CHAPTER-1
INTRODUCTION
INTRODUCTION

Mental health is “a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community”[1].

1.1 PSYCHIATRIC DISORDER

Psychiatric disorders are characterized by imbalances between person’s thinking, perception and behaviour. The patient usually remains upset, suffers from extreme anxiety, feels lack of freedom or behaves unexpectedly to a stressful life conditions. Dispute or disagreement between the person and society cannot be considered as psychiatric disorder but it depends on individual’s behaviour, psychology and biological dysfunction. The psychiatric disorders often lead to severe diseases like CVS (cardiovascular) disorder, diabetes, cancer, obesity etc. Literatures showed good health is always linked with the positive mental health [2].

1.1.1 Classification of psychiatric disorder

Psychiatric disorders are classified into two major categories.

a. ICD-10 (1992)

b. DSM-IV-TR (2000)

In ICD-10 (International Classification of Diseases, 10th Revision, 1992), WHO has classified various mental and behavioural disorders (MBD’s) in chapter ‘F’ which codes them from F00 to F99 (Table 1). Several versions of ICD-10 are also available. American Psychiatric Association (APA’s) has classified mental disorders given as DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revision, 2000) [2].
Table 1: Mental and behavioural disorders according to ICD-10

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Code</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F00-F09</td>
<td>Organic, including symptomatic disorders</td>
</tr>
<tr>
<td>2</td>
<td>F10-F19</td>
<td>Mental and behavioural disorders due to psychoactive substance use</td>
</tr>
<tr>
<td>3</td>
<td>F20-F29</td>
<td>Schizophrenia, schizotypal and delusional disorders</td>
</tr>
<tr>
<td>4</td>
<td>F31-F39</td>
<td>Mood (affective) disorders</td>
</tr>
<tr>
<td>5</td>
<td>F40-F48</td>
<td>Neurotic, stress-related and somatoform disorders</td>
</tr>
<tr>
<td>6</td>
<td>F50-F59</td>
<td>Behavioural syndromes associated with physiological disturbances and physical factors</td>
</tr>
<tr>
<td>7</td>
<td>F60-F69</td>
<td>Disorders of adult personality and behaviour</td>
</tr>
<tr>
<td>8</td>
<td>F70-F79</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>9</td>
<td>F80-F89</td>
<td>Disorders of psychological development</td>
</tr>
<tr>
<td>10</td>
<td>F90-F98</td>
<td>Behavioural and emotional disorders with onset usually occurring in childhood and adolescence</td>
</tr>
<tr>
<td>11</td>
<td>F99</td>
<td>Unspecified mental disorders</td>
</tr>
</tbody>
</table>

In DSM-IV-TR system, five separate axes are considered for thorough evaluation of mental health status of an individual patient (Table 2).

**Table 2: Five axes of DSM-IV-TR**

<table>
<thead>
<tr>
<th>AXIS I</th>
<th>Clinical psychiatric diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AXIS II</td>
<td>Personality disorders and mental retardation</td>
</tr>
<tr>
<td>AXIS III</td>
<td>General medical conditions</td>
</tr>
<tr>
<td>AXIS IV</td>
<td>Psychosocial and environmental problems</td>
</tr>
<tr>
<td>AXIS V</td>
<td>Global assessment of functioning: current and in past one year (rated on a scale)</td>
</tr>
</tbody>
</table>

It is a useful approach for the diagnosis of patient. Similarly ICD-10 also has multi-axial classification system.
Psychiatric disorders can also be classified as Psychosis and Neurosis, in former patient is not aware of his illness and refuses to take treatment, while in later insight is present. Psychosis includes schizophrenia and affective mood disorders (mania, depression, bipolar disorder). Neurosis includes obsessive compulsive disorder (OCD), phobia, anxiety, post traumatic disorders etc [3]. Psychiatric disorders are generally associated with the abnormal activity of neurotransmitters, which are the endogenous chemical that communicates information throughout the brain and body; mainly dopamine and serotonin are involved [4].

