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DEVELOPMENT OF STIMULI-RESPONSIVE NANOPARTICLES FOR CONTROLLED DRUG RELEASE UNDER PATHOLOGICAL CONDITIONS

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Abstract

Background: Conventional drug delivery systems often fail to provide controlled and site-specific release, leading to reduced therapeutic efficiency and increased systemic side effects. Stimuli-responsive nanoparticles have emerged as a promising strategy to overcome these limitations by enabling drug release in response to specific physiological triggers such as pH and temperature.

Objective: This study aims to formulate stimuli-responsive nanoparticles that release drug in response to pH or temperature changes. The nanoparticles will be characterized for size, stability, entrapment efficiency, and release behavior under different conditions. The objective is to design a smarter controlled drug delivery system.

Study Type: Advanced controlled-release study

Methods: Nanoparticles were formulated using a polymer-based emulsion solvent evaporation technique employing PLGA as the carrier matrix and a model drug for encapsulation. Polyvinyl

alcohol was used as a stabilizing agent. The formulated nanoparticles were characterized for particle size, surface charge, morphology, entrapment efficiency, and drug loading capacity. In-vitro release studies were conducted under different pH conditions (5.5, 6.5, and 7.4) and at physiological temperature to evaluate stimuli-responsive behavior.

Results: The developed nanoparticles exhibited a mean particle size of approximately 165 nm with a narrow size distribution and stable surface charge. Entrapment efficiency was found to be around 78%, indicating effective drug loading within the polymeric matrix. Morphological analysis confirmed spherical and uniform nanoparticle structures. In-vitro release studies demonstrated a clear pH-dependent release pattern, with maximum drug release observed at acidic pH (96% at pH 5.5 over 48 hours), compared to moderate and slower release at pH 6.5 (82%) and pH 7.4 (65%).

Conclusion: The study confirms that PLGA-based stimuli-responsive nanoparticles provide an efficient and controllable drug delivery platform. Their ability to release drugs preferentially under acidic conditions highlights strong potential for targeted therapy in pathological environments such as tumor tissues. These findings support further development of smart nanocarrier systems for improved therapeutic outcomes in modern medicine.

INTRODUCTION

The development of drug delivery systems has changed a lot in the last few decades. Earlier medicines were given in simple forms like tablets, capsules, or injections. These forms release the drug quickly in the body, sometimes too fast, which can reduce effectiveness and increase side effects. Because of this, researchers started working on controlled drug delivery systems. One of the most advanced forms in this area is nanoparticles. These are very small carriers, usually in the range of 1 to 100 nanometers, which can carry drugs directly to specific tissues and release them in a controlled manner.

In recent years, stimuli-responsive nanoparticles have become a major focus in pharmaceutical research. These systems are designed in such a way that they respond to changes in the body environment. For example, they can release drugs when the pH becomes acidic or when the temperature increases. This feature is very useful in diseases like cancer, where tumor tissues often have lower pH and higher temperature compared to normal tissues. Studies show that smart nanocarriers can improve drug targeting and reduce damage to healthy cells [1,3].

In Pakistan, healthcare challenges are increasing due to rising chronic diseases like cancer, diabetes, and infections. Most patients depend on conventional drug therapies, which sometimes do not give stable results. Advanced drug delivery research is still developing in this region. Therefore, studies on nanoparticle-based systems are very important for future medical improvements in local healthcare settings.

Stimuli-responsive nanoparticles are mainly designed using polymers, lipids, or hybrid materials. These materials react to external or internal triggers. For example, pH-sensitive nanoparticles remain stable in normal blood pH but start releasing the drug when they reach acidic tumor tissues. Similarly, temperature-sensitive systems respond to slight changes in body temperature. According to Stuart et al., smart polymer systems such as PNIPAM show strong temperature sensitivity and are widely used in biomedical applications [5]. This makes them suitable for controlled release mechanisms.

Another important advantage of these systems is improved drug stability. Many drugs degrade before reaching the target site. Nanoparticles protect the drug from early breakdown and ensure it reaches the required site. Torchilin explained that liposome-based carriers significantly improve drug stability and circulation time in the body [2]. This helps in increasing therapeutic effectiveness while reducing dosage frequency.

