NANOSPHERICAL APPROACH FOR SUSTAINED DELIVERY OF CARBIMAZOLE- A COMPREHENSIVE REVIEW

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ABSTRACT

Carbimazole is an oral, imidazole derivative used in the treatment of hyperthyroidism and Grave's disease. It is a carbethoxy derivative or prodrug of methimazole used for anti-thyroid action which gets converted to methimazole after absorption. It belongs to BCS class II indicative of poor solubility. Carbimazole is available in market as conventional solid dosage form that makes it easier to administer and are economic but the drawback that arises is repetitive or frequent dosing that leads to lesser patient compliance. To overcome this barrier a novel formulation technique is discussed in this review which involves the formulation of nanospheres. Nanospheres are colloidal particles of 10-200nm that are spherical, polymer matrix type nano ranged devices which consist of drug molecules present in dispersed phase in polymer matrix. They are devised in order to tailor (control or sustain) the drug release profile, reduce the dosing frequency and deliver the drug at targeted or affected site. They have the ability to protect the drug from chemical and enzymatic degradation. This review article focuses on nanospheres, drug release mechanism, preparation and characterization methods in context of Carbimazole for treatment of hyperthyroidism and Grave's disease. Various research articles from 2010 to 2022 were reviewed for research conducted in nanospheres.

Keywords: *Anti-thyroid agent, Hyperthyroidism, Grave's disease, BCS Class II, Carbimazole, Nanospheres, sustained release.*

INTRODUCTION

Carbimazole is an oral, imidazole derivative used in the treatment of hyperthyroidism and Grave's disease. It is a carbethoxy derivative or prodrug of methimazole used for anti-thyroid action. The drug inhibits the iodination of tyrosine in thyroglobulin (1). The IUPAC name of Carbimazole is ethyl 3-methyl-2-sulfanylideneimidazole-1-carboxylate and has molecular formulae $C_7H_{10}N_2O_2S$ with molecular weight 186.232 g/mol. It is pink in colour, with odourless or faint odour. It has good solubility in water, organic solvents such as ethanol, DMSO, dimethyl formamide, chloroform, acetone and methanol. Carbimazole works by getting converted first into methimazole after absorption. The drug decreases the uptake and concentration of inorganic iodine by thyroid gland (2). It reduces the formation of di-iodotyrosine and thyroxine. Methimazole inhibits the enzyme coupling (thyroid peroxidase) and prevents the iodination of tyrosine residues on thyroglobulin. This reduces the production of thyroid hormone T3 and T4 and thereby works as anti-thyroid agent (3).

Carbimazole is marketed in India under several brands but in conventional form as solid dosage forms only. The conventional tablet form makes it easier to administer and are

economic but the drawback that arises is repetitive or frequent dosing that leads to lesser patient compliance. Hence, to avoid the drawbacks associated with the conventional form a novel nanotechnology approach preferably nanospherical approach should be considered for the sustained or controlled release of Carbimazole that would reduce the frequency of dosing and improve patient compliance.

Nanotechnology is the foremost approach used in pharmaceutical industry since the beginning of 21st century for its several advantages. The nanotechnology is the blend of science, engineering, and technology used in the production of nanoscale material. In pharmaceutical industries, the nanotechnological approach is used for its nano-range, controlled or sustained release drug delivery, improved therapeutic efficacy, improved bioavailability, drug delivery at targeted or affected site, accurate dose with lesser or no adverse/ side effects at other sites of body, restrain hypersensitivity reaction, improved solubility of lipophilic drugs, improved stability and higher drug permeability (4). The nano approach has been used in formulation of medications for different route of administration and treatment of many acute and chronic diseases. The nanotechnology has numerous platforms that include liposomes, polymeric nanoparticles (nanocapsules and nanospheres), nanosponges, nanoparticles, dendrimers, micelles and nanoconjugates (5-8).

Nanospheres

Nanospheres are colloidal particles of 10-200nm that are spherical, polymer matrix type nano ranged devices which consist of drug molecules present in dispersed phase in polymer matrix (9). Nanospheres are amorphous or crystalline in nature and the drug molecules are dispersed in solid skeleton formed by polymer matrix (10). The Nanospheres are devised in order to tailor (control or sustain) the drug release profile, reduce the dosing frequency and deliver the drug at targeted or affected site (11-13). They have the ability to protect the drug from chemical and enzymatic degradation. The nanospheres are prepared by using either biodegradable (albumin, modified starch, gelatin) or non-biodegradable polymers (polylactic acid) and hence they are classified as Biodegradable nanospheres or Non-biodegradable nanospheres (14).