1.1.2 Types of psychiatric disorder

a. Depression

According to WHO, depression is the third most prevalent disease across the world. Psychotic depression is characterized by the presence of severe depression along with psychosis but there is absence of mania associated with bipolar disorder [5,6].

b. Anxiety

Anxiety is most commonly occurring mental disorder which includes phobias like panic, anxiety, post-traumatic stress and separation anxiety. Anxiety is more prevalent in developed countries and prevalent rate is higher in women than in men [7].

c. Bipolar disorder

Bipolar disorder is much more related to mood disturbance compared to thought disturbance. Person suffering from bipolar disorder experiences mood fluctuations like mood elevations (mania) and depression, with variable intensity and persistence rate. Arousals of psychotic symptoms are manifested in the person’s mood. Patient may hear voices that led them more depressed, patients with elevated mood feels that they are special, have super powers and can do amazing things. It occurs more in women [8].

d. Schizophrenia

Schizophrenia is associated with interferences in the thinking, perception and social behaviour. The psychotic symptoms persist for at least six months, and lead to the
decreased functional ability of the person. The symptoms and duration of schizophrenia are subjected to inter-subject variation. Eugen Bleuler, a Swiss psychiatrist coined the word “Schizophrenia” for the first time in 1908 in medical history. It was derived from the combination of Greek words “skhizein” means split and “phren” means mind. So Bleuler emphasizes that this disorder was due to the breaking of the associative threads or the destruction of the forces that connect one function to the next. The prevalence rate for schizophrenia across the globe is 0.5% to 1%. It affects men at an early age than women. Patients with schizophrenia pose high risk for suicide [6].

Schizophrenia can be classified as:

a. Paranoid type: These patients have delusions and hallucinations but their cognitive functions are not affected (do not show derailment of speech).

b. Disorganized type: People show major or inappropriate changes in speech and behaviour. They are indulged in own thoughts, activities and behaviour and remain busy at looking and caring them.

c. Catatonic type: These patients show typical disorganized behaviour, like catatonic immobility, waxy flexibility and wild agitation with pacing excitably. They appear odd and repeatedly show unusual behaviours by making faces or shaking the body.

d. Undifferentiated type: Patients show many symptoms of schizophrenia which cannot be classified into one single class.

e. Residual type: These patients have history of schizophrenia but the symptoms are no longer present. They have some leftover symptoms like negative beliefs, unusual ideas that are not fully delusional, social withdrawal, inactivity and flat affect. An unusual perceptual experience is also evident [9].

e. Schizophreniform disorder

It is similar to schizophrenia except that the symptoms persist for less than six months. The illness may completely resolve or may persist and progress to other
psychiatric diagnoses, such as schizophrenia, bipolar disorder or schizoaffective disorder.

**f. Schizoaffective disorder**

The disorder is associated with the symptoms of both schizophrenia and mood disturbance occurring concurrently or vary with time from one to another.

**g. Drug induced psychosis**

Use of certain CNS active drugs causes the appearance of psychotic symptoms. Some of these drugs are marijuana, cocaine, LSD, amphetamines and alcohol. When these drugs are washed off from the biological system, the symptoms of psychosis disappear. Suitable medical treatment is required to remove the symptoms of psychosis.

**h. Organic psychosis**

Physical illness or a head injury, sometimes results in psychosis, known as Organic psychosis. But it should be confirmed by thorough medical examination (e.g. tests, investigations, brain scan).

**i. Brief psychotic disorder**

When the person is suffering from major stress in life (e.g. death of family member), some psychotic symptoms suddenly appear which persists for one month or less.

**j. Delusional disorder**

The disorder is associated with very strong disbeliefs and is not accompanied by any perception changes or hallucinations. It doesn’t affect a person’s functional ability.

**k. Frequent mental distress**

It is characterized by poor mental health (like stress, depression and emotional distress) of a person for more than 14 days; during last one month.
1.1.3 Symptoms of psychiatric disorder

There are no well-defined features to differentiate between various types of psychiatric disorders. It is necessary to review the patient’s history, cluster of symptom and long term patient’s observations during the treatment period. Clinical symptoms may vary among individuals and with the age and different stages of disease. Some of the symptoms associated with psychosis are thought disorder, delusions, hallucinations, abnormal affect, disorganized behaviour, cognitive difficulties etc.

The symptoms are further classified as “positive symptoms”, “negative symptoms” and “disorganized symptoms”. In positive symptoms, abnormal behaviour like delusions and hallucinations are more prominent. Negative symptoms include social withdrawal and lack of normal behaviour (speech, motivation etc). Disorganized symptoms are characterized by disorganized speech, abnormal/unpredictable behaviour [10].

