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FORMULATION AND EVALUATION OF NANO EMULSION CONTAINING ANTI- ALZHEIMERS DRUG FOR BRAIN TARGETING

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ABSTRACT

Nanotechnology has a wide range of uses in the food business, including the development of Nano-structured materials such as nanoparticles and Nano emulsions. Nano emulsions have been found to offer a number of advantages over regular emulsions, including improved optical clarity, kinetic stability, and bioavailability. While Nanoemulsions are seen to be one of the most promising food delivery technologies, their use is still restricted while their impacts on human health and food safety are studied. An emulsion is a biphasic system in which one phase is dispersed in the other phase as minute droplets with diameters ranging from 0.1 to 100 micrometers. It's a thermodynamically unstable system that can only be stabilized by adding an emulsifying agent (emulsifier).

INTRODUCTION

Nanotechnology has a wide range of uses in the food business, including the development of Nano-structured materials such as nanoparticles and Nano emulsions. Nano emulsions have been found to offer a number of advantages over regular emulsions, including improved optical clarity, kinetic stability, and bioavailability. While Nanoemulsions are seen to be one of the most promising food delivery technologies, their use is still restricted while their impacts on human health and food safety are studied. Nano emulsions are Nano-sized emulsions used to improve active medicinal component distribution. These are thermodynamically stable isotropic systems in which an emulsifying agent, such as surfactant and co-surfactant, is used to combine two immiscible Liquids to produce a single phase. NE droplets are usually between 20 and 200 nanometers in size. The size and form of particles dispersed in the continuous phase are the primary differences between emulsion and NE. An emulsion is a biphasic system in which one phase is dispersed in the other phase as minute droplets with diameters ranging from 0.1 to 100 micrometers. It's a thermodynamically unstable system that can only be stabilized by adding an emulsifying agent (emulsifier). The dispersed phase is also referred to as the internal phase or the discontinuous phase, whereas the outer phase is referred to as the dispersion medium, the external phase, or the continuous phase. Intermediate or interphase refers to the emulsifying agent. A NE is a fine oil/water or water/oil dispersion stabilized by an interfacial coating of surfactant molecules with droplet sizes ranging from 20 to 200

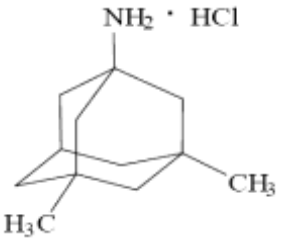
nanometers. Nanoemulsions are transparent because of their small size. There are two types of Nano emulsions. Avoiding the effect of solubility and solvent competition they cannot be avoided during solution crystallization

DRUG PROFILE

Memantine Hydrochloride: Memantine Hydrochloride is the hydrochloride salt of memantine, a low-affinity, voltage-dependent, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist.

Generic Name: Memantine, **Brand Name:** Namenda, Namenda XR, **IUPAC Name:** 3, 5- dimethyl adamantan-1-amine hydrochloride**, Molecular Weight:** 215.76

Molecular Formula: $C_{12}H_{21}NHcl$**, Structural Formula:**



Physical Description: Memantine hydrochloride appears as off-white fine powder. It is bitter in taste. **Melting Point:** 290-295 °C**, Solubility:** Solubility in water (100 mM), DMSO (43 mg/ ml), Ethanol (43 mg/ml). **Pka (strongest basic):** 10.7

Mechanism of Action: Memantine is a clinically useful drug in many neurological disorders, including Alzheimer's disease. The principal mechanism of action of memantine is believed to be the blockade of current flow through channels of N-methyl-d-aspartate (NMDA) receptors--a glutamate receptor subfamily broadly involved in brain function. Surprisingly, other drugs that block NMDA receptor channels, such as ketamine, exhibit serious deleterious effects. The unusual therapeutic utility of memantine probably results from inhibitory mechanisms shared with ketamine, combined with actions specific to memantine. These potentially important differences between memantine andketamine include effects on gating of blocked channels and binding of memantine to two sites on NMDA receptors. Because modulation of NMDA receptor activity can increase or decrease excitability of neuronal circuits, subtle differences in the mechanisms of action of NMDA receptor antagonists can strongly impact on their clinical effects.

