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Autocatalytic Acidification in Poly(Lactic-Co-Glycolic Acid) Nanoparticles: Effects on the Chemical Stability of the Encapsulated Substance and Control by Alkaline Excipients

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Abstract: This article analyzes the process of autocatalytic acidification occurring in poly(lactide-co-glycolide) (PLGA) nanoparticles and its effect on the chemical stability of encapsulated substances. Based on a literature review, the study examines the decrease in internal pH of nanoparticles caused by the accumulation of carboxyl groups during PLGA degradation, as well as the impact of this process on the stability of proteins, peptides, and acid-sensitive substances. In addition, the effects of factors such as particle size, glycolide content, molecular weight, terminal group type, and matrix porosity on the kinetics of acidification were evaluated. The effectiveness of alkaline additives in stabilizing internal pH and their potential effects on matrix morphology and drug release kinetics were comparatively analyzed. The findings demonstrate the need to monitor internal pH in PLGA nanoparticles and to consider autocatalytic acidification at the early stages of formulation design.

Keywords: PLGA nanoparticles, autocatalytic acidification, internal pH, polymer degradation, chemical stability, encapsulation, alkaline additives, controlled drug release, matrix porosity, pharmaceutical nanotechnology.

1. Introduction

It is no accident that PLGA is called the “workhorse” of pharmaceutical nanotechnology: it is biocompatible, its degradation products are the body's own natural metabolites, and its degradation rate can be tuned from weeks to months through the lactide-to-glycolide ratio. As Makadia and Siegel have noted, PLGA is widely used precisely as a biodegradable carrier capable of controlled release [1].

However, the very property that makes this polymer so useful — its controlled hydrolysis — is at the same time the source of its greatest problem. Each cleavage of an ester bond generates one free carboxyl group. Because a nanoparticle is, from a diffusional standpoint, a semi-closed system, these acids cannot immediately escape to the exterior and instead accumulate within the matrix. The acid, in turn, catalyzes further hydrolysis, so that the process takes on an exponential character. Fu and co-authors were among the first to visually demonstrate the existence of an acidic environment inside degrading PLGA microspheres [2-3].

The practical severity of the problem is such that, in some measurements, the internal pH has been reported to fall to around 2. Under such conditions proteins denature, peptide bonds are cleaved, and acid-sensitive small molecules decompose. As a result, a formulation may be published with a high encapsulation efficiency, yet within a few months practically none of the active substance remains intact within it[4].

The stability problem is not unique to synthetic polyesters. It remains a central issue for natural biopolymers as well. Studies carried out at the Institute of Polymer Chemistry and Physics of the Academy of Sciences of the Republic of Uzbekistan have examined in depth the structure and stability of chitosan-based nanosystems. In particular, Nurgaliyev and Rashidova demonstrated the significance

of chitosan nanoparticles as nanocarriers owing to their biodegradability and biocompatibility, modeled the formation of a chitosan ascorbate nanostructure using density functional theory (DFT), and showed that such nanoparticles can improve the stabilization and controlled release of ascorbic acid [5]. This approach, aimed at understanding stability at the level of molecular interactions, is methodologically close to the direction of the present work. Vokhidova and Rashidova, for their part, studied how synthesis conditions affect the morphology of chitosan-stabilized nanoparticles, showing that the structure of the stabilizing polymer determines the final state of the nanosystem [6]. Sarymsakov and Yunusov analyzed the prospects for creating polymer-based drugs [7], while Kudyshkin and co-authors synthesized graft copolymers of chitosan with acrylic acid, demonstrating that chemical modification of the chitosan chain makes it possible to control the properties of the material [8].

A review of the available literature reveals two serious gaps.

First, the measurement of internal pH is not standardized: different research groups use fluorescent probes, EPR spectroscopy, microelectrodes, or NMR methods, and for the same formulation these can yield results differing from one another by 1–2 pH units. **Second**, alkaline excipients are usually evaluated only from the standpoint of raising pH, while their side effects on matrix morphology and release kinetics are rarely measured together with their primary benefit.

The scientific novelty of this work is aimed precisely at closing the second gap: acidification and the release profile are treated not as separate parameters but as two manifestations of a single chemical process[9]. The study seeks answers to the following questions:

1) What hierarchy exists among the formulation parameters that govern the rate of autocatalytic acidification?

2) Is there a quantitative relationship between the decline in internal pH and the loss of the substance?

3) How effective are alkaline excipients, and what "price" do they exact on the release profile?

4) What minimal methodological standard is needed for measuring internal pH?

2. Materials and methods

2.1. Type of study

This work was carried out as a structured systematic review, based on a version of the PRISMA guidance adapted for reviews.

2.2. Search strategy

The search was conducted in the Scopus, Web of Science Core Collection, PubMed, and ScienceDirect databases. In addition, regional sources — the Uzbekistan Journal of Polymers and publications of the Academy of Sciences of the Republic of Uzbekistan — were reviewed manually. Search date: not specified in the source document; time range: [10]. The following logical query was applied:

(PLGA OR "poly(lactic-co-glycolic acid)") AND (nanoparticle OR microsphere*) AND ("internal pH" OR "microclimate pH" OR acidification OR autocatalytic) AND (stability OR degradation OR excipient)*

2.3. Inclusion and exclusion criteria

The analysis included peer-reviewed, full-text publications; particle systems based on PLGA (or PLA/PGA); works reporting quantitative data on internal pH, acidification, or degradation, together with at least one physicochemical characteristic (size, PDI, ζ-potential, EE%). Conference abstracts, in-silico-only studies, publications providing no information on the internal environment, systems in which the PLGA fraction was below 50%, and duplicate publications were excluded[11-12].

2.4. Data extraction

The following indicators were extracted from each publication into a single format: lactide/glycolide ratio; molecular weight (Mw); end-group type (ester- or acid-terminated); synthesis method; mean

diameter; PDI; ζ-potential; EE% and DL%; method and value of internal pH measurement; incubation conditions; substance loss; excipient type and concentration; and change in the release profile.

2.5. Quality assessment and analysis

Publications were sorted into three tiers of methodological completeness (high, moderate, and low reliability). The analysis was performed by thematic synthesis. Because of the high degree of heterogeneity among protocols (see section 3.5), a formal meta-analysis was not conducted.

3. Results

3.1. Phased kinetics of acidification

Based on the sources analyzed, the process can be divided into three phases (Figure 1).

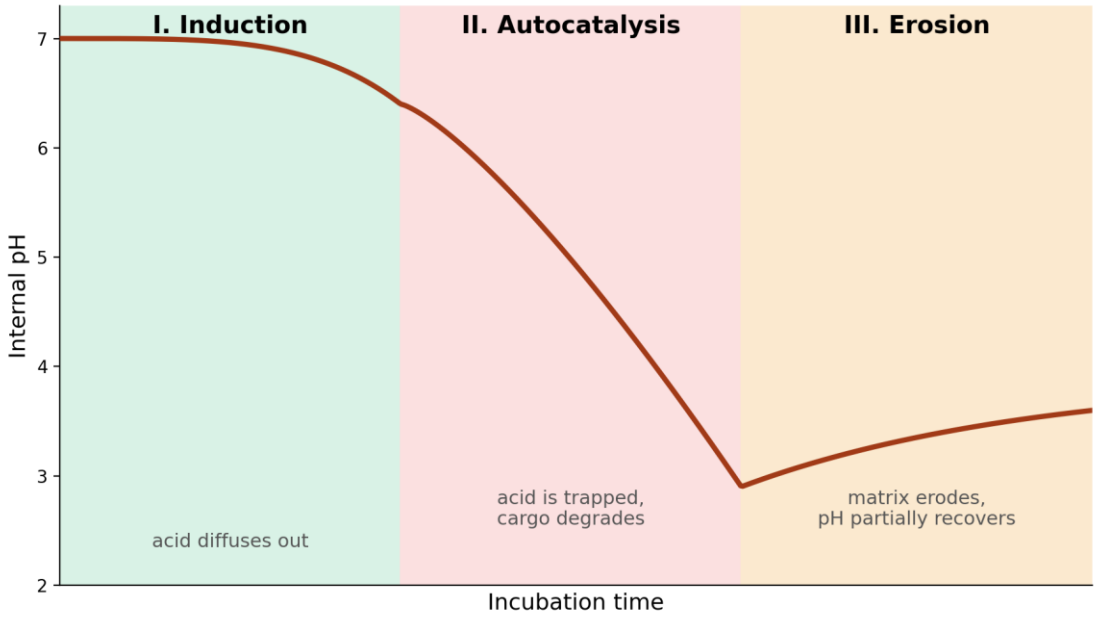

Figure 1. The three phases of autocatalytic acidification in a PLGA nanoparticle and the dynamics of internal pH (schematic)

Phase I — Induction. Water penetrates the matrix and hydrolysis begins, but the acids formed still manage to escape by diffusion. At this stage, release of the substance proceeds mainly through diffusion.

Phase II — Autocatalysis. Once the number of chain scissions exceeds a critical threshold, the rate of carboxyl-group formation outpaces the rate at which they can escape, and the hydrolysis rate constant increases several-fold. It is precisely in this phase that the bulk of the encapsulated substance undergoes chemical breakdown. As Houchin and Topp have shown, the destruction of peptides and proteins within the PLGA matrix is largely driven by reactions that proceed in an acidic environment [13].

Phase III — Erosion. The polymer chains are converted into water-soluble oligomers, the matrix disintegrates, the acids escape to the exterior, and the pH partially recovers. By this point, however, the substance may already have been lost.

An important methodological conclusion follows from this: a short-term stability study that captures only Phase I (for example, a 7-day observation) provides almost no reliable information about the formulation.

3.2. Hierarchy of factors governing acidification

Table 1. Factors governing acidification in PLGA nanoparticles

Factor	Direction of effect	Relative strength	Mechanism
Particle radius	Increases as size increases	High	The diffusion path for the acid becomes longer
Glycolide fraction	Accelerates as fraction increases	High	Glycolide linkages are more susceptible to hydrolysis
End-group type	Free COOH intensifies autocatalysis	Moderate–high	Higher initial acid concentration
Molecular weight	Accelerates as it decreases	Moderate	A larger number of chain ends
Matrix porosity	Diminishes as it increases	Moderate	An escape route opens up for the acid
External-medium buffering	Has little effect on internal pH	Low	The buffer does not reach the interior

Particular attention should be paid to the last row of the table. In many studies the in vitro test is carried out in phosphate buffer, and because the external pH remains stable at 7.4, the formulation is judged to be "stable." In reality, however, the internal environment functions as an independent chemical reactor — this is one of the most common interpretive errors in the field.

3.3. Risk categories of substances by acid sensitivity

High-risk group — proteins and peptides: tertiary structure is lost, and aggregation and deamidation are observed. For such substances, using PLGA without a stabilizing excipient is, in practice, not advisable [14].

Moderate-risk group — small molecules bearing amide, lactone, or complex ester bonds, including certain antibiotics. These undergo partial decomposition, and the degradation products may be toxic.

Low-risk group — acid-resistant hydrophobic substances (many cytostatics, steroids). For these, acidification is not so much a chemical problem as a kinetic one, distorting the release profile.

3.4. The dual effect of alkaline excipients

When an alkaline excipient is incorporated into the matrix, beneficial and harmful consequences arise simultaneously (Figure 2).