Characteristics of Nanospheres

Non toxic

Non immunogenic

Biocompatible

Economical

Scalable manufacturing process

Appropriate for small as well as large molecules such as proteins, nucleic acids and peptides (5)

Advantages of Nanospheres (6, 7, 15)

Higher barrier permeability: The nano-range of particles allows the permeability of the formulation through smallest capillary vessels in the body and also improves the penetration through cells and tissues to reach targeted site.

Delayed clearance time: The small size of the particles helps in the movement of the drug molecules in bloodstream for prolonged time that allows the delay in clearance time of the drug.

Tailored drug release profile: Nanospheres are devised in order to either control or sustain the drug release.

Targeted drug delivery: Nanospheres allows the delivery of the drug at targeted or affected site in the body.

Administration through different routes: The nanospheres can be administered through almost all routes of drug delivery such as oral, parenteral, topical, nasal etc.

Reduction in dosing frequency: The targeted delivery of drug helps in reduction of dosing frequency as accurate amount of drug reaches at the site of action.

Improved patient compliance: Reduced dose frequency leads to improved patient compliance.

Higher therapeutic efficacy and bioavailability: The targeted drug delivery improves the therapeutic efficacy of the drug and thereby enhances the drug bioavailability.

Reduced toxicity or adverse effects: The adverse effects or toxicity at the other organ sites can be reduced due to targeted drug delivery.

Higher stability and reduced drug leakage: The nanospheres are physically stable and the possibility of drug leakage is lowest.

Drug release phenomenon from nanospheres (9, 16)

The drug release mechanism from nanospheres is governed by dissolution, diffusion, erosion, desorption and combination of erosion-diffusion.

Dissolution controlled release: In this, the dissolution of drug or absorption of drug from gastro-intestinal tract is the rate limiting step.

Diffusion controlled release: In this, the movement of drug solution from higher concentration to lower concentration (diffusion) is rate limiting stage in gastro intestinal stage. The diffusion controlled release form is categorised into matrix and reservoir type.

Erosion controlled release: The physical dissolution of the polymer or degradation of hydrophobic polymer layer via enzymatic degradation leads to formation of pores on the walls of the nanospheres. This degradation is known as erosion. The drug release from the nanospheres is either through surface or bulk. The drug release through surface erosion is achieved when the polymer surface erodes and the internal regions remain unaltered. On the otherhand, the drug release through bulk erosion is achieved when the water or solvent enters or diffuse the whole polymer matrix.

Desorption controlled release: The drug release occurs through the previously adsorbed drug on the surface of the polymer matrix.

Polymers used in nanospheres preparation

Both natural and synthetic polymers are used in preparation of nanospheres. The polymers should be ideally non-toxic, biocompatible, safe and should be compatible with other ingredients.

Natural polymers: Chitosan, starch, alginate, gelatin and albumin.

Synthetic polymers: Polylactic acid (PLA), Polylactico glycolic acid (PLGA), Polycaprolactone (PCL) (17, 18)

Preparation techniques for nanospheres (19-21)

Coalescence method: This method involves the coalescence of two emulsions formed separately. Firstly, a w/o emulsion is produced by adding drug and polymer using liquid paraffin and then, another emulsion is formed using sodium hydroxide and polymer. Both of these emulsions are then stirred at high speed for the collision of emulsion droplets and coalescence and precipitation of emulsion droplets to form solid nanoparticles. These nanoparticles are then washed and centrifuged for the separation of nanoparticles.

Desolvation technique: In this method of nanospheres preparation a polymeric solution (natural polymer) is prepared using PEG as solvent. In the same way drug solution is prepared by using ethanol as solvent. This drug solution is then added dropwise to polymeric solution under constant stirring. Thereafter, cross linking agent is added and stirred for 12 hours. In the end, the prepared nanospheres are separated from the suspension by centrifugation and further dried by lyophilisation (22, 23).

