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Review Article

# The Challenges and Novel Approaches in the Nanoparticle Formulation of DPP Inhibitors

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**ABSTRACT**

Drug delivery methods based on nanoparticles have shown great promise in the effective administration of medicinal drugs, such as inhibitors of Dipeptidyl Peptidase (DPP). In the treatment of type 2 diabetes, DPP inhibitors are commonly used, and their formulation as nanoparticles offers numerous advantages, such as enhanced bioavailability, controlled release, and targeted delivery. However, several challenges exist in formulating DPP inhibitors into nanoparticles, including drug stability, particle size control, and sustained release kinetics. This review article aims to discuss the challenges associated with nanoparticle formulation of DPP inhibitors and highlight recent innovative approaches to overcome these limitations.

**Keywords:** DPP inhibitors, Nanoparticle, Lipid-based.

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## INTRODUCTION

Nanoparticle formulation of DPP (Dipeptidyl Peptidase) inhibitors presents both challenges and novel approaches in drug delivery. DPP inhibitors are used in the treatment of type-2 diabetes, they act by inhibiting the enzyme responsible for degrading incretin hormones, which regulate blood sugar levels. The utilization of nanoparticles as carriers for DPP inhibitors offers several advantages including targeted distribution to certain areas, better bioavailability, controlled release, and improved medication stability. However, there are also challenges associated with this formulation approach.[1]

### Nanoparticle synthesis

Developing nanoparticles with the desired size, morphology, and drug-loading capacity can be challenging. The selection of appropriate materials and formulation techniques is critical to achieve optimal drug encapsulation efficiency and stability.[2]

### Drug release kinetics

Controlling the release of DPP inhibitors from nanoparticles is crucial to maintain therapeutic drug levels over an extended period. Achieving sustained release profiles that mimic the physiological requirements of DPP inhibitor dosing can be a complex task.[3]

### Stability and storage

Nanoparticles must remain stable during storage and transportation to maintain their drug-loading capacity and prevent premature drug release or degradation. Stability challenges include particle aggregation, drug leakage, and changes in physical or chemical properties over time.[2]

### Targeting and tissue penetration

Efficient delivery of DPP inhibitors to the target tissues, such as the pancreas or the gastrointestinal tract, is essential for optimal therapeutic outcomes. Achieving effective targeting and deep tissue penetration of nanoparticles can be challenging due to physiological barriers and variability in patient-specific factors.[3]

### Safety and toxicity

The safety of nanoparticle formulations must be thoroughly evaluated, considering factors such as potential toxicity, immune response, and clearance from the body. Understanding the long-term effects of nanoparticles and their potential accumulation in specific organs is crucial for ensuring patient safety.[4]

### Novel approaches to overcome these challenges include

Surface modification: Coating nanoparticles with ligands or targeting moieties that interact with specific receptors or tissues

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can enhance their cellular uptake and targeting capabilities. Triggered drug release at the intended location can be achieved by functionalizing the surface of the nanoparticle with molecules that react to environmental stimuli, such as pH or enzyme activity.[5]

## Combination therapies

Nanoparticle formulations can be designed to incorporate multiple therapeutic agents, such as DPP inhibitors along with other anti-diabetic drugs or synergistic compounds. This approach can provide enhanced efficacy and improved patient compliance by reducing the number of separate drug administrations.[6]

## Stimuli-responsive systems

Controlled drug release at predetermined sites or upon demand can be achieved by creating nanoparticles that react to external stimuli like light, temperature, or magnetic fields. These responsive systems can provide precise spatiotemporal control over drug release, optimizing therapeutic outcomes.[7]

## Co-delivery systems

Combining DPP inhibitors with other therapeutic agents or drug carriers, such as nanoparticles loaded with insulin or glucose-lowering drugs can enhance the overall treatment efficacy. Co-delivery systems can address multiple aspects of diabetes management and potentially offer synergistic effects.[1]

## Nanotechnology-based imaging

Drug distribution, release kinetics, and therapeutic response can all be monitored in real time with the help of imaging techniques integrated into nanoparticle formulations. Treatment optimization can be greatly aided by tracking the non-invasive activity of DPP inhibitors through the use of imaging agents like fluorescent dyes or contrast agents.[1]

## Active targeting strategies

To improve the efficacy and selectivity of drug delivery, nanoparticle surfaces can be modified by adding ligands or antibodies that bind and recognize receptors that are overexpressed in the target tissues. In addition to decreasing off-target effects, this active targeting strategy can enhance medication accumulation at the intended location.[8]

