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In Vitro Dissolution Studies of Nanopharmaceuticals in Drug Delivery System

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Abstract:
Nanopharmaceuticals represent an emerging field where the sizes of drug particles or a therapeutic delivery system work at the nanoscale. Nanotechnology can offer the advantages of increasing solubility and bioavailability of delivering drugs. Nearly 40% of drugs coming to the market nowadays are having poor solvency-related issues and 70% of molecules in the discovery are in effect fundamentally insoluble in water, a long-standing issue is the difficulty of delivering the appropriate dose of a particular active agent to the specific disease site. The poor solubility of many drugs along with a slow dissolution rate is a major research and industrial problem for pharmaceutical scientists and industries. Nanopharmaceuticals have enormous potential in addressing this failure of traditional therapeutics which offers site-specific targeting of active agents. Such precision targeting via nanopharmaceuticals reduces toxic systemic side effects, resulting in better patient compliance.
The present work aimed to prepare and develop chlorothiazide (CTZ) andLisinopril nanoparticles for rapid and complete release by nano techniques to solve the problem of poor water solubility and bioavailability.CTZ and Lisinopril nanoparticles have to prepare by solvent evaporation method under an ultra-sonication process. Prepared nanoparticles were evaluated for yield, drug loading, and entrapment efficiency studies.CTZ and Lisinopril nanoparticles are to be characterized for drug and polymer interaction by using FT-IR and DSC. The morphological characteristics of the formulation can be studied. In vitro drug dissolution study of a drug, diffusion has to be performed by using the Dissolution and Disintegration apparatus, and Drug-like properties, Molecular properties, and Biological activity scores are calculated.

Objectives:
1. The aim is to investigate the performance of in-vitro studies of Nanopharmaceuticals of Diuretic drugs and Antihypertensive drugs
2. The desirable quality attributes of Nanopharmaceuticals and to enhancedissolution rate and bioavailability as compared to the raw materials.
3. To study the potential and usefulness of the quality-by-design approach, in understanding the related parameters for the preparation and processing of nanoparticles to the target area by techniques and tools.
4. Increase in relative bioavailability, enhanced solubility, and dispersion rate of the drug from the Nanosuspension formulation.

I. Introduction:

Oral delivery of drug formulations has been the most preferred route of drug administration for almost a century, however, significant challenges exist. For many years, more than 90% of the approved drugs have either poor solubility orpermeability or both issues. Poor solubility of drugs has been estimated to bethe cause of low bioavailability they involve many challenges such as decreased physical or chemical stability of excipients and drugs in aqueous solutions, poordrug solubility and absorption to macromolecules at the site of administration, degradation by enzymes, limited access to the site of action, as well as the need for sustained drug release system. To overcome these drawbacks nanoscaled products are being used.

Previous studies have been carried out to improve the bioavailability of these drugs including the sustained release of drug preparation of salts, solid dispersions, co-crystal formulations, and supramolecular complexes. However, these methods have some problems, considering alternative technologies, including nanotechnology, which resolves the problem of poor bioavailability of Biopharmaceutics. The Increase in interest in Nanotechnology-based drug delivery systems had been the key factor in the design and development of numerous novel dosage forms and complex delivery therapies such as liposomes, nanoemulsions, nanosuspensions, nanocrystals, polymeric nanoparticles, solid lipid nanoparticles. Several nanoparticulate nanosuspension preparations are currently undergoing clinical investigations for the delivery ofa wide range of therapeutics antibiotics, anti-inflammatories, etc. Some of the drugs

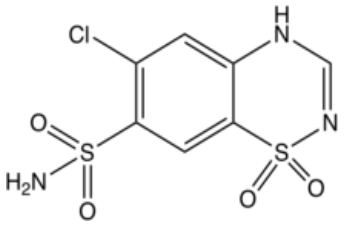
List of marketed products that were prepared using differentnanotechnology-based techniques

Name of Drug	Category	Particle Size
Nifedipine	Antihypertension	15 µm
5 Fluorouracil	Anticancer	0.26 – 0.6 µm
Amoxicillin	Antibiotic	118nm