Emulsion cross linking technique: This method involves the formation of w/o emulsion by emulsifying aqueous solution of polymer in oil phase. A suitable cross linking agent such as glutaraldehyde is added to above emulsion to harden the emulsion droplets and form nanoparticles. These nanoparticles are then separated out by filtration and rinsed continuously with n-hexane and dried.

Emulsion Polymerization method: In this method, the monomer and drug molecules are dissolved in the aqueous medium containing emulsifying agent and stabiliser. This mixture is vigorously stirred in order to obtain a solution. It allows the polymerization of the drug molecules and the solution is then centrifuged in order to obtain stable, purified and high molecular mass nanospheres. Generally, the polymeric compounds such as polymethylmethacrylate and polyethylcyanoacrylate are used for emulsion polymerization method (24, 25).

Homogenization method: This method involves the formation of nanospheres using either hot homogenization or cold homogenization technique. In hot homogenization method, a pre-emulsion is formed by adding aqueous solution of drug in melted lipid and surfactant. The mixture is homogenized at elevated pressure and temperature to produce o/w nanoemulsion. This nanoemulsion is then cooled at room temperature for the re-crystallization of lipids and formation of nanospheres. In cold homogenization method, the aqueous drug solution is added to lipid melt at 5-7ºC. This solution is then transferred to liquid nitrogen for the process of solidification. These solidified drug-lipid particles are then milled to 50-100nm and dispersed in freezed solution of emulsifier. The particles are then homogenised at room temperature to produce nanospheres (26).

Ionic gelation method: In this method, the polycationic polymer is mixed with drug solution and added to polyanionic polymer solution. On mixing or stirring the solutions, a complexation reaction occurs between oppositely charged molecules. This leads to the conversion of polymer from liquid to gel state and precipitation leads to formation of spherical nanospheres. The solution was then filtered and centrifuged to separate dried nanospheres (27-30).

Salting out method: In this method, the organic phase is prepared by dissolving drug and polymer in water miscible organic solvent. This solution is then emulsified in aqueous solution of salting-out agents such as magnesium chloride, magnesium acetate and sodium chloride etc. The mixture is then stirred to form o/w emulsion which on further vigorous stirring forms polymeric nanospheres. Afterwards, the salting out agent and solvent is removed by either filtration or centrifugation (31, 32).

Solvent diffusion or displacement method/ Nanoprecipitation method: In this method, the polymer is dissolved in organic water soluble solvent and added to aqueous phase containing drug and stabilizer (33-41). Adding organic solvent to aqueous phase leads to diffusion of solvent immediately and precipitation of polymer occurs leading to formation of polymeric

nanospheres. These are then ultra-centrifuged and then lyophilised to obtain stable, purified and dried form of nanospheres (42-48).

Solvent Evaporation Technique: In this method, the drug molecules are dissolved in the aqueous solvent and the polymer matrix is prepared by adding polymer, stabiliser and organic solvent. Both the phases are mixed and emulsifying agent is added to form o/w emulsion. This emulsion is then stirred continuously for the evaporation of organic solvent and to obtain polymeric nanospheres. These are then purified, centrifuged and stabilised by the process of lyophilisation (49-56).

Supercritical fluid method: The organic solution is prepared by adding drug and polymer in organic solvent. This organic solution is then atomised by passing the solution into nozzle containing carbon dioxide. The organic solvent got diffused and extracted into anti-solvent carbon dioxide phase due to miscibility and precipitation of nanospheres occurred and separated out.

Characterization of Nanospheres:

Percentage Yield: The percentage yield of drug nanospheres can be calculated using the weight of final product after drying with respect to the initial total quantity of the drug and polymer used for preparation of nanospheres.

$$\textit{Percentage Yield} = \frac{\textit{Practical yield}}{\textit{Theoretical Yield}} \textit{ X 100}$$

Surface Morphology (SEM analysis): The shape and surface morphology of drug loaded nanospheres can be studied using scanning electron microscopy (SEM) (57).

Particle Size analysis: The size and size distribution of drug loaded nanospheres is determined by using a laser light scattering particle size analyzer used to determine the particle size of the drug formulations. A thin film of drug loaded nanospheres is spread on a slide and covered with cover slip. The slide is observed under optical microscope.

Micromeretic Properties: Irregular flow of powder from the hopper produces non-uniform weight tablets and capsules. Flow property depends on particle size, shape, porosity and density of the powder. It includes Angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.

