Kailash V Vilegave et al /J. Pharm. Sci. & Res. Vol. 12(3), 2020, 351-355

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Recent Advances in Nanocapsules and Nanoparticles

Kailash V Vilegave*, Ravindra S Chauhan, Swapnil M Pawar, Komal R Malankar, Nitin R Pal, Aishwarya A Ingle, Agnes Sara Sabu

Dept. of Pharmaceutics, VT's Shivajirao S Jondhle College of Pharmacy, Asangaon- 412 601, Tq. Shahapur, Dist. Thane, MS, India

Abstract

Nanotechnology encompasses the understanding of the fundamental physics, chemistry, biology and technology of nanometre-scale objects. Nanotechnology refers to the creation and utilization of materials whose constituents exist at the nanoscale; and, by convention, be up to 100 nm in size. Nanotechnology explores electrical, optical, and magnetic activity as well as structural behavior at the molecular and sub molecular level. Nanotechnology offers multiple benefits in treating chronic human diseases by site-specific and target-oriented delivery of medicines. Recently, there are a number of outstanding applications of the nanomedicine like chemotherapeutic agents, biological agents, immunotherapeutic agents etc. in the treatment of various diseases. Nanocapsules involve utilization of nanotechnology for the benefit of human health and well-being. 5-fluorouracil is an antineoplastic agent. 5-flurouracil is used for enhances the activity by method of nanoparticles. Phenytoin is used as anticonvulsant. Phenytoin is used to decrease the hepatic damage in our body.

Keywords: Nanotechnology, Nanocapsules, phenytoin, 5-fluro uracil, nanoparticles

INTRODUCTION

The past 50 years have showed major advances in the control of disease brought about with the use of drugs [1]. Nanotechnology can be defined as a branch of science and engineering dedicated to study, control, and manipulate Nano scale materials, having dimensions of 100 nm or less [2]. Nanotechnology is the term derived from the Greek word "Nano" meaning "dwarf"(short man)[3]. Particles of size between 1 and 100 nm are termed as nanoparticles [2]. Tremendous growth in nanotechnology has opened up novel fundamental and applied frontiers in materials science and engineering, such as nano biotechnology, bionanotechnology, quantum dots, surface-enhanced Raman scattering (SERS), and applied microbiology [4].Nanomedicine involves utilization of nanotechnology for the benefit of human health and well-being [3].

Nanomedicine research aims at developing therapeutic agents to address chronic and serious human diseases. Progress in nanomedicine research for cancer therapy has provided new opportunities for the development of multi-functional nanocarriers with the potential to improve tissue and organ specific intracellular delivery of anticancer drugs with minimal off target toxicity [5].

NANOPARTICLES

Pharmaceutical nanoparticles are defined as solid, submicron-sized (less than 100 nm in diameter) drug carrier that may or may not be biodegradable[6]. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents so as to achieve the site specific action of the drug at the rationale rate and dose. Polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties[6]. The term nanoparticle is a combined name for both nanospheres and nanocapsules. Nanospheres are matrix system in which drug is uniformly dispersed, while nanocapsules are the system in which the drug is surrounded by a unique polymeric membrane[6].

Advantages of nanoparticles [7]:

NPs show number of advantages, which include:

1. Ease of preparation
2. Increased bio-availability
3. Increased residence time in the body
4. Site specific drug targeting

Limitations [6]

In spite of these advantages nanoparticles do have limitations like:

1. Altered physical properties which lead to particle – particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms due to smaller size and larger surface area.
2. Smaller the particles size greater the surface area and this property makes nanoparticles very reactive in the cellular environment.
3. Small particles size results in limited drug loading and burst release. These practical problems have to be sorted out before nanoparticles can be used clinically or made commercially available.

NANOCAPSULES

Nanocapsules as characteristic class of nanoparticles, are made up of one or more active materials (core) and a protective matrix (shell) in which the therapeutic substance may be confined. Nanocapsules have been developed as drug delivery systems for several drugs by different routes of administrations such as oral and parental. Reduce the toxicity of drugs. Polymeric nanoparticles are named nanocapsules when they contain a polymeric wall composed of non-ionic surfactants, macromolecules, phospholipids and an oil core [8].

