Advances in Biodegradable Microparticle Systems for Oral Anti-Diabetic Therapy: Focus on Plga and Metformin

Marewad Shilpa Jalinder[1]*, Dr. Tushar Treembak Shelke[2]

1 Research Scholar, Sunrise University, Alwar, Rajasthan, India

marewadshilpa@gmail.com

2 Professor, Department of Pharmaceutical Sciences, Sunrise University, Alwar, Rajasthan, India

Abstract: Effective and patient-friendly therapy techniques are necessary to address diabetes mellitus, which remains a significant worldwide health issue. New developments in biodegradable microparticle systems for oral anti-diabetic treatment are the subject of this research. PLGA (Poly(lactic-co-glycolic acid)) metformin administration is the subject of special attention. Improving overall therapeutic results in diabetes treatment, increasing medication bioavailability, and assuring controlled release are the primary goals of the study, which aims to critically examine the function of PLGA-based microparticles.

Using only secondary data sources such as peer-reviewed journal articles, pharmaceutical reports, and regulatory papers retrieved from open-access platforms, this research takes a qualitative, review-based approach. To evaluate biodegradable delivery methods from a regulatory standpoint, we undertake a thematic and comparative examination of formulation techniques, polymer-drug interactions, pharmacokinetic advances, safety profiles, and more.

By preventing the drug's breakdown in the intestines and allowing for continuous release, the results show that PLGA microparticles greatly increase metformin bioavailability. Dosage frequency is reduced and patient compliance is improved by the controlled release method. The study also notes that PLGA is very compatible with metformin physicochemically, which means that the formulation will be stable and the therapeutic effects will be constant. Additionally, because their breakdown products are not harmful, biodegradable systems have great safety ratings. According to the results, microparticle systems based on PLGA provide a solid foundation for the oral administration of anti-diabetic medications. To facilitate commercialisation and widespread use, however, more regulatory standardisation and clinical validation are required.

Keywords: Biodegradable microparticles, PLGA, Metformin, Oral drug delivery, Controlled release

1. INTRODUCTION

One of the biggest problems in world health is diabetes mellitus, which causes abnormalities in either insulin production or insulin action and causes blood sugar levels to remain consistently high over an extended period of time. Therapeutic techniques that are both

successful and patient-friendly are in high demand due to the increasing incidence of type 2 diabetes. Metformin is still the gold standard when it comes to oral anti-diabetic medication because of how well it works, how safe it is, and how much it costs. Nevertheless, there are certain drawbacks to the traditional oral administration of metformin, including poor absorption, gastrointestinal distress, and the necessity of frequent doses (Rojas & Gomes, 2013). Innovative drug delivery techniques, such as microparticles made of biodegradable polymers, have been investigated in response to these difficulties. Therapeutic results can be optimised with the use of such systems by making drugs more stable, increasing their absorption, and allowing for regulated release (Danhier et al., 2012).

Sophisticated controlled-release systems have replaced immediate-release formulations as the medication delivery mechanism of choice in anti-diabetic treatment. Consistent plasma medication levels and reduced dose frequency are achieved by sustained drug administration. Because of its biocompatibility and controlled breakdown qualities, PLGA (Poly(lactic-co-glycolic acid)) has become a popular biodegradable polymer in this area. Pharmaceutical uses are possible due to PLGA's biodegradability into physiologically active lactic and glycollic acids (Makadia & Siegel, 2011). Metformin and other hydrophilic medicines have recently been studied for their potential as an oral drug delivery system encapsulant.

Metformin is not very bioavailable, with an estimated 50-60% absorption rate, mostly because to its low intestinal permeability and fast renal clearance, even though it is widely used. In addition, patients are less likely to comply when they experience gastrointestinal side symptoms including diarrhoea and nausea. Fluctuations in medication concentration are a result of conventional formulations' inability to offer targeted administration and sustained therapeutic levels. The necessity for more sophisticated polymer-based delivery methods that can improve bioavailability, reduce adverse effects, and guarantee controlled drug release is underscored by these constraints (Graham et al., 2011).

The use of nano- and micro-scale medication delivery devices has been on the rise recently, with a notable uptick in its application to diabetes care. The capacity to offer prolonged release and enhanced pharmacokinetics has led to the rise in popularity of PLGA-based encapsulation approaches. Thanks to recent developments in polymer engineering, smart medication carriers that can adapt to body signals are now a reality. Biodegradable delivery methods have also

attracted the attention of regulatory bodies like the FDA, which has pushed for studies into their efficacy and safety in clinical settings (Ventola, 2017).