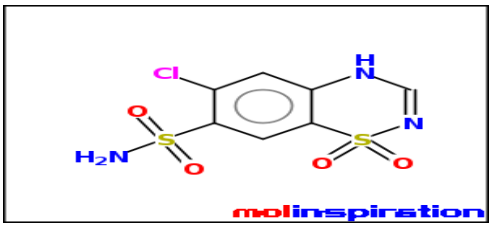
Lately, nanosuspension has turned out to be one of the budding dosage forms for water-insoluble drugs. Nanosuspensions can be defined as colloidal dispersions and biphasic systems comprising drug particles suspended in an aqueous medium, where the dispersed particles are less than 1 µm in diameter. These dispersed particles are stabilized with the help of a stabilizer. Apart from the simplicity and benefits of nanosuspensions, they are also easy to scale up, superior in drug loading, and use no harmful substances. In nanosuspensions, the Nano size particles provide a large drug surface area enhancing the dissolution rate, improving the overall bioavailability, and causing rapid onset of action for poorly soluble drugs.

Thiazide diuretics are an FDA-approved class of drugs that inhibit the reabsorption of 3% to 5% of luminal sodium in the distal convoluted tubule of the nephron. Because of poor solubility in the acidic pH of the stomach, they exhibit partial and erratic absorption. Despite its increasing solubility with the increasing pH of the lower intestine, the drug continues to remain largely unabsorbed, as it is less permeable in the intestinal region. The purpose of this study was to enhance the dissolution rate of Diuretics (Chlorothiazide) in gastric media so that the permeability through the stomach membrane can be increased for Diuretic nanosuspensions processed using optimized conditions and by controlling the critical process parameters (CPP) and material attributes (CMA) to stabilize nanosuspension with quality attributes; particularly average particle size, dissolution, and bioavailability

Chlorothiazide



STRUCTURE: Drug-like properties



NS (=O)(=O)c1cc2c(cc1Cl)NC=NS2(=O)=O

Chlorothiazide: Calculation of molecular properties and bioactivity score

miLogP	0.02
TPSA	118.70
natoms	17
MW	295.73
nON	7
nOHNH	3

nviolations	0
nrotb	1
Volume	196.55

Molecular Properties Prediction and Drug-Likeness by Molinspiration :

Molecular Properties Prediction. Physicochemical parameters play a vital role in the generation and determination of the bioactivity of any compound. Molinspiration, a web-based software, was used to explore the various parameters such as miLogP, TPSA, MW, nON,nOHNH,n violations, n rot b, volume, and drug-likeness.

MiLogP (octanol/ water partition coefficient) was calculated by the method developed by Molinspiration as a sum of fragment-based contributions and correction factors and used to predict the permeability of molecule across the cell membrane the value is 0.02.

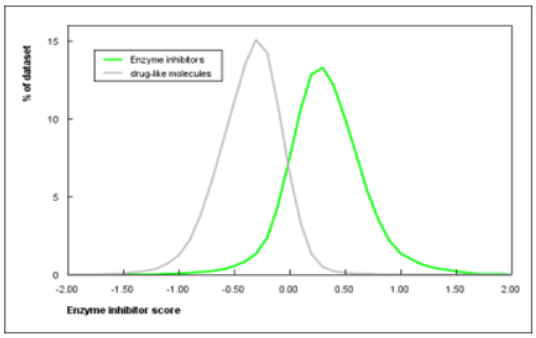
Topological Polar Surface Area (TPSA) is calculated based on the methodologypublished by Ertl et al. as the sum of fragment-based contributions in which O- and N-centered polar fragments are to be considered and calculated by surface areas that are occupied by oxygen and nitrogen atoms and by hydrogen atoms attached to them. TPSA has been used for characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood- brain barrier permeability here the value is 118.70.