Due to the miniscule size, nanocapsules possess greater capability to take on an extensive range of applications with extremely high efficient reproducibility. The production of nanocapsules depends on their application and pharmaceutical, biochemical, electrical, optical or magnetic characteristics [9].

Objectives [10, 11, 12, 13]

1. Optimum therapeutic- drug concentration in the blood or in tissue may be maintained over a prolonged period of time.
2. Pre- determined release rates of extended period of time may be achieved.
3. Duration for short half- life drug may be increased.
4. By targeting the site of action, side effects may be eliminated.
5. Frequent dosing and wastage of the drug may be reduced or excluded.
6. Better patient compliance may be ensured.
7. Better treatment of many chronic illnesses. eg Cancer, Asthma, Arthritis.
8. Increased bioavailability.
9. Sustenance of the total amount of drug administered over the period dose periods.
10. Prevention from first pass metabolism and gastrointestinal tract degradation.
11. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
12. Targeting the drug molecule towards the affected tissue or organ make smaller the toxicity to the normal tissues.
13. Versatile and pH dependent system release the drug whenever the body demands.
14. Biocompatibility.
15 Various routes of administration are available including oral, nasal, parenteral, intra-ocular etc.
16.These are the bulk drugs so dose reduction is intended.
17. Currently marketed formulations lack target specificity for various chronic diseases.
18. Some other side effects are associated with currently marketed formulations**.**

DRUG SELECTON CRITERIA FOR NANOCAPSULES:-

Nanoparticles consisting of human therapeutic drugs are suggested as a promising strategy for targeted and localized drug delivery to tumour cells. In this study, 5-fluorouracil (5-FU) encapsulated chitosan nanoparticles were prepared in order to investigate potentials of localized drug delivery for tumour environment due to pH sensitivity of chitosan nanoparticles.

Optimization of chitosan and 5-FU encapsulate nanoparticles production revealed 148.8±1.1 nm and 243.1±17.9 nm particle size diameters with narrow size distributions, which are confirmed by scanning electron microscope (SEM) images. The challenge was to investigate drug delivery of 5-FU encapsulated chitosan nanoparticles due to varied pH changes.

To achieve this objective, pH sensitivity of prepared chitosan nanoparticle was evaluated and results showed a significant swelling response for pH 5 with particle diameter of ~450 nm. In vitro release studies indicated a controlled and sustained release of 5-FU from chitosan nanoparticles with the release amounts of 29.1–60.8% due to varied pH environments after 408 h of the incubation period. pH sensitivity is confirmed by mathematical modeling of release kinetics since chitosan nanoparticles showed stimuli-induced release. Results suggested that 5-FU encapsulated chitosan nanoparticles can be launched as pH-responsive smart drug delivery agents for possible applications of cancer treatments.

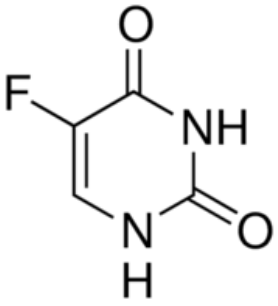
3) DRUG SUITABLE FOR NANOCAPSULES [14, 15, 16, 17, 18, 19]

3.1) Drug profile: 5-Fluorouracil

Description:

5-fluorouracil is an antineoplastic agent which acts as an antimetabolite. 5-fluorouracil is a nucleobase analogue that is uracil in which the hydrogen at position 5 is replaced by fluorine, approval for treatment of multiple solid tumors including colon, rectal, breast, gastric, pancreatic, ovarian, bladder and liver cancer.

Structure:



Chemical Formula : $C_4H_3FN_2O_2$
Molecular Weight : 130.08 g/mol
IUPAC : 5-fluoro-1H-pyrimidine-2, 4-Dione
Melting Range : 282°C to 283°C
Appearance : White to off-white crystalline powder.
Action and Use : Antineoplastic antimetabolite agent, antifungal agent
Mainly it's used in cancer treatment.
Solubility : Soluble in DMSO (5mg/ml), dimethyl formamide (5mg/ml), methanol (1mg/ml) or hot water (1mg/ml).
Storage and Stability : 5-fluorouracil in NS (800 mg in 100 mL) in PVC bags may be frozen for up to 79 days, thawed in a microwave oven, and then stored for up to 28 days at 5°C ± 3°C without major changes in concentration.

