Chapter 2

Literature Review

Management of Dyslexia and ADHD

2.1 Introduction: ADHD

Attention-deficit hyperactivity disorder (ADHD) was first descripted in 1980 as a developmental condition characterized by distractibility and inattention with or without associated hyperactivity. (1) The highest prevalence is in Children of school age. Approximately 11% of children 4-17 years of age (6.4million) have been diagnosed with ADHD as of 2011. (2) 3–7% of such cases have been reported in the USA and less than 1% in the UK with a worldwide reporting of 8–12% cases.

Classification of Diseases

ADHD is internationally diagnosed on basis of two distinct classifications.

In the Diagnostic and Statistical Manual of Mental Disease 4thEdition (DSMIV), it is characterized by inattention, persistent hyperactivity and impulsivity, differentially stated in three subtypes: primarily hyperactive/impulsive, primarily inattentive, or combined type. (3) However, according to International Classification of Diseases 10th edition (ICD-10, extensively used in Europe, for the diagnosis of hyperkinetic disorder presence of all three behavior is must, and thus has no subtypes. (4)

2.1.1 Cause and Symptoms

2.1.1.1 Causes

ADHD is the most ubiquitous childhood developmental disorder with no clear neurobiological etiology. However, advancement in brain imaging and molecular genetics shows hypo function of dopaminergic neurons in the basal ganglia and frontal lobes in ADHD. (5, 6)

2.1.1.2 Symptoms

As per American Academy of Pediatrics, ADHD is most frequently occurring neurobehavioural disorder in childhood. Children with ADHD present with symptoms of hyperactivity, inattention, distractibility and impulsivity. Compared with the general population, individuals with ADHD carry a higher risk of learning disabilities, mood disorders, anxiety, and disruptive behavioral disorders. As children mature, the resulting impairments may persist, resulting in higher rates of accidents, lower high school graduation rates, difficulty in the workplace, and poorer psychosocial functioning. (7, 8)

ADHD is associated with significant deficits in many areas of functioning, including cognitive, emotional, academic, and interpersonal domains. (9) One of the sources of morbidity and disability associated with ADHD are cognitive deficits like executive functioning (EFDs), working memory, and problem solving. (10-12) Children with ADHD commonly exhibit impairments in executive functioning, (13, 14) and their presence is associated with increased risk of grade retention and academic underachievement, relative to ADHD youth without such deficits. (15-17)

2.1.2 Diagnosis

In the UK and US, diagnosis is based on a structured clinical interview together with symptoms rated by parents and teachers in different settings (i.e. home, school and the community) using diagnostic scales. The evaluation Consensus guidelines have been published regarding the diagnosis and management of ADHD. (18, 19) Guidelines recommend core ADHD diagnostic procedures that include interview with parents/caregivers, medical examination, teacher reports, rating scales, educational assessment and vision and hearing assessment. Parental perceptions indicate between 45 and 91% compliance with these recommendations. (20)

2.1.3 Treatment

There is no cure for ADHD. The symptoms, however, can be managed with a combination of medications and psychotherapy. Psychostimulants (e.g. methylphenidate (MPH) and amphetamine, which are potent inhibitors of the dopamine transporter) are the first choice of medication for ADHD disorder, and they have been in use since 1937.

For more than half a century the treatment of ADHD has been dominated by the use of catecholaminergic psychostimulants. (21) Report describing an immediate and often dramatic improvement in the academic performance and conduct of children with behavioural disturbances when they were given racemic amphetamine (DL-amphetamine). (22) Lisdexamfetamine (LDX), a D-amphetamine prodrug increased therapeutic window with a greater separation between efficacy and unwanted psychostimulant side effects than those produced by once-daily amphetamine or MPH medications. Furthermore, because LDX is pharmacologically inactive, it would also have a lower potential for abuse. (23)

MPH products are generally based on racemic DL-threo-MPH(DL-MPH),which is available in immediate-release form as Ritalin, and as once-daily formulations, e.g. Metadate SR, Concerta and the transdermal patch, Daytrana. In a move to improve on the benefit/risk profile of DL-MPH, the more potent enantiomer in the racemate, i.e. D-MPH, has been introduced to the market as Focalin and Focalin XR.

More recently, the noradrenaline reuptake inhibitor, atomoxetine (Strattera) non-stimulant catecholaminergic drug has been introduced for ADHD treatment. (24, 25) The weak selective dopamine reuptake inhibitor, bupropion (Wellbutri), has also been used off-label for treating ADHD, but it has only very moderate efficacy. (26) Modafinil represents another class of psychostimulant, have off-label use to explore its potential in the management of ADHD.

Non-stimulant pharmacotherapy, α_2-Adrenoceptor agonists, e.g. clonidine and guanfacine, have been used off-label as second-line therapies in ADHD for many years, especially when patients have co morbid conditions. (27) In randomized, double-blind, placebo-controlled, clinical trials extended-release guanfacine has been reported statistically to significantly improve ADHD symptoms in children and adolescents. (28)

Adherence to treatment is a challenge with most chronic disorders, and ADHD is no exception. Discontinuation and non-adherence among patients who are prescribed ADHD medication vary with the definition of adherence and the method used to measure. Analysis of large claims databases show that, on average, patients discontinue ADHD medication in less than 1 year after the first prescription. (7) The need for multiple doses, inflexibility of medication duration, and inability to swallow tablets or capsules are additional considerations when treating patients with ADHD.

2.1.4 Patented Product of Modafinil

Some of the patented products of modafinil are listed in the Table 2.1. Modafinil has promising approach for formulating in the different delivery systems. It acts on Central nervous system (CNS). Oral administration result in poor bioavailability because of its insolubility and heavy first pass metabolism. Thus a focus on solubility enhancement, will serve as a good approach to overcome the drawback of limited absorption.

Table 2.1 Patented Products of Modafinil

Work Done	Comment	Reference
Intranasal Delivery Of Modafinil (US Patent No.: US7989502)	The method may be implemented with an intranasal p'ceutical delivery device loaded with a modafinil composition & adapted to deliver the dosage to the upper third of the nasal cavity.	Greco Mary Ann Katherine et. al. (29)
Formulation and process for the preparation of Modafinil (US Patent No.: US8173169B2)	The tablet was bioequivalent to PROVIGIL®. Tablet prepared by a dry granulation method.	Mohannad Shawer et.al. (30)

2.2 Introduction: Dyslexia

The word dyslexia is made up of two different parts: dys meaning not or difficult, and lexia meaning words, reading, or language. Thus Dyslexia in Greek means 'difficulty with words'.

As per International Dyslexia Association (IDA), Dyslexia is a disability of learning, from neurobiological origin, and is categorized by problems with correct word understanding and decoding abilities, which typically is an outcome of scarcity in the phonological element of language. (31-33)

Internationally, dyslexia has no single definition however it is generally accepted as designating a cognitive disorder related to reading and speech. The World Federation of Neurology explain that though dyslexic person is intelligent, face a difficulty in learning to read. (34) The National Institute of Neurological Disorders and Stroke definition also adds, "difficulty with spelling, phonological processing (the manipulation of sounds), and/or rapid visual-verbal responding."

The National Institutes of Health estimates that about 5-10% of school-aged children and total of 15% of the United States population are affected by learning disabilities, mostly with problems in language and reading. The condition appears in all ages, races and income

levels. Occasionally balance, movement and rhythm are also affected. The percentage of males and females having dyslexia is nearly the same. In 2014, Hachmann concluded that dyslexia is due to short-term memory loss for sequential instruction. (35)

Classification of Disorder

The dyslexia is classified as "specific primary dyslexia or developmental dyslexia" and "secondary dyslexia".

2.2.1 Cause and Symptoms

2.2.1.1 Causes

The dyslexia, which is stated to be of unknown origin, is referred to as "specific primary dyslexia or developmental dyslexia". Dyslexia is based on recognition and not on vision. This view is representative of the widely accepted belief of the medical profession that this form of dyslexia is caused by an inability of the brain to recognize what the eyes see.
Dyslexia caused by obvious conditions such as prolonged absence from school, psychological problems, or obvious (generally cortical) brain defects is identified as "secondary dyslexia".