1.1.4 Causes of psychiatric disorder

There are several reasons that are responsible for psychosis and it varies from person to person and according to type of particular disorder. Some of the causes are:

   a. Genetic factor: Several different genes are involved in schizophrenia and other psychotic disorders.

   b. Chemical imbalance in brain was found to be associated with several major psychiatric disorders, like too high levels of neurotransmitters dopamine, serotonin and their interplay. Sometimes norepinephrine and glutamate systems are also involved.

   c. Enlarged ventricles in brain that lead to incomplete or weaker development of brain and its parts.

   d. Less brain activity in frontal lobes and brain injury.

   e. Viral infection (prenatal exposure to influenza virus/ or if the mother is suffering from influenza during pregnancy, the fetus may have more chances of getting schizophrenia).
f. Birth complications: e.g. loss of oxygen (anoxia), forceps delivery and fetal distress may cause brain damage that may lead to schizophrenia later.

g. Excessive stress: due to traumatic life events like death of loved ones, stressful environment in family or jobs, increases the risk of relapse.

h. Poor coping skills: Patients inability to handle stress, lack of social skills, inability to relax will trigger the onset of schizophrenia or the relapse.

i. Use of psychoactive drugs, like cannabis, alcohol, caffeine, etc.

j. Migration, discrimination, childhood trauma, separation in families, parenting factors, child abuse, family history, etc [11].

**Treatment**

Antipsychotics are used for the treatment of various types of psychosis. The term “neuroleptics” are synonymously used that means “taking hold of the nerves”. These drugs decreases or eliminates the delusions and hallucinations and help the people to think more clearly. It also decreases negative or disorganized symptoms.

**1.2 ANTIPSYCHOTIC DRUGS**

Antipsychotic drugs are used in the treatment of various psychotic disorders and associated symptoms. The term major tranquilizers, neuroleptics, ataractics, anti-schizophrenic drugs, D2 receptor blockers are synonymously used [3].

**1.2.1 Classification of antipsychotic drugs**

Antipsychotic drugs can be broadly classified as Typical and Atypical type, depending upon their mechanism of action (Fig 1). Typical antipsychotics act by blocking dopamine (D2) receptors whereas atypical antipsychotics act by other mechanisms.
1.2.2 Mechanism of action of antipsychotic drugs

Generally the antipsychotics act by decreasing the dopamine level in the brain. These drugs act by blocking the D$_2$-receptors present in specific regions of brain, like mesolimbic–mesocortical system, nigro-striatal system and tubero-infundibular system. The D$_2$-receptors present in the mesolimbic system is responsible for emotional reactions while extrapyramidal side effects are controlled due to the D$_2$-receptors present in other systems.
receptors present in nigro-striatal system. Blockage of D₂ receptor in tubero-infundibular system controls the hyperprolactinaemia (Fig 2) [2].

Fig 2: Distinct areas of brain for D₂ blockade action

Typical antipsychotics (like chlorpromazine) are least potent and are highly sedative and it acts by blocking D₂ receptors. Haloperidol is highly potent but causes more extrapyramidal symptoms (e.g. acute muscular dystonia, Parkinsonism, akathisia, malignant neuroleptic syndrome, tardive dyskinesia). The second generation (atypical) antipsychotics acts by blocking 5-HT₂ and α-adrenergic receptors and may or may not block D₂ receptors. These drugs have tremendous advantages over conventional antipsychotics since they are more effective against negative symptoms of schizophrenia and hence cause less extrapyramidal symptoms and are less sedating. It includes clozapine, olanzapine, quetiapine, ziprasidone, risperidone etc. Risperidone is one of the most effective drugs used in the treatment of schizophrenia [12].