PHARMACOKINETICS:-

1. **Absorption:** 5-Flourouracil is absorbed by oral and parenteral administration In that oral administration is 28-100%.
2. **Distribution:** approximately 22% of total body water; penetrates extracellular fluid and third space fluids (e.g., malignant effusions and ascitic fluid).
3. **Metabolism:** Hepatic. The catabolic metabolism of fluorouracil results in degradation products (e.g., CO2, urea and α-fluoro-ß-alanine) which are inactive.
4. **Excretion:** Seven percent to 20% of the parent drug is excreted unchanged in the urine in 6 hours; of this over 90% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver.

MECHANISM OF ACTION:

5-FU acts in several ways, but principally as a thymidylate synthase (TS) inhibitor. Interrupting the action of this enzyme blocks synthesis of the pyrimidine thymidine, which is a nucleoside required for DNA replication. Thymidylate synthase methylates deoxyuridine monophosphate (dUMP) to form thymidine monophosphate (dTMP). Administration of 5-FU causes a scarcity in dTMP, so rapidly dividing cancerous cells undergo cell death via thymineless death.Calcium folinate provides an exogenous source of reduced folinates and hence stabilizes the 5-FU-TS complex, hence enhancing 5-FU's cytotoxicity.

Pharmacokinetics properties of 5- Fluorouracil

Sr.No.	Pharmacokinetics Parameters	Data
1.	Daily dose (mg/ml)	50mg/ml
2.	Number of dose per day	Once a day
3.	Therapeutic concentration range (mg/ml*hr)	50mg/ml per hour
4.	Tmax (hr)	3.5 ± 1.7 hour
5.	Bioavailability (%)	28to 100%
6.	Protein binding (%)	8-12%
7.	Volume of distribution (L)	8-11 L/m2
8.	clearance (mg/ml)	IV bolus: 350-850 $mL/min/m^2$; dependent on dose, schedule, and route of administration; nonlinear pharmacokinetics due to saturable degradation ;interference with fluorouracil degradation markedly prolongs its half-life6 continuous infusion: clearance increases
9.	Half-life (hr) [$T_{1/2}$]	10-20 minutes
10.	Metabolism	hepatic 80%
11.	Metabolites	
	active metabolite(s)	FdUMP, FUTP, and FdUTP
	inactive metabolite(s)	dihydrofluorouracil
12.	Elimination	60-80% excreted as respiratory CO2; 2-3% by biliary system. urine <10% as intact drug.

Materials And Methods[27]

Table no.1 :- list of Chemicals Used:-

Sr no.	Chemicals
1	Chitosan
2	5-Fluorouracil
3	TPP

Table 2 :- List Of Instrument Used:-

Sr no.	Instrument
1	Magnetic stirrer
2	Sonicator
3	Centrifugation
4	Hot air oven
5	FTIR
6	DSC

Preparation of Nanoparticles[27] :

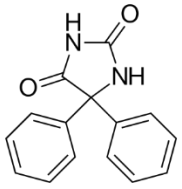
Chitosan nanoparticles were produced based on ionic gelation of TPP with chitosan after chitosan was dissolved in 1% (v/v) acetic acid solution to make up chitosan concentrations at 0.50, 0.75, 1.00, 1.25, 2.50, and 5.00 (mg/mL). Tween 80 (0.5% (v/v)), as a resuspending agent, was added to chitosan solutions in order to prevent particle aggregation, and then chitosan solutions were raised to pH 4.6–4.8 with 1 N NaOH. TPP was dissolved in distilled water to maintain TPP solutions of 0.50, 0.75, 1.00, 1.25, 2.50, and 5.00 (mg/mL). All solutions were filtered through 0.22 micron filter (Millipore). Prepared chitosan solutions were flushed mixed with TPP solutions with a volumetric ratio of 2.5: 1 (v/v) (chitosan: TPP) under magnetic stirring at room temperature. The formation of chitosan-TPP nanoparticles started spontaneously via the TPP-initiated ionic gelation mechanism. Nanoparticles were purified by centrifugation at 12000 rpm for 30 min. Supernatants were discarded and suspended in water, and the chitosan nanoparticles were then freeze-dried before further use or analysis.