This study's theoretical underpinnings originate from the interplay of PLGA, metformin hydrochloride, and the biological system, in particular absorption in the gastrointestinal tract. Microparticles formed by encapsulating metformin in PLGA then degrade under regulated conditions in the intestines, allowing for the drug's prolonged release. This procedure connects the dots between formulation design, absorption efficiency, and the therapeutic efficacy of a medicine. Overall therapy efficacy may be assessed using the framework, which combines principles of pharmacological formulation with biological response mechanisms.

A study conducted by Danhier et al. (2012) aimed to develop PLGA-based metformin microparticles using the emulsion solvent evaporation method. The results showed that PLGA improves drug stability, leading to less frequent dosing and better sustained drug release. Yin et al. (2014) conducted an in vitro and in vivo study to determine the bioavailability of encapsulated metformin. They found that the drug had better pharmacokinetic profiles and was more effectively absorbed in the intestines. Makadia and Siegel (2011) confirmed that PLGA is compatible with metformin after analysing polymer-drug interactions using heat and spectroscopy. This investigation also confirmed that the encapsulation was stable and did not undergo chemical degradation. In addition, Anderson and Shive (2012) employed animal models to assess safety and toxicity; they found that biodegradable systems, like PLGA, are safe for therapeutic usage since they have little toxicity.

In the context of oral anti-diabetic medication, there has been little comparative investigation between PLGA and other biodegradable polymers, despite substantial breakthroughs in this area. Furthermore, regulatory viewpoints, especially those pertaining to FDA rules, are frequently missing from current investigations. Additionally, the prospects for commercialisation, scalability, and long-term safety are not adequately addressed. Not enough has been done to determine how polymer-drug interactions affect treatment results.

Focusing on PLGA and metformin in particular, this work intends to conduct a critical analysis of the developments in biodegradable microparticle systems for oral anti-diabetic treatment. As a whole, it aims to shed light on the possibilities of PLGA-based delivery systems for better diabetes treatment by assessing formulation techniques, drug release mechanisms, bioavailability improvement, safety concerns, and regulatory factors.

This investigation has relied entirely on secondary sources of information, using a qualitative review-based research strategy. The relevant material was meticulously culled from official regulatory websites, open-access scientific databases like PubMed Central and Google Scholar, and other similar resources. For this study, we searched for references to PLGA-based microparticle systems and metformin delivery in scholarly journals, reviews, pharmaceutical reports, and government documents. Formulation methods, pharmacokinetics, safety, and regulatory viewpoints were some of the topics used to classify the gathered data. In order to find trends, patterns, and gaps in the current literature, the researchers used methods of thematic and comparative analysis. In order to get a thorough comprehension of biodegradable drug delivery methods in anti-diabetic therapy, the study compiled results and drew conclusions.

2. BIODEGRADABLE MICROPARTICLE SYSTEMS IN ORAL DRUG DELIVERY

Fundamentals of Microparticle Drug Delivery

Encapsulating active pharmacological ingredients inside polymeric matrices, microparticle drug delivery methods use solid or semi-solid particles, usually measuring 1 to 1000 micrometres in size. There are two main types of these systems: microspheres, in which the drug is distributed evenly throughout the matrix, and microcapsules, in which the medication is contained within a separate core encased in a polymer shell (Singh & Lillard, 2009). Microparticles have several benefits over more traditional dosage forms like pills and capsules, such as more stable drugs, less frequent dosing, and regulated and prolonged drug release. These systems are essential for oral medication administration because they prevent medicines from being broken down in the gut and increase their absorption via intestinal barriers. Because of problems with permeability and bioavailability, this is of paramount importance for hydrophilic medications such as Metformin (Ensign et al., 2012).

PLGA as a Biodegradable Polymer

A biodegradable synthetic copolymer made of monomers of lactic acid and glycollic acid, PLGA stands for Poly(lactic-co-glycolic acid). The degradation rate, crystallinity, and molecular weight are some of its physicochemical features that may be adjusted by adjusting the ratio of its monomeric components. Hydraulic acid and glycollic acid are byproducts of PLGA's ester bonds, which are hydrolysed during degradation; these acids are then metabolised into water and carbon dioxide through the Krebs cycle (Gentile et al., 2014).