Pharmacokinetics:

Absorption:

1. Bioavailability of approximately 100%.
2. Food has no effect on the absorption of memantine.
3. T max: 3-7 hours.

Distribution:

Protein Binding: low (45%).

Metabolism and Elimination:

- Little metabolism
- The majority of an administered dose eliminated as the parent drug via
    - The kidney : 75% to 90%
    - The faeces : 10% to 25%
- A small amount of the drug is converted to three polar metabolites.
    N-glucuronide,
    6- Hydroxyl memantine,
    1-Nitro-deaminated memantine.
- Terminal elimination half-life of about 60-80 hours.

Memantine Hcl is a psycho analeptic anti-dementia medication used to treat Alzheimer's disease in those who have moderate to severe symptoms. Memantine is an amantadine derivative that works as an NMDA receptor antagonist. It possesses antagonistic activity at the type-3 serotonergic (5-HT3) receptor with potency comparable to the NMDA receptor, but lower antagonistic activity at the

nicotinic acetylcholine receptor. Memantine is a prescription medication used to treat moderate to severe dementia (confusion) caused by Alzheimer's disease. It is not a cure for Alzheimer's disease, but it may help with memory, alertness, and daily functions. This medicine works by inhibiting the function of a natural molecule in the brain called glutamate, which is connected to Alzheimer's disease symptoms. Memantine is a medication that has been shown to be effective in the treatment of a variety of neurological illnesses, including Alzheimer's disease. The blocking of current flow via channels of N-methyl-D aspartate (NMDA) receptors, a glutamate receptor subfamily widely engaged in brain function, is thought to be the mechanism of memantine.

Side effects of memantine hydrochloride include:

- Dizziness
- Headache
- Constipation
- High blood pressure (Hypertension)
- Shortness of breath
- Acute kidney failure

Contraindications

- Hypersensitivity to product or components

EXCIPIENTS:

Oleic acid: It is used as oil phase for formulating nanoemulsion, performing dual role as component of delivery system and enhancing penetration. The usage of oleic acid is prevalent as a component in many foods in the form of triglycerides. It has substantially increased the penetration ability through the nasal mucosa.

PEG 400: It has been used in nasal delivery formulations, intravenous injections, and oral administration. Propylene glycol (PG), which is not a polymer but is miscible in water, was also used as a co-solvent in our study to examine the feasibility of nano or micro-emulsion.

TWEEN 20: It is a non-ionic detergent widely used in biochemical applications. It is necessary to accommodate the large interfacial areas generated were determined prior to emulsion formulation. It has been used as an emulsifying agent for the preparation of stable oil-in-water emulsions

METHOD USED FOR THE STUDY

Ultrasonic Emulsification: Solubility of memantine was determined in various oils, surfactants and co-surfactants. Excipients with maximum solubility were further chosen for preparing the mixtures in different ratios (surfactant: co-surfactant and oil: Smix) to determine a suitable combination of oil, surfactant and co-surfactant. To the combinations that gave absolute transparency when mixed with Milli-Q water, drug was added till the concentration of 10mg/ml. The finalized samples were vortexed and kept overnight.

ANALYTICAL METHOD OPTIMIZATION

Number of analytical methods is available for estimation of memantine hydrochloride such as ultra violet spectroscopy,DSC, SEM and FTIR.

UV VISIBLE SPECTROSCOPY:

Standard curve of memantine hydrochloride in phosphate buffer (pH6.8): 10mg of memantine hydrochloride was dissolved in 100ml mixture of phosphate buffer with pH6.8 by proper ultra-sonication for 5-10 minutes and further dilutions were made by using phosphate buffer (pH6.8) to obtain concentrations ranging 1,2,3,4,and 5µg/ml. The absorbance of solution was measured at 254nm by using UV Visible spectrophotometer. The readings obtained are tabulated in table and values was given in graph

Standard curve of memantine hydrochloride in distilled water: 10mg of memantine hydrochloride was dissolved in 100ml of distilled water by proper ultra-sonication for 5-10 minutes and further

dilutions were made by using distilled water to obtain concentrations ranging 1, 2, 3, 4, and 5µg/ml. The absorbance of solution was measured at 254nm by using UV Visible spectrophotometer. The readings obtained are tabulated in table and values was given in graph.