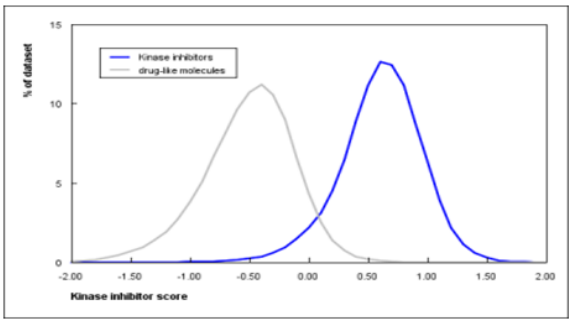
Molecular volume developed by molinspiration is based on group contributions. The number of rotatable bonds (n rot b) is 1. It is a simple topological parameterthat measures molecular flexibility. It is a very good descriptor of the oral bioavailability of a drug. A rotatable bond is defined as any single non-ring bond, bounded to a nonterminal heavy (i.e., nonhydrogen) atom the value is 17. Amide C–N bonds are not considered because they are having high rotational energy barriers.

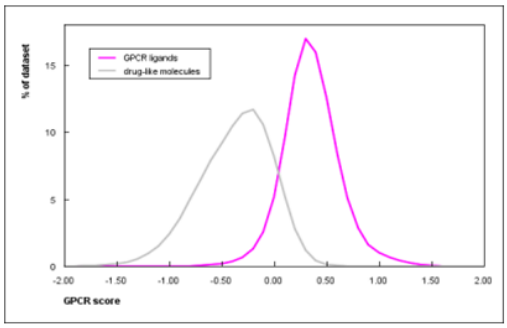
Molinspiration bioactivity score :

GPCR ligand	-0.69
Ion channel modulator	-0.45
Kinase inhibitor	-0.95
Nuclear receptor ligand	-1.20
Enzyme inhibitor	0.18
Protease inhibitor	-0

Drug likeness may be defined as a complex balance of various molecular properties and structural features which determine whether the particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility, and of course presence of various pharmacophoric features influence the behavior of molecules in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability

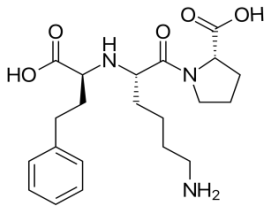




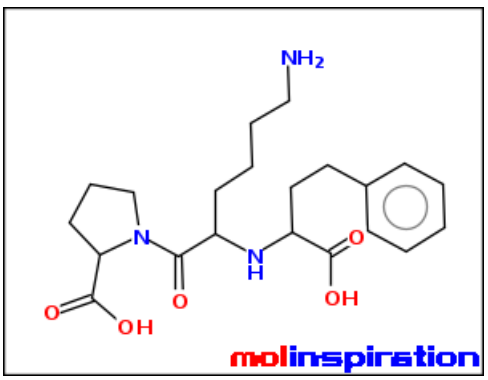


The angiotensin-converting enzyme inhibitor, lisinopril, has an oral bioavailability of 25 percent +/- 4 percent, which is unaffected by food. It prevents the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor. It is approved by FDA for the management of hypertension. Lisinopril has a poor bioavailability of ~25%. Its time to peak concentration is 7hours. The peak effect of lisinopril is about 4 to 8 hours after administration. The purpose of this study was to enhance the dissolution rate and bioavailability of Lisinopril in gastric in oral administration by using Nanosuspension processed using optimized conditions and by controlling the critical process parameters (CPP) and material attributes (CMA) to stabilize nanosuspension with quality attributes; particularly average particle size, dissolution, and bioavailability.

Lisinopril



STRUCTURE: Drug-like properties



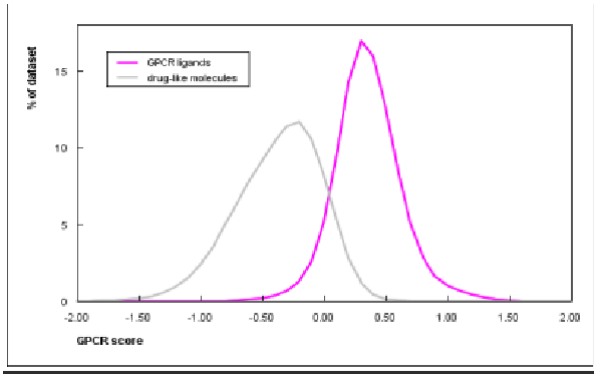
NCCCCC(NC(CCc1ccccc1)C(=O)O)C(=O)N2CCCC2C(=O)O
N~2~-(1-carboxy-3-phenylpropyl)lysylproline