DRUG PROFILE: - PHENYTOIN [23, 24]

DESCRIPTION

This study evaluated the in vivo anticonvulsant effect of a spray-dried powder for reconstitution containing phenytoin-loaded lipid-core nanocapsules. Phenytoin-loaded chitosan-coated nanocapsules and their redispersed powders have good gastrointestinal stability, and are able to control drug release in simulated gastric and intestinal fluids. Besides that, the reconstituted powder containing chitosan-coated nanocapsules exhibited improved anticonvulsant activity against seizures induced by pilocarpine in mice, compared to the non-encapsulated drug, representing an important approach in anticonvulsant treatments for children and adults.

STUCTURAL FORMULA:-



CHEMICAL FORMULA :- $C_{15}H_{12}N_2O_2$
MOLECULAR WEIGHT: - 252.268

IUPAC: - 5, 5-diphenylimidazolidine-2, 4-Dione.

MELTING RANGE: - 295-298^{0}C.

APPEARANCE: - Orange liquid with an orange and vanilla flavour.

ACTION & USE: - Protect against seizures by causing voltage-dependent block of voltage gated sodium channels.

SOLUBILITY :- soluble in alkali 165 pg /ml at pH 9.1 borate buffer.

STORAGE & STABILITY: - Phenytoin was **stable** at 23-25 degrees C for 48 h. However, small but statistically significant decreases in **phenytoin** concentrations were observed in samples that were **stored** for 24 h or longer at 37 degrees C. These changes may not be clinically significant.

PHARMACOKINETICS:-
1) Absorption: - Phenytoin is completely absorbed. Peak plasma concentration is attained approximately 1.5-3 hours, and 4-12 hours after administration of the immediate release formulation and the extended release formulation, respectively. It should be noted that absorption can be markedly prolonged in situations of acute ingestion.
2) Distribution: The volume of distribution of phenytoin is reported to be approximately 0.75 L/kg.
3) Metabolism:-Phenytoin is extensively metabolized and is first transformed into a reactive arene oxide intermediate. It is thought that this reactive intermediate is responsible for many undesirable phenytoin adverse effects such as hepatotoxicity, SJS/TEN, and other idiosyncratic reactions. The arene oxide is metabolized to either a hydroxyphenytoin or phenytoin dihydrodiol metabolite, although the former accounts for about 90% of phenytoin metabolism.
4) Excretion: The majority of phenytoin is excreted as inactive metabolites in the bile. An estimated 1-5% of phenytoin is eliminated unchanged in the urine.

MECHANISM OF ACTION
Although phenytoin first appeared in the literature in 1946, it has taken decades for the mechanism of action to be more specifically elucidated. Although several scientists were convinced that phenytoin altered sodium permeability, it wasn't until the 1980's that this phenomenon was linked to voltage-gated sodium channels. Phenytoin is often described as a non-specific sodium channel blocker and targets almost all voltage-gated sodium channel subtypes. More specifically, phenytoin prevents seizures by inhibiting the positive feedback loop that results in neuronal propagation of high frequency action potentials.

MATERIALS AND METHODS [26]:-

Table 1: List of Chemical Used:-

SR no.	Ingredients
1	HPMC
2	PEG 6000
3	Phenytoin
4	Ethanol

Table 2:- List of Instrument Used:-

SR no.	Instrument
1	Magnetic stirrer
2	Sonicator
3	Centrifugation
4	Hot air oven
5	FTIR
6	DSC

PREPARATION OF PHENYTOIN NANOPARTICLES [26]:-
Phenytoin nanoparticles were prepared by solvent evaporation method.22 Required HPMC E15was weighed and dissolved in 10 ml of distilled water and later 1.25 % PEG 6000 was added with the mixture. Likewise, weighed phenytoin drug was dissolved in 5mL of ethanol and was injected into aqueous HPMC E15 solution in mechanical stirrer till it was mixed uniformly. The mixture was later on poured and entirely dried up in a flask of rotary evaporator on a rotating speed with 80 rpm with the water bath at 60°C. The obtained dry film on the walls of the rotating flask was shaken with 5mL of ethanol and the resulting suspension was subjected to sonication at 60% amplitude for 60 sec in a probe Sonicator. Then, the sediment is removed by centrifugation at 10,000rpm for 15 min at 37°C and finally the sedimented phenytoin nanoparticles were dried.