Characterization of pure drug:

Fourier Transform Infrared (FT-IR) studies: For the pure drug, Fourier transform infrared (FT-IR) spectra were obtained. The spectra were recorded in a thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 400-4000 1/cm at the spectral resolution of 201/cm.

Differential Scanning calorimetry (DSC): Thermal analysis of pure curcumin, were recorded on a DSC (NETZSCH DSC 204). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 10 C/min was employed with nitrogen pursing. Powder samples (15-30 mg) was weighed into an aluminium pan and analyzed as sealed with pin holes and an empty aluminium pan was used as reference.

Scanning Electron Microscopy (SEM): The surface characteristics of Memantine hydrochloride and oleic acid,PEG 400, and Tween 20 was studied by SEM (vegan3 tescan). The specimens were scanned with an electron beam of acceleration potential of 10 kV and the images were collected as secondary electron mode.

RESULTS AND DISCUSSION

UV-VIS spectrum: Memantine Hydrochloride: UV-VIS spectrum of memantine hydrochloride in phosphate buffer PH 6.8 was determined and spectrum was shown in graph no.1. it gave a peak at 302nm, the lamda max which is similar to the obtained reference.

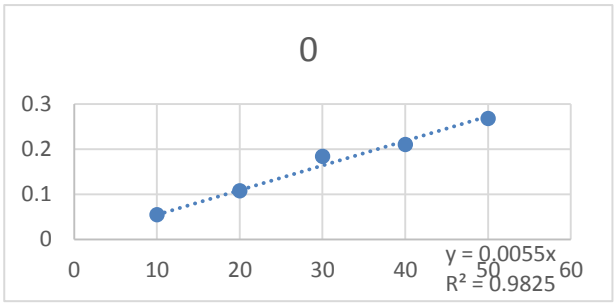
UV- VIS spectrum: Memantine hydrochloride: UV-VIS spectrum of memantine hydrochloride in distilled water was determined and spectrum was shown in graph no.2. It gave a peak at 302nm, the lambda max which is similar to the obtained reference.

FTIR analysis

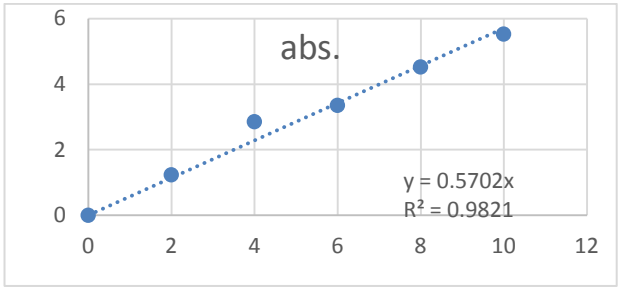
FTIR Of Memantine HCl drug formulation: The infrared (FT-IR) spectra were obtained in a KBr pellets using a FT-IR spectrometer spectrum one at resolution 4cm-1 from 4000 to 400 cm-1. Typical FT-IR spectra of novel memantine showed absorption at the following wave number in cm-1 2978.73, 2941.58, 2859.39, 1511.78, 1455.27, 1355.83, 436.30 and 448.78. FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements of an organic compound. Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational frequencies, leading to frequency shifts and splitting in absorption peaks. The FTIR spectrum of samples showed characteristic absorption bands which were comparable with absorption bands of individual sample. The results illustrated that, there were no chemical instabilities in drug-excipient combinations.