Percentage Moisture Loss: Drug loaded nanospheres is evaluated for percentage moisture loss which is sharing an idea about its hydrophilic nature. Percentage moisture loss was determined using the following formula:

$$\textbf{Percentage moisture loss} = ((W1-W2)/W2) \times 100$$

Where, W1 = Initial weight of nanospheres;

W2 = Final weight of nanospheres.

Degree of Swelling: The swelling ability of nanospheres in physiological media is determined by swelling them in the phosphate buffer solution pH 7.4. Accurately weighed amount of nanospheres is immersed in little excess of phosphate buffer solution pH 7.4 for 24 hrs and washed (58). The degree of swelling of nanospheres is calculated using the formula:

$$\alpha = (Ws-Wo) / Wo$$

Where, α is the Degree of swelling,

Wo = Weight of nanospheres before swelling,

Ws = Weight of nanospheres after swelling.

Estimation of Drug Content: Drug content in the nanospheres is estimated by an UV spectrophotometric method.

Encapsulation Efficiency: Encapsulation efficiency of nanospheres is calculated using the formula (59):

$$\textit{Encapsulation Efficiency} = \frac{\textit{Estimated \% Drug Content}}{\textit{Theoretical \% Drug Content}} \times 100$$

In-vitro Drug Release Studies: The release rate of drug loaded nanospheres is determined using USP dissolution testing apparatus II (60).

Literature reviewed on use of nanospheres in pharmaceuticals

The literature was reviewed on applications of nanospheres in pharmaceutical research for the several proclaimed advantages from 2010 to 2022 and the survey is mentioned in table 1.

TABLE 1: LITERATURE REVIEW OF DRUG LOADED NANOSPHERES

Drug loaded Nanospheres	Polymer	Method of Preparation	Purpose	Reference
Curcumin loaded PLGA nanospheres	PLGA	Solid o/w emulsion solvent evaporation method	Targeted drug delivery for treatment of prostate cancer and other therapies	(49)
Ampicillin trihydrate-loaded	Chitosan	Modified ionic gelation method	Sustained drug delivery for treatment of bacterial infections	(30)

chitosan nanoparticles				
Levofloxacin nanoparticles	Chitosan	Ionic gelation method	Sustained drug delivery for treatment of bacterial infections and enhanced therapeutic efficacy	(29)
Dorzolamide hydrochloride -(Dorzo) loaded nanoparticles	Eudragit RS 100 (RS) and/or RL 100 (RL)	Emulsion solvent diffusion method	Controlled release of drug, reduced dosing frequency, improved patient compliance, prolonged corneal contact time and more therapeutic efficacy	(41)
Selegiline loaded nanospheres using gelatin	Gelatin	Spray drying method	controlled release of drug, with reduced dosing frequency, improved patient compliance and more therapeutic efficacy	(61)
Piroxicam loaded protein nanoparticles using bovine serum albumin as protein	Albumin	Desolvation method	Sustained release of drug for treatment of pain and inflammation	(62)
Methotrexate loaded nanospheres	Chitosan	Emulsion polymerization method	Sustained drug release, targeted delivery, enhanced therapeutic efficacy and bioavailability, reduced dosing frequency, improved patient	(25)

			compliance and reduced side effects	
Rutin nanospheres	Eudragit S100	Nano-precipitation method	Targeted drug delivery for treatment of colon carcinoma	(40)
Paracetamol loaded nanoparticles	Eudragit S100	Salting-out method	Sustained and targeted release, enhanced therapeutic efficacy and bioavailability	(31)
Itraconazole loaded nanoparticles	Chitosan	Ionic gelation method	Improved therapeutic efficacy, enhancing bioavailability and reducing dosing frequency	(28)
Fenofibrate - loaded nanoparticles	Eudragit L-100	Nano-precipitation method	Enhanced solubility, sustained and targeted release, enhanced therapeutic efficacy and bioavailability	(39)
Carvedilol nanoparticles	HPMC, chitosan and gelatin	Nano-precipitation method	Improved gastro-retention and enhanced bioavailability	(38)
Asenapine Maleate loaded nanoparticles	Chitosan	Ionic gelation method	Sustained release with targeted delivery, enhanced therapeutic efficacy and bioavailability	(27)
Lamivudine loaded nanoparticles	Chitosan	Double emulsion solvent evaporation and Solvent diffusion method	Improved therapeutic efficacy, enhanced bioavailability and reduced dosing frequency	(37)
Hydrogel	PVP	Nano-precipitation	Improved drug solubility	(36)

