



EVALUATION OF NANOPARTICLES FOR NOSE TO BRAIN DELIVERY

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Permeability, antidepressant.

Abstract: -

Nanoparticles ranges between 1 & 100nm in diameter & chemically are active. Polymers or macromolecules are included in drug delivery system in controlled-release manner. Polymeric nanoparticles are suitable for delivery at target site through nasal route, as nasal drug delivery system has enormous advantages like effective permeability , good bioavailability. So can be used as first-line treatment in emergency cases to achieve rapid therapeutic effects. Fluoxetine has drug category of Selective Serotonin Reuptake Inhibitors (SSRIs) which is approved to treat the mental diseases & can be delivered through nasal route rapidly & efficiently.

INTRODUCTION:-

Nanoparticles are defined as particle of matter that ranges between 1 and 100 nm in diameter. They are chemically very active. Nanoparticles are used for various Such

purpose , such as medical treatment & using in different branches of industry production

for example - Solar and oxide full fuel battery for energy storage. Nanoparticles are also used in our daily /everyday products such as cosmetics or clothes, sunscreens, deodorant ETC.

Different possible ways to synthesis the nanoparticles. were put forward after the Feynman's discovery.

- 1) Top-down approach
- 2) Bottom up method

Both the method differs in themselves in quality of the nanoparticles, time consumed by the synthesis and the expenditure for the synthesis.

1. Top down approach: Includes breaking down of the big or as a whole material to the Nano - size

particle. This can be performed by various, modern Engineering techniques as precision engineering and lithography.

2. Bottom-up: - It including constructing or building up the atom by atom or molecule by molecule by physiochemical methods. In a nanoscale range by standard handling of atoms and molecules.

Nanoscience:- Study of Nanoparticles ranging 1 to 100 Nano meter.

Nanotechnology:- Practical uses of the nanoparticles in modern science.

Type of Nanoparticles

Nanoparticles are classified into different types on the basis of size , morphology, physical or chemical properties.

- 1) carbon based nanoparticles
 - 2) Ceramic nanoparticles
 - 3) metal nanoparticles
 - 4) semi-conductor nanoparticles
 - 5) lipid baled nanoparticles
 - 6) Polymeric nanoparticles
- 1) Carbon based nanoparticles: - This It includes two important material carbon nanotube (CNTs) and fullerenes. There is 100 times stronger than steel therefore mainly used in structural reinforcement carbon nanotubes (CNTs) are allotropes of Carbon with a nanostructure. fullerene are also allotropes of carbon and its molecules consist of carbon atom that are connected by single and double bond. Example: - C60 fullerene and shortened single-walled carbon nanotube (SWNTs)
 - 2) Ceramic nanoparticles: - Ceramic nanoparticles are the type of inorganic solids, and it's made up of oxides, carbide, carbonate and phosphate. They have high flame retardant and chemical inertness. They are used in Photocatalysis

Photodegradation of dyes, drug delivery system. Example:

- Calcium, titanium, silicon etc.
- 3) Metal Nanoparticles: - TH is prepared from metal precursors. They can be obtained from chemical electrochemical or Photochemical methods. Example: Gold, Copper, Silver
 - 4) Semiconductor Nanoparticles: - Semiconductor nanoparticles established in the periodic table in groups 11-VI, 111-V or IV-VI. They having both metal or non-metal properties in it. They widely used in Photocatalysis Photo-Optics etc. example: - Ge, N, Gap from group III-V. Silicon and germanium from group VI
 - 5) lipid- based nanoparticles: - It is found in spherical in shape with diameter ranging from to 100 nm. There It is used in biomedical field cu a drug carrier and delivery or RNA release in cancer therapy.
 - 6) Polymeric nanoparticles: - The Polymeric nanoparticles are based on. organic compound on depending on their formulation they have structure like Nano capsules or nanospheres in shape nanosphere particles have matrix like structure as well a Nano capsules particle have core-shell Structure The particle size range between the 1 to 1000 nm.