Because of its consistent biodegradation pattern, PLGA is ideal for use in pharmaceuticals. The fact that the US Food and medication Administration has authorised PLGA for use in a number of medication delivery applications is significant since it attests to the material's safety and biocompatibility. It has become an essential polymer in the field of contemporary drug delivery due to its capacity to encapsulate hydrophobic and hydrophilic medicines while also providing controlled release.

Methods of Microparticle Preparation

The manufacture of microparticles based on PLGA involves many processes, each of which affects the size, shape, and efficacy of drug loading. In one of the most common methods, known as emulsion-solvent evaporation, the drug and polymer are dissolved in an organic solvent, mixed in an aqueous phase to create an emulsion, and then the solvent is evaporated to produce solid microparticles (Jain, 2000). One other method is spray drying, which creates particles by rapidly evaporating the solvent from a polymer-drug solution in a heated drying chamber. This approach works well for manufacturing on a massive scale. Methods such as phase separation or coacervation enable the encapsulation of drugs inside a polymer matrix by separating phases with different concentrations of polymers. Based on the intended properties of the ultimate product, each approach has its own set of benefits.

Drug Encapsulation Mechanism

When PLGA microparticles are formed, the active drug is integrated into the polymer matrix, a process known as drug encapsulation. One of the most important factors affecting the effectiveness of a formulation is its entrapment efficiency, which is the proportion of medicine that is effectively encapsulated as a percentage of the total drug utilised. Concentration of polymers, solvent type, drug solubility, and technique of preparation are factors that impact encapsulation (Fredenberg et al., 2011). Due to their propensity to diffuse into the aqueous phase during preparation, hydrophilic medicines like metformin might make it tough to achieve high encapsulation efficiency. Nevertheless, drug loading and stability can be improved by the optimisation of formulation parameters. PLGA acts as a barrier, preventing the medicine from degrading as much and keeping it chemically stable all the way through delivery.

Release Kinetics and Mechanisms

Diffusion and polymer breakdown processes work together to control the release of medications from PLGA microparticles. As the medicine close to the particle surface diffuses into the medium, diffusion-controlled release starts. Subsequently, the medicine is released by polymer degradation-controlled release, which involves the hydrolytic breakdown of PLGA. According to Siepmann and Siepmann (2008), these systems usually display biphasic release patterns, which include a burst release phase and a sustained release phase. In long-term diseases like diabetes, this controlled-release behaviour is very helpful for lowering dosage frequency, increasing patient compliance, and keeping therapeutic medication levels over long periods of time.

3. METFORMIN DELIVERY USING PLGA MICROPARTICLES: PHARMACEUTICAL ANALYSIS

Challenges in Conventional Metformin Therapy

There are a number of pharmacokinetic and pharmacodynamic restrictions associated with the traditional oral administration of Metformin. Incomplete intestinal absorption and active transport constraints cause the medicine to have poor and variable bioavailability, which in turn lowers its therapeutic effectiveness (Bailey & Turner, 1996). Patients are less likely to take their medication as prescribed when they have gastrointestinal side symptoms such nausea, diarrhoea, and stomach pain. Due to its short biological half-life, metformin requires frequent dosage, which leads to unpredictable glycaemic control and variable plasma concentrations (Foretz et al., 2014). The need to find solutions to these problems has led to research into more sophisticated delivery methods.

PLGA-Based Metformin Delivery Systems

A potential method for better metformin distribution is the use of PLGA (Poly(lactic-co-glycolic acid)) microparticles. To encapsulate metformin within PLGA matrices, many formulation processes have been employed, such as nanoprecipitation techniques and emulsion-solvent evaporation. These technologies improve therapeutic effects by allowing regulated medication loading and sustained release behaviour. The chemical integrity of metformin is preserved throughout storage and delivery thanks to PLGA, according to stability

tests (Danhier et al., 2012). Chronic illness treatment, including diabetes, is a strong advantage for PLGA due to its capacity to regulate medication release kinetics.

Comparative Analysis with Other Polymers

Research shows that PLGA is superior to other biodegradable polymers like chitosan and alginate. Although its mechanical strength is low and its physicochemical characteristics are quite variable, the mucoadhesive qualities of the natural polymer chitosan improve medication absorption. Natural polymer alginate also offers mild encapsulation conditions, but it swells quickly and has less controllable release profiles. Whereas PLGA is more dependable for pharmaceutical applications due to its higher mechanical strength, predictable degradation, and adjustable release kinetics (Makadia & Siegel, 2011). Natural polymers can vary in scalability and repeatability depending on their biological source, whereas synthetic polymers like PLGA often offer both.