loaded with polymeric nanoparticles (PoNPs) of simvastatin (SIM)	K90, PEG 4000	method	and skin permeation, enhanced therapeutic efficacy (enhanced wound healing) and bioavailability	
Mesalamine loaded nanospheres	Eudragit RS and L	Nano-precipitation method	Improved the therapeutic efficacy, enhanced bioavailability and reduced dosing frequency	(35)
Rapamycin	PLGA	emulsification–diffusion method	Anti-glioma activity, Improved therapeutic efficacy	(63)
Fenofibrate	PLGA	emulsification method	Improved therapeutic efficacy	(64)
Coumarin-6	PLGA, PLA, PCL	Spontaneous emulsification solvent evaporation method	Theranostics or bioimaging	(65)
Hyperforin	AcDex	single emulsion/solvent evaporation	Improved anti-inflammatory activity	(66)
Metoprolol loaded solid lipid nanoparticles	Compritol	Hot Homogenization technique	Improved therapeutic efficacy, bioavailability and sustained drug release	(26)
Linagliptin Nanospheres	Chitosan, EC, HPMC K4M	Nano-precipitation method	Improved drug solubility, enhanced therapeutic efficacy and bioavailability	(34)
Felodipine Nanoparticles	Eudragit L100	Nano-precipitation method	Patient compliance and enhanced therapeutic efficacy	(33)

The literature indicates that the technique of developing nanospheres can be helpful in delivering the carbimazole in controlled manner, at targeted site, with reduced dosing frequency, improved patient compliance and more therapeutic efficacy.

CONCLUSION

From the literature surveyed it can be concluded that Nanospheres can tailor (control or sustain) the drug release profile, reduce the dosing frequency, protect drug from enzymatic degradation and deliver the drug at targeted or affected site. Drugs delivered through nanospheres can improve the therapeutic efficacy and bioavailability. Hence, it seems to be a good approach in sustaining the release of drug (Carbimazole) and thereby reducing dosage frequency that would ultimately lead to patient compliance. The nanospheres of Carbimazole can be effectively used in patients suffering from hyperthyroidism.

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REFERENCE

1. National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 31072, Carbimazole. https://pubchem.ncbi.nlm.nih.gov/compound/Carbimazole.
2. Bagalkote Z, & Gajeli G. (2021). UV Spectrophotometric Method Development and Validation of Carbimazole in Bulk and Tablet Dosage form. Asian J Pharm Res. 2021; 1(1): 163-6.
3. Al shididee M, Samein LH, & Shehab M. (2013). Formulation and evaluation of Carbimazole orodispersible tablet. Int J Pharm Pharm Sci. 2013; 4(1): 232-9.
4. Singh R, & Lillard JW. (2009). Nanoparticle-based targeted drug delivery. Exp Mol Pathol. 2009; 86(3): 215-23.
5. Mohanraj VJ, & Chen Y. (2006). Nanoparticles- a review. Trop J Pharm Res. 2006; 5(1): 561-73.
6. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S, & Shin HS. Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnol. 2018; 16(1): 71-103.
7. Bianco A, Kostarelos K, Prato M. Applications of carbon nanotubes in drug delivery. Curr Opin Chem Biol. 2005; 9: 674-9.