'Dyslexia' defined by many researchers and organizations around the world are purely descriptive or represent fundamental theories. These definitions for the disorder, defined as dyslexia, encompass a number of reading skills, deficits and difficulties with a number of causes rather than a single condition. (36, 37) Although an exact cause has not been identified, studies have identified differences in the way sound and visual information are processed between persons with and without dyslexia. Children with dyslexia demonstrate problems with their phonological memory. Phonological memory, also called phonological coding, describes the ability to encode and store phonological information in the memory. Research has found that poor readers have difficulty using phonological memory to encode and store verbal information. (38)

Bateman (1890), defined dyslexia as a form of verbal amnesia in which the patient has lost the memory of the conventional meaning of graphic symbols. On 21st December 1895,

James Hinshelwood, an optic surgeon from Glasgow, Scotland, published an article in the journal "The Lancet" on the issue of visual memory and word blindness. Vellutino (1981, 2004) stated that dyslexics have difficulties establishing verbal associations, perhaps due to phonological decoding problems. Moreover, there exists a relationship between phonological deficits and short-term memory deficits in normal readers. (39, 40)

The role of short-term memory in dyslexia has been demonstrated by several earlier studies which reported a reduced memory span in dyslexia, mostly constraining it as a specifically verbal impairment. (41-45) Shayne (2010) claimed that phoneme awareness is essential to learning to read. (46)

These findings are more considerable when Margaret Snowling, an English psychologist, during the 1980s and 1990s described dyslexics' deficits in phonological tasks and short-term memory. (47)

Also Pennington has shown that reading ability depends on single word recognition, as well as on the ability to process words in a text. (48) Denckla (1976) also described coding or naming deficits. (49) Rudel (1976) suggested that dyslexics' memory deficits only exist for language information; the results were confirmed by other studies. [46] Additionally, individuals with dyslexia whose language is not English may show greater degree of working memory impairment. (50) Recent findings in 2011 proposed that dyslexic person have trouble in study of sequential data. (51)

2.2.1.2 Symptoms

In primary childhood, signs that correlate with a later diagnosis of dyslexia comprise a deficiency of phonological awareness and tardy onset of speech and, also easy distraction by background noise. (52) Dyslexia is commonly associated problem of mirror writing and reading letters and words backwards. These deeds are observed in many children while they learn to read and write, and not measured in defining features of dyslexia.

2.2.2 Diagnosis

Signs of effort in identifying or producing rhyming words, or counting syllables words in numbers – both of which depends upon phonological awareness may be seen in school aged

children. (53) Difficulty in segmenting words into distinct sounds or blend them when producing words, representing reduced phonemic alertness may also be seen.(54) Moreover, difficulties with naming things or word retrieval are associated with dyslexia. (55) Complications persist into adolescence and adulthood and might also accompany problems with memorization, foreign language learning, summarizing stories and reading aloud. Adults having dyslexia can also read with good comprehension, still they tend to read slowly than those without a learning trouble and perform poor in spelling tests or when reading nonsense words – a measure of phonological awareness. (56)

2.2.3 Treatment

Current treatment of dyslexia is carried out using a team of neurologist, a pediatrician, and special education instructors. Focus of treatment is usually on the specific learning problems of affected individuals. The usual method is to identify the specific weaknesses and tailor the treatment to concentrate on those areas. Dyslexia is a condition and not a disease and hence medicine is not used generally to treat it. Occasionally, medicines are used for co-existing conditions like Attention Deficit-Hyperactivity Disorder (ADHD). (57)

Allopathic Treatment

Allopathic medical treatment for dyslexia includes use of anti-motion drugs, such as Cyclizine [Marezine], Meclizine [Antivert], Dimenhydrinate [Dramamine] addressing the symptoms of balance and coordination which results from visual perception alterations; stimulant drugs such as Methylphenidate [Ritalin, Cylert] to address symptoms of low self-esteem, restlessness, and distractibility, and 'nootropic' drugs, a class of drugs believed to improve cognitive function. The stimulant drugs may be more effective for learning disorders related to ADHD or ADD than for dyslexia. (58) The drug Piracetam, a nootropic, has been observed to have positive effects on dyslexia symptoms, improving verbal ability, speed and accuracy of reading, and short term memory in dyslexic patients. However Piracetam has not been approved for use in the United States by the Food and Drug Administration (FDA) and has legal issues.

Clinical Trials

Clinical Trials. Gov. Dyslexia Clinical Trials has a list of ongoing clinical trials. Some of the ongoing trials involve are:

1) Medicines containing dopamine may help with reading, spelling and writing
2) The use of the medication atomoxetine to treat patients with ADHD and dyslexia.

- NCT00111371: Dopaminergic Enhancement of Learning and Memory in Healthy Adults and Patients with Dyslexia
- NCT00191048: The use of the medication atomoxetine to treat patients with ADHD and dyslexia.
- NCT02429739: Working Memory Training for Children with Dyslexia. (Study Completion Date: April 2016)

Recently Concluded Clinical Trials

- Medication Atomoxetine (Strattera), a norepinephrine reuptake inhibitor used in the treatment of ADHD, has a role in treating dyslexia.(25)
- The National Institutes of Health completed ten years study to investigate the biological and educational constraints of children with learning disabilities, with a focus on treatment and links between assessment and treatment. The project evaluated prevention and treatment of reading and writing disabilities, the genetic contribution to subtypes of dyslexia, the relationship between brain variables and dyslexia, and the brain's response to treatment for dyslexia. Genetic and brain imaging studies were an ongoing part of the study.
- Using computer-based visual and auditory multimedia training in developmental dyslexia to improve writing performance.
- United States Patent 3940485 discloses a pharmacotherapy of dyslexia by treatment and pre-treatment of dyslexia by improving sequential scanning and ocular fixation abilities and therapeutic compounds.

Some of the clinical trials in Dyslexia and ADHD are listed in Table 2.2.

Table 2.2 Clinical Trial in Dyslexia and ADHD

Sr. No	Study Title	Interventions	Locations
1	Speech and short-term memory functions in dyslexia: a combined MEG and EEG study	-	Laboratory of CBRU, Institute of Behavioural Sciences, University of Helsinki, Helsinki, Uusimaa, Finland
2	Dyslexics' visual attention field	Passing tests in dyslexics	U1028 INSERM - CNRS UMR 5292 Equipe Imp Act, Bron, France
3	Dyslexia, motor control and proprioception	Evaluation of motor learning and written language	Inserm U1093, Dijon, Bourgogne, France
4	Working memory training for children with dyslexia	Behavioral: Working memory Training	Sorlandet Hospital, Arendal, Aust-Agder, Norway
5	Dopaminergic enhancement of learning and memory in healthy adults and patients with dyslexia	Drug: Levodopa	Dept. of Neurology, University Hospital of Muenster, Muenster, North-Rhine Westphalia, Germany
6	Treatment with Atomoxetine hydrochloride in children and adolescents with ADHD	Drug: Atomoxetine	Rolling Hills Estate, California, United States
7	Effects of Atomoxetine on brain activation during attention and reading tasks in patients with ADHD & comorbid dyslexia	Drug: Atomoxetine	Yale University School of Medicine New Haven, Connecticut, United States
8	Treatment of ADHD with Atomoxetine in children & adolescents with ADHD & comorbid Dyslexia	Drug: Atomoxetine	Irvine, California, United States
9	Comparison of Atomoxetine and placebo in children with ADHD and/or reading disorder (RD)	Drug: Atomoxetine Hydrochloride	Gent, Belgium
10	Interventions for children with attention and reading disorders	Drug: Methylphenidate Behavioral: Intensive reading instruction	Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States. University of Texas Health Science Center, Houston, Texas, United States

2.2.4 Patented Product of Vinpocetine

Russian Patent No.2212890 relates to infusion solution used for improvement of cerebral circulation comprising Vinpocetine, Ascorbic Acid, Benzyl Alcohol, Sodium Pyrosulfite, sorbitol, Tartaric acid and water.

Russian Patent No.2262931 relates to a pharmaceutical composition as a solid medicinal formulation possessing cerebro-vasodilating and nootropic activity and comprising vinpocetin, piracetam as active components.

Us patent no 20160038552 A1 disclose that Vinpocetine is a drug that has been observed to have positive effects on dyslexia symptoms; improving cognitive function such as learning, memory, concentration, focus, attention and mood.

2.3 Formulation Approaches to Improve Oral Bioavailability

Recent progress in combinatorial chemistry has led to the generation of a large number of new compounds. Today, a large percent of these new chemical entities (NCEs) in addition to many existing drugs often show poor solubilization behavior which leads to poor oral bioavailability with wide intra and inter subject variation and present formulators with considerable technical challenges.

Some of the approaches have been highlighted to improve oral bioavailability in Fig. 2.1. one of them is lipid-based formulations have attracted great deal of attention. Truly, best rational method is to incorporate lipophilic drugs into inert lipid vehicles such as oils, liposomes, self-emulsifying formulations, surfactant dispersions, microemulsions and self-micro-emulsifying formulations.(59, 60) This could lead to increased solubilization with concomitant modification of their pharmacokinetic profiles, leading to increase in therapeutic efficacy.

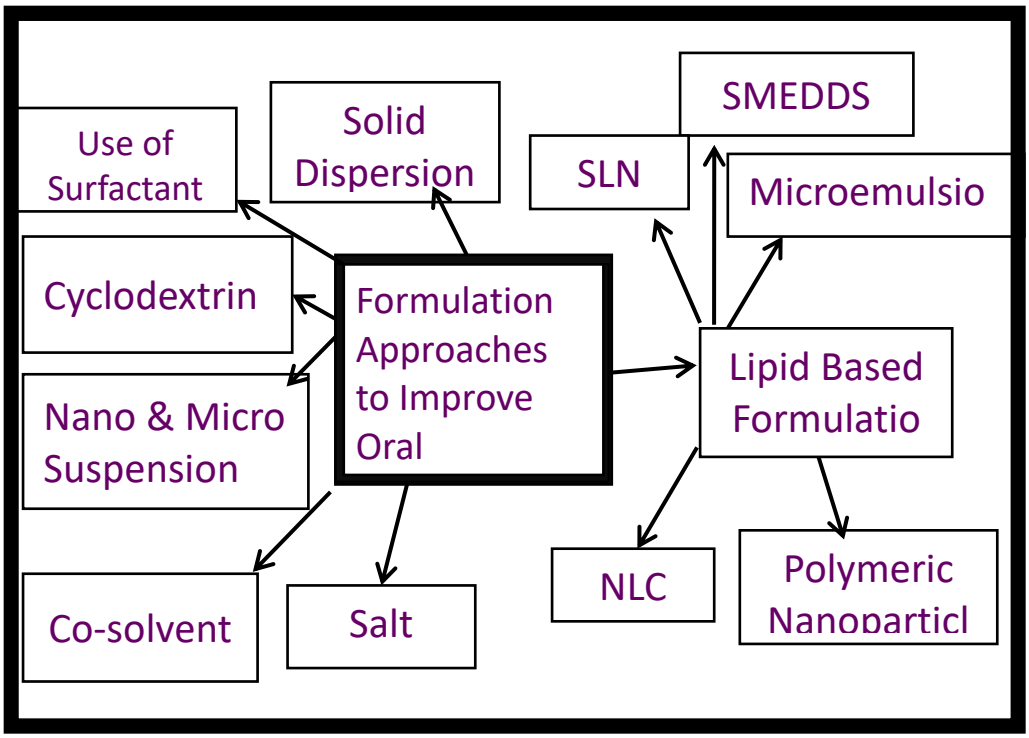

Fig. 2.1 Formulation Approaches to Improve Oral Bioavailability

2.4 Self-microemulsifying Drug Delivery System (SMEDDS)

For drug substances which exhibit poor aqueous solubility but sufficient lipophilic properties, it will be a novel approach to dose them in a pre-dissolved state, e.g. in a lipid formulation. It will be helpful in minimizing the energy associated between a solid-liquid phase transitions and provide a better output for the slow dissolution process after oral intake. Lipid formulations include lipid solutions, micelle formulation, emulsions, microemulsions, self-microemulsifying drug delivery systems or self-emulsifying drug delivery systems or self-nanoemulsifying drug delivery systems. (61, 62) Table 2.3 represents proposed classification system of lipid formulations based on the polarity of the blend describe by Pouton. (63)

The most straightforward lipid based formulation is a lipid solution, classified as a Type I formulation. The obvious advantage of this formulation is its relative simplicity. Nonetheless, these formulations are highly dependent on the digestion process and suffer from low solvent capacity. Unless the drug is sufficiently lipophilic (log P>4), formulation as an oil solution is limited to highly potent compounds. Solvent capacity can be increased

by adding surface active agents as is the case in type II and III formulations. In addition, the most polar formulations, comprising of hydrophilic surfactants and represented by class III, often exhibit self-emulsifying properties. (59)

Table 2.3 Properties of Type I, II, III and IV Lipid Formulations

Sr. No.	**ingredient**	**Features**	**Advantages**
Type I	Oils	Not- disperse	Suitable for capsule
Type II	Oils, water	SEDDS formed	On dispersion lose Solvent
Type IIIA	Oils, surfactants, Co-solvents	SEDDS/ SMEDDS formed	Clear
Type IIIB	Oils, surfactants, cosolvents	SMEDDS with water-soluble components and low oil content.	Clear
Type IV	Co-solvents with water-soluble surfactants	form micellar solution	good solvent capacity

2.4.1 Mechanism of Self-emulsification

The free energy (ΔG) associated with emulsification process is given by the equation:

$$\Delta G = \Sigma N_i \pi r_i^2 \sigma$$

In which "N" is number of droplets with radius "r" and "σ" is interfacial energy. From the equation it can be confirmed that Spontaneous formation of the interface between water and the oil phase is not favored energetically. The emulsification process is associated with the ease to which water penetrates the oil-water interface creating liquid crystalline phases. This results in swelling at the interface causing ease of emulsification. (64) The additional mechanisms by which lipid based delivery systems enhance the absorption of lipophilic drugs are as follows:

2.4.1.1 Enhanced Dissolution/ Solubilization

The presence of lipids in the GI tract stimulates gallbladder contractions leads to biliary and pancreatic secretions including bile salts (BS), phospholipids (PL) and cholesterol. These products, along with the gastric shear movement, form a crude emulsion supports the solubilization of the co-administered lipophilic drug. Lipids in the GI tract provoke delay in gastric emptying, i.e. gastric transit time is increased. As a result, the residence time of the co-administered lipophilic drug in the small intestine increases which enables better dissolution of the drug at the absorptive site, and thereby improves absorption.(65)

2.4.2 Absorption Mechanism for Self-microemulsification

SMEDDS causes reduction in first pass metabolism due to intestinal lymphatic transport of highly lipophilic drugs, and thus directly or indirectly bioavailability increase. Moreover, luminal drug solubility may also increase effectively.(66) In the gastric environment, lipids enhances the secretion of phospholipids and bile salts, including cholesterol, allowing formation of phospholipids/ bile salts/ cholesterol micelles which enhance solubilization, as shown in Fig. 2.2 and Fig. 2.3.

It is clear that certain lipids and surfactants (like Tween) may reduce the activity of pgp efflux, moreover decrease metabolism.(66, 67)

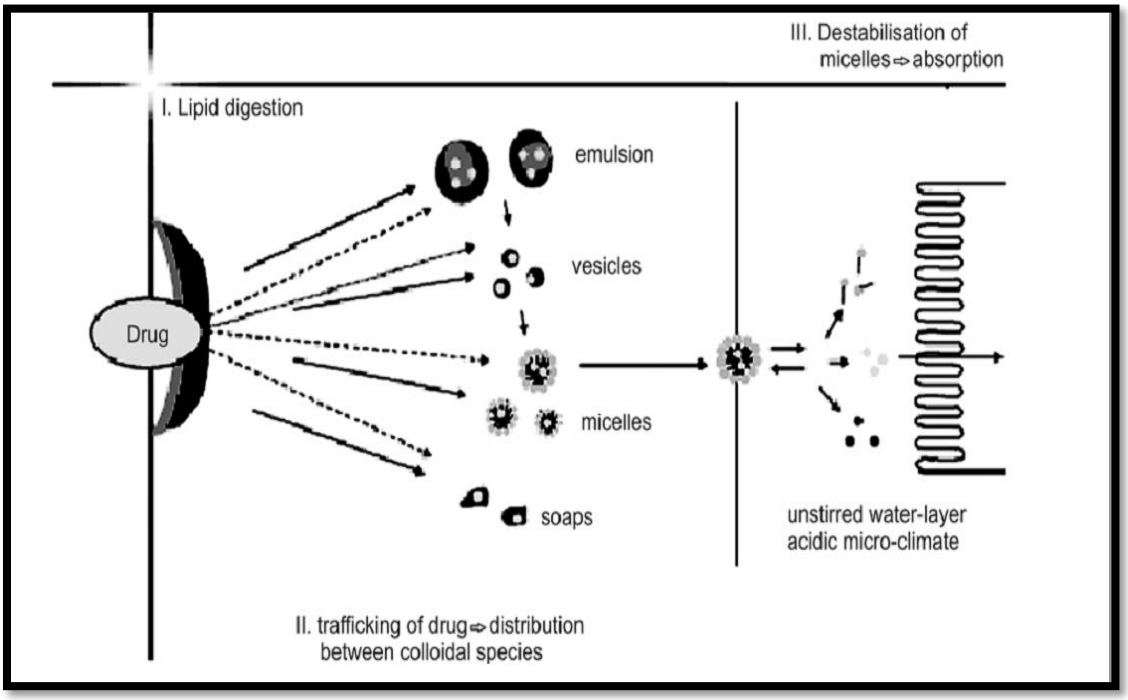

Fig. 2.2 Intestinal Pre-absorptive Processes (61)

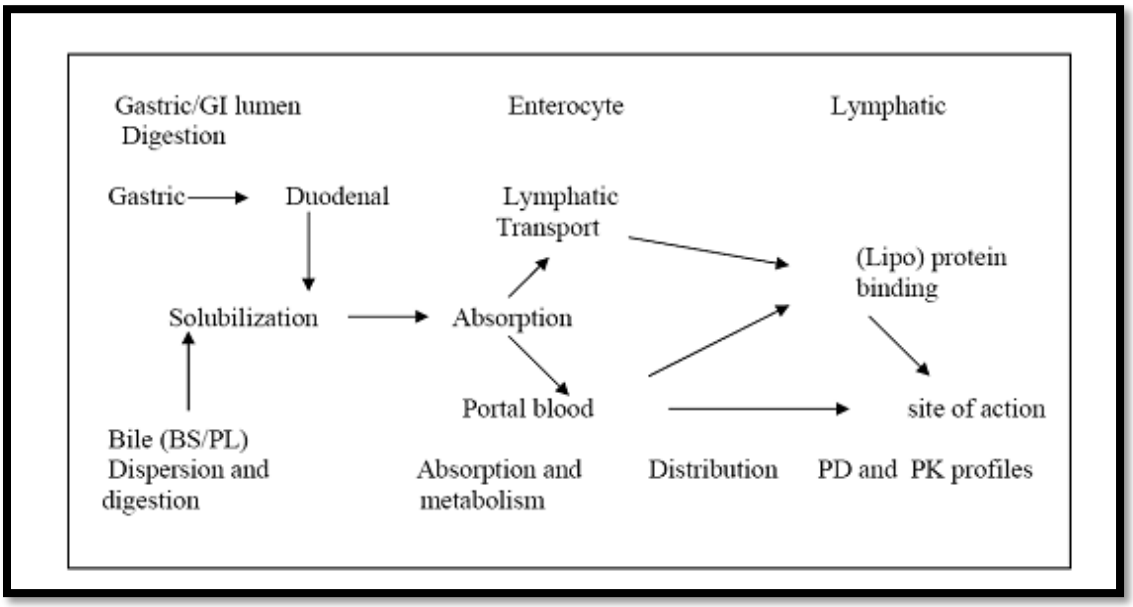

Fig. 2.3 Fate of SEDDS and SMEDDS Following Oral Administration and Mechanisms Proposed for Bioavailability Enhancement of Drug (61)

2.4.3 Composition of SMEDDS

The SMEDDS are composed of the oil, surfactant and co-surfactant. Individual components must be biocompatible, non-toxicity, with clinical acceptance. Emulsifiers must be added in an appropriate concentration range so that mild and non-aggressive formulation is obtained. The importance is, therefore, on the use of GRAS (generally regarded as safe excipients). (68)

2.4.3.1 Oil

It is one of the most vital excipients in the SMEDDS formulation. It solubilizes high quantities of the lipophilic drug or enables self-emulsification. It can increase the portion of lipophilic drug that is transported via the intestinal lymphatic system, and hence increase absorption through the GI tract depending on the nature of triglyceride molecule. For preparation of SMEDDS, use different amount of both LCT and MCT. Saturated (for example, lauric, myristic and capric acid) and unsaturated fatty acids (for example, oleic acid, linoleic acid and linolenic acid) have penetration enhancing property of their own and they have been studied since a long time. Fatty acid esters i.e., ethyl or methyl esters of lauric, myristic and oleic acid have also been employed as the oil phase. (69) Hydrolyzed vegetable oils or Modified oils have been recognized for forming stable emulsification systems. Novel semi synthetic medium chain derivatives with surfactant properties, are effectively substituting the regular medium chain triglyceride oils in the Formulation of Self Emulsifying Oil (SEOFs).

2.4.3.2 Surfactant

Surfactant can be used alone or in combination. Generally, its concentration varies from 30 – 60% w/w to form stable SMEDDS. Surfactant opted must be able in lowering the interfacial tension and form film on globule.(65) Surfactant used to stabilize microemulsion system could be nonionic or ionic, which governs interactions of aqueous phase with hydrophilic end of surfactant. For pharmaceutical applications, ionic surfactants are not preferred due to very high toxicological concerns compared to non-ionic surfactants. (65)

Non-ionic surfactants are regarded as safe for oral use. Industry have faith in lipid-based products and successfully marketed. The 50 g/Kg for oral and 5 g/Kg for intravenous LD50 values have been reported for surfactants of non-ionic nature.(64, 65)

Commercially available surfactants are polysorbate 80 (Tween 80), polyoxyl 35 castor oil (Cremophor EL), polysorbate 20 (Tween 20), Labrafil M-2125CS, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), sorbitan mono-oleate (Span 80), d-α-tocopherol polyethylene glycol 1000 succinate (TPGS), Solutol HS-15, polyoxyl 40 stearate and various polyglycolyzed glycerides including Labrafil M-1944CS, Labrasol, Gellucire 44/14. (70) Low HLB (3-6) surfactants are favored for the formulation of w/o microemulsion, and surfactants with high HLB (8-18) are favored for the formation of o/w microemulsion. Surfactants with HLB greater than 20 frequently require the presence of co-surfactants to lessen their effective HLB to a value within the range required for microemulsion formation. (71)

2.4.3.3 Co-surfactant

For the fabrication of SMEDDS, high concentration of surfactant is required in order to reduce interfacial tension and harmful effects of surfactant. Therefore, co-surfactants are used along with surfactant to decrease the concentration of surfactants. [100] Selection of proper co-surfactant is necessary for the efficient design of SMEDDS.[101] Organic solvents like ethanol, propylene glycol, polyethylene glycol are able to dissolve large amount of either drug or hydrophilic surfactant in lipid base and are suitable for oral delivery, so they can be used as co-surfactant for SMEDDS. Interface flexibility has been increase by co-surfactant. Characteristic like surfactant-partitioning has change leads to alter curvature and HLB. Moreover gel or crystalline structure has destroy.

Hydrophilic co-surfactants are mainly alcohols of intermediate chain length like pentanol, hexanol and octanol, known to lessen the oil/water interface and permit the spontaneous formulation of microemulsion.(65)

2.4.3.4 Co-solvent

Solvents can even act as co-surfactants in SMEDDS systems. Huge amounts of the drug solubilize in lipophilic base or in organic solvents and are suitable for oral application in SMEDDS to enhance solubility and stability of SMEDDS. (64) Examples are: Alcohols: ethanol, ethylene glycol, propylene glycol; Amides: 2-pyrrolidone, caprolactam; Ester: ethyl propionate, tributyl citrate, acetyl triethyle citrate.

2.4.3.5 Polymer

Polymer can enhance viscosity of the preparation. Polymer matrix ranges from 5 -40% of the total composition. They are incorporated for different application such as in-situ gelling system mucoadhesion, sustained drug release, permeation enhancer. Examples are: Carbopol 934, chitosan, hydroxyl propyl methyl cellulose, polycarbonate. (72)

2.4.4 Formation of SMEDDS

Preformulation studies are carried out for the selection of oil, surfactant and co-surfactant. For that solubility of drug in various oils and surfactant/co-surfactant is find out then prepare a series of SMEDDS system containing drug in oils, surfactants/co-surfactants mixture (Smix) and construct phase diagram. From diagram, optimization ratio of different excipients, which will solubilize the entire dose of drug in an acceptable volume of preparation, can be found out. The incorporated drug may change the self-emulsifying efficiency or may not affect it at all. SMEDDS are known to be more sensitive towards any changes in the ratio of excipients.

The pseudo-ternary phase diagrams were constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature. Oil phase, and Smix (surfactant: co-surfactant ratio) were prepared by varying concentration from 9:1 to 1:9 and weighed in the same screw-cap glass tubes and vortexes. Each mixture was then slowly titrated with aliquots of distilled water and stirred at room temperature to attain equilibrium. The mixture was examined visually for transparency. After equilibrium was reached, the mixtures were further titrated with aliquots of distilled water until they showed the turbidity. Clear and isotropic samples were deemed to be within the microemulsion region.(65)

2.4.4.1 Advantages of SMEDDS

SMEDDS has various advantages. (64, 65)

a) Enhanced oral bioavailability, which leads to reduction in dose.
b) Provide consistent profiles of drug absorption.
c) Targeting in GIT.
d) Protect drug in gut.

Fine oil droplets empty rapidly from the stomach and promote wide distribution of drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall. Ease of manufacture and scale up is one of the most important advantages. Peptide that hydrolyses by enzyme can deliver by SMEDDS.

When polymer is incorporated in a composition of SMEDDS; internal phase have drug which gives prolonged release of medicament, and absorb by the lymphatic system, can bypass first pass metabolism. Moreover, Increase the dissolution and permeability of drug.

2.4.4.2 Limitation of SMEDDS

There is certain limitation of SMEDDS. (73)

a) Limitation for formulation to assess by in vitro models.
b) To stabilize globules, high amount of Surfactant/ Co-surfactant is required

2.4.5 Marketed Formulation of SMEDDS

Marketed Formulation of SMEDDS are represented in Table 2.4

Table 2.4 Marketed Formulation of SMEDDS

Drug	Trade Name	Company	Dosage form	Indication
Amprenavir	Agenerase®	GSK	SGC	HIV antiviral
Bexarotene	Targretin®	Ligand	SGC	Antineoplastic
Calcitriol	Rocaltrol®	Roche	SGC	Calcium regulator
Cyclosprorine A/I	Neoral®	Novartis	SGC	Immune suppressant
Cyclosprorine A/II	Sandimmune®	Novartis	SGC	Immune suppressant
Cyclosprorine A/III	Gengraf®	Abbott Laboratories	HGC	Immune suppressant
Fenofibrate	Lipirex®	Sanofi- Aventis	HGC	Antihyper-lipoproteinemic
Ibuprofen	Solufen®	Sanofi- Aventis	HGC	NSAID
Ritonavir	Norvir®	Abbott laboratories	SGC	HIV antiviral
Saquinavir	Fortovase®	Hoffmann-LaRoche.	SGC	HIV antiviral
Tretinoin	Vesanoid®	Roche	SGC	Antineoplastic
Valproic acid	Convulex®	Pharmacia	SGC	Anti-epileptics

2.5 Nasal Drug Delivery System: An Approach for Brain Targeting

Nasal pathway has been used for drugs acting on CNS via systemic and targeted drug delivery, over the oral and parenteral routes. The reason are: (74, 75) Vascularized nasal epithelium with larger surface area for drug absorption is devoid of first pass metabolism resulting in direct transport of absorbed drug into the systemic circulation. Noninvasive route having ease of application and self-administration is possible.

2.5.1 Anatomy of The Nasal Cavity

Human nasal cavity with a total surface area of 180 cm^2, is separated by the nasal septum in two parts. The cavity is entirely lined by the nasal mucosa. It is among the anatomical structures forming the physical barriers of the body's immune system.

Nasal cavity covers the external opening, the nostrils, the pharynx, where it joins to the rest of the respiratory system shown in Fig. 2.4. (76, 77)

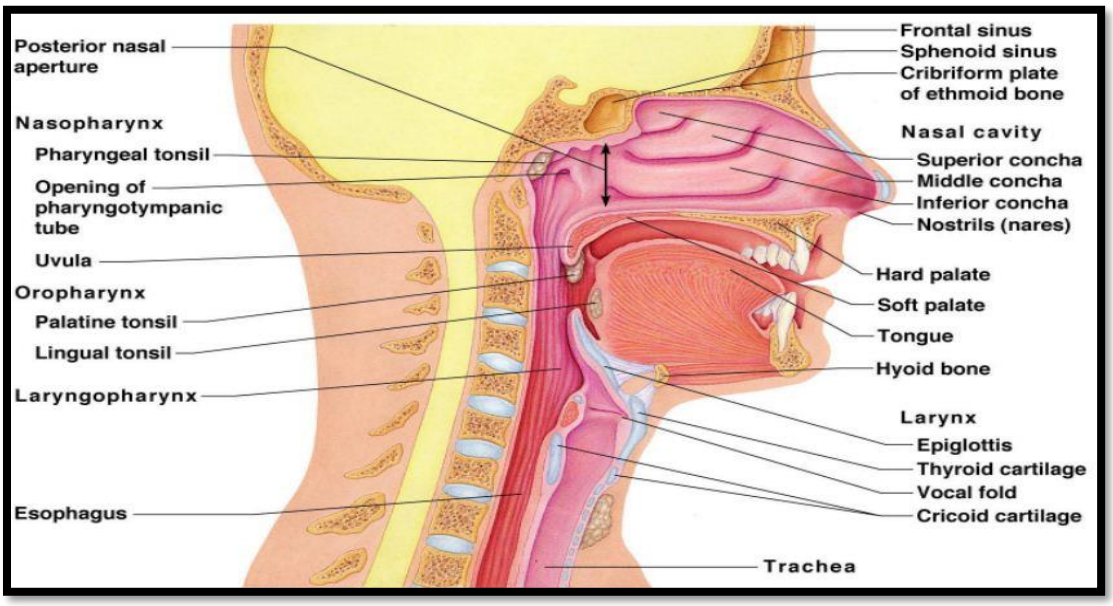

Fig. 2.4 Anatomy of Nasal Cavity

2.5.1.1 Nasal Vestibule

Inside nostrils, the anterior part of the nasal cavity is nasal vestibule. It refers to the passages through which air reach to respiratory system. (77)

2.5.1.2 Respiratory Section

Superior, middle and inferior turbinate are the three conchae comprises by each nostril. (77) Basement membrane, lamina propria, epithelium are the part of nasal respiratory mucosa and are responsible for drugs delivery. Structure and permeability of nasal pathway discussed in Table 2.5.

Table 2.5 Structural Sections of Nasal Cavity and Their Impact on Permeability (77-79)

Area	Features	Permeability
vestibule	• Hairs • Keratinized, stratified, squamous epithelial cells • Sebaceous glands present	Least permeable
Atrium	• Trans epithelial region • at anterior stratified squamous cells and at posteriorly pseudostratified cells with microvilli	Less permeable
Respiratory	• Pseudostratified ciliated columnar cells with microvilli • Presence of serous glands, nasolacrimal duct and goblet cells • Rich blood supplied	Most permeable region
Olfactory	• Specialized ciliated nerve cells	Direct access to cerebrospinal fluid
Nasopharynx	ciliated cells at upper part and squamous epithelium at lower part	nasal cavity drainage

2.5.1.3 Olfactory Region

At top of the nasal cavity, it is positioned and up to septum and lateral wall it prolongs. This is directly exposed to the external environment. This section composed of receptors. (77, 78)

2.5.2 Nose to Brain Delivery

Effective concentration of drug in brain is required for pharmacological treatment of CNS disease/disorders. For that drugs are able to cross the BBB/ BCSF barrier.(77) One of the approach is the nasal delivery to bypass blood brain barrier, thus permitting direct drug delivery to the CNS.

2.5.2.1 Advantages of Nasal Route

Delivery of drug through nasal route has various advantages. **(79, 80)** It provides easy accessibility and needle free drug application. Self-administration of the drug is possible. Patient compliance is improved as compared to parenteral routes. It would be effective in emergency therapy. It provides good penetration, especially of lipophilic and low molecular weight drugs. It provides quick absorption and fast commencement of action due to a comparatively large absorptive surface and high vascularization. It avoids the hepatic first-pass metabolism and hence possesses a potential for dose reduction compared to oral delivery. Additionally intranasal administration of vaccine can deliver directly to lymphatic tissue and facilitates secretory immune response at distant mucosal sites.

2.5.2.2 Disadvantages of Nasal Route

Nasal route has certain disadvantages. (80) The drug permeability can be affect by mucociliary clearance. Some of the drugs have limited solubility show inadequate absorption. Irritation in nasal cavity can occur by some drugs. Degradation of drug by metabolism in the nasal route. Drugs administered chronically is less appropriate to delivered through intranasal route. Volume delivered into nasal cavity is constrained to 25–200 μl. Nasal congestion due to allergies or cold adversely affects it. There is inadequate understanding of mechanisms; less established models at this stage and high Inter-individual variability are some of the additional limitation to this approach.

2.5.2.3 Mechanism of Nasal Absorption

CNS and Nasal mucosa is connected through extra neuronal or intraneuronal pathways. (77-79)

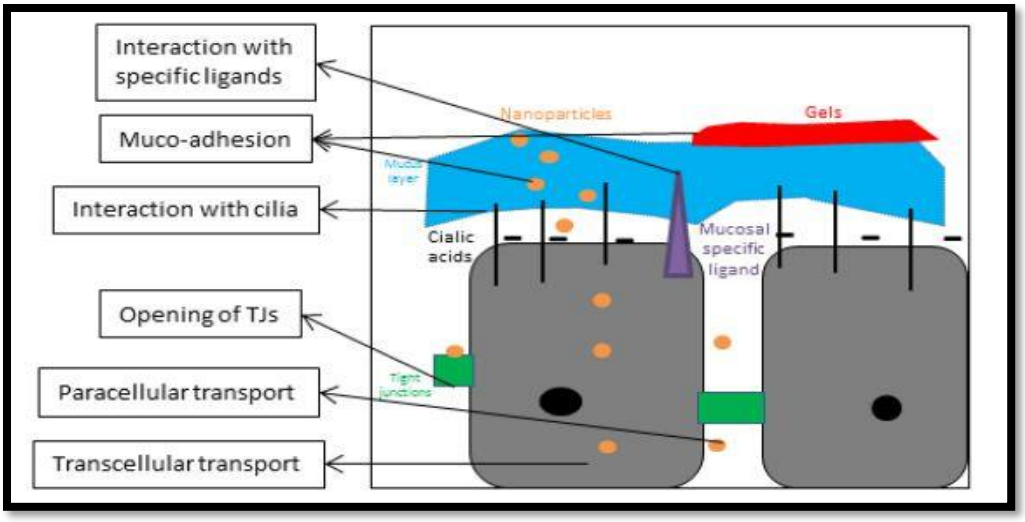

Fig. 2.5 Mechanism of Nasal Transport of Drug Molecule

Absorbance of drug from the nasal cavity is shown in fig. 2.5 and contribute as first step in absorption. Drugs with charge or higher molecular weight find difficulty in crossing it; however unchanged, small drugs easily permit through this layer. Mucin is the principle protein of the mucus and has property to bind to the solutes and hinder diffusion of drug molecules.

2.5.2.4 Blood Supply to Nasal Cavity

Blood reach vasculature of nasal cavity accomplish the various functions of cavity which are mucociliary clearance, heating and humidification, immunological functions and olfaction. (80) These arteries are: 1) blood supply to the vestibule by artery 'branches of the facial', 2) a branch of maxillary artery is 'Sphenopalatine, 3) a branch of ophthalmic artery is 'Anterior Ethmoidal'

2.5.3 Strategies to Improve Nasal Absorption

There are some methods used for successfully enhancement of nasal drug absorption are: (81, 82)

- **Permeation enhancer:** Permeation enhancers are of distinct categories and have been Examined to improve the nasal absorption like cyclodextrins, surfactants, fatty acids, Bile salts, etc.
- **Nasal enzymes inhibitors:** Various kinds of enzyme inhibitors such as protease and

Peptidase is utilized to minimize metabolism of drug in nasal cavity.

- **Structural modification:** Without altering the pharmacological action of drug, drug structure modification of can be done, resulting in improvement of nasal absorption.
- **Prodrug approach:** Inactive chemical moiety, which becomes active at the target site is called prodrug and is mainly used to improve solubility, taste, odor, and stability.
- **Bioadhesive polymer:** To improve the absorption of the drug and nasal residence bioadhesive polymers are used. They improve the drug retention time inside the nasal cavity by making an adhesive force between nasal mucosa and formulation, which leads to minimization of mucociliary clearance of formulation.
- **Particulate drug delivery:** Carriers are used for encapsulation of drug, prevent exposure of drug to nasal environment and improving the retention capacity.

2.5.4 Mucoadhesive Drug Delivery System

Mucoadhesion polymers, on hydration become adhesive to mucosa, have a property of mucoadhesion, remain adhere for a particular period, and release a drug for extended time. (79) By means of interfacial forces, two things are held together is a characteristic of Bioadhesion and is an integral phenomenon. (83)

2.5.4.1 Mechanism of Mucoadhesion

Several theories have been put forward to explain the mechanism of polymer-mucus interactions that lead to mucoadhesion. Contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the same. Following this, the penetration of the bioadhesive into the tissue crevices. Hydration of the polymer plays a very important role in bioadhesion. During hydration, dissociation of hydrogen bonds of the polymer chains occurs. The polymer-water interaction becomes greater, making the polymer chains available for penetration of mucus. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs.(79) The factors which affect mucoadhesion are contact time, contact pressure and the diffusion coefficient of the polymer.

2.5.4.2 Theories of Mucoadhesion

Table 2.6 Theory of Mucoadhesion (84)

Sr. No.	Theory	Statements	Mechanism
1.	Wetting theory	Positive spreading coefficient of polymer.	Mucus membrane contact with polymer by its spreading property.
2.	Electronic theory	At the interface of double layer Electron must transfer.	Attractive electrostatic forces between the polymer and glycoprotein mucin network.
3.	Diffusion theory	Bioadhesive polymer and mucus glycoprotein must be similar for extreme diffusion and solubility	Flexible polymer chain and physical entanglement of mucin strands
4.	Adsorption theory	Strong primary forces: hydrogen bonds, covalent bonds, ionic bonds, weak secondary force & Vander Waal's forces.	Chemical bond resulting from Surface forces

2.5.4.3 Characteristics of Ideal Bioadhesive Polymers

Ideal bioadhesive polymers have certain characteristics. Most important is, should be compatible and inert. (84) It should possess its property in liquid and solid state, and should have an optimal molecular weight. For both hydrophilic and hydrophobic drug its response remained same. It should penetration enhancement property, show specificity and stimulate endocytosis, specificity for attachment to particular tissue/cell, as well enzyme inhibition property.

2.6 Basic Concept of Microemulsion

2.6.1 Background of Microemulsion

Hoar and Schulman introduced microemulsion concept early in 1940s. Microemulsion is an optically isotropic and thermodynamically intact a system of oil, water and anamphiphile. In some respects, microemulsions considered as nano-scale versions of emulsions, i.e., droplet type dispersions either of oil-in water (o/w) or of water-in-oil (w/o), with a size range of 1 nm-100 nm.(85) It has well dispersed particles having

diameter less than one-fourth wavelength of visible light, i.e. Less than approximately 120 nm, do not refract light and therefore micro emulsion appear transparent to the eye compared to simple emulsion. Bioavailability problems due to dissolution can be overcome, and solubilization of poorly soluble drugs (particularly BCS class II or class IV), can be enhanced by microemulsions. Systems protect incorporated drugs against oxidation, enzymatic degradation and enhance membrane permeability.(86)

2.6.2 Structure of Microemulsions

The mixture of water oil and surfactants is capable of forming a wide variety of structures and phases, depending on the proportion of components. The flexibility is a crucial factor in regard of surfactant. Bicontinuous structures do not exist (Fig. 2.6) if a very rigid film of surfactant is present.(87)

Besides microemulsions, structural examinations can reveal the existence of regular emulsions, anisotropic crystalline hexagonal or cubic phases, and lamellar structures depending on the ratio of the components. The internal structure of a microemulsion vehicle is very important for the diffusivity of the phases, and also for the diffusion of a drug in the respective phases.

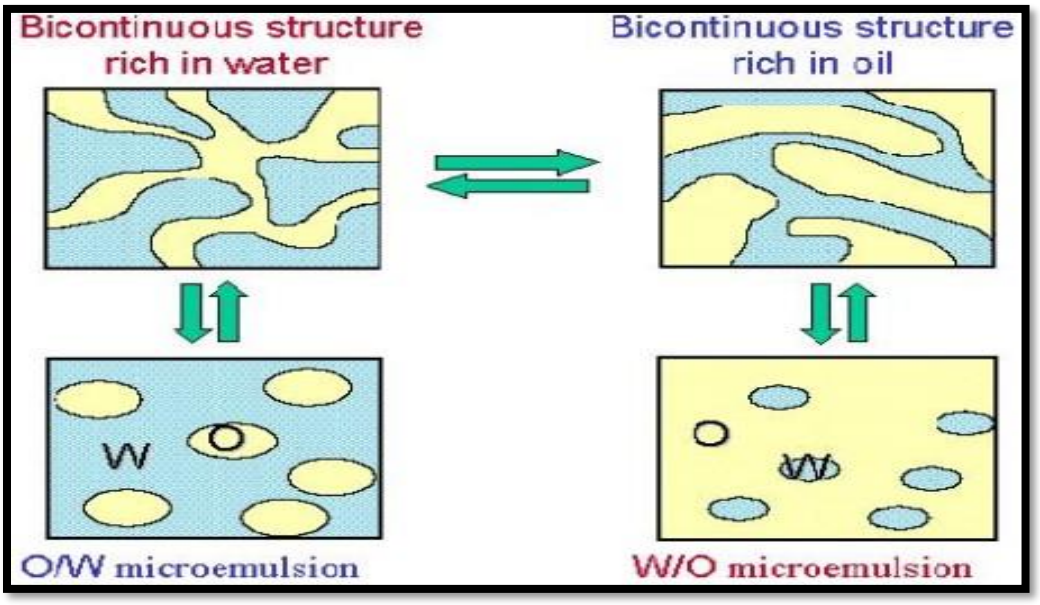

Fig. 2.6 Bicontinuous Structure of Microemulsion System (7)

2.6.3 Methods for Constructing Phase Diagram

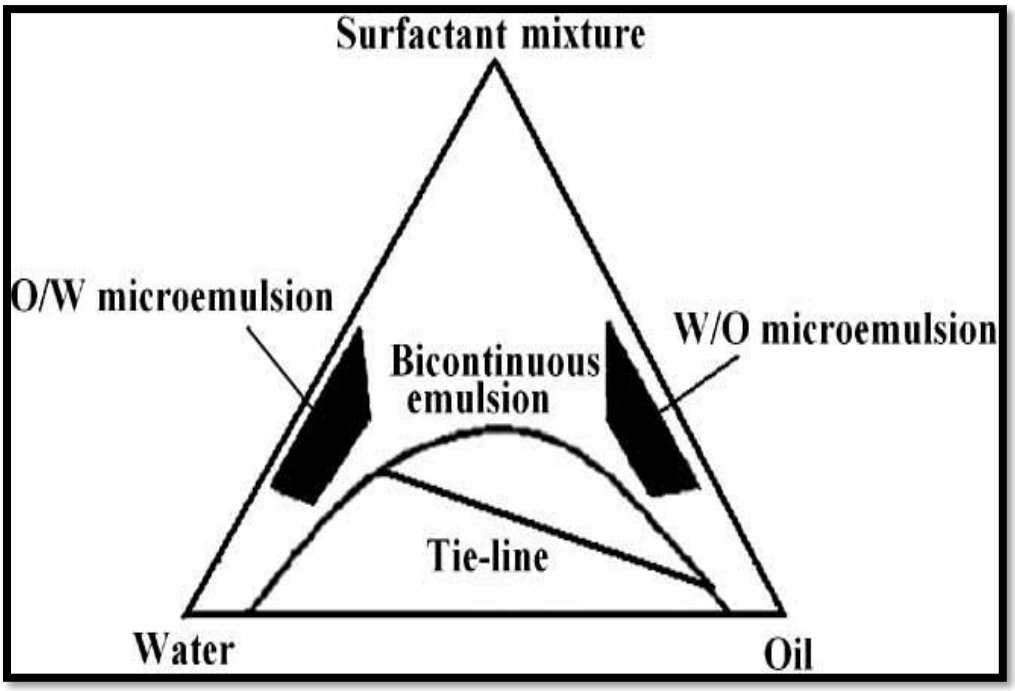

Fig. 2.7 Pseudo ternary Phase Diagram of Oil, Water and Surfactant

Phase diagrams should be constructed to define the extent and nature of the microemulsion regions and surrounding regions (Fig. 2.7). Several methods can be used to achieve the same. In one of the methods, prepared a different composition. Other regions can be identified by their characteristic optical structure. These diagrams are complicated and time consuming to prepare. (88)

In another method, microemulsion region can be located by titration method. At a constant ratio of s/cos, various combinations of oil and s/cos are produced. The water is added dropwise, after the addition of each drop, the mixture is stirred and examined. The

appearance (transparency, opalescence and isotropy) is recorded along with the number of phases. Thus, an appropriate delineation of the boundaries can be obtained in which it is possible to refine through the production of compositions point by point beginning with the four basic components.

2.6.4 Preparation of Microemulsion

Basic components for microemulsion system has been same as discussed in the section 2.4.3 composition of SMEDDS, beside this component water is additional part of the system. Phase titration and phase inversion method are used for the preparation of microemulsion.(88)

2.6.4.1 Phase Titration Method

Phase titration method utilised for microemulsions preparation. Phase diagram construction is a methodology to study the effect of mixing of component to formulate a microemulsion.

2.6.4.2 Phase Inversion Method

Dispersed phase in excess quantity or extreme temperature, may inverse phase of microemulsions with changes in particle size that affect drug release both *in vitro* and *in vivo*.

2.6.5 Advantages of Microemulsion Based Systems

Microemulsions, a thermodynamically stable system, are easy to prepare and requires no significant energy involvement during preparation. It improves effectiveness of drug, rendering total dose to be reduced and hence lowering side effects. Drug release from the system with pseudo zero order kinetics, also depend on the partition of drug volume, transport rate of the drug and dispersed phase. Compare to normal microemulsion system mucoadhesive system shows promising advantages over simple system. (88) Mucoadhesive microemulsion increases the contact time of formulation with nasal mucosa and reduce chances of draining out of formulation. It provides sustain delivery and increases nasal absorption due to incorporation of permeation enhancer.

2.6.6 Limitations of Microemulsion

Factors which limit the use of microemulsion in pharmaceutical applications are: The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons. (88)

2.6.7 Advanced Method for Characterization of Mucoadhesive Microemulsion (89)

2.6.7.1 Scattering Techniques for Microemulsions Characterization

Small-angle x-ray scattering (SAXS), small-angle neutron scattering (SANS), and static as well as dynamic light scattering are widely applied techniques in study of size, shape and dynamics of the components of microemulsions.

2.6.7.2 Static Light Scattering Techniques

These techniques have been widely used to determine droplet size and shape of microemulsion. Here, the intensity of scattered light is generally measured at various angles and for different concentrations of microemulsion.

2.6.7.3 Dynamic Light Scattering Techniques

Due to Brownian motion, the scattering intensity fluctuations of droplets can analyze by photon correlation spectroscopy

This technique allows the determination of z-average diffusion coefficients. Using the stokes-Einstein equation, in absence of inter particle interactions, hydrodynamic radius of particles, r_h, can be determined from the diffusion coefficient

$$D = kT/6\pi\acute{\eta}r_h \quad \text{------ (6)}$$

Where, k is Boltzmann constant, T is the absolute temperature and ή is the viscosity of the medium.

2.6.7.4 Nuclear Magnetic Resonance Studies

Using nuclear magnetic techniques, dynamics of microemulsions and its structure can be studied. With the use of magnetic gradient present on the samples, the Fourier transform pulsed-gradient spin-echo (FT-PGSE) technique work and it allows rapid and simultaneous determination of the self diffusion coefficients (in the range of 10^4 to 10^{12} m^2/s) of many components. (90)

2.6.7.5 Interfacial Tension

Measuring the interfacial tension, formation and properties of microemulsion can be studied. Ultra low values of interfacial tension are correlated with phase behavior, particularly existence of surfactant phase or middle phase microemulsion in equilibrium with aqueous and oil phases. Spinning drop apparatus can measure the ultra-low interfacial tension. Interfacial tension is derived from the measurement of the shape of a drop of the low density phase, rotating it in cylindrical capillary filled with the high density phase.(89)

2.6.7.6 Electrical Conductivity Measurements

To determine the nature of the continuous phase and to detect the phase inversion phenomenon, the electrical conductivity measurements are highly useful. A sharp increase in conductivity in certain w/o microemulsion systems was observed at low volume

fractions and such behavior was interpreted as an indication of a 'percolative behavior' or exchange of ions between droplets before the formation of bicontinuous structures.(89)

2.6.7.7 Mucoadhesive Strength (91)

Mucoadhesive strength is known as the force to detach formulation from nasal mucosal tissue, for determining the mucoadhesive strength by modified balance, show in Fig. 2.8. A small section of nasal mucosa of sheep/goat was cut and tied or fixed on 2 glass vial with the help of rubber band or thread, stored at 37°C ±2°C for 10 minute and then 50 mg of gel was placed on nasal mucosa on first vial. Second vial was fixed in inverted position to the underside of the same balance, after this the height of both vials were adjusted and come in intimate contact for 5 minute to ensure contact between nasal mucosal tissue and in situ gel formulation. Then weight was added gradually on the other side of balance, until vials detached, it expresse the strength or stress in dyne/cm².

Stress is calculated by the formula

Detachment Stress (dyne/cm²) = M × G ÷ A

Where,

G - acceleration due to gravity, M - weight required for detachment of two vials in gm, A - Area of tissue exposed.

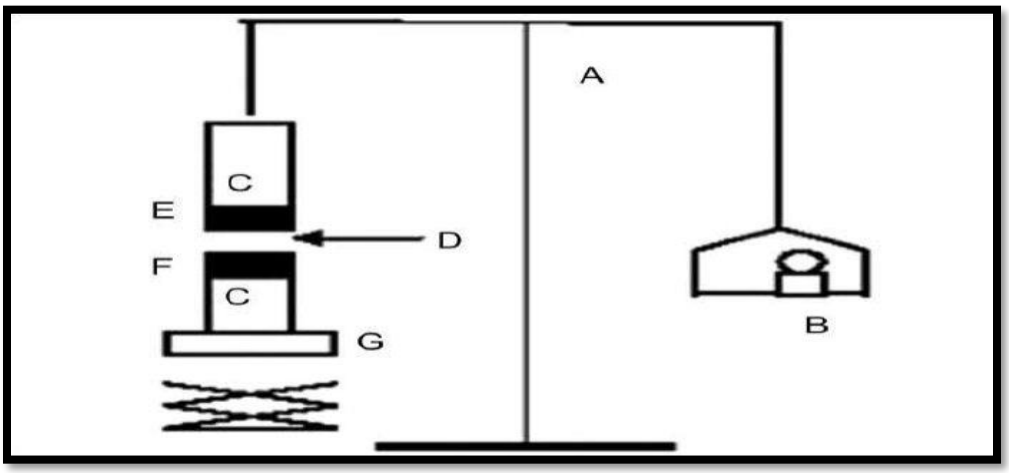

Fig. 2.8 A Modified Balance, B Weights, C Glass Vial, E, F Membrane, G Height Adjustable Pan

2.6.7.8 *In vitro* Diffusion Study of Mucoadhesive Microemulsion (92)

Franz diffusion cell has been used for *in vitro* diffusion study of microemulsion. Dialysis (22µm pore size) or cellophane membrane (12000-18000 mol wt cut off) with diffusion area 8 cm^2 has used. Phosphate buffer (pH 6.4-6.6), is placed into the acceptor chamber and formulation containing drug is placed in donor chamber. At predetermined time point, 1ml sample has been withdrawn from receiver chamber and analyze, replace sample volume with equal amount of phosphate buffer after each sampling.

2.6.7.9 *In vitro* Permeation Study of Mucoadhesive Microemulsion (93)

Fresh nasal tissue section of goat/sheep obtains from slaughter house and mount on franz diffusion cell. Phosphate buffer (pH 6.4-6.6) is placed into the acceptor chamber and formulation was placed in donor chamber, at predetermined time point, 1ml sample has been withdrawn from acceptor chamber and analyze, replace sample volume with same amount of phosphate buffer after each sampling.

Permeability Coefficient Calculated from the Slope of the Graph;

$P = Slope \times Vd \div S$

Where, P = permeability coefficient.

Vd = volume of the donor solution

S = surface area of tissue

Differential Scanning Calorimetry (DSC), X-Ray Diffraction and Fourier Transform Infra Red Spectroscopy (FTIR) Studies: used for drug and polymer interaction, compatibility and to check matrix formation.

2.7 Patented Microemulsion Product

Table 2.7 List of Patented Microemulsion Product

Drug	Name of Excipients	Comment	Reference
Clonazepam	S- polyoxyethylene-35-ricinoleate O-medium chain triglyceride Cos- Polysorbate 80	Rapid delivery of Clonazepam to the brain more effectively by intranasal administration.	Vyas et.al.2006 (94)
Diazepam	S- Tween 80 O- ethyl laurate, ettyloleate Cos- propylene glycol, ethanol	Rapid onset of Diazepam by intranasal route and increased bioavailability.	Lianil, et al 2002. (95)
Nimodipine	S-Cremophore RH 40, Labrasol, O-IPM, Labrafil M 1944 Cos-transcutol, ethanol	Maximum solubility of Nimodipin, no nasal toxicity, therapeutic effect improved.	Zhang et al.2004. (96)
Eucalyptus oil	S- tween 80, span 80 O- drug itself Cos- PEG 400	Rapid onset of action Oil, used for aroma therapy and for the treatment of migraine.	Tiwari and Bajaj, 2007.(97)
Sumatriptan Succinate	S-macragol glyceride Cos-transcutol, fatty acid ester of polyglycerol O- MCT MP- polycarbophil	Enhanced rate and transport of Sumatriptan succinate, help in decrease the dose and maximize therapeutic index.	Vyas et.al.2006. (98)
Progesterone and Indomethacine	S- tween 80/40, Span 20 O- Isopropyl myristate Cos-isobutanol	High solubilization capacity for both drugs	Nandi et al, 2003. (99)

*O-Oil, S-Surfactant, Cos-Cosurfactant, MP-Mucoadhesive polymer

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