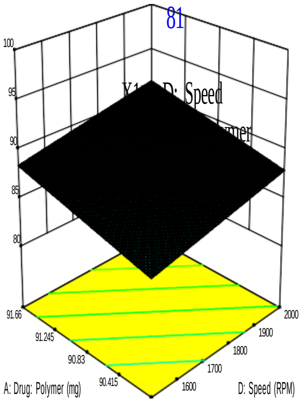
Factor Coding:

Actual

CDR(T8) (%)

96

81



B: Volume of Internal Phase = 12.5 C: PVA Concentration = 0.875

CDR(T8)(%)

90

85

80

CDR(T8)(%)

91.66

91.245

90.83

A: Drug: Polymer (mg)

90.415

90

0.75

0.8

0.85

0.9

C: PVA Concentration (mg)

1

0.95

90

1500

(c)

(d)

Figure 4.32: Response Surface Plot: (a) Drug Polymer Ratio and Internal Phase Concentration, (b) Internal Phase Concentration and Drug Polymer Ratio, (c) PVA concentration and Drug Polymer Ratio and (d) Speed and Drug: Polymer Ratio on % CDR (Y4)

Establishing Design Space and Control Strategy

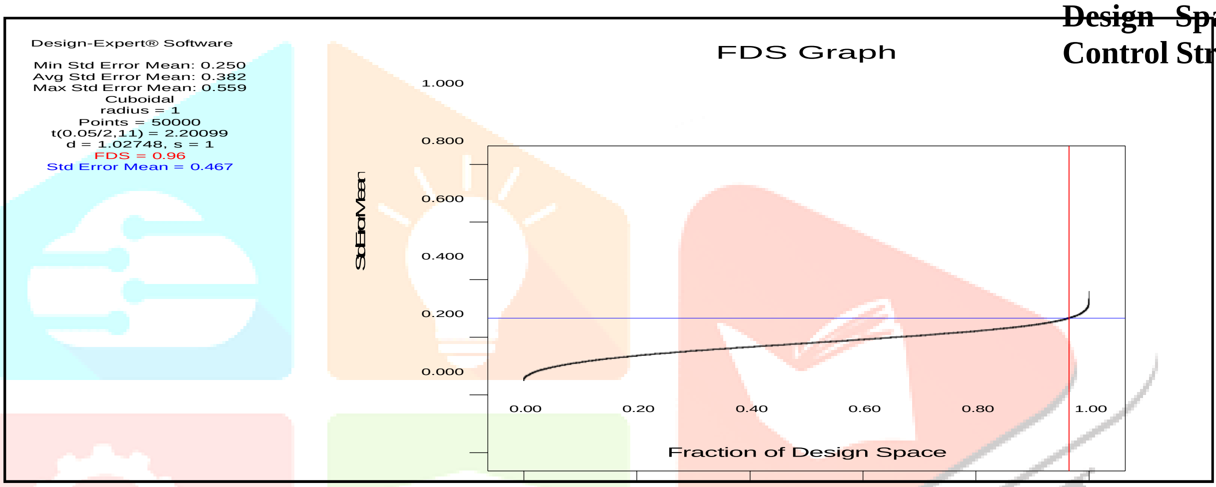


Figure 4.33: FDS Graph

Fraction of Design Space Graph shows the relationship between design space volume and prediction error quantity indicating fraction (percentage) prediction error or lower. A good design will have a flatter and lower curve than a poor design as shown in figure 4.32. Flatter means the overall prediction error will be constant. Lower means the overall prediction error will be smaller. FDS should be at least 0.8 or 80% of exploration, and 100% for robustness testing. In the extraction of mucilage FDS was 0.956 or 95%, which indicating robust Standard error of prediction relates to the prediction interval around a predicted response at a given pair of factor levels.

Validation:

From the polynomial equations generated in response using intensive grid and integrated search was done over the experimental field and one formulation was selected. The predicted and experimental values of selected batch responses and the percentage error indicate high prognostic ability using RSM optimization. The percentage error varied between 0.6 and 1.9 from contrast of experimental responses with those of anticipated responses indicating validity of the applied model.