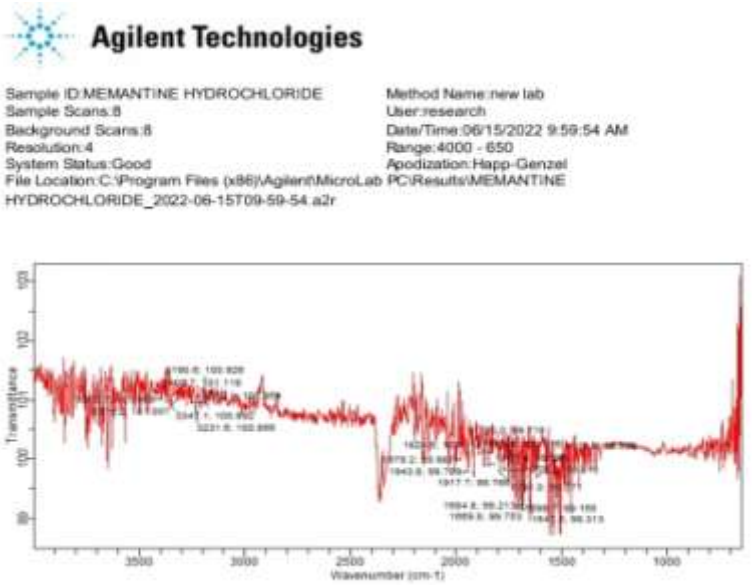
DSC analysis: Thermal analysis of pure curcumin, were recorded on a DSC (NETZSCH DSC 204). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 10 C/min was employed with nitrogen pursing. Powder samples (15- 30 mg) was weighed into an aluminium pan and analyzed as sealed with pin holes and an empty aluminium pan was used as reference. The surface characteristics of Memantine hydrochloride and oleic acid, PEG 400 and Tween 20 was studied by SEM (vegan3 tescan). The specimens were scanned with an electron beam of acceleration potential of 10 kV and the images were collected as secondary electron mode.

Concentration(µg/ml)	Absorbance
0	0
1	0.0545
2	0.1075
3	0.1839
4	0.2102
5	0.2679

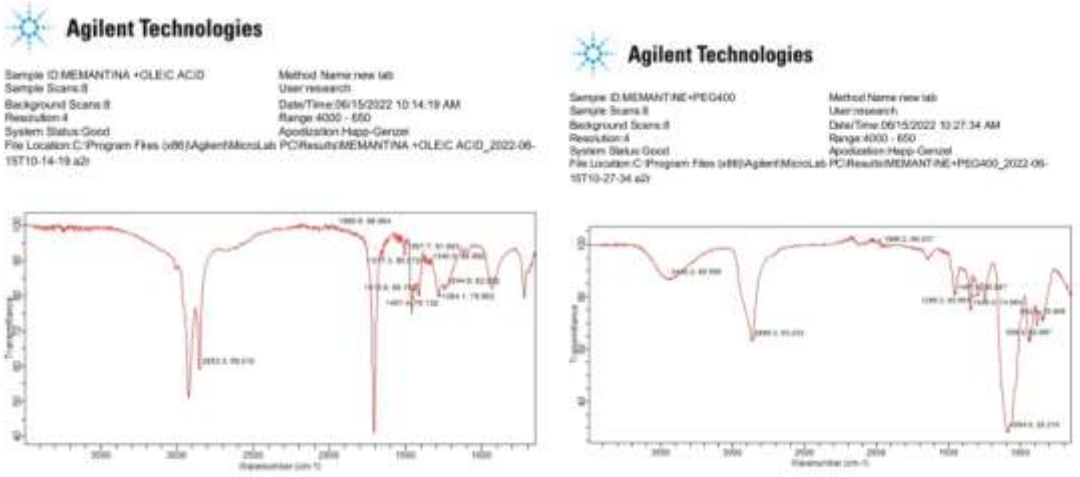


Concentration(µg/ml)	Absorbance
0	0
2	0.400
4	0.510
6	0.850
8	0.920
10	1.00





FTIR of Memantine HCl + Oleic acid



Agilent Technologies

Sample ID:MEMANTINE+TWEEN20
Sample Scans:8
Background Scans:8
Resolution:4
System Status:Good
File Location:C:\Program Files (x86)\Agilent\MicroLab PC\Results\MEMANTINE+TWEEN20_2022-06-15T10-20-08.a2r