1) In the recent years, biodegradable Polymeric nanoparticles (PN)have attracted great attention as potential drug carriers

2) the application of Polymeric nanoparticles is controlled delivery of Drugs, ability to target organs/tissue, as Carriers ability for DNA in gene therapy & ability to delivery proteins Due to their small size property demand has been raised of Polymeric nanoparticles. Because of the controlled released type, it's therapeutic index and bioavailability can be enhanced.

Polymers

Polymer- huge molecules with large molecular mass also termed as macromolecules. Constructed by combining small units called monomers with the help of covalent bonds. Complete process of manufacturing polymers is termed or coined as polymerization. No. of polymers & monomer which helps to make a polymer is known as Degree of polymerization hence a formula is derived

Degree of polymerization \times weight of monomers = Average molecular weight of polymers.

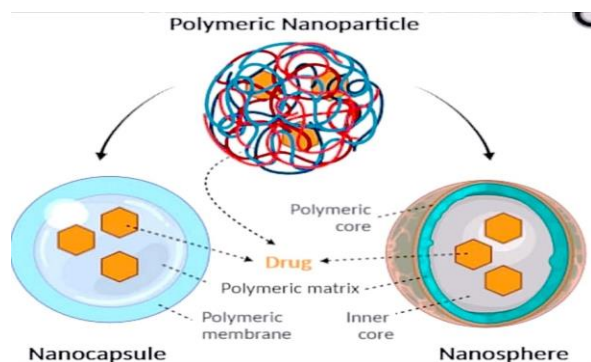


Fig: - polymers We have studied here about the how polymers are included in drug delivery system in controlled release manner.

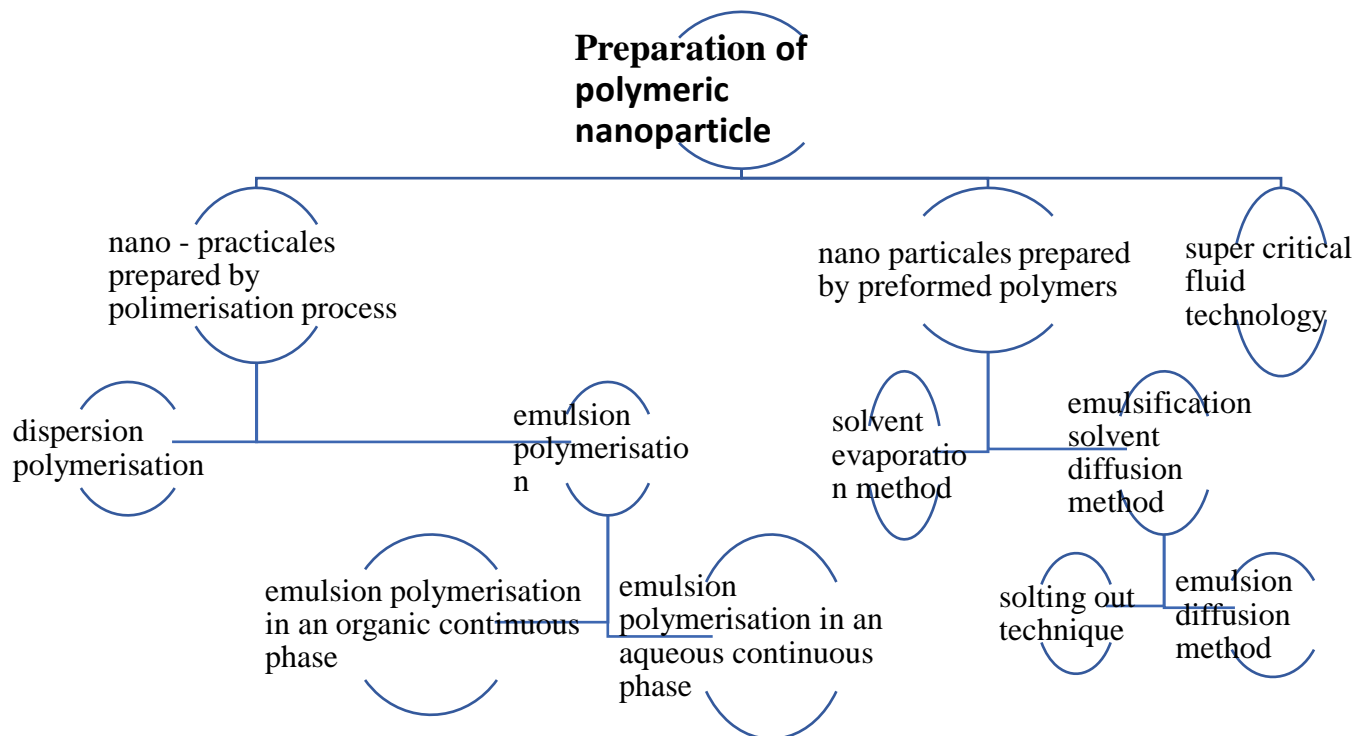
1] Drug-polymer Conjugates: In this method the pharmaceutical active agents are attached to the back of polymer chain so that they help to increase the action of cellular internalization and to get the exact amount of the required drug at target organ (site).