## Combination with gene therapy

Combining DPP inhibitors with gene therapy approaches, such as RNA interference or gene editing technologies, can provide a synergistic effect in managing type-2 diabetes. Nanoparticles can be engineered to simultaneously deliver DPP inhibitors and genetic material to modulate gene expression or target specific genetic mutations associated with the disease.[8]

## Multifunctional nanoparticles

Designing nanoparticles with multiple functionalities can offer enhanced therapeutic capabilities. For instance, the inclusion of imaging agents in the formulation of the nanoparticles, such as contrast agents for Positron Emission Tomography (PET) or Magnetic Resonance Imaging (MRI), can allow for real-time tracking of drug distribution and therapeutic response.[8]

## Biomimetic nanoparticles

Developing nanoparticles that mimic biological structures or functions can improve their biocompatibility and targeting ability. Biomimetic nanoparticles can be engineered to resemble components of cells or extracellular matrices, allowing for enhanced interactions with biological systems and potentially improved drug delivery efficiency.[8]

## Challenges

### *Scalability*

Transitioning nanoparticle formulations from laboratory-scale to large-scale manufacturing can pose challenges in maintaining consistent quality, reproducibility, and scalability. A major problem is making sure that nanoparticle production procedures are scalable while yet keeping the required drug encapsulation stability and efficiency.[9]

## Regulatory considerations

Nanoparticle formulations of DPP inhibitors may require additional regulatory considerations compared to conventional drug formulations. Safety evaluations, toxicology studies, and appropriate characterization methods specific to nanoparticles need to be established to ensure regulatory compliance.[10]

## Clearance and biodegradation

Understanding the fate of nanoparticles in the body, including their clearance pathways and potential accumulation in organs, is crucial for assessing long-term safety. The biodegradability of nanoparticles and the clearance mechanisms through the liver, kidneys, or lymphatic system should be thoroughly investigated.[10]

## Manufacturing complexity

The fabrication of nanoparticles with precise size, shape, and drug-loading capacity often requires specialized manufacturing techniques and equipment. Overcoming the challenges associated with complex nanoparticle synthesis processes, scale-up, and quality control can be resource-intensive and time-consuming.[10]

## Patient variability

Nanoparticle formulations may exhibit variable responses and efficacy among different patient populations due to individual variations in physiological factors, such as metabolism, immune response, or disease stage. Tailoring nanoparticle formulations

to account for patient-specific factors can be a challenge in personalized medicine approaches.[11]

## Immunogenicity

Nanoparticles can trigger immune responses in the body, leading to the clearance of the nanoparticles or potential adverse reactions. Addressing the immunogenicity of nanoparticle formulations is crucial to ensure their long-term safety and effectiveness.[11]

## Stability in biological fluids

Nanoparticles may undergo various physical and chemical changes when exposed to biological fluids, such as serum or gastrointestinal fluids. Maintaining the stability of DPP inhibitor-loaded nanoparticles under physiological conditions is essential for their successful delivery and therapeutic efficacy.[11]

## Manufacturing cost

Developing nanoparticle formulations with DPP inhibitors at a reasonable cost can be challenging. The choice of materials, manufacturing processes, and quality control measures can significantly impact the overall production cost, which may affect the accessibility and affordability of these formulations.[12]

## Toxicity considerations

While nanoparticles offer numerous advantages, they can also pose potential toxicity risks. The toxicity profile of nanoparticles is influenced by various factors, including their size, content, and surface charge. Thorough evaluation of the biocompatibility and potential toxicity of nanoparticle formulations is necessary to ensure patient safety.[12]

## Regulatory approval

Novel nanoparticle formulations of DPP inhibitors may require additional regulatory approvals and rigorous testing before they can be clinically used. Demonstrating their safety, efficacy, and superiority over existing formulations can be a complex and time-consuming process.[12]

## Pharmacokinetics and bio distribution

Understanding the pharmacokinetic profile and biodistribution of nanoparticle-based DPP inhibitors is essential for optimizing their therapeutic efficacy. The size, surface characteristics, and formulation composition of nanoparticles can affect how quickly they circulate through tissues and are eliminated from the body.[12]

## Scale-up and reproducibility

Transitioning from small-scale laboratory synthesis to large-scale manufacturing of nanoparticle formulations can present challenges in terms of maintaining batch-to-batch consistency, reproducibility, and quality control. Developing robust and scalable manufacturing processes is crucial for the widespread application of nanoparticle-based DPP inhibitors.[13]