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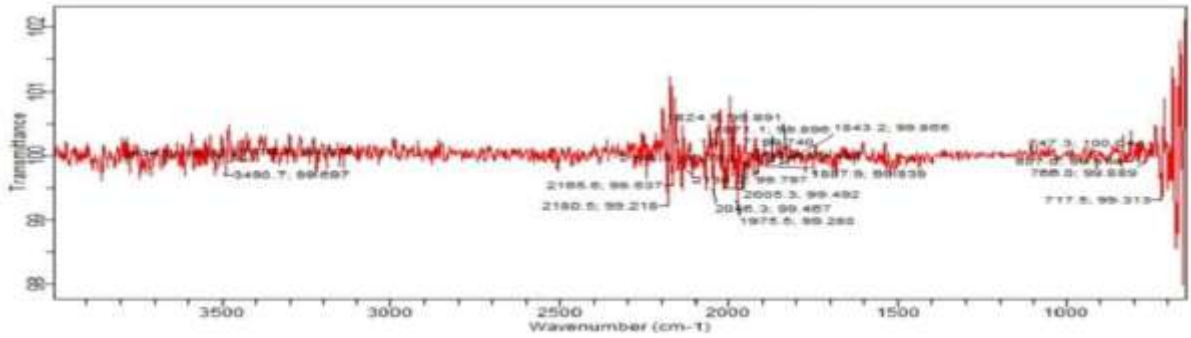
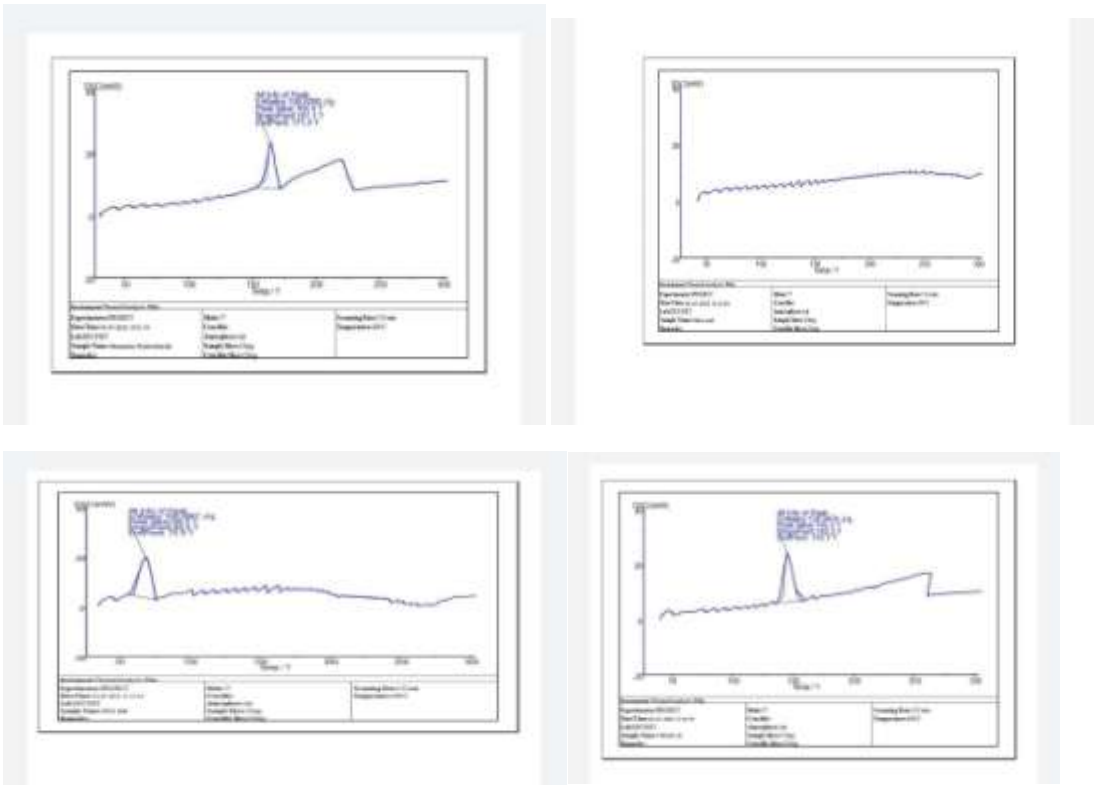
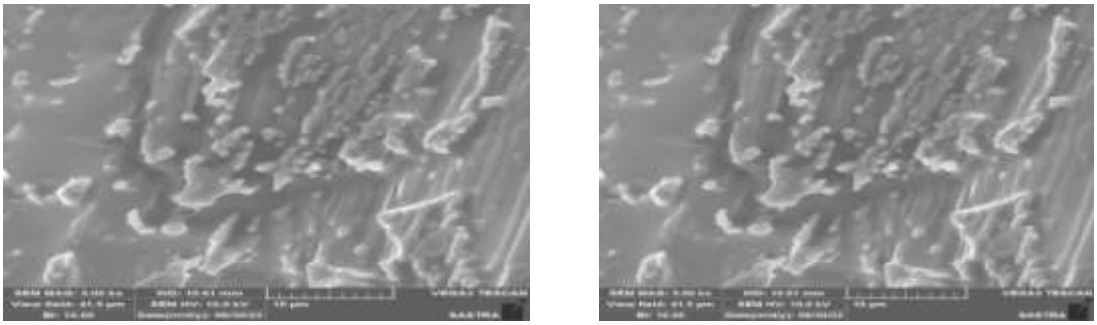