2] Encapsulated drug polymer: In this method the drug is entrapped into the polymer to improve the Spreading ability and serum steadiness to get a low level in drug immunogenicity by a regulated spreading to the target location.

General method of preparation of polymeric nanoparticle

Polymeric nanoparticles can be prepared by either polymerization of monomer or from the pre-formed polymer

Preparation of polymeric nanoparticle



1. Nano Particles prepared by polymerization process:

- This method is derived from field of latex engineering to produce nanoparticles and are based on in-situ polymerization of monomer in various media.

-The Birnbach and Speiser 1st Polymerized nanoparticles (NP) for Pharmaceutical use adopting Two types of Polymerization processes

- 1) Dispersion polymerization (DP)
- 2) Emulsion Polymerization (EP)

1.1. Dispersion polymerization:

- Dispersion polymerization (DP) is conducted using monomer, an initiator solvent in which newly formed polymer is insoluble

- the Precipitates as a particle and polymer forms in Continuous phase.

- in aqueous monomer solution nucleation is directly induced

-When these chains exceed a critical chain length, small particles are formed by aggregation of growing polymer chains and precipitates from continuous phase.

-When sufficient stabilizer cover particles, stable colloidal particles are formed by coalescence of these precursor particles with themselves and with their aggregates.

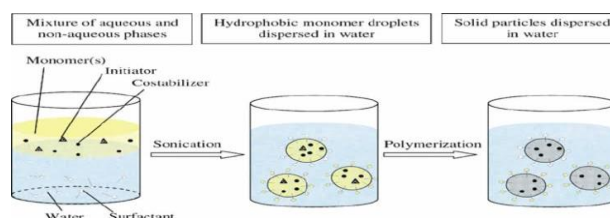


Fig - Dispersion polymerization

1.2 Emulsion Polymerization (EP): Is a method in which the monomer is emulsified in non- solvent containing micelles and stabilizer monomer droplet.

- In the in the presence of initiator the polymerization is perform either radical or iron depending upon type of initiator.

-The particle size obtained by the EP are smaller (100-300nm) than the original stabilizes monomer droplet in a continuous phase.

-The emulsion performed by using either organic or aqueous media, as continuous phase for production polymer.

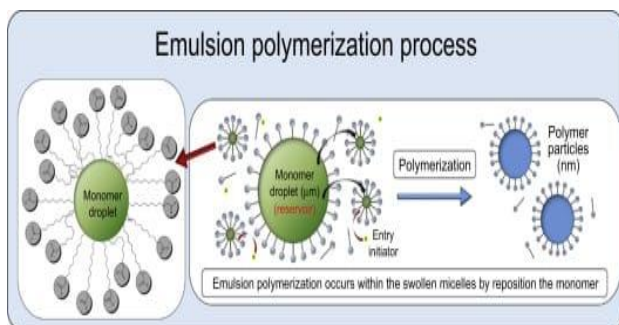


Fig: Emulsion Polymerization

2. Nanoparticles prepared from the preformed polymers:

2.1 Solvent evaporation method:

-In this method the solution of polymer is prepared in organic solvent such as chloroform ethyl acetate and dichloromethane.