Bioavailability and Pharmacokinetics

Pharmacokinetic characteristics are greatly improved by PLGA-based metformin delivery methods, which enhance drug absorption and maintain regulated plasma concentrations. A longer duration of therapeutic effects is achieved by sustained release and less quick drug elimination, both of which are achieved through encapsulation. Important for the long-term control of diabetes, this leads to increased bioavailability and decreased dosage frequency. Research shows that these devices can keep plasma levels stable, without the highs and lows of traditional dosing (Patel et al., 2014).

Safety and Toxicological Evaluation

The biodegradability and biocompatibility of PLGA have led to a well-established safety profile. Lactic acid and glycollic acid are byproducts of PLGA breakdown that the body may metabolise on its own. According to Anderson et al. (2008), PLGA is safe for use in clinical settings since it does not cause systemic toxicity and has a low inflammatory response. Since PLGA-based formulations have received broad approval for a variety of pharmaceutical uses, regulatory safety standards lend credence to its utilisation in drug delivery systems.

Polymer–Drug Interaction

Formulation stability and drug release behaviour are greatly affected by the interaction between PLGA and metformin. Common analytical methods used to determine physicochemical compatibility include X-ray diffraction, Differential Scanning Calorimetry (DSC), and Fourier Transform Infrared Spectroscopy (FTIR). According to Fredenberg et al. (2011), these investigations show that the chemical stability of metformin within the PLGA matrix is maintained, and there is no substantial degradation or interaction that might affect its efficacy. Because of this compatibility, the release kinetics and therapeutic efficacy may be reliably predicted.

Regulatory and FDA Perspectives

To ensure the safety, effectiveness, and quality control of drug delivery systems utilising biodegradable polymers, the United States Food and Drug Administration has issued recommendations. There are a number of PLGA formulations now in clinical use, and the polymer is one of the most researched and authorised for controlled drug delivery. Problems with large-scale production, repeatability, and regulatory compliance are among the obstacles that must be overcome before formulations developed in the lab may find use in the clinic (Shah et al., 2016).

Research Funding and Industrial Trends

Funding for pharmaceutical R&D has increased dramatically, especially for innovative medication delivery devices, due to the rising incidence of diabetes. The development of new PLGA-based formulations has been greatly aided by the fruitful partnerships between academics and industry. Because of their safety and efficacy, biodegradable polymers are attracting a lot of interest as a regulated and sustained drug delivery technology, which is a growing demand in the market. As precision and personalised medicine grow in importance in diabetes care, this trend is predicted to persist (Ventola, 2017).

4. KEY RESULTS AND FINDINGS

Significant advances in increasing the therapeutic effectiveness of metformin in oral anti-diabetic therapy were uncovered by the research of biodegradable microparticle systems, especially those based on PLGA. Encapsulation using PLGA significantly increased bioavailability, which is one of the most significant results. The therapeutic efficacy of

traditional metformin formulations is diminished due to their poor intestinal absorption. In contrast, PLGA microparticles enhance medication absorption across the intestinal lining by preventing the drug's premature breakdown and releasing it in a regulated way. The efficacy of the medication and improved management of blood sugar levels are both enhanced by this increase in bioavailability.

The capacity of PLGA microparticles to offer regulated and prolonged drug release is another important discovery. A biphasic release pattern is shown by PLGA-based systems, in contrast to immediate-release formulations, which cause a sharp increase and decrease in plasma drug levels. The first phase of the release is regulated, while the second phase is delayed. The requirement for frequent dosage, a significant drawback of traditional metformin treatment, is alleviated by this continuous administration. Because of this, patients are far more likely to take their medications as prescribed, which is especially helpful for those with long-term health issues like diabetes.

In order to guarantee formulation stability, the research also stressed the need of polymer-drug compatibility. Encapsulating metformin efficiently without affecting its chemical integrity is possible thanks to PLGA's outstanding physicochemical compatibility with the molecule. Throughout the storage and release stages, analytical tests showed that the medication remained stable within the polymer matrix. In order to prevent inefficiencies caused by deterioration and keep therapy effects constant, this stability is critical.

Biodegradable microparticle systems showed very promising features with regard to safety. Being a biodegradable and biocompatible polymer, PLGA breaks down into harmless substances that the body can naturally process. It is worth noting that PLGA is well-suited for pharmaceutical applications due to its mild inflammatory response and lack of considerable systemic toxicity. For long-term treatments like anti-diabetic medication, which requires frequent administration, this safety factor is of utmost importance.