During the independent variable characterization study, the impact of the parameters Drug Concentration (mg), internal Phase Volume (mL), PVA Concentration (mg) and Speed (RPM) were assessed. The criteria considered of response % yield-Y1, E.E. (Y2), Particle Size (µm) and

% CDR are between 75-85%, 80-90 %, 8-15 µm and 85-95 % respectively. This study lead to the knowledge space and ultimately design space from a multidimensional combination of intensity, solvent volume and time leads to the acceptable operating ranges for isolating mucilage with respect to target product profile. Design space shown in figure 4.34 and 4.35 also called as overlay plot which is shaded region with yellow color indicates that region of successful operating ranges.

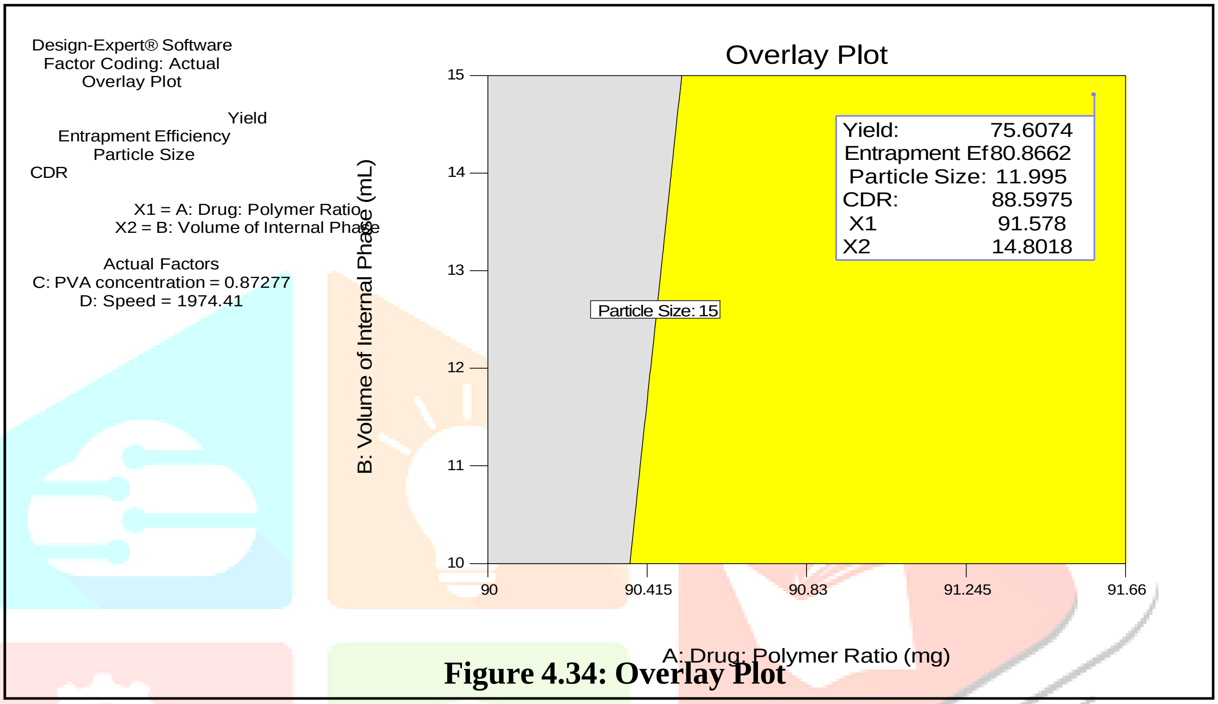


Figure 4.34: Overlay Plot

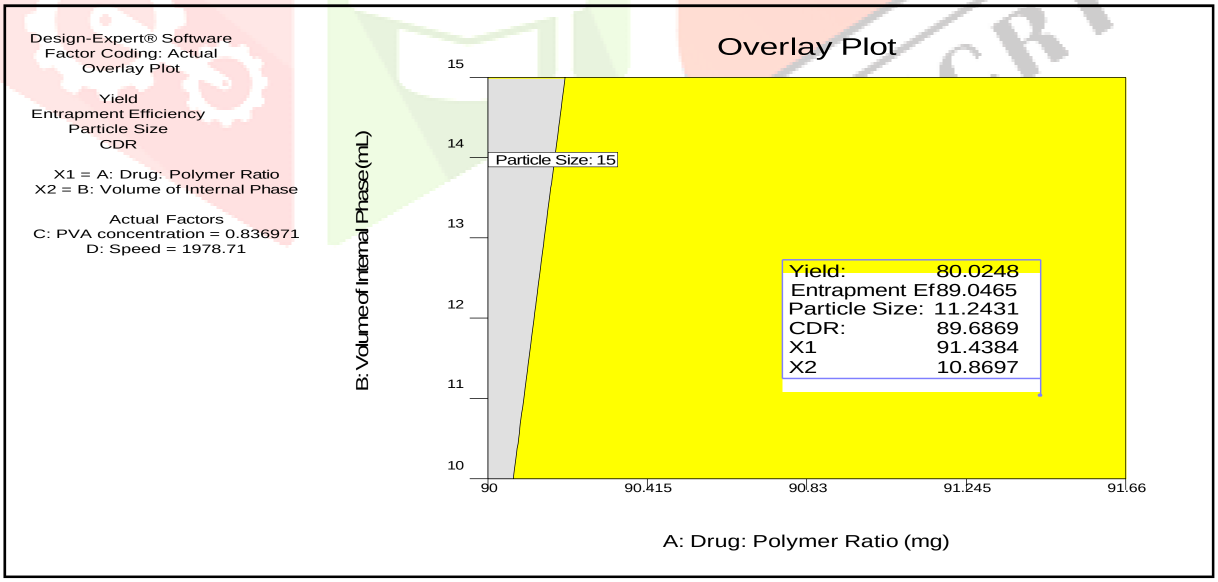


Figure 4.35: Overlay Plot

Check point analysis of Validation Batches

Two extra designs, check point formulation batches FEMS1 & FEMS2 were developed and predicted and experimental values of dependent variables were compared using a pooled t - test at 95% confidence interval, 4- degree of freedom and $p < 0.05$ of two batches FEMS1 & FEMS2 thus starting validity of created model.