-The encapsulated drug to be dissolve in a polymer solution and organic phase is emulsified with an aqueous phase containing surfactant to obtain oil / water emulsion.

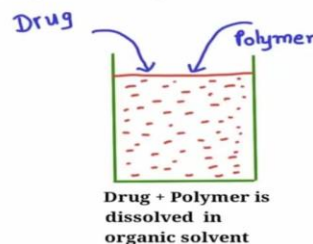
-The organic solvent is then evaporated either at elevated temperature of the under reduced pressure.

-The surfactant used in emulsion formation include poloxamers, polysorbate 80, polyvinyl alcohol (PVA).

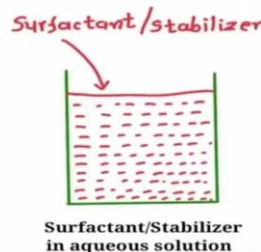
-The size of nanoparticles is depending on size of emulsion droplets forms prior to solvent evaporation.

- The size can be controlled by the number of factors including stirring rate, type and amount. Viscosity of organic aqueous phase and temperature of emulsification.

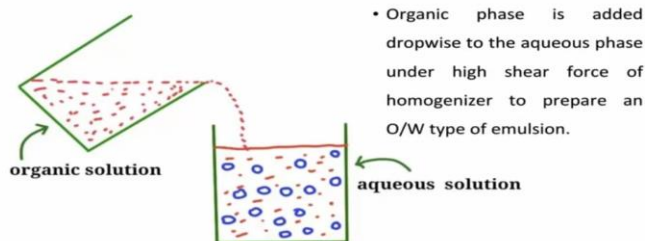
Step 1: Preparation of organic phase



Step 2: Preparation of aqueous solution of surfactant / surface stabilizer



Step 3: Emulsification



Step 4: Evaporation of solvent and precipitation of nano-particles

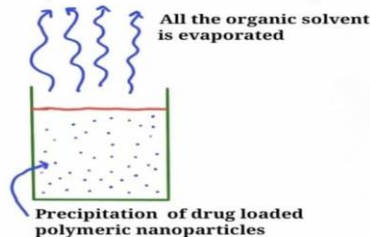


Fig: solvent evaporation method

2.2 Emulsification solvent diffusion method

- The emulsification solvent diffusion method is a modified version of solvent evaporation techniques.

-The techniques employ use of water miscible solvent such as methanol and acetone along with the non-polar solvent. which where use as organic phase.

- Solubility of polar organic solvent in water, they spontaneously diffuse into the aqueous phase. and an interfacial turbulence is created between two phases leading to precipitation of droplets as small as polymeric non-particle.

-The above techniques utilize organic solvent which are hazardous to environment then other various technique such as salting out technique and emulsification solvent diffusion techniques were developed.

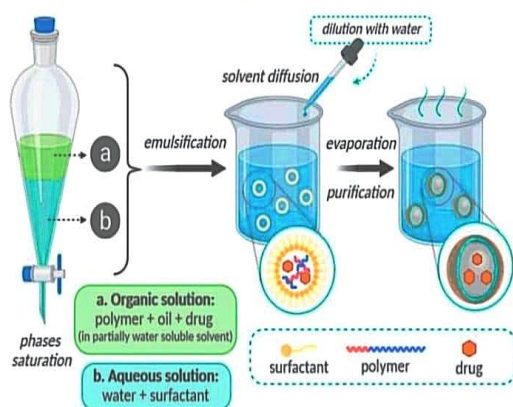


Figure 3. Schematic representation of the emulsification/solvent diffusion method.

2.2.1 salting out technique

- This method is based on the separation of the water- miscible solvent phase from aqueous solution promoted by the salting out effects

- Water is added to the emulsion obtained by the addition of a solution of polymer and drug emulsified in an aqueous gel containing salting-out agent and colloidal stabilizer.

- As a consequence of dilution, acetone diffuse into water resulting in particle formation.

- However, this technique can be used only for the loading lipophilic drug.

2.2.2 Emulsion diffusion method

- Is a slightly modification method of salting out technique.