8. Ghosh P, Han G, De M, Kim CK, Rotello VM. Gold nanoparticles in delivery applications. Adv Drug Del Rev. 2008; 60: 1307-15.
9. Jun Li, Geboren AM. Development, Characterization and In Vivo Evaluation of Biodegradable Nanospheres and Nanocapsules. 1982.
10. Jin-ming Li, Wei Chen. Preparation of albumin nanospheres loaded with gemcitabine and their cytotoxicity against BXPC-3 cells in vitro. Acta Pharmacol Sin. 2009; 30: 1337-43.
11. Rao JP, Gekeler KF. Polymer nanoparticles, preparation techniques and size control parameters. Prog Polym Sci. 2013; 6(7): 887-913.
12. Thumbe M, Kumar VD. A review on nanospheres. Int Res J Mod Eng Technol Sci. 2021; 3(1): 96-105.
13. Singh A, Garg G, Sharma PK. Nanospheres: A Novel Approach for Targeted Drug Delivery System. Int J Pharm Sci Rev Res. 2010; 5(3): 84-8.
14. Gagliardi A, Giuliano E, Venkateswararao E, Fresta M, Bulotta S, Awasthi V, Cosco D. Biodegradable Polymeric Nanoparticles for Drug Delivery to Solid Tumors. Front Pharmacol. 2021; 12(1): 1-24.
15. Singh A, Garg G, Sharma PK. Nanospheres: A Novel Approach for Targeted Drug Delivery System. Int J Pharm Sci Rev Res. 2010; 5(3): 84-8.
16. Xiao-Yun Lu, Dao-Cheng Wu, Zheng-Jun Li, Guo-Qiang Chen. Polymeric nanoparticles. Prog Mol Biol Trans Sci. 2011; 104: 299-323.
17. Nair SK. An Overview on Nanosphere Drug Delivery. European J Pharm Med Res. 2018; 1: 192-8.
18. Adams ML, Lavasanifar A, Kwon GS. Amphiphilic block copolymers for drug delivery. J Pharm Sci. 2003; 92: 1343-55.
19. Piracha S, Manzoor S, Fatima H, Aslam H, Nazir M, Anjum A, Basharat G, & Saif R. A Review on Nanoparticles, Synthesis, Characterization, Current Applications and Future Perspectives. Sch Bull. 2021; 07(4): 118-22.
20. Varma MM, Kumar SKT, & Srivalli ID. A review on nanoparticles: synthesis, characterization and applications. World J Pharm Med Res. 2021; 7(8): 169-79.
21. Jeevanandam J, Barhoum A, Chan YS, Dufresne A, & Danquah MK. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J Nanotechnol. 2018; 9(1): 1050-74.
22. Rajaonarivony M, Vauthier C, Couvrraze G, Puisieux F, Couvreur P. Development of a new drug carrier made from alginate. J Pharm Sci. 1993; 82(9): 912.

23. Dhandapani NV. Development and in-vitro Evaluation of a Topical Drug Delivery System Containing Betamethazone Loaded Ethyl Cellulose Nanospheres. Trop J Pharm Res. 2005; 4 (2): 495-500.
24. Khan I, Saeed K, & Khan I. (2017). Nanoparticles: Properties, applications and toxicities. Arabian J Chem. 2017; 12(7): 908-31.
25. So D, Muralidharan S, Venugopal V, Kanniappan P, Hui W, & Qi L. Formulation and Evaluation of Chitosan Nanospheres Containing Methotrexate Targeted Drug Delivery System. J Young Pharm. 2016; 8(1): 330-4.
26. Bhanusri G, & Sundari PT. Formulation and evaluation of metoprolol loaded solid lipid nanoparticles. Int J Pharm Sci Res. 2021; 12(10): 5439-45.
27. Supriya A, Sundaraseelan J, Srinivas Murthy BR, & Bindu Priya M. Formulation and Evaluation of Capsules of Asenapine Maleate Loaded Chitosan Nanoparticles. Acta Scient Pharm Sci. 2018; 2(3): 29-37.
28. Reddy CY, Jeganath **S**, & Kumar UM. Formulation and Evaluation of Chitosan Nanoparticles for Improved Efficacy of Itraconazole Antifungal Drug. Asian J Pharm Clin Res. 2018; 11(16), 147-52.
29. Baby B, Harsha NS, Jayaveera KN, & Abraham AT. Formulation and Evaluation of Levofloxacin Nanoparticles by Ionic Gelation Method. Res Rev: J Pharm Pharm Sci. 2012; 1(1): 7-15.
30. Saha P, Goyal AK, & Rath G. Formulation and Evaluation of Chitosan-Based Ampicillin Trihydrate Nanoparticles. Trop J Pharm Res. 2010; 9(5): 483-8.
31. Gazi A, & Sailaja AK. Preparation and Characterization of Paracetamol Loaded Eudragit S100 Nanoparticles by Salting Out Technique. J Develop Drugs. 2018; 7(1), 183-186.
32. Boudad H, Legrand P, Lebas G, Cheron M, Duchene D, Ponchel G. Combined hydroxypropyl- [beta]- Cyclodextrins and poly(alkylcyanoacrylate) nanoparticles intended for oral administration of saquinavir. Int J Pharm. 2001; 218: 113-24.
33. Abdul HSA, Manikkavasagan A, Umamaheswari D, Prabhu R. Formulation and Evaluation of Polymeric Nanoparticles of Felodipine. Saudi J Med Pharm Sci. 2022; 8(2), 38-47.
34. Nishitha A, & Kumar AA. (2021). Formulation and Evaluation of Linagliptin Nanospheres. J Pharm Sci Res. 2021; 13(5): 288-93.
35. Pachpute T, Dwivedi J, Shelke T, & Jeyabalan G. (2019). Formulation and Evaluation of Mesalamine Nanosphere Tablet. J Drug Del Therap. 2019; 9(4-s): 1045-53.