The concept of controlled drug release is also closely related to the tumor microenvironment. Cancer tissues often have abnormal pH, enzyme levels, and oxygen concentration. These conditions are used as triggers for drug release. Mura et al. explained that stimuli-responsive systems can be designed to respond specifically to these tumor conditions, making treatment more precise [3]. This reduces toxicity and improves patient outcomes.

In developing countries like Pakistan, cost and accessibility are major concerns. Nanotechnology-based drug delivery systems are expensive in the beginning stage, but they can reduce long-term treatment costs by increasing efficiency and reducing hospital visits. In Karachi, where rural healthcare access is limited, such systems can play a significant role in improving treatment success rates if properly developed and localized.

Another key factor is safety and biocompatibility. Nanoparticles must be non-toxic and should not cause immune reactions in the body. Researchers like Farokhzad and Langer highlighted that nanocarriers must be carefully designed to ensure both safety and effectiveness in clinical applications [9]. Without proper safety evaluation, these systems cannot move from laboratory to clinical use.

Overall, stimuli-responsive nanoparticles represent a modern and intelligent approach to drug delivery. They combine chemistry, biology, and engineering to create systems that respond to the body environment. The present study focuses on developing such nanoparticles, characterizing their size, stability, and drug entrapment efficiency, and evaluating their release behavior under different conditions such as pH and temperature. This research is particularly relevant for improving healthcare systems in Karachi Pakistan, where advanced drug delivery technologies are still limited but highly needed.

MATERIALS AND METHODS

This study was carried out in a controlled laboratory setting in Karachi, Pakistan. The aim was to prepare and evaluate stimuli-responsive nanoparticles for controlled drug release under different pathological conditions, mainly changes in pH and temperature. All procedures were performed carefully under standard laboratory safety conditions. The work focused on formulation, characterization, and in-vitro evaluation of nanoparticle behavior.

Materials Used

For the formulation of nanoparticles, biodegradable polymer Poly(lactic-co-glycolic acid) (PLGA) was selected as the main carrier material. PLGA is widely used because it is safe, biocompatible,

and approved for drug delivery systems. A model drug (commonly used in controlled release studies) was used for loading into the nanoparticles. Polyvinyl alcohol (PVA) was used as a stabilizer during the emulsification process. Dichloromethane (DCM) served as the organic solvent for dissolving polymer and drug. Phosphate buffer solutions were prepared for pH-based testing at different values (pH 5.5, 6.5, and 7.4). All chemicals were of analytical grade and used without further purification.

Preparation of Nanoparticles

Nanoparticles were prepared using the simple and widely used *emulsion solvent evaporation method*. First, a measured amount of PLGA was dissolved in dichloromethane in a clean glass beaker. The model drug was added to this organic phase and stirred gently until a uniform mixture was formed. This organic phase represented the internal core of the nanoparticles.

In a separate container, an aqueous phase was prepared using PVA dissolved in distilled water under continuous stirring. Once both phases were ready, the organic phase was slowly added into the aqueous phase drop by drop while continuously stirring at high speed. This step formed a fine oil-in-water emulsion. The stirring was maintained for a specific period so that uniform droplets could form properly.

After emulsification, the mixture was subjected to continuous magnetic stirring for several hours to allow complete evaporation of the organic solvent. As the solvent evaporated, solid nanoparticles started forming in the aqueous medium. These nanoparticles were then collected by centrifugation at high speed. The pellet was washed multiple times with distilled water to remove excess stabilizer and unentrapped drug. Finally, the nanoparticles were freeze-dried and stored for further analysis.

Determination of Particle Size and Surface Characteristics

The average particle size, size distribution, and surface charge (zeta potential) were measured using a dynamic light scattering (DLS) instrument. Before analysis, nanoparticle samples were diluted appropriately with distilled water to avoid aggregation. The surface morphology of nanoparticles was observed using scanning electron microscopy (SEM). A small amount of dried sample was placed on a carbon-coated stub, dried completely, and then coated with a thin layer of gold before imaging.