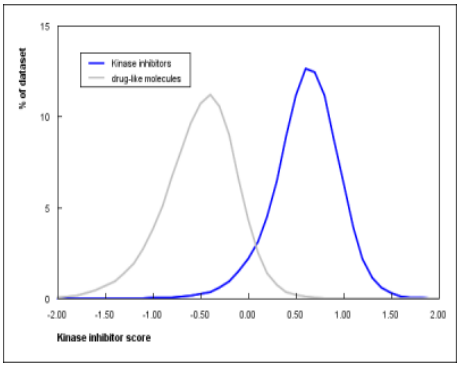
Lisinopril: Calculation of molecular properties and bioactivity score

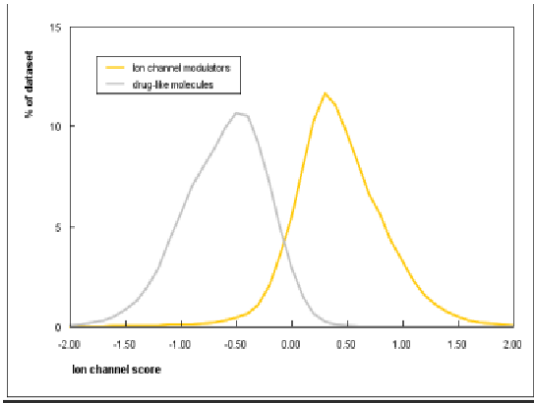
miLogP	-2.44
TPSA	132.96
natoms	29
MW	405.50
nON	8
nOHNH	5
nviolations	0
nrotb	12
Volume	384.36

Molinspiration bioactivity score

GPCR ligand	0.60
Ion channel modulator	0.35
Kinase inhibitor	0.01
Nuclear receptor ligand	0.12
Enzyme inhibitor	0.91
Protease inhibitor	0.39





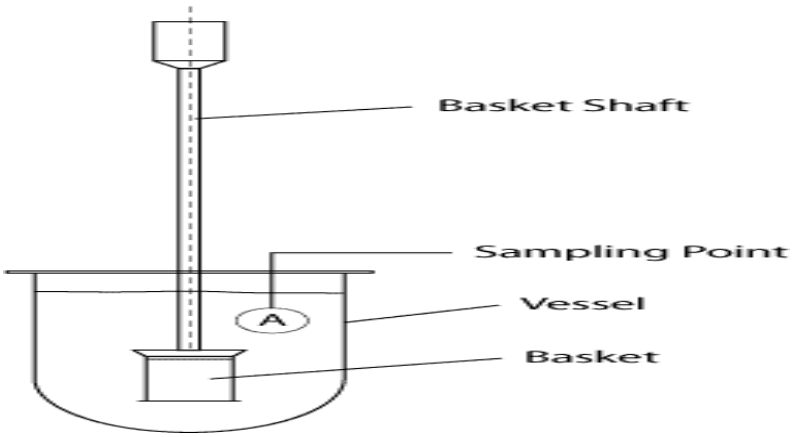


II. Materials and Methods:

- In Vitro Release Methods Drug release from nano-sized dosage forms canbe assessed using one of the following three categories, namely, sample and separate (SS), continuous flow (CF), and dialysis membrane (DM) methods. A few novel methods that use voltammetry, and turbidimetry, are also used.