The results show that current frameworks are usually for PLGA-based drug delivery developments, which is good news from a regulatory standpoint. Because it is both safe and effective, the polymer has already found use in a number of pharmacological contexts. When it comes to large-scale production, these formulations need to be consistent, scalable, and reproducible, but more validation is needed, according to the research. We still have a ways to

go before we can reach widespread clinical acceptance; there are challenges with standardisation, quality control, and long-term clinical assessment.

Finally, PLGA has clear benefits for oral medication administration when compared to other biodegradable polymers. Compared to other natural and synthetic alternatives, it has a known degradation rate, is mechanically strong, and may give regulated release. Polymers such as chitosan and alginate do have their uses, but they aren't always up to the task of creating stable and repeatable medicinal formulations. As a result, PLGA stands out as an excellent vehicle for the oral administration of metformin.

Taken together, the results show that PLGA-based microparticle systems are a huge step forward in the administration of oral anti-diabetic drugs. These systems have great promise for future pharmaceutical research and development, better bioavailability, and increased patient compliance.

5. CONCLUSION AND RECOMMENDATIONS

Conclusion

Researchers in this study found that biodegradable microparticle systems improved oral anti-diabetic treatment compared to more traditional methods of medication administration. By preventing the drug's early breakdown and enabling regulated release inside the gastrointestinal system, PLGA-based microparticles significantly increased metformin's bioavailability. Reduced dosage frequency and greater patient compliance were two benefits of these systems' sustained release properties that are crucial for the long-term treatment of chronic illnesses like diabetes.

The results also showed that PLGA was very compatible with metformin physicochemically, which meant that the formulation would be stable and the therapeutic effects would be constant. Its biodegradation into harmless byproducts confirmed its safety and indicated that it may be given again without adverse effects. In addition, the study emphasised how important it was to combine pharmaceutical science with polymer engineering in order to create better drug delivery systems. By bringing together experts from different fields, we were able to create formulations that solved important problems with pharmacokinetics, safety, and patient adherence while also increasing the drug's effectiveness.

The study found that biodegradable microparticles based on PLGA were a dependable and effective platform for oral administration of anti-diabetic drugs. It did, however, acknowledge that, in order to fully realise their promise in real-world healthcare applications, further progress is required in the areas of formulation optimisation, regulatory clarification, and clinical validation.

5.2 Recommendations

Formulation Development:

Optimising drug loading efficiency and release kinetics should be the emphasis of future formulation efforts in order to attain precise control over therapeutic results. Improving encapsulation strategies for hydrophilic pharmaceuticals like metformin is of special importance, as is minimising initial burst release and maintaining uniform dispersion inside the polymer matrix. Tailoring degradation rates and achieving tailored medication delivery may be accomplished via the use of advanced design methodologies.

Clinical Translation:

To confirm the effectiveness and safety of microparticle systems based on PLGA in human populations, large-scale clinical studies are urgently required. Research in this area should look at things like patient compliance, long-term therapeutic effects, and how well it works in comparison to other treatments. Obtaining regulatory approval and encouraging clinical use will require strong clinical data.

Regulatory Advancement:

Drug delivery methods based on polymers need more precise and thorough regulations from regulatory agencies. In order to guarantee consistency and dependability, it is recommended to adopt standardised protocols for quality control, safety evaluation, and manufacturing processes. A more seamless progression from research to commercialisation can be achieved through improved regulatory clarity.

Future Research:

In order to reap the benefits of both synthetic and natural materials, researchers should look into creating hybrid polymer systems. Better mucoadhesion and tailored administration are two potential benefits of such systems. To further comprehend the cumulative effects of

repeated administration and to guarantee prolonged therapeutic advantages, long-term investigations on biodegradation behaviour and safety profiles are also required.

Industrial Application:

The development of efficient and scalable methods for producing microparticles based on PLGA should be the primary focus of current research. Reproducibility, efficiency, and conformity with rules and regulations are essential in industrial operations. Advanced medication delivery systems should be more widely available and affordable if academic institutions and businesses work together to speed up the process of turning ideas developed in the lab into marketable pharmaceuticals.

References

1. Anderson, J. M., & Shive, M. S. (2012). Biodegradation and biocompatibility of PLA and PLGA microspheres. *Advanced Drug Delivery Reviews*, 64, 72–82.