## Long-term stability

Ensuring the long-term stability of nanoparticle formulations is crucial to maintain their integrity and drug release properties over extended periods. Factors such as storage conditions, formulation composition, and manufacturing processes need to be optimized to prevent particle aggregation, drug degradation, or loss of drug-loading capacity.[13]

## Clearance and toxicity

Understanding the clearance pathways of nanoparticles from the body and their potential accumulation in organs or tissues is important for assessing their long-term safety. Additionally, investigating potential toxic effects of nanoparticle formulations on various physiological systems, such as liver, kidney, or immune system, is essential to ensure patient safety.[14]

## Cost-effectiveness

Developing nanoparticle-based formulations can involve higher production costs compared to conventional drug formulations. Finding a balance between the therapeutic benefits and the cost-effectiveness of these formulations is an important consideration for their practical application.[14]

## Novel Approaches

### *Nanoparticle-cell interactions*

Understanding the interactions between nanoparticles and cells/tissues can enable the design of nanoparticles with improved cellular uptake, intracellular trafficking, and release of DPP inhibitors. Molecular-level research on the interactions between nanoparticles and cells can direct the creation of more effective and focused delivery methods.[14]

## Combination with nanosensors

Integrating nanosensors within nanoparticle formulations can enable real-time monitoring of drug release and therapeutic response. These nanosensors can provide feedback on drug efficacy and enable personalized dosing strategies for DPP inhibitors.[1]

## Bio responsive nanoparticles

Drug release that is site-specific and improved therapeutic results can be achieved by creating nanoparticles that react to particular biological cues, such as pH, enzyme activity, or glucose levels. When a disease-specific environment or physiological shift occurs, bio responsive nanoparticles can be designed to release DPP inhibitors.[1]

## Nanoparticles for mucosal delivery

Utilizing nanoparticle formulations for mucosal delivery routes, such as oral, nasal, or pulmonary administration, can provide non-invasive and patient-friendly alternatives to parenteral

administration. Developing nanoparticles that can effectively traverse mucosal barriers and deliver DPP inhibitors to target tissues can improve treatment outcomes and patient compliance.[1]

### Personalized medicine approaches

Incorporating patient-specific factors, such as genetic variations or disease characteristics, into the design of nanoparticle formulations can enable personalized medicine approaches. Tailoring the nanoparticle formulation to individual patients' needs can improve treatment efficacy and minimize adverse effects.[1]

### Combination with targeting strategies

Combining nanoparticle-based DPP inhibitors with targeting strategies, such as ligand-mediated targeting or magnetic targeting can enhance their specificity and accumulation at the desired site of action. Targeting strategies can improve drug delivery to specific tissues or cells, enhancing therapeutic efficacy while minimizing off-target effects.[15]

### Hybrid nanoparticle systems

Developing hybrid nanoparticle systems that combine different types of nanoparticles or materials can offer synergistic advantages. For example, combining polymeric nanoparticles with inorganic nanoparticles or lipid-based systems can provide enhanced drug encapsulation, controlled release, and improved stability.[15]

### Stimuli-responsive controlled release

Designing nanoparticles with stimuli-responsive properties can enable controlled and triggered drug release. Temperature, pH, or enzyme-sensitive materials are examples of stimuli-responsive components that can be used to control the release of DPP inhibitors in response to particular physiological conditions.[15]

### Advanced imaging techniques

By incorporating cutting-edge imaging methods like Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), or fluorescence imaging into nanoparticle formulations, medication delivery and therapeutic response can be visualized and tracked in real-time. Imaging-guided approaches can optimize treatment outcomes and facilitate personalized medicine.[15]

### Combination with immunomodulatory agents

Combining nanoparticle-based DPP inhibitors with immunomodulatory agents can enhance their therapeutic efficacy by modulating the immune response associated with type 2 diabetes. This approach aims to address the underlying inflammatory processes and immune dysregulation observed in the disease.[16]

## CONCLUSION

The nanoparticle formulation of DPP inhibitors presents exciting opportunities for improving the treatment of type 2 diabetes. By addressing the challenges associated with drug delivery, novel approaches can enhance therapeutic outcomes, patient compliance, and overall efficacy while minimizing potential side effects.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**DPP:** Dipeptidyl Peptidase; **RNA:** Ribonucleic acid; **PET:** Positron Emission Tomography; **MRI:** Magnetic Resonance Imaging.

## AUTHOR'S CONTRIBUTIONS

All the authors contributed equally for review of literature, concept making, writing, and proofreading.