DISSCUSSION
Phenytoin nanoparticles are more compatible than 5 fluoro uracil nanoparticles. Solvent evaporation method is more preferable than ion gelation method

CONCLUSION
For Phenytoin:
In this research to improve the efficacy of Phenytoin anticonvulsant activity. In order to accomplish the goal, controlled release individual Phenytoin nanoparticles were prepared and filled in with capsules to make them a single-unit dosage form.
For 5-fluorouracil:
In this study, chitosan nanoparticle formation was optimized in terms of localized drug delivery systems for cancer treatment studies., chitosan nanoparticles were demonstrated as pH sensitive with respect to instantaneous swelling (pH: 3 to 5) and shrinking (pH: 5 to 7.4) responses. 5-FU encapsulation of chitosan nanoparticles achieved as ~70% with ~250 nm diameter size, indicating potential use for drug delivery applications. Additionally, release profiles demonstrated significant dependence on pH, leading chitosan nanoparticles as good candidates for use in tumour localized drug delivery.

REFERENCE

1. Vilegave Kailash, Gali Vidyanagar, Chandankar Pratibha, Patil Ashwini, Kharjul Mangesh, Virendra Jagtap. Stability study in biological environment of Niosomes: Future targeted drug delivery system
2. Abhilash M., Valarmathy K., Babu P. A. S. 2010. Antimicrobial activity of ethanolic extracts of various plant leaves against selected microbial species. EJEAFChe, 9 (8): 1378-1382.
3. Muhammad Idrees, Role Of Nanotechnology In Medical Sciences: A Review, Muhammad Idrees. / Vol 5/ Issue 1/ 2015 / 14-24
4. Siavash Iravani, Green synthesis of metal nanoparticles using plants, Green Chem., 2011, 13, 2638
5. Ana Cadete, Ana Olivera, Magnus Besev, Pradeep K. Dhal, Lídia Gonçalves, António J. Almeida, Guillaume Bastiat, Jean-Pierre Benoit, María de la Fuente, Marcos Garcia-Fuentes, María José Alonso & Dolores Torres. Self-assembled hyaluronan Nanocapsules for the intracellular delivery of anticancer drugs https://www.nature.com/articles/s41598-019-47995-8.pdf.
6. Konwar Ranjit, Ahmed Abdul Baquee Department of Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS), Hatkhowazpara, N Azara, Guwahati, India. Nanoparticle: An Overview of Preparation, Characterization and Application Nanoparticle: An Overview of Preparation, Characterization and Application Nanoparticle: An Overview of Preparation, Characterization and Application Nanoparticle: An Overview of Preparation, Characterization and Application , ISSN-2230-8407
7. Mukarram Anees, Muhammad Irfan Masood, Mahwish Ilyas, Talib Hussain, Muhammad Ammad. Nanoparticles as a Novel Drug Delivery System A Review, Pakistan Journal of Pharmaceutical Research (Vol.2, No. 2).
8. G Nilewar, P.B. Mute, P.P. Talhan, S Thakre, Nanocapsules: Nano Novel Drug Delivery System ISSN: 2347 - 7881(Volume 5, Issue 6).
9. Pavankumar Kothamasu, Hemanth Kanumur, Niranjan Ravur, Chiranjeevi Maddu, Radhika Parasuramrajam, and Sivakumar Thangavel. Nanocapsules: The Weapons for Novel Drug Delivery Systems, BioImpacts, 2012, 2(2), 71-81.
10. Johann Michael Kohlberg Wolfgang Fritzsche, Preparation of Nanostructures Technische Universität Ilmenau, Thuringia, Germany.
11. Ibrahim Khana, Khalid Saeedb, Idrees Khanc Nanoparticles: Properties, applications and toxicities,.2017.05.011.