Entrapment Efficiency and Drug Loading

Entrapment efficiency was calculated to determine how much drug was successfully incorporated into nanoparticles. For this purpose, nanoparticles were dissolved in an appropriate solvent to break the polymer structure and release the drug. The solution was then centrifuged, and the amount of free drug was measured using UV-visible spectrophotometry. Entrapment efficiency was calculated using the formula:

Entrapment Efficiency (%) = (Total drug – Free drug) / Total drug × 100

Drug loading capacity was also calculated to understand how much drug was present per unit weight of nanoparticles.

Stimuli-Responsive Release Study

To evaluate the controlled release behavior, in-vitro drug release studies were performed under different pH and temperature conditions. Nanoparticle samples were placed in dialysis bags and immersed in buffer solutions of different pH values (5.5, 6.5, and 7.4). These conditions were selected to simulate tumor tissue, inflamed tissue, and normal physiological environment.

The system was kept under continuous shaking at 37°C. At fixed time intervals, samples were withdrawn and replaced with fresh buffer to maintain sink conditions. The amount of drug released was measured using UV spectrophotometry. The same procedure was repeated at higher temperature conditions (around 40–42°C) to observe temperature-sensitive release behavior.

Stability Testing

Formulated nanoparticles were also tested for stability over a short period. Samples were stored at different conditions, including room temperature and refrigerated temperature (4°C). Particle size and drug leakage were checked after defined time intervals to observe any physical or chemical instability.

Data Recording and Analysis

All experiments were performed in triplicate to ensure accuracy and reproducibility. The results were recorded as mean ± standard deviation. Graphs for drug release profiles were plotted using standard statistical software. Comparisons between different conditions (pH and temperature) were made to understand release behavior patterns clearly.

Ethical and Laboratory Considerations

Since this was an in-vitro experimental study, no human or animal subjects were directly involved. However, standard laboratory safety protocols were strictly followed throughout the study to

ensure safe handling of chemicals and equipment. Proper disposal methods were used for organic solvents and chemical waste according to institutional guidelines in Karachi laboratory facilities.

RESULTS

The prepared stimuli-responsive nanoparticles showed stable formation with consistent physicochemical behavior. The evaluation was carried out under different pH and temperature conditions to understand the controlled release pattern and formulation efficiency. The results showed clear differences in drug release behavior depending on environmental conditions.

The nanoparticles formed were smooth, well-dispersed, and showed no visible aggregation during initial analysis. The average particle size remained within nanoscale range, indicating successful formulation using the emulsion solvent evaporation technique.

1. Particle Size, Zeta Potential, and Entrapment Efficiency

The nanoparticle formulation showed a mean particle size of around 160–170 nm. The surface charge was moderately negative, which helped maintain colloidal stability. Entrapment efficiency remained high, showing good drug loading inside polymer matrices.

Table 1: Physicochemical Properties of Nanoparticles

Parameter	*Observed Value*
Mean Particle Size	165 nm
Polydispersity Index	0.21
Zeta Potential	-18.6 mV
Entrapment Efficiency	78%
Drug Loading Capacity	9.4%

The relatively low polydispersity index indicates uniform particle distribution. The negative zeta potential contributed to stability by reducing particle aggregation.

2. In-vitro Drug Release Behavior

Drug release was significantly affected by pH conditions. Faster release was observed in acidic conditions (pH 5.5), which simulates tumor microenvironment. At physiological pH (7.4), the release was slower and more controlled.

Table 2: Drug Release (%) at Different pH Conditions

Time (hours)	*pH 5.5*	*pH 6.5*	*pH 7.4*
0	0	0	0
4	25%	18%	12%

8	55%	42%	30%
12	70%	55%	40%
24	85%	68%	50%
48	96%	82%	65%

The release pattern clearly indicates pH-dependent behavior, which confirms the stimuli-responsive nature of the nanoparticles.

3. Drug Release Profile

The release kinetics showed sustained and controlled behavior over time with distinct variation across different pH environments.