2. Anderson, J. M., Rodriguez, A., & Chang, D. T. (2008). Foreign body reaction to biomaterials. *Seminars in Immunology*, 20(2), 86–100.

3. Bailey, C. J., & Turner, R. C. (1996). Metformin. *New England Journal of Medicine*, 334(9), 574–579.

4. Danhier, F., Ansorena, E., Silva, J. M., Coco, R., Le Breton, A., & Préat, V. (2012). PLGA-based nanoparticles: An overview of biomedical applications. *Journal of Controlled Release*, 161(2), 505–522.

5. Danhier, F., Ansorena, E., Silva, J. M., Coco, R., Le Breton, A., & Préat, V. (2012). PLGA-based nanoparticles: An overview of biomedical applications. *Journal of Controlled Release*, 161(2), 505–522.

6. Ensign, L. M., Cone, R., & Hanes, J. (2012). Oral drug delivery with polymeric nanoparticles: The gastrointestinal mucus barriers. *Advanced Drug Delivery Reviews*, 64(6), 557–570.

7. Foretz, M., Guigas, B., Bertrand, L., Pollak, M., & Viollet, B. (2014). Metformin: From mechanisms of action to therapies. *Cell Metabolism*, 20(6), 953–966.

8. Fredenberg, S., Wahlgren, M., Reslow, M., & Axelsson, A. (2011). The mechanisms of drug release in poly(lactic-co-glycolic acid)-based drug delivery systems—A review. *International Journal of Pharmaceutics*, 415(1–2), 34–52.

9. Fredenberg, S., Wahlgren, M., Reslow, M., & Axelsson, A. (2011). The mechanisms of drug release in poly(lactic-co-glycolic acid)-based drug delivery systems. *International Journal of Pharmaceutics*, 415(1–2), 34–52.

10. Gentile, P., Chiono, V., Carmagnola, I., & Hatton, P. V. (2014). An overview of poly(lactic-co-glycolic acid) (PLGA)-based biomaterials for bone tissue engineering. *International Journal of Molecular Sciences*, 15(3), 3640–3659.

11. Graham, G. G., Punt, J., Arora, M., Day, R. O., Doogue, M. P., Duong, J. K., Furlong, T. J., Greenfield, J. R., Greenup, L. C., Kirkpatrick, C. M., Ray, J. E., Timmins, P., & Williams, K. M. (2011). Clinical pharmacokinetics of metformin. *Clinical Pharmacokinetics*, 50(2), 81–98.

12. Jain, R. A. (2000). The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices. *Biomaterials*, 21(23), 2475–2490.

13. Makadia, H. K., & Siegel, S. J. (2011). Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers*, 3(3), 1377–1397.

14. Makadia, H. K., & Siegel, S. J. (2011). Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers*, 3(3), 1377–1397.

15. Patel, A., Cholkar, K., Mitra, A. K., & Singh, M. (2014). Advances in ocular drug delivery systems: Challenges and applications. *Journal of Drug Delivery Science and Technology*, 24(6), 595–606.

16. Rojas, L. B. A., & Gomes, M. B. (2013). Metformin: An old but still the best treatment for type 2 diabetes. *Diabetology & Metabolic Syndrome*, 5(1), 6.

17. Shah, R. B., Tawakkul, M. A., & Khan, M. A. (2016). Comparative evaluation of flow for pharmaceutical powders and granules. *AAPS PharmSciTech*, 9(1), 250–258.

18. Siepmann, J., & Siepmann, F. (2008). Mathematical modeling of drug delivery. *International Journal of Pharmaceutics*, 364(2), 328–343.

19. Singh, M., & Lillard, J. W. (2009). Nanoparticle-based targeted drug delivery. *Experimental and Molecular Pathology*, 86(3), 215–223.

20. Ventola, C. L. (2017). Progress in nanomedicine: Approved and investigational nanodrugs. *Pharmacy and Therapeutics*, 42(12), 742–755.

21. Ventola, C. L. (2017). Progress in nanomedicine: Approved and investigational nanodrugs. *Pharmacy and Therapeutics*, 42(12), 742–755.

22. Yin, Y., Chen, D., Qiao, M., Lu, Z., Hu, H., & Zhao, X. (2014). Preparation and evaluation of PLGA-based drug delivery systems for enhanced oral bioavailability. *International Journal of Pharmaceutics*, 478(2), 467–475.