1.3 RISPERIDONE

Risperidone is a benzisoxazole derivative used for treatment of various psychiatric conditions including schizophrenia. The chemical structure of risperidone is shown in Fig 3.
Fig 3: Structure of risperidone

1.3.1 Physicochemical properties

IUPAC name: 3- [2- [4- (6- fluoro- 1, 2-benzisoxazole-3-yl) piperidino] ethyl] -2-methyl- 6, 7, 8, 9- tetrahydro- 4H- pyridol [1, 2-a] pyrimidine- 4- one

Official in: British Pharmacopoeia (BP) 2005

Appearance: It is available as white or off-white powder

Molecular formula: C_{23}H_{27}FN_4O_2

Molecular weight: 410.49 Daltons

Solubility: It is insoluble in water (soluble at pH 4 only)

Soluble in methanol and dilute acid

Melting point: 170°C

Log P: 2.5

pKa: 8.24 (it is a weak base due to the presence of 2 tertiary amines)[13,14].

1.3.2 Pharmacology

Risperidone binds to dopamine, histamine, muscarinic, α-adrenergic and serotonin receptors. Blockage of dopamine transmission in various areas of brain is responsible for its therapeutic benefit in schizophrenia and others psychological issues. When compared to clozapine, it is more potent and safe as it exhibits lesser adverse effects like seizure precipitation and extrapyramidal symptoms [3].
1.3.3 Pharmacokinetics

Absorption: Risperidone is well absorbed orally and has bioavailability of 70%. Peak plasma concentration is achieved within 1-2 hours. Food has no effect on absorption of risperidone.

Distribution: It is rapidly distributed and has volume of distribution 1 to 2 L/kg.

Metabolism: It is metabolized (at the alicyclic site of pyrimidinone ring) by cytochrome P-450 2D6 enzymes to 9-hydroxy risperidone which is equally active as the parent drug but exhibits less permeability to blood brain barrier (BBB) as compared to risperidone. The pharmacological action of risperidone is a result of cumulative effect of both the moieties.

Elimination: The risperidone shows half-life of 3 hours in extensive, 11 hours in intermediate and 20 hours in poor metabolizers respectively. After one week 70% of drug is excreted in urine and 14% in faeces. It is also excreted through milk, so it not indicated in nursing mother [15].

Plasma protein binding: 88% of risperidone and 77% of 9-hydroxy risperidone binds to plasma protein [13].

1.3.4 Therapeutic uses/ indications

It is used in the treatment different types of schizophrenia, psychiatric disorders, affective symptoms, behavioural disturbances, aggressiveness, conduct and other disruptive behaviour disorders in children.

1.3.5 Contraindications

Due to the absence of safety data risperidone is contraindicated for the persons who are allergic to it, in pregnant and lactating women and for the children less than 5 years.

1.3.6 Drug interaction

Risperidone interacts with several drugs like artemether, carbamazepine, donepezil, fluoxetine, galantamine, indinavir, itraconazole, lumefantrine, paliperidone,
paroxetine, tacrine, tacrolimus, terbinafine, ziprasidone, voriconazole, vorinostat, zuclopenthixol, triprolidine, tetrabenaize, etc [16].

1.3.7 Marketed formulations of risperidone

1. **Risperidone tablets:** It is available in various dosage strengths of 0.25, 0.5, 1, 2, 3 and 4 mg tablets.

2. **Risperidone oral solution:** It is available as 1 mg/ml oral solution.

3. **Risperidone rapidly or mouth dissolving tablets:** This is the latest advancement for managing acute psychosis. Risperidone is available as M-Tab. It is especially designed for children and elderly patients, who have swallowing problems. The disintegration time for M-tab is approximately 29 seconds. It is available as 0.5, 1, 2, 3 and 4 mg tablets [17].

4. **Long acting parenteral risperidone:** USFDA has recently approved Risperdal® Consta™, a microsphere preparation designed to be administered Intramuscularly (IM). It is available in high dose of 25 to 50 mg for IM gluteal injection. It suffers from the drawback that an initial oral dose should be provided along with this injection. After three weeks, the microsphere releases the drug and maintains the therapeutic levels for six weeks (Fig 4). To maintain the steady state plasma levels (for 4-6 weeks) it should be administered bi-weekly. Usually steady state can be achieved after 4th injection of risperidone [18,19]. Risperidone formulation is available as injection, powder for suspension, extended release 12.5mg, 25mg, 37.5mg and 50mg [20].
1.4 VESICULAR SYSTEMS

Vesicular systems are prepared by the self-assembly of the lipids/surfactants to form the bilayers where an aqueous space is present in the core. It was first reported by Bingham et al in 1965. Vesicular systems include liposomes, niosomes, transferosomes, ethosomes etc. Drug delivery via vesicular system offer many advantages like increased solubility, high permeability, acts as a carrier for various drugs which exhibits different solubility. It also acts as drug reservoirs, allows drug targeting and control release. It prolongs the residence time of drug in the body, reduces toxicity (if selective uptake is achieved), improves bioavailability and reduces cost of therapy, delays elimination of rapidly metabolizable drug. These systems are widely used in different fields of science like immunology, membrane biology, diagnostic techniques and genetic engineering [21].