## SUMMARY

Nanoparticle-based delivery systems for DPP inhibitors hold promise for improving type-2 diabetes treatment by enhancing drug stability, targeted delivery, and controlled release. Challenges include issues with synthesis, stability, scalability, and regulatory compliance. Novel approaches, such as surface modifications, combination therapies, stimuli-responsive systems, and bio-responsive nanoparticles, can address these obstacles, improving efficacy and patient compliance. However, challenges related to cost, immunogenicity, and long-term safety need to be addressed before widespread clinical application.

## REFERENCES


1. Kasina SVSK, Baradhi KM. Dipeptidyl Peptidase IV (DPP IV) Inhibitors. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. PMID: 31194471.
2. Mitchell, M.J., Billingsley, M.M., Haley, R.M.*et al*. Engineering precision nanoparticles for drug delivery.*Nat Rev Drug Discov*, 2021;20:101-24. https://doi.org/10.1038/s41573-020-0090-8.
3. Makrilakis K. The Role of DPP-4 Inhibitors in the Treatment Algorithm of Type 2 Diabetes Mellitus: When to Select, What to Expect. Int J Environ Res Public Health. 2019;16(15):2720. doi: 10.3390/ijerph16152720. PMID: 31366085; PMCID: PMC6696077.
4. Sharma S, Parveen R, Chatterji BP. Toxicology of nanoparticles in drug delivery. Curr Pathobiol Rep. 2021;9(4):133-44. doi: 10.1007/s40139-021-00227-z. PMID 34840918, PMCID PMC8611175.
5. Yoo J, Park C, Yi G, Lee D, Koo H. Active Targeting Strategies Using Biological Ligands for Nanoparticle Drug Delivery Systems. Cancers (Basel). 2019;11(5):640. doi: 10.3390/cancers11050640. PMID: 31072061; PMCID: PMC6562917.
6. Souto EB, Souto SB, Campos JR, Severino P, Pashirova TN, Zakharova LY, *et al.* Nanoparticle delivery systems in the treatment of diabetes complications. Molecules. 2019;24(23):4209. doi: 10.3390/molecules24234209, PMID 31756981, PMCID PMC6930606.
7. Pham SH, Choi Y, Choi J. Stimuli-responsive nanomaterials for application in antitumor therapy and drug delivery. Pharmaceutics. 2020;12(7):630. doi: 10.3390/pharmaceutics12070630, PMID 32635539, PMCID PMC7408499.
8. Dehaini D, Fang RH, Zhang L. Biomimetic strategies for targeted nanoparticle delivery. Bioeng Transl Med. 2016;1(1):30-46. doi: 10.1002/btm2.10004, PMID 29313005, PMCID PMC5689512.

9. Paliwal R, Babu RJ, Palakurthi S. Nanomedicine scale-up technologies: feasibilities and challenges. AAPS PharmSciTech. 2014;15(6):1527-34. doi: 10.1208/s12249-014-0177-9. PMID 25047256, PMCID PMC4245446.
10. Zielińska A, Carreiró F, Oliveira AM, Neves A, Pires B, Venkatesh DN, *et al.* Polymeric nanoparticles: production, characterization, toxicology and ecotoxicology. Molecules. 2020;25(16):3731. doi: 10.3390/molecules25163731, PMID 32824172, PMCID PMC7464532.
11. Zhao R, Lu Z, Yang J, Zhang L, Li Y, Zhang X. Drug delivery system in the treatment of diabetes mellitus. Front Bioeng Biotechnol. 2020;8:880. doi: 10.3389/fbioe.2020.00880, PMID 32850735, PMCID PMC7403527.
12. Li SD, Huang L. Pharmacokinetics and biodistribution of nanoparticles. Mol Pharm. 2008;5(4):496-504. doi: 10.1021/mp800049w. PMID 18611037.
13. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, *et al.* Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics. 2018;10(2):57. doi: 10.3390/pharmaceutics10020057, PMID 29783687, PMCID PMC6027495.
14. Donahue ND, Acar H, Wilhelm S. Concepts of nanoparticle cellular uptake, intracellular trafficking, and kinetics in nanomedicine. Adv Drug Deliv Rev. 2019;143:68-96. doi: 10.1016/j.addr.2019.04.008. PMID 31022434.
15. Murar M, Albertazzi L, Pujals S. Advanced optical imaging-guided nanotheranostics towards personalized cancer drug delivery. Nanomaterials (Basel). 2022;12(3):399. doi: 10.3390/nano12030399, PMID 35159744, PMCID PMC8838478.
16. Shao S, Xu Q, Yu X, Pan R, Chen Y. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. Pharmacol Ther. 2020;209:107503. doi: 10.1016/j.pharmthera.2020.107503. PMID 32061923, PMCID PMC7102585.


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