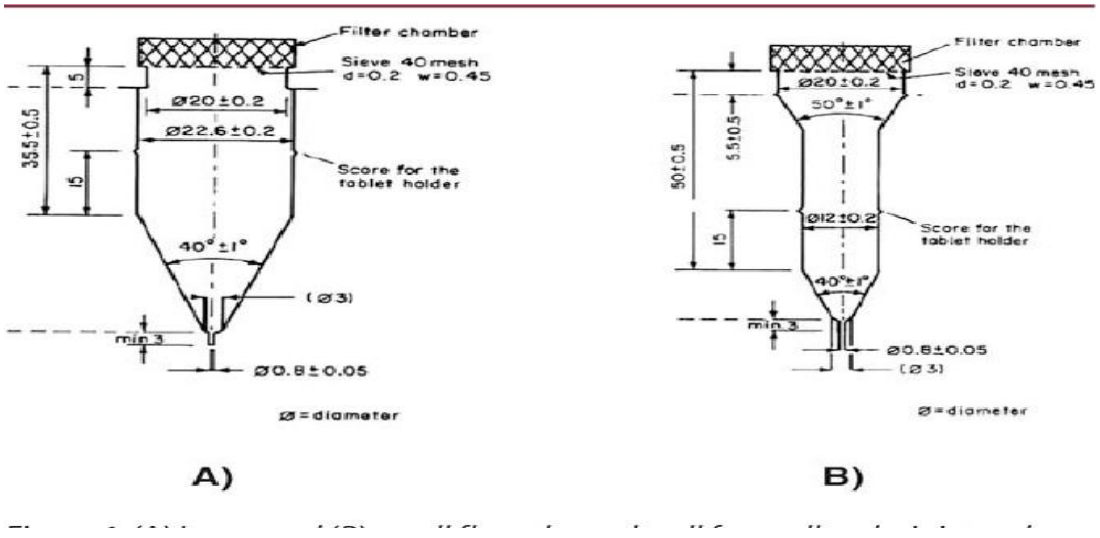
- Sample and Separate: The nanoparticulate dosage form is introduced into the release media that is maintained at a constant temperature, after which drug release is assessed by the sampling of the release media (filtrate or supernatant) or the nanoparticles. there are several adaptations to the SS method, with differences noted in set-up, container size, mode of agitation, and sampling techniques. Commonly reported set-ups to include USP I (basket), USP II (paddle), or vials and generally depend on the volume of release media used in the in vitro release study nanoparticulate dosage forms

(a) USP I (basket): 900 mL buffer at 100 rpm
(b) USP II (paddle): 900 mL buffer at 100 rpm;
(c) USP IV (flow through cell): 900 mL buffer at a flow rate of 1.6 mL/min (peristaltic pump, closed loop) through a cell (internal diameter = 25 mm) and
0.2 μm membrane disc filter;
(d) dialysis bag (MWCO 12 kDa, inner volume = 7 mL) placed into a USP II(paddle) in vitro release test