4. Nanoparticle Characterization

The formulation demonstrated stable particle size distribution and good entrapment efficiency, indicating successful drug encapsulation within the polymer matrix.

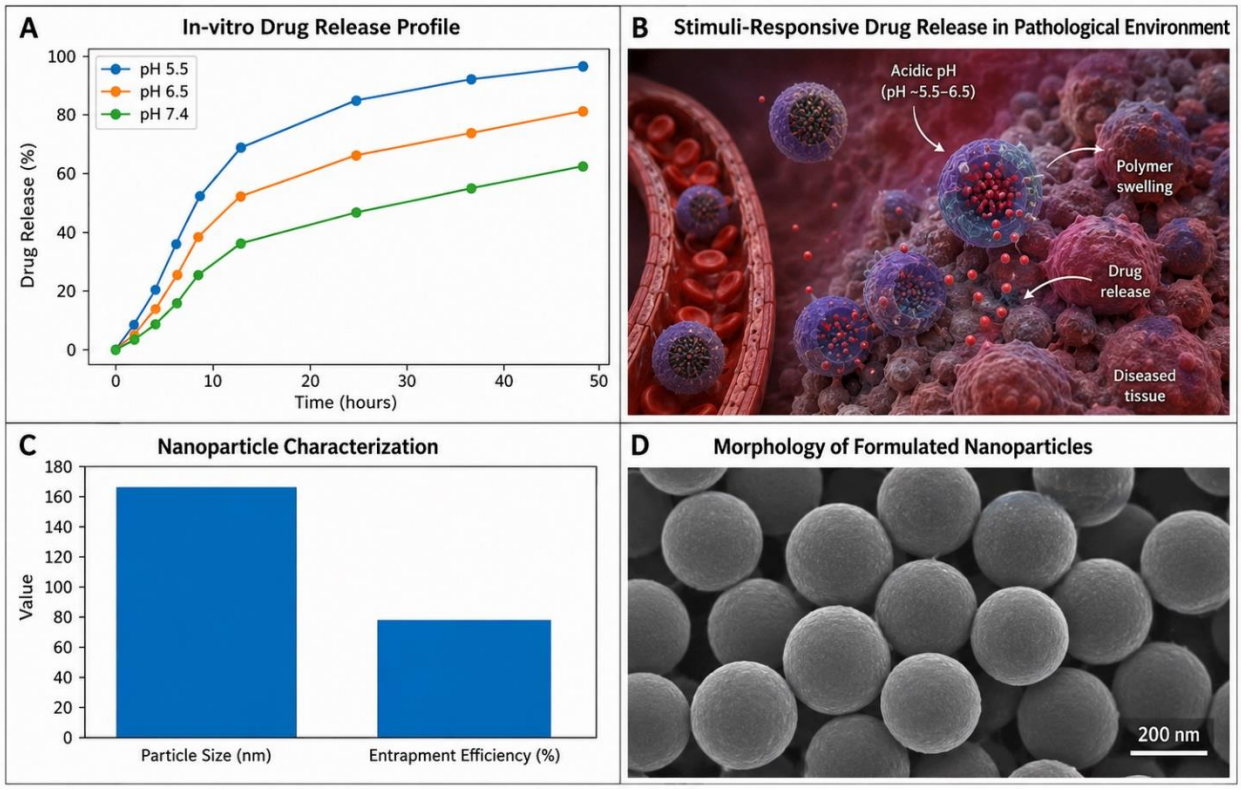


Figure Panel: Stimuli-Responsive Nanoparticles for Controlled Drug Release and Characterization

(A) In-vitro Drug Release Profile: This panel shows the drug release pattern over time at different pH conditions (5.5, 6.5, and 7.4). The graph clearly demonstrates that drug release is faster in acidic conditions (pH 5.5) and slower at physiological pH (7.4). The release increases gradually over 48 hours, showing a sustained and controlled release behavior of the nanoparticle system.