Table 4.43: Validation Batches (FEMS1 & FEMS2): Predicted Response

Batch No	Drug Con.- mg (X1)	Int. Phase Vol.-mL (X2)	PVA Con.- mg (X3)	Speed- RPM (X4)	Yield- % (Y1)	E.E.- % (Y2)	P.Size- µm (Y3)	CDR T8- % (Y4)
FEMS 1	91.57	14.8	0.87	1974.41	75.6	80.86	11.99	88.59
FEMS 2	91.43	10.86	0.83	1978.71	80.02	89.04	11.24	89.68

Table 4.44: Validation Batches (FEMS1 & FEMS2): Actual Response

Batch No	Drug Con.- mg (X1)	Int. Phase Vol.-mL (X2)	PVA Con.- mg (X3)	Speed- RPM (X4)	Yield- % (Y1)	E.E.- % (Y2)	P.Size- µm (Y3)	CDR T8- % (Y4)
FEMS 1	91.57	14.8	0.87	1974.41	81.34	81.01	11.01	87.96
FEMS 2	**91.43**	**10.86**	**0.83**	**1978.71**	**85.32**	**88.55**	**11.89**	**88.71**

% Cumulative Drug Release Profile:

Table 4.45: % Cumulative Drug Release Profile OZ Microsponge (FEMS1 and FEMS2)

Time (hr)	**FEMS1 (Mean ± S.D.) (n = 3)**	**FEMS2 (Mean ± S.D.) (n = 3)**
0	0	**0**
1	25.13±1.48	**26.89±1.21**
2	35.33±1.23	**38.61±2.43**
3	43.95±1.56	**47.31±1.09**
4	50.72±2.75	**54.82±1.23**
5	62.77±2.43	**62.48±1.56**
6	71.42±2.75	**75.51±2.82**
7	80.13±1.36	**82.16±1.12**
8	87.96±0.29	**88.71±1.39**