DSC analysis



Scanning Electron Microscopy (SEM):



CONCLUSION

The aspects surrounding the available techniques of preparation and the physical characterization of nano emulsions detailed in this review will furnish the formulator with a wide basis on the available techniques for preparation of nanoemulsions, as well as the technologies for characterisation of the prepared nanoemulsions, according to specific needs. Nano emulsions are common place in many applications including in pharmaceutical industries. This is because of their versatility as an efficient carrier system to deliver active ingredients to the targeted delivery sites.

REFERENCES

1. Mayank Handa, Therapeutic potential of nanoemulsions for targeting Alzheimer's disease.Department of Pharmaceutics.(2021);26(12),2881-2888.
2. Elisabetta Gavini, Paolo Giunchedi, and Maria Cristina Bonferoni ,Approach in the treatment of CNS disorders and brain diseases,Department of chemistry and pharmacy. (2020);12(2):138.
3. Atinderpal Kaur,Kuldeep Nigam, Sukriti Srivastava,A New approach to treat Alzheimer's disease,Journal of microencapsulation,(2020);37(5),355-365.
4. Devika Lomate, Arun Mahajan and Mayuri Tapkir. Nasal drug delivery. A Promismy approach for brain targeting. World Journal of pharmacy and pharmacueticlas sciences,(2019);8(10):477-491.
5. Bappaditya Chatterjee, Hira Choudhury.Targeted drug delivery to brain via intranasal nanoemulsion. International Journal of Pharmaceutics,(2019);565:258-268.
6. Gurupreet- Department of pharmaceutical sciences- Colloidal dispersion system. 2018;18(5): 781-789.
7. Paula.Espitia,Nanoemulsion characterization ,Journal of pharmaceuticals science.(2018);18(1),264-285.
8. Tushar Hemant Nikam, ,Development and application in parental drug delivery.Advance Pharmaceutical Journal,(2018);3(2),43-54.
9. Sagar Kishor savale, Hitendra Mahajan. Nose to Brain:A Versatile mode of drug delivery system.Indian Journal of Novel Drug Delivery ,(2016);8(3):123-132.
10. Srikanth C S.shinde, N.B Mahale , S.R Chaudhani and R.S Thorat. Recent Advances in Brain targeted drug delivery system. World Journal Of Pharmaceutical Research,(2015);4(5):542-559.
11. Rohit Rajendra Bhosale, Nano emulsion in advanced drug delivery.Journal of pharmaceutics.(2014);2(1):122-127.
12. Marta Tages, Eva Ramos-Fernandez, Bertran Salvador. The blood brain barrier- structure, function therapeutic approaches to cross it. Molecular Membrane Biology.(2014);31(5):150-167.
13. Chandrakanth,.Direct Nose -to-brain drug delivery via integrated nerve pathways bypassing the blood brain barrier. Allied Health Jornals,(2013);10(7):957-972.
14. Ashu Johri, M Flint, Mitochondria dysfunction in neurodegenerative diseases.Journal of pharmacology and experimental Therapeutics,(2012);342(3):619-630.
15. Vikram Lohar , Sandeep Singhal, Vimal Arora.Approach to better drug delivery.International journal of pharmacuetical reseach(2012);4(1):15-21.
16. Eva Bollen- Phosphodiesterases in neurodegenerative disorders.International union of biochemistry and molecular biology life. 2012;64(12).
17. Charles Lovelyn ,Antony A. Altama, Current state of nanoemusion in drug delivery, Journal of Biomaterial and nanobiotechnology, (2012);2, 626-639.
18. Nitin sharma ,Mayank Bansal, A new concept of delivery system,Chronicles of young scientists,(2012);1(2),2-6.