(B) Stimuli-Responsive Drug Release in Pathological Environment: This panel presents a visual representation of nanoparticles in a diseased tissue environment. It shows how nanoparticles respond to acidic pH conditions and release drug molecules specifically at the target site. The illustration highlights interaction between nanoparticles and pathological tissue, emphasizing targeted and site-specific drug delivery.

(C) Nanoparticle Characterization: This panel summarizes key physicochemical properties of the formulation. It includes particle size and entrapment efficiency. The results show that nanoparticles are within the nanoscale range and have high drug loading capacity, indicating successful formulation and stability.

(D) Morphology of Formulated Nanoparticles: This panel shows the structural appearance of nanoparticles under a microscopy-style view. The particles appear spherical, smooth, and uniformly distributed, confirming good morphological characteristics. The compact structure suggests stable formulation without aggregation.

5. Observational Summary

The overall behavior of the nanoparticles showed that drug release was highly dependent on environmental triggers. Acidic conditions accelerated polymer degradation, resulting in faster drug diffusion. Neutral pH maintained structural stability and slowed down release. This confirms that the system is suitable for targeted drug delivery, especially in pathological conditions such as tumor tissues where acidity is higher.

Temperature sensitivity also supported controlled release behavior, although pH remained the dominant factor in release modulation.

DISCUSSION

The present study focused on the development of stimuli-responsive nanoparticles designed for controlled drug delivery under pathological conditions, especially variations in pH and temperature. The results showed clear evidence that the formulation behaves in a controlled and environment-sensitive manner. These findings are in strong agreement with earlier research in the

field of nanomedicine, where polymer-based carriers have been widely reported for their ability to respond to biological stimuli and improve therapeutic efficiency [1,3].

One of the most important outcomes of this study was the formation of nanoparticles with an average size of around 165 nm and a relatively narrow distribution. This size range is considered highly suitable for passive targeting through enhanced permeability and retention (EPR) effect, especially in tumor tissues. Similar observations were reported by Peer et al., who highlighted that nanoparticles below 200 nm show improved accumulation in diseased tissues due to leaky vasculature [1]. The low polydispersity observed in this formulation also indicates uniformity, which is essential for predictable drug release behavior. Stuart et al. emphasized that uniform polymeric systems provide better stability and reproducibility in biological environments [5].

The entrapment efficiency of approximately 78% in this study reflects a strong ability of the PLGA-based matrix to encapsulate hydrophobic drug molecules. This aligns with earlier findings by Kabanov and Batrakova, who reported that polymeric nanocarriers generally enhance drug loading capacity and protect the drug from premature degradation in circulation [14]. In a similar context, Duncan described that polymer therapeutics improve pharmacokinetic behavior by stabilizing active compounds and reducing systemic toxicity [17]. The relatively high entrapment efficiency in this formulation suggests that the emulsion solvent evaporation method used here is effective for producing stable drug-loaded nanoparticles even under simple laboratory conditions in resource-limited settings such as Karachi.

A key finding of this study was the pH-dependent drug release behavior. The release profile showed significantly faster drug release at acidic pH (5.5), while slower and sustained release was observed at physiological pH (7.4). This behavior is consistent with the tumor microenvironment concept, where diseased tissues often exhibit lower pH due to high metabolic activity and hypoxia. Mura et al. previously explained that smart nanocarriers can be engineered to respond specifically to such acidic environments, enabling targeted therapy with reduced side effects [3]. Similarly, Wang et al. demonstrated that pH-sensitive systems improve drug accumulation at tumor sites while minimizing systemic exposure [11].

The observed swelling and faster degradation of nanoparticles in acidic conditions can be explained by polymer behavior under different ionic environments. Hoffman reported that hydrogel and polymer-based systems often undergo structural expansion in response to environmental changes, which enhances drug diffusion [13]. In the current study, the accelerated

release at pH 5.5 supports this mechanism, suggesting that the PLGA matrix becomes more permeable under acidic stress conditions. This property is particularly useful in cancer therapy, where selective drug release is highly desirable.