1.4.1 Different types of vesicular systems

Different types of vesicular system like conventional liposomes, transferosomes, ethosomes and niosomes have been shown in Fig 5.
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Vesicular systems namely liposomes, transferosomes and ethosomes are principally composed of phospholipids, which offer similar advantages like biodegradable, biocompatible, high entrapment efficiency, provide targeted controlled and prolonged release with improved drug delivery across the skin. They also suffer from the common drawbacks due to the presence of phospholipids like variable purity of phospholipids, expensive, chemical instability, prone to oxidative degradation and hydrolysis, high production cost as the handling of phospholipids require inert/cryogenic atmosphere. In addition, these systems also exhibit drawbacks like sedimentation, fusion of vesicles during storage, drug leakage from the vesicular formulations, scale up and sterilization issues, difficult to obtain products with reproducible properties, short half-life, suitable for parenteral administration but cannot withstand in presence of bile salts when given orally.

Notably, niosomes offer similar advantages as that of liposomes. It principally composed of non-ionic surfactants that are cost effective, inert and stable than phospholipids. It does not require any special conditions during its preparation (low
temperature & inert atmosphere), can withstand in presence of bile salts \textit{in-vivo}, increased half life, serves as solubilizing agent for poorly soluble drugs. Surfactant properties will modify the structure of stratum corneum and render them loose and more permeable to drugs. In view of these facts, niosomes are generally preferred over other vesicular systems in drug delivery system [22,23].

1.5 NIOSOMES

1.5.1 Definition

Niosomes are type of vesicular drug delivery systems, where an aqueous space is entrapped within bilayer structures formed by the self assembly of non-ionic surfactants, along with the cholesterol and charge inducer. They are similar to liposome structurally and show similar \textit{in-vitro} and \textit{in-vivo} behaviour. The aqueous space is present in the core and polar groups are in contact with them, whereas the bilayer assembly of hydrophobic tail is shielded away from that [24]. The typical structure of niosomes is shown in Fig 6.

![Fig 6: Typical structure of niosomes](image)

1.5.2 Classification of niosomes

Niosomes can be classified depending on the lamellarity, size and specialized niosomes as shown in Table 3 [25,26].
Table 3: Classification of niosomes

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>According to the lamellarity</td>
<td>Multi-lamellar vesicles (MLV) 1-5µm in size</td>
</tr>
<tr>
<td></td>
<td>Large unilamellar vesicles (LUV) 0.5-1µm</td>
</tr>
<tr>
<td></td>
<td>Small unilamellar vesicles (SUV) 25-500nm</td>
</tr>
<tr>
<td>According to the size</td>
<td>Small niosomes (100nm-200nm)</td>
</tr>
<tr>
<td></td>
<td>Large niosomes (800nm-900nm)</td>
</tr>
<tr>
<td></td>
<td>Big niosomes (2µm-4µm)</td>
</tr>
<tr>
<td>Specialized niosomes</td>
<td>Proniosomes</td>
</tr>
<tr>
<td></td>
<td>Surfactant ethosomes</td>
</tr>
<tr>
<td></td>
<td>Elastic niosomes</td>
</tr>
<tr>
<td></td>
<td>Polyhedral niosomes</td>
</tr>
<tr>
<td></td>
<td>Discomes</td>
</tr>
<tr>
<td></td>
<td>Aspasome</td>
</tr>
</tbody>
</table>