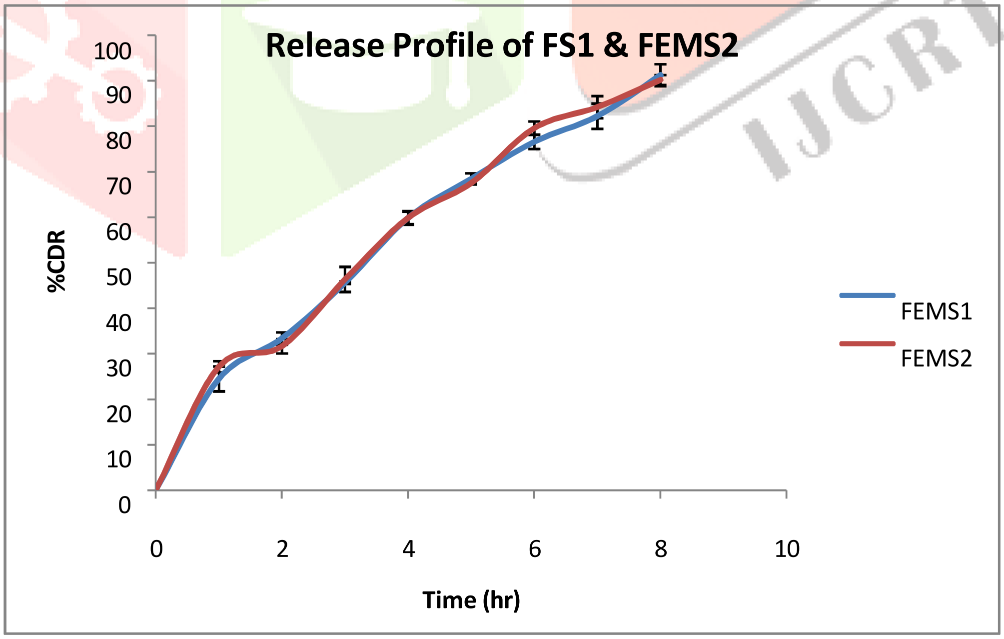


Figure 4.36: % Cumulative Drug Release Profile of OZ Microsponge (FEMS1-FEMS2)

Selection of Optimized Formulation

FEMS2 was found and selected validated optimized Batch with having particle size of 11.89 µm,

% Yield of 85.32%, CDR of 88.71 % and desirability factor of 0.792 which was further used for subsequent loading into gel for topical drug delivery system.

Analysis of Optimized Formulation 4.3.4.1.12.1.

FTIR Spectrum of FEMS2

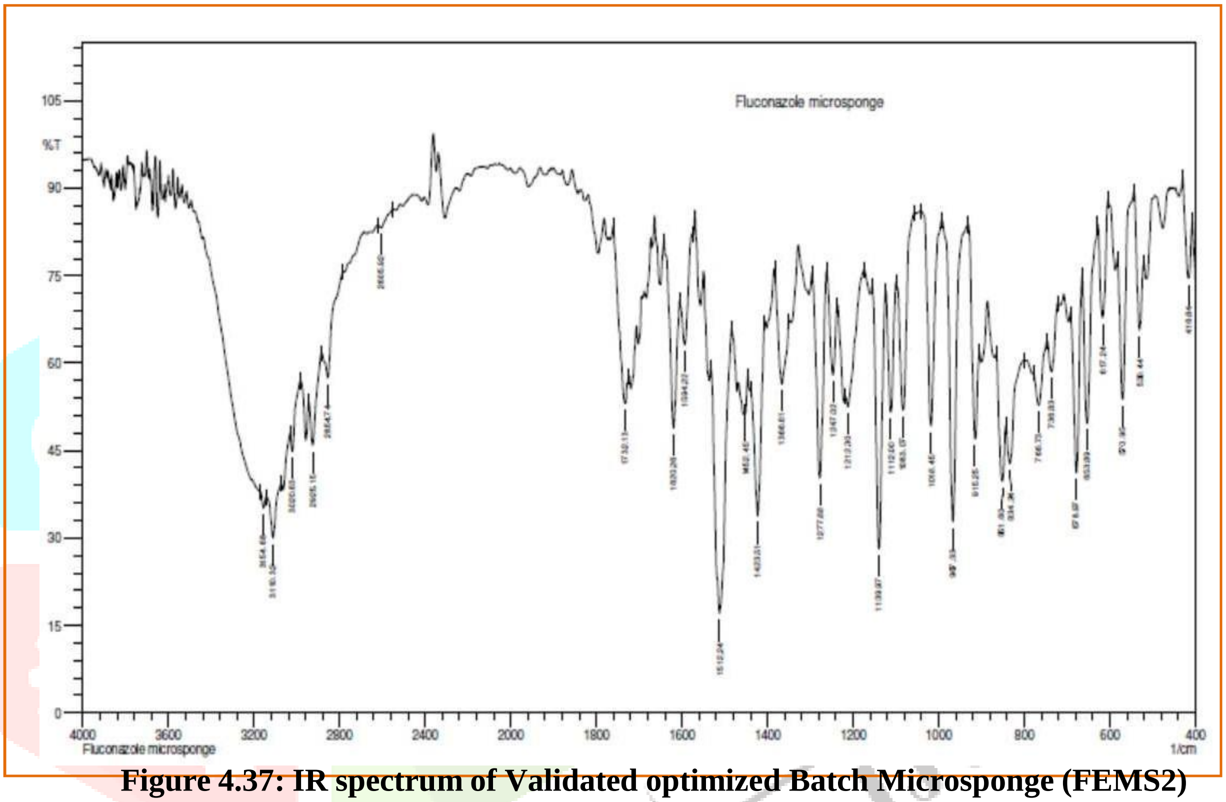


Figure 4.37: IR spectrum of Validated optimized Batch Microsponge (FEMS2)