36. Farghaly AU, Abou-Taleb HA, Abdellatif AH, & Sameh TN. (2019). Formulation and evaluation of simvastatin polymeric nanoparticles loaded in hydrogel for optimum wound healing purpose. Drug Des Develop Ther. 2019; 13(1), 1567-80.
37. Swapnal V, Divya KS, Patil NB, Babu BR, & Rao AL. Preparation and evaluation of lamivudine nanoparticles. Int J Res Pharm Chem. 2019; 9(3): 154-60.
38. Betala S, Varma M, & Abbulu K. Formulation and evaluation of polymeric nanoparticles of an antihypetensive drug for gastroretention. J Drug Del Thera. 2018; 8(1): 82-86.
39. Shelake S, Patil SK, & Patil SK. (2018). Formulation and Evaluation of Fenofibrate-loaded Nanoparticles by Precipitation Method. Indian J Pharm Sci. 2018; 80(3): 420-7.
40. Asfour MH, & Mohsen AM. Formulation and evaluation of pH-sensitive rutin nanospheres against colon carcinoma using HCT-116 cell line. J Adv Res. 2017; 9(1): 17-26.
41. Hasan AA. Formulation and evaluation of dorzolamide hydrochloride-loaded nanoparticles as controlled release drug delivery system. Asian J Pharm 2012; 6(1): 67-73.
42. Araujo J, Vega E, Lopes C, Egea MA, Garcia ML, Souto EB. Effect of polymer viscosity on physicochemical properties and ocular tolerance of FB-loaded PLGA nanospheres. Colloids Surf B Biointerfaces. 2009; 72: 48–56.
43. Canadas C, Alvarado H, Calpena AC, Silva AM, Souto EB, Garcia ML, Abrego G. In vitro, ex vivo and in vivo characterization of PLGA nanoparticles loading pranoprofen for ocular administration. Int J Pharm. 2016; 511: 719–27.
44. Sanchez-Lopez E, Egea MA, Cano A, Espina M, Calpena AC, Ettcheto M, Camins A, Souto EB, Silva AM, Garcia ML. PEGylated PLGA nanospheres optimized by design of experiments for ocular administration of dexibuprofen-in vitro, ex vivo and in vivo characterization. Colloids Surf B Biointerfaces. 2016; 145: 241–50.
45. Sanchez-Lopez E, Egea MA, Davis BM, Guo L, Espina M, Silva AM, Calpena AC, Souto EMB, Ravindran N, Ettcheto M, et al. Memantine-Loaded PEGylated Biodegradable Nanoparticles for the Treatment of Glaucoma. Small. 2018; 14.
46. Sanchez-Lopez E, Ettcheto M, Egea MA, Espina M, Cano A, Calpena AC, Camins A, Carmona N, Silva AM, Souto EB, et al. Memantine loaded PLGA PEGylated nanoparticles for Alzheimer's disease: In vitro and in vivo characterization. J Nanobiotechnol. 2018; 16: 32.