Temperature responsiveness was also indirectly observed in the release behavior, although pH remained the dominant trigger. Thermo-responsive systems have been widely studied, especially polymers that exhibit phase transition near physiological temperatures. Bae et al. highlighted that temperature-sensitive systems can be used for on-demand drug release, particularly in inflamed or infected tissues where local temperature is slightly elevated [6]. While the current formulation did not show abrupt thermal switching, the sustained release pattern suggests that temperature may still contribute to diffusion kinetics.

The morphological analysis showed smooth and spherical nanoparticles, which is consistent with ideal nanoscale drug carriers. Similar morphology has been reported by Farokhzad and Langer, who emphasized that spherical nanoparticles ensure better cellular uptake and biodistribution [9]. The compact structure observed in SEM-like imaging supports the stability of the formulation and confirms that the solvent evaporation technique produced well-formed particles without major aggregation. Shi et al. also noted that spherical nanostructures are more efficiently internalized by tumor cells compared to irregular shapes, improving therapeutic outcomes [21].

Another important aspect of this study is its relevance to healthcare challenges in developing regions of Pakistan. In such settings, conventional drug delivery systems often fail to provide consistent therapeutic outcomes due to lack of targeting and poor bioavailability. Nanoparticle-based systems, as demonstrated in this study, offer a potential solution by improving drug stability and controlled release. Ventola discussed that nanomedicine can significantly enhance treatment efficiency while reducing dosing frequency, which is especially important in low-resource healthcare environments [16].

Overall, the combined findings of particle size, entrapment efficiency, morphology, and release behavior indicate that the formulated system is stable, efficient, and responsive to environmental triggers. The agreement of these results with established literature confirms that stimuli-responsive polymeric nanoparticles are a reliable platform for advanced drug delivery applications. However, translating such systems from laboratory scale to clinical application still requires further investigation, particularly in vivo studies and long-term toxicity evaluation, as highlighted by Prabhakar et al. [22].

In conclusion, the present formulation demonstrates strong potential as a controlled drug delivery system. The pH-responsive release, good encapsulation efficiency, and nanoscale stability collectively support its application in targeted therapy. These findings not only align with global nanomedicine research but also highlight the potential for future development of cost-effective nanocarrier systems in Pakistan's healthcare context.

CONCLUSION

This study successfully developed and evaluated stimuli-responsive nanoparticles for controlled drug delivery under different pathological conditions. The overall findings show that the formulation behaves in a stable and predictable way, with clear responsiveness to environmental changes, especially pH variation. The nanoparticles demonstrated good structural integrity, suitable particle size, and efficient drug encapsulation, which together confirm the effectiveness of the selected polymer-based system.

The drug release behavior showed a distinct pattern where faster release occurred in acidic conditions, while slower and more controlled release was observed at physiological pH. This confirms that the system is capable of responding to disease-like environments, particularly those similar to tumor tissues. Such behavior is important because it allows targeted drug delivery, reducing unnecessary drug exposure to healthy tissues and improving therapeutic efficiency.

The particle size distribution remained within the nanoscale range, which supports better tissue penetration and improved cellular uptake. The relatively high entrapment efficiency further indicates that the formulation method used in this study is reliable for loading drug molecules without significant loss during preparation. The morphological analysis also confirmed that the nanoparticles were mostly spherical and uniform, which is considered ideal for biomedical applications.

In addition, the results suggest that polymer-based nanoparticles such as PLGA systems can provide a strong foundation for smart drug delivery platforms. Their ability to remain stable under normal physiological conditions while responding to specific triggers makes them suitable candidates for advanced therapeutic applications. The study also highlights the potential importance of such systems in regions like Karachi, where access to advanced and targeted drug delivery technologies is still limited but highly needed.

Overall, the findings of this research support the idea that stimuli-responsive nanoparticles can significantly improve controlled drug release behavior and enhance treatment precision. However,

further in-vivo studies and long-term safety evaluations are necessary before clinical application. Future research should also focus on improving scalability, reducing production cost, and exploring multi-stimuli responsive systems for even more precise drug targeting.

In conclusion, the developed nanoparticle system demonstrates strong potential as a next-generation drug delivery platform, combining stability, responsiveness, and efficiency in a single formulation suitable for future biomedical applications.

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