Table 4.46: IR Peaks of Validated optimized Batch Microsponge (FEMS2)

Type of Vibration	Observed Wave number cm^{-1})	Peak obtained in mixture cm^{-1})
C=N Stretching	1600-1700	1630.86
C-F Stretching	1000-1400	1178.39
C-H Stretching	3000-3100	3106.83
C=O Stretching	1690-1760	1736.09

6. SUMMARY AND CONCLUSION

SUMMARY

The QbD system offers product quality and consistency. MDS can be used to deliver controlled release topical DDS

CHAPTER-I Provides introduction to Skin, Topical Gel, QbD, DoE, Microsponge-methods of preparation, applications, and characterization, Disease and its Treatment, Drug and Excipients profile.

CHAPTER-II provides the aim, objective and plan of investigation to carry out formulation and development of Oxaprozin Microsponges loaded Topical Gel.

CHAPTER-III discusses past work Topical Gel, QbD, DoE, Microsponge, Drug and Polymer in a review of the literature..

Chapter-IV discusses in detail methodology of Oxaprozin Microsponges using EC and ERS 100 polymers for Preformulation, Preliminary selection of formulation and process variable, CQAs, QbD approach, DoE, Characterization of MS, Check Point Analysis and MS loaded Gel. Further, this chapter describes preparation of Oxaprozin microsponges and evaluation for % yield, % Entrapment efficiency, % drug content, SEM, FTIR spectral studies, and *% CDR*. Preparation of optimized microsponges gels was evaluated for *In vitro* diffusion studies, Anti- Fungal Study and primary skin irritation studies. It also describes the results and discussion of the thesis. Production yield and loading efficiency were calculated for all the microsponge formulations average of three determinations was considered and was found to be reproducible. The loading efficiency of the microsponge formulations were from **80%-90%.** The FTIR spectrum of microsponge formulations shows the characteristic bands and all other peaks observed with individual compound have remained unaffected in microsponges formulations indicates microsponges formed were not a chemical reaction product, hence, the drug exists in original form and available for the biological action. SEM suggests the optimized microsponges were finely spherical, uniform in shape, no intact drug crystals are seen visually and inner structure was consisted of porous in nature with void spaces. The comparative dissolution profiles and regression coefficient values were also discussed. Further chapter describes the study of

.

Chapter-VI briefly explains the discussion of the whole thesis with brief summary and conclusion.

Chapter-VII briefly explains references.

CONCLUSIONS

Microsponge containing Aceclofenac sodium or Oxaprozin was prepared by a quasi emulsion diffusion method using Eudragit RS100 and Ethyl cellulose using QbD approach. All the were subjected for for % yield, % Entrapment efficiency, % drug content, **s**canning electron microscopy, FTIR spectral studies, and *in vitro* drug release studies, the low SD and CV values indicate drug content was uniform and reproducible in all the formulations.

The IR spectral analysis suggested compatibility between the drug and formulation additive. The drug exists in original form and available for the biological action.

The dissolution parameters were studied by using dissolution software PCP DISSO V.3 for microsponges formulations which proved increase in drug concentration, drug release was decreased.

he microsponges which gave better physical, morphological and % encapsulation in either of the polymers were selected for incorporation into the Topical gel formulations. Various Topical gel formulations with Oxaprozin or Aceclofenac in free form and in microsponges delivery system were formulated and the in-vitro release studies were carried out.

By considering all the results of Check Point Analysis the microsponges formulations and further proceed for topical gel formulations and Characterization of same. It shows that the release of drug from microsponges incorporated into the Topical gel, follow Higuchi (matrix) diffusion model. No changes found after stability analysis for a period of 3 months.

From the study it can be concluded that it is possible to design a topical polymeric microsponges formulation for anti fungal drug Oxaprozin and Aceclofenac may increase efficacy and patient compliance which are of prime importance. However, in – vivo experiments are essential to establish the actual usefulness of these microsponges.

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