1.5.3 Composition of niosomes

Surfactants: Surfactant is the principle component in bilayer formation of the niosomes. Surfactants are amphiphilic in nature and it contains both the polar and non-polar parts within the same molecule. Non-polar part can be alkyl, fluoroalkyl or steroidal in nature that are attached by ether, amide or ester bonds with different hydrophilic head groups. The hydrophilic head groups may be glyceryl molecule, ethylene oxide, crown ether, sugar, amino and sorbitan groups etc [27]. Among the surfactants, non-ionic type is of prime importance. They are stable, exhibits no or minimal toxicity and interaction and are considered compatible with other formulation ingredients and endogenous substances in the body tissues. In addition, non-ionic surfactant play versatile role in pharmaceutical formulations like they can be used as antifoaming agent, wetting agents, detergents, emulsifying agents, solubilising agents etc. They act by decreasing the surface tension and facilitate the penetration of drug (acts as penetration enhancers) across the biological membranes. Different types of non-ionic surfactant used to prepare niosomes are glycerol and glyceryl esters, sorbitan esters, polysorbates, macrogol ethers, crown ethers, gemini surfactant and bola surfactant. Spans and tweens are most widely used non-ionic surfactant. Chemically span is the sorbitan ester of fatty acid and tween is the polyoxyethylene
derivative of spans. Some important properties and chemical structure of spans and tweens are given in Table 4 and Fig 7.

Table 4: Non-ionic surfactants and their properties

<table>
<thead>
<tr>
<th>Non-ionic surfactants</th>
<th>Name</th>
<th>Molecular weight</th>
<th>HLB Value</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Span 20</td>
<td>Sorbitan monolaurate</td>
<td>346</td>
<td>8.6</td>
<td>C_{18}H_{34}O_{6}</td>
</tr>
<tr>
<td>Span 40</td>
<td>Sorbitan monopalmitate</td>
<td>403</td>
<td>6.7</td>
<td>C_{22}H_{42}O_{6}</td>
</tr>
<tr>
<td>Span 60</td>
<td>Sorbitan monostearate</td>
<td>431</td>
<td>4.7</td>
<td>C_{24}H_{46}O_{6}</td>
</tr>
<tr>
<td>Span 80</td>
<td>Sorbitan monooleate</td>
<td>429</td>
<td>4.3</td>
<td>C_{24}H_{44}O_{6}</td>
</tr>
<tr>
<td>Tween 20</td>
<td>Polyoxyethylene sorbitan monolaurate</td>
<td>1128</td>
<td>16.7</td>
<td>C_{58}H_{114}O_{26}</td>
</tr>
<tr>
<td>Tween 40</td>
<td>Polyoxyethylene sorbitan monopalmitate</td>
<td>1284</td>
<td>15.6</td>
<td>C_{62}H_{122}O_{26}</td>
</tr>
<tr>
<td>Tween 60</td>
<td>Polyoxyethylene sorbitan monostearate</td>
<td>1312</td>
<td>14.9</td>
<td>C_{64}H_{126}O_{26}</td>
</tr>
<tr>
<td>Tween 80</td>
<td>Polyoxyethylene sorbitan monooleate</td>
<td>1310</td>
<td>15.0</td>
<td>C_{64}H_{124}O_{26}</td>
</tr>
</tbody>
</table>
Fig 7: Chemical structure of spans, tweens and cholesterol
**Cholesterol:** Cholesterol is one of the important excipient which is added to prepare stable niosomes. Cholesterol improves the packing of bilayers and increases the rigidity of the vesicles, by intercalating themselves between the bilayers and forms less leaky vesicles [28].

**Charge inducers:** Charge inducers like dicetyl phosphate, stearylamine, diacylglycerol provides the electrostatic stabilization of the vesicles, which prevents the aggregation of vesicles [29].

### 1.5.4 Method of preparation of niosomes

Several methods for the niosomes preparation have been documented in the literature. Selection of these methods depends on numbers of factors like number of bilayers, vesicle size, entrapment efficiency, intended use etc. Various methods used for the preparation of niosomes are listed below:

- a. Thin film hydration method
- b. Ether injection method
- c. Reverse phase evaporation
- d. Sonication method
- e. Multiple membrane extrusion method
- f. Micro fluidization
- g. Hydration of proniosomes
- h. Freeze and thaw method (FAT)
- i. Dehydration rehydration method (DRM)
- j. Trans membrane pH gradient method

### 1.5.5 Evaluation of niosomes

Niosomes can be evaluated for various parameters like:

- a. Morphology: It can be analyzed by scanning electron microscopy (SEM), transmission electron microscopy (TEM), freeze fractured microscopy, optical microscopy technique, etc.