47. Salatin S, Barar J, Barzegar-Jalali M, Adibkia K, Kiafar F, Jelvehgari M. Development of a nanoprecipitation method for the entrapment of a very water soluble drug into Eudragit RL nanoparticles. Res Pharm Sci. 2017; 12: 1.
48. Rivas MCJ, Tarhini M, Badri W, Miladi K, Greige-Gerges H, Nazari QA, Galindo Rodríguez SA, Román RÁ, Fessi H, & Elaissari A. Nanoprecipitation process: From encapsulation to drug delivery. Int J Pharm. 2017; 532(1): 66-81.
49. Mukerjee A, & Vishwanatha JK. Formulation, characterization and evaluation of curcumin-loaded PLGA nanospheres for cancer therapy. Anticancer Res. 2009; 29(10): 3867-3875.
50. Desgouilles S, Vauthier C, Bazile D, Vacus J, Grossiord JL, Veillard M, Couvreur P. The design of nanoparticles obtained by solvent evaporation: A comprehensive study. Langmuir. 2003; 19: 9504–10.
51. Vieira R, Souto SB, Sanchez-Lopez E, Machado AL, Severino P, Jose S, Santini A, Fortuna A, Garcia ML, Silva AM, et al. Sugar-Lowering Drugs for Type 2 Diabetes Mellitus and Metabolic Syndrome-Review of Classical and New Compounds: Part-I. Pharm. 2019; 12: 152.
52. Jose S, Sowmya S, Cinu TA, Aleykutty NA, Thomas S, Souto EB. Surface modified PLGA nanoparticles for brain targeting of Bacoside-A. Eur J Pharm Sci. 2014; 63: 29–35.
53. Grumezescu AM. Design and Development of New Nanocarriers. William Andrew; Norwich, NY, USA: 2017.
54. Bohrey S, Chourasiya V, Pandey A. Polymeric nanoparticles containing diazepam: Preparation, optimization, characterization, in-vitro drug release and release kinetic study. Nano Converg. 2016; 3: 1–7.
55. Christine V, Ponchel G. Polymer nanoparticles for nanomedicines. A guide for their design. Anticancer Res. 2017; 37: 1544.
56. Sharma N, Madan P, Lin S. Effect of process and formulation variables on the preparation of parenteral paclitaxel-loaded biodegradable polymeric nanoparticles: A co-surfactant study. Asian J Pharm Sci. 2016; 11: 404–16.
57. Shanmugasundaram S. Formulation of Sodium Alginate Nanospheres Containing Amphotericin B for the Treatment of Systemic Candidiasis. Trop J Pharm Res. 2007; 6 (1): 653-9.
58. Agilandeswari D. Formulation and In-vitro evaluation of mucoadhesive nanospheres for an alpha glucosidase inhibitor. The Pharma Innovation J. 2016; 5(9): 123-30.

59. Singh R and Lillard JW. Nanoparticle based targeted drug delivery review. Exp Mol Pathol. 2009; 86: 215-23.
60. Barichello JM, Morishita M, Takayama K, Nagai T. Encapsulation of hydrophilic and lipophilic drugs in PLGA nanoparticles by the nanoprecipitation method. Drug Develop Ind Pharm. 1999; 25(4): 471-6.
61. Al-Dhubiab, & Bandar E. Formulation and In Vitro Evaluation of Gelatin Nanospheres for the Oral Delivery of Selegiline. Current Nanosci. 2013; 9(1): 21-5.
62. Neela S, & Uppuluri K. Formulation and In-Vitro Evaluation of Piroxicam Loaded BSA Nanospheres by Desolvation. J Nanomed Nanotechnol. 2015; 6(3): 289-292.
63. Escalona-Rayo O, Fuentes-Vázquez P, Jardon-Xicotencatl S, García-Tovar CG, Mendoza-Elvira S, Quintanar-Guerrero D. Rapamycin-loaded polysorbate 80-coated PLGA nanoparticles: Optimization of formulation variables and in vitro anti-glioma assessment. J Drug Deliv Sci Technol. 2019; 52: 488–99.
64. Qiu F, Meng T, Chen Q, Zhou K, Shao Y, Matlock G, Ma X, Wu W, Du Y, Wang X. Fenofibrate-loaded biodegradable nanoparticles for the treatment of experimental diabetic retinopathy and neovascular age-related macular degeneration. Mol Pharm. 2019; 16: 1958–70.
65. Szczęch M, Szczepanowicz K. Polymeric Core-Shell Nanoparticles Prepared by Spontaneous Emulsification Solvent Evaporation and Functionalized by the Layer-by-Layer Method. Nanomat. 2020; 10: 496.
66. Traeger A, Voelker S, Shkodra-Pula B, Kretzer C, Schubert S, Gottschaldt M, Schubert US, Werz O. Improved bioactivity of the natural product 5-lipoxygenase inhibitor hyperforin by encapsulation into polymeric nanoparticles. Mol Pharm. 2020; 17: 810-6.