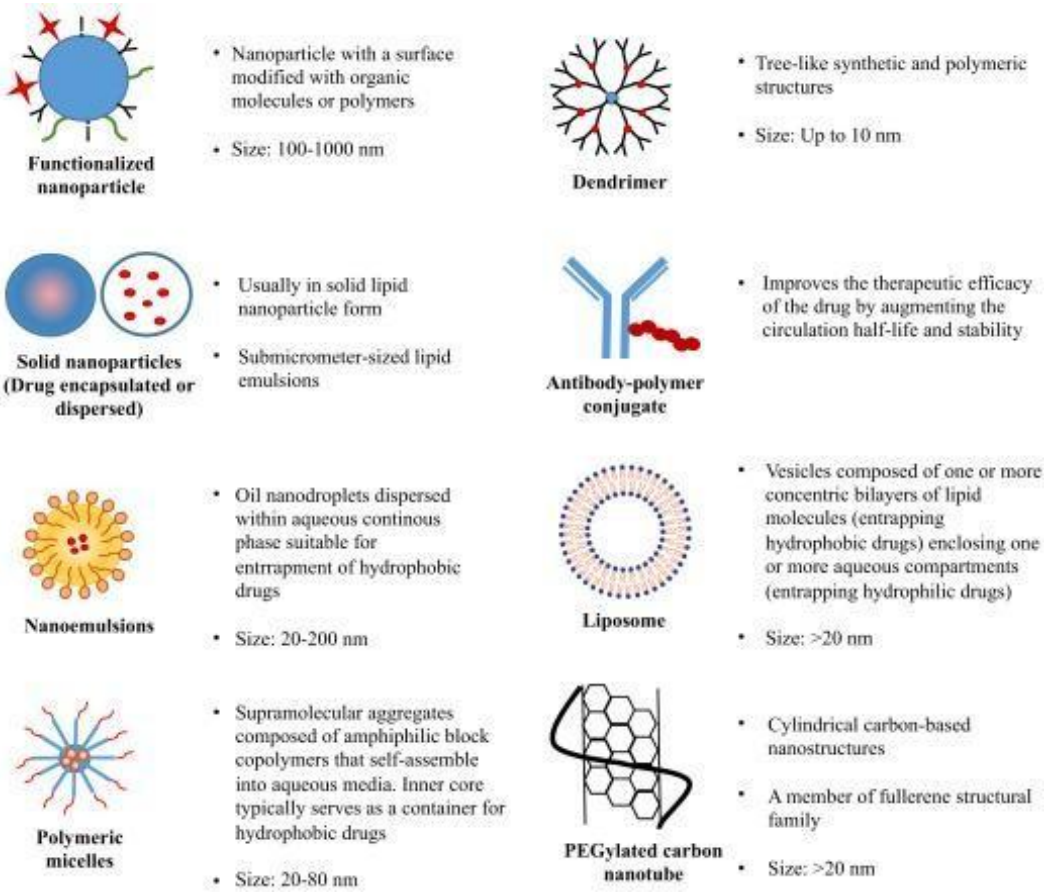
USP (BASKET) DISSOLUTION APPARATUS

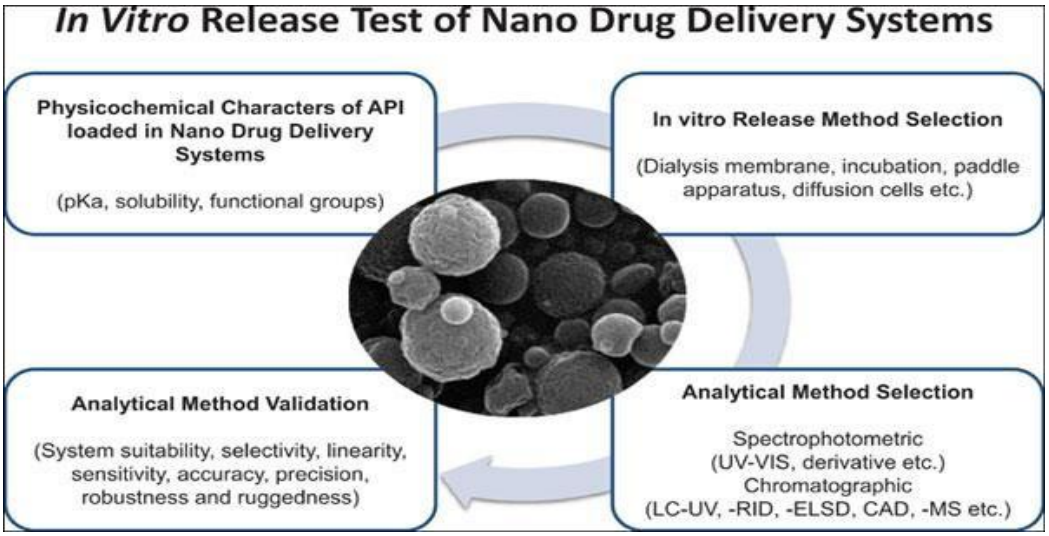
Continuous Flow: In the CF method, drug release from the nanoparticulate dosage form is monitored using the USP IV apparatus or a modification thereof.



Drug release occurs as a result of buffer or media constantly circulating through a column containing the immobilized dosage form and is monitored by collecting the eluent at periodic intervals

FLOW THROUGH CELL





III. Conclusion:-

For novel dosage forms like nanoparticles where no regulatory or compendial standards exist, in vitro drug release assessment assumes greater significance in serving as an indicator of product quality and performance. A plethora ofmethods have been used, each with its advantages and drawbacks concerning ease of set-up, sampling, and rapid buffer replacement. My objective is to enhance the dissolution rate and bioavailability of diuretic drugs with Nano Suspensions and their release in vitro methods which should simulate in vivo conditions, there release mechanisms, and enhance therapeutic activity.

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