- b. Vesicle size, size distribution and polydispersity index: Vesicle size, size distribution and polydispersity index can be determined by photon correlation spectroscopy, dynamic light scattering or laser beam based equipments.
c. Zeta potential measurement: Zeta potential can be analyzed by Zetasizer which is based on the electrophoretic light scattering (ELS).

d. Entrapment efficiency: The entrapment efficiency of the drug in niosome formulation can be determined by techniques like dialysis, centrifugation and size exclusion chromatography. The entrapment efficiency of the drug can be calculated by:

\[
\% \text{ Entrapment Efficiency} = \left( \frac{\text{Total amount of drug added} - \text{free drug}}{\text{Total amount of drug added}} \right) \times 100
\]

e. Bilayer rigidity, homogeneity and compatibility study: It can be analyzed by proton-Nuclear Magnetic Resonance (p-NMR), Differential Scanning Calorimetry (DSC) and Fourier Transform Infra Red Spectroscopy (FTIR).

f. \textit{In-vitro} drug release: It can be evaluated by dialysis method using dialysis bag of defined pore size under the simulated conditions.

g. Stability study: The stability of the niosome formulation can be analyzed in various extreme stress conditions like temperature, pH, bile salts etc. and can be examined for visual appearance, drug content, vesicle size, zeta potential and entrapment efficiency.

h. \textit{In-situ} and \textit{in-vivo} studies using suitable animal models.

\textbf{1.5.6 Mechanism for uptake of niosomes}

The niosome formulation uptake in the body cell occurs \textit{via} different mechanisms like fusion of niosome outer bilayers with the plasma membrane, adsorption at cell surface, lipid transfer between the niosomes and cell and endocytosis.

\textbf{1.5.7 Applications of niosomes}

Various therapeutic applications of niosomes are documented the in literatures like:

- Pulmonary delivery
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- Protein and peptide delivery
- Transdermal delivery of drugs
- In neoplasia
- In leishmaniasis
- Immunological application
- Ophthalmic drug delivery
- Targeting of bioactive agents
- Diagnostic imaging
- Also used for sustained release and localized drug action [30,31]

1.6 PRONIOSOMES

Proniosomes are the non-ionic surfactant based vesicular system that overcomes the problems of physical instability of aqueous niosome dispersions (aggregation, fusion and leakage) or any other vesicular drug delivery system. It can be hydrated with hot water to give niosomes when required. Proniosomes exhibit certain advantages like high encapsulation efficiency, capable of incorporating drugs with wide range of solubility (e.g. lipophilic, hydrophilic and amphiphilic). It is easy to control particle size distribution and an inert or nitrogen atmosphere is not required for stability maintenance. All these characteristics make proniosomes a unique system for effective drug delivery in different formulation.

1.6.1 Advantages of proniosomes

- Overcomes the problem of physical instability like fusion, aggregation, sedimentation and leakage on storage.
- Prevents the hydrolysis of entrapped drugs.
- Ease in handling and storage.
- Ease in transportation, distribution, storage, scale up and sterilization.
- Release can be sustained, controlled and prolonged using proniosomes.
1.6.2 Classification of proniosomes

Proniosomes can be classified into two categories:

(a) Dry granular proniosomes

(b) Liquid crystalline proniosomes

(a) Dry granular proniosomes

It is a dry free flowing powder which upon hydration with hot water produces niosomes. It can be prepared by coating the layer of surfactant over water soluble carrier like sorbitol or maltodextrin. When they get hydrated, the water soluble carrier dissolves and led to the formation of niosomes.

(b) Liquid crystalline proniosomes

It can be prepared by mixing different ingredients like lecithin, non-ionic surfactants and alcohol. After heating, once the resulting mixture gets melted, small amount of water is added and heated again till the uniform mass is obtained (proniosomes). These proniosomes get converted into niosomes after get hydrated with hot water. Since, the final product exhibits gel like consistency it can be easily used as transdermal drug delivery systems. When the proniosomes comes in contact with water in the skin; it gets converted into the niosomes and acts by same mechanism as niosomes does. These formulations are highly stable, show high entrapment efficiency; cause no damage to the stratum corneum, acts as penetration enhancers due to the presence of non-ionic surfactants, involves use of biocompatible excipients, etc. These systems are analyzed in a similar manner as niosomes.