-Differs mainly because organic solvent is only partially miscible with water and it's previously saturated with water.

-In order to reach an initial thermodynamics equilibrium between water and organic phase.

- After addition water and organic phase is observed and a Nano particle suspension is formed.

3. Supercritical fluid technology.

- recently discovered hyperbolic drug presented a problem of low solubility, poor bioavailability and irregular absorption after oral administration.

- supercritical fluid is a substance at a temperature and pressure above its critical temperature and pressure where it does not condense or evaporated to from a liquid or gas.

- supercritical fluid are useful in a precipitation of micro to Nano range of particles in a pure and encapsulated forms.

-most widely utilized supercritical fluid is carbon dioxide.

- technique after small particles however the formation of larger drug crystal could not be prevented of these techniques and enable formation of dry nanoparticles.

-In the use of super critical carbon dioxide or nitrogen the supercritical fluid has become attractive alternative because they involve use of environment friendly solvents.

- the supercritical fluid has been widely applied for preparation of micro particles.

Advantage of Nanoparticle:

- 1) They can be consolidated in other pharmaceutical drug delivery processes.
- (2) The particular polymer and its potential to adapt drug delivery from polymeric nanoparticles have been beneficial for cancer treatment.
- 3)

It's transferred a greater concentration of Active agent to a specific site.
 4) Improves the stability of any volatile agents, simply and affordable manufacture in huge volume by a multiple of process.
 5) Nanoparticles provide an effective way of drug delivery over oral and intravenous method of drug delivery.

Intranasal Delivery for Brain targeting:

1] The severe or long-lasting drug treatment for various neurodegenerative and psychiatric disorders are difficult to handle from different point of view.
 2] The low bioavailability and restricted brain exposure of oral drugs.
 3] The rapid ADME process causes side effects and also due to high dose of the medicine produces the disruption to patient also the reason for low brain penetration of the compound is due to the Blood Brain Barrier which protects against the chemical substance from foreign body.
 4] Intranasal drug delivery helps to cross the Blood Brain barrier effectively. And also reduces the side effect of the dose.

Nasal drug delivery system

Most of the drug are efficient to provide their therapeutic effect at their specific site but in case of CNS or central nervous system Drug Delivery process it may fail or unable to even

read their as they have to cross the blood-brain barrier and blood cerebrospinal fluid by area because the barriers are very complex and defensive and most of the drugs are deficient to cross them easily

so, there is an approach of drug delivery through olfactory nerves and off that passed from the nose to the brain

that is the intended route is going to be divided to brain by passing the blood-brain barrier delivery through

Intranasal route avoids the contact to blood brain barrier also we can avoid pre-systemic metabolism international beauty credential

for delivery to brain also it has enormous advantage that it will require low dose of drug it can be convenient trouble free and first-line treatment in emergency cases we can transfer the drugs through nasal mucosa to the CNS to achieve the faster and great drug absorption as it is more permeable and neutral PH

Advantages and Dis-advantages of nasal drug delivery system:

Advantages:

1. permability of nasal mucosa is high
2. self-administration of drug
3. easy to use by patient
4. sub epithelial tissue is highly vascularized
5. within 30 min absorption is happened
6. highly suitable route for peptides
7. higher bioavailability

Disadvantages:

1. Many drugs are not able to administered through nasal route
2. highly using this route damage the nasal mucosal layer
3. once the drug is administered it cannot be withdrawn
4. limited volume of drug delivery
5. pathogenic condition can affect the bioavailability
6. compounds or drug with high molecular weight cannot be administered by this route

Mechanism of drug release: Generally, this mechanism is carried out by this way the polymeric drugs from their physical chemical barrier

1. Hydration and diffusion:

In this process the polymeric nanoparticle is allowed to swell by hydration subsequently released through diffusion

2. Enzymatic reaction:

rupturing of the polymeric dosage form at the site of delivery by an enzymatic reaction A so resulting the release of drug from entrapped inner core

3. Dissociation and de-adsorption:

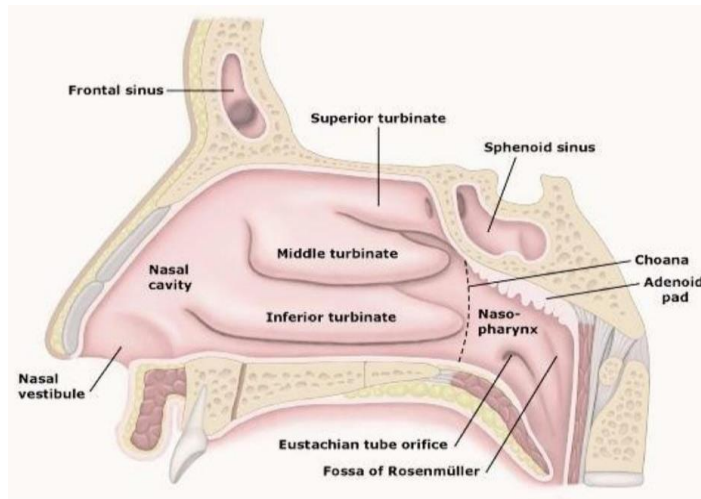
Dissociation of the drug from the polymer and its de adsorption from the swelled nanoparticles

Nasal Anatomy and Physiology:

Nasal Anatomy ----

The nose is a structure that lies on middle of face & is inevitable part of our respiratory system. It is a major & continued route of airway to enter the body.

The whole nasal cavity is approximately 5cm high & 10cm long having dual chamber. Nose consist of two halves having total resistance of approximately 50% to respiratory airflow from nostrils which are two openings of nasal cavity to alveoli, which are essential for breathing process. Each half of nasal cavity have bony scroll like turbinate, there are of three types inferior turbinate, median turbinate & superior turbinate. This turbinate is responsible for turbulent airflow through nasal portion which results into better connectivity between mucosa present in nasal passage & inspired air leading to humidification & regulation of temperature. As we go at lower part of nasal cavity, it again bends at nasopharynx area. Therefore, at nasopharynx area impaction of particles occur as air stream increases the velocity. So, from the nasopharynx part particles are expelled out by mucociliary clearance (MCC).



Nasal physiology-----

With function perspective nasal cavity can be divided into three regions

1) Vestibular region which is at lower part & limited.

It is covered by epithelium having protective functions against microbes & also protect from water loss called stratified squamous epithelium.

2) The respiratory region which occupies most of the region of nasal cavity & is necessary for absorption of drugs. It consists of epithelium which allows humidification of incoming breath called pseudo stratified columnar epithelium.

3) olfactory region, as name indicates contains the smell receptors at small patch of columnar cells.

Factors Influencing Nasal Drug Absorption:

A] Drug related factors:

1) Molecular weight: higher the molecular weight lowers the absorption of through nasal route of administration, bioavailability is inversely proportional to the molecular weight. 2) Chemical form: Drug in its salt or ester form may affect absorption. 3) Polymorphism: Dissolution rate and solubility of the drugs depends on the polymorphism of the drug, so it is important

to check the polymeric stability of drug.

4) Solubility and dissolution rate: lower the particle size of the drug higher the solubility and dissolution rate of the drug.

5) Lipophilicity: higher the Lipophilicity of the drug, it increases the permeation of the drug through nasal mucosa.

6) PK and partition coefficient: Unionized drugs case of an easily absorbed in the case of nasal absorption check the polymorphic stability of drug.

B] Factors related to formulation:

1) pH and mucosal irritancy: The optimum pH of the drug is specified to 4.5-6-5 pH which didn't cause Nasal irritation and prevents the bacterial growth in the mucosal membrane. 2)

Osmolarity: Maintenance of the osmolarity of the drug is important it Causes Constriction of epithelial mucosa and affect the absorption of drug.

3) Viscosity: Permeation of the drug depends on the Viscosity of the drug, higher the viscosity great the Contact time with nasal mucosa hence higher the absorption of drug.

4) Buffer capacity: Nasal formulation are about 25 to 200µL in volume adequate formulations is necessary to maintain the pH in situ. 5)

Molecular weight and size: lower the molecular weight and smaller the size of the drug in higher rate of absorption.

6) Area of nasal membrane exposed: Drug deposition in the nose at the anterior portion of the nasal cavity have slower clearance due to the low ciliated portion.

C] Physiological factors:

1) Effect of deposition on absorption: When the drug is deposited on the anterior portion of nasal mucosa It provides A higher nasal residence time. which increases absorption of the drug. 2)

Nasal blood flow: Nasal mucosa is highly Vascularized Network of blood vessels. Vasoconstrictions and vasodilation the blood vessel will affect the adsorption of the drug.

3)Effect of enzymatic activity: Stability of

the drug is affected by the various enzymes present in the nasal mucosa different which leads to change in different characteristics of the drug. 4)

Effect of mucociliary clearance: mucociliary clearance is inversely proportional and to absorption of drugs administered which is inversely dependent on the residence time.

5) Effect of pathological condition: Presence of the pathogens on the nasal mucosa layer of the host will affect the amount of the drug absorption.

Antidepressants:

1) Antidepressants works by raising levels of certain neurotransmitters in brain.

2) Depression is associated with deficiency of one or more monoamines, which are of 3 types- Serotonin, Norepinephrine & Dopamine.

3) Upregulation of postsynaptic receptors also leads to depression, Due to abnormal genes also cause depression.

Classification of Antidepressant:

A] Selective serotonin reuptake inhibitors (SSRIs): -ex. Fluoxetine, Sertraline, Paroxetine, Citalopram

B] Serotonin and norepinephrine reuptake inhibitors (SNRIs):
ex: Duloxetine, venlafaxine

C] Tricyclic antidepressants (TCAs): -
ex: Amoxapine, amitriptyline, Protriptyline

D] Monoamine oxidase inhibitors (MAOIs)
ex: Phenelzine, Selegiline

E] Atypical antidepressants:
ex: Bupropion, trazadone, Nefazodone, Vilazodone.

Drug profile

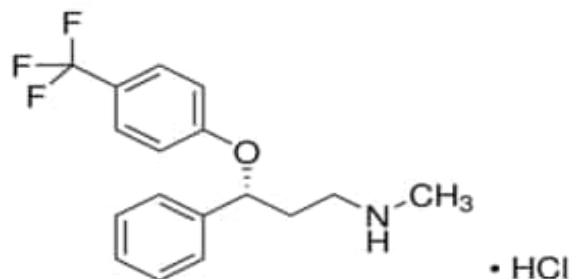
FLUOXETINE HYDROCHLORIDE:

Chemical name: Methyl ([3phenyl13
[4(trifluoromethyl)phenoxy] propyl) amine

CAS number: 54910-89-3

Molecular formula: C₁₇H₁₈F₃NO.HCl

Structural formula:



Appearance: white or almost white crystalline powder.

Odor: odor-less.

Melting point: 179 °C -182 °C.

Solubility: Slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and in methylene chloride.

Drug category: it is an antidepressant drug of the SSRI type.

Purity: Fluoxetine HCl is anhydrous or contains one-half molecule of water of hydration. It contains not less than 98.5 percent and not more than 102.0 percent of CHF NO. HCl, calculated on the anhydrous and solvent-free basis.

Ultraviolet spectrum: Maximum spectrum absorption at + 263 nm.

Beer's law range: 50-250 µg/ml.

Dose (tablets): 80 mg/day

BCS Classification: BCS Class-I

Half-life: 24-72 hours.

Conclusion:

Drug delivery via nasal mucosa to the brain, to treat the depression is very advantageous, without pre-systemic metabolism. The goal of present research is the preparation of novel

nanoparticle drugs to treat depression in efficient way. SSRIs like fluoxetine can be given by nasal route to treat the depression by interfering with reuptake of serotonin.

The mechanism followed by polymeric nanoparticles to release is of different ways -

1. hydration & diffusion in which nanoparticles subsequently release through diffusion.

2. Enzymatic reaction in which dosage form is ruptured to release at target site dissociation of drug takes place from polymer & de-adsorption takes place from swelled nanoparticles.

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