12. Alihosseini, faezeh; ghaffari, solmaz; dabirsiaghi, ali reza and haghighat, setareh. Freeze-drying of ampicillin solid lipid nanoparticles using mannitol as cryoprotectant. Braz. J. Pharm. Sci. 2015, vol.51, n.4, pp.797-802. ISSN 2175-9790.
13. S. H. Ansari, Farha Islam, and Mohd, Saeem. Journal of Advanced Pharmaceuticals Technology & Reseach, Volume-8 Issue-5, March 2019, ISSN: 2278-3075 .
14. Clinical studies with 5-fluorouracir a. R. Curreri,fredj. Ansfield, fordea. Mciver,f harrya. Waisman,and Charles heidelberger, Vol. 18, May, 1958.
15. Laurence Galanti, Massin P Lebitasy, Jean-Daniel Hecq, Julie Cadrobbi, Danielle Vanbeckbergen, Jacques Jamart. Long-Term Stability of 5-Fluorouracil in 0.9% Sodium Chloride after Freezing, Microwave Thawing, and Refrigeration, v.62(1); Jan-Feb 2009 PMC2826915.
16. Rustum YM. Biochemical rationale for the 5-fluorouracil leucovorin combination and update of clinical experience. J Chemother 1990 ;(2 Supply 1):5-11. (K22:K-6761)
17. Ning Zhang, Ying Yin, Sheng-Jie Xu, and Wei-Shan Chen 5-Fluorouracil: Mechanisms of Resistance and Reversal Strategies, 2008 Aug; 13(8): 1551–1569
18. Andrea Botticelli , Marina Borro,Concetta Elisa Onesti, Giovanna Gentile . Degradation Rate of 5-Fluorouracil in Metastatic Colorectal Cancer: A New Predictive Outcome Biomarker, 10.1371 journal.pone.0163105.
19. Paul Mccarron, David Woolfson ,Siobhán Keating, Sustained Release of 5-Fluorouracil from Polymeric Nanoparticles Volume52, Issue12December 2000,Pages 1451-1459.
20. Gaurav Goel James J. Lee, Pharmacokinetically Guided Dose Adjustment of 5-FU—A Critical Element Toward Personalized Medicine, Vol. 13, No. 1, 1-2.
21. Drug Koichi Hirata, Noboru Horikoshi, Keisuke Aiba, Minoru Okazaki, Ryuichi Denno, Kazuaki Sasaki, Yasuyuki Nakano, Hikaru Ishizuka, Yasuhide Yamada, Shinji Uno, Tetsuo Taguchi and Tetsuhiko Shirasaka Pharmacokinetic Study of S-1, a Novel Oral Fluorouracil Antitumor. 2000 Vol. 5, 2000–2005, August 1999.
22. Tiantian He ,Elie Hatem, Laurence Vernis, a potential new therapeutic perspective for an old drug,Journal of Experimental & Clinical Cancer Research volume 34,Article number: 152 (2015)
23. Rajan Seda, Tıglı Aydın, Mehlika Pulat, 5-Fluorouracil Encapsulated Chitosan Nanoparticles for pH-Stimulated Drug Delivery: Evaluation of Controlled Release Kinetics, Volume 2012, Article ID 313961, 10 pages doi:10.1155/2012/313961.
24. Tripathi K D. Antiepileptic drug: essentials of medical pharmacology 8th edition 2018.
25. Vilegave Kailash, Gali Vidyasagar, Chandankar Pratibha, Patil Ashwini, kharjul Mangesh, Virendra Jagtap. Niosomes (nonionic surfactant vesicles) preparation & stability in biological environment, 2013, 1(1): 1-9.
26. Chitra Karthikeyini Senthilvel, Kavitha Karuppaiyan*, Muthu Mohammed Jamal Moideen Development of Capsules Filled with Phenytoin and Berberine Loaded Nanoparticles- A New Approach to Improve Anticonvulsant Efficacy ,Indian Journal of Pharmaceutical Education and Research, vol 53 issue 3 Jul-Sep, 2019.
27. 5-Fluorouracil Encapsulated Chitosan Nanoparticles for ph-Stimulated Drug Delivery: Evaluation of Controlled Release Kinetics R. Seda Tığlı Aydınand Mehlika Pula. Volume 2012, Article ID 313961.