1.6.3 Mechanism of drug transport from proniosomes

The transport mechanism of niosomes and proniosomes through the skin is shown in Fig 8.
Application of proniosome gel on the skin essentially requires hydration to convert them into niosome. Drug release and permeation across the skin depends on the nature of drug and excipients in niosomes. Proniosome formulation contains non-ionic surfactants and phospholipids; which can act as penetration enhancer. The niosomes are effectively adsorbed, fuses with skin layer and loosens the integrity of lipid of stratum corneum and thus increases the diffusion of drug across it.

1.6.4 Application of proniosomes

Some of the applications of proniosomes are mentioned below:

a. Drug targeting

b. Treatment of cancer

c. Treatment of leishmaniasis

d. Delivery of peptide drugs

e. Use to examine immune response

f. Localized as well as sustained release of drugs

g. Transdermal drug delivery systems

h. As a carriers for haemoglobin [30]
1.7 NIOSOMES FOR ORAL DRUG DELIVERY OF RISPERIDONE (SELECTION CRITERIA)

Liposomes, ethosomes and transfersomes require phospholipids as one of the formulation component, which has certain limitations like they are costly, have variable purity grade, undergo rapid degradation by hydrolysis and oxidation. Production is costly and cryogenic conditions are required. In contrast to this, niosomes are microscopic vesicles that are formed from self-assembly of non-ionic surfactant in aqueous media resulting in closed bilayer structure. These non-ionic surfactants are non-toxic, biocompatible, cheap, easily available and stable at ordinary conditions of temperature and pressure. Niosomes increases the solubility of poorly soluble drug and act as intestinal permeation enhancers. Thus augments high permeability of the formulations across the intestinal mucosa. Notably, non-ionic surfactants are strong inhibitors of cytochrome P-450 enzymes responsible for metabolism of risperidone in liver. Due to high rate of metabolism, risperidone exhibit poor pharmacokinetic profile which reduces its therapeutic efficacy in psychic disorders. In view of these facts present study was designed to formulate risperidone niosomes using non-ionic surfactants that will delay its rate of metabolism and improve its pharmacokinetic profile significantly.

1.8 PRONIOSOMES FOR TRANSDERMAL DRUG DELIVERY OF RISPERIDONE (SELECTION CRITERIA)

Transdermal drug delivery system (TDDS) is known as suitable alternative to overcome the issues associated with oral route. TDDS increases the therapeutic efficacy of several drugs that are associated with GI-irritation, low absorption, hepatic “first-pass” metabolism. It prevents the conversion of drug into undesirable metabolite that may cause side effects. Fluctuations in drug plasma level associated with multiple dosing can be reduced by formulating the drug as TDDS. When compared to oral formulations, equivalent therapeutic effect can be elicited with lower dose of drug through TDDS. TDDS offers better patient compliance with reduced inter & intra-patient variability, due to simplified dosage regimen. Self-administration is possible and easy to terminate the drug input at any time. TDDS of various psychotropic drugs e.g. selegiline, rivastigmine, methylphenidate has already been approved FDA and are available commercially. However, the stratum corneum is the major barrier, when drugs are given as TDDS.
Vesicular systems like niosomes and proniosomes interact with the horny layer and increase the permeability of drug across the stratum corneum. Presence of surfactants serves as penetration enhancer and facilitates dermal delivery leading to higher localized drug concentration. It also acts as drug reservoir and provides the controlled release of drug. Further the release rate can be adjusted by changing the composition or by surface modification. Proniosomes are usually dry powder or gel which can be hydrated just before use resulting in the formation of niosomes. Proniosome gel when applied to skin under occlusive conditions, they are hydrated with the skin moisture and converted to niosomes. Proniosomes also provides ease of transportation, distribution, storage and dosing.

TDDS is suitable for potent drugs; risperidone belongs to this category, having the dose of 1-2 mg. It has the molecular weight of 410.49 daltons (drugs with mol.wt. <500 daltons are suitable candidate for TDDS). It has Log P of about 2.5 (sufficiently lipophilic to be formulated as TDDS). It undergo hepatic first pass metabolism, so TDDS can be a suitable alternative for the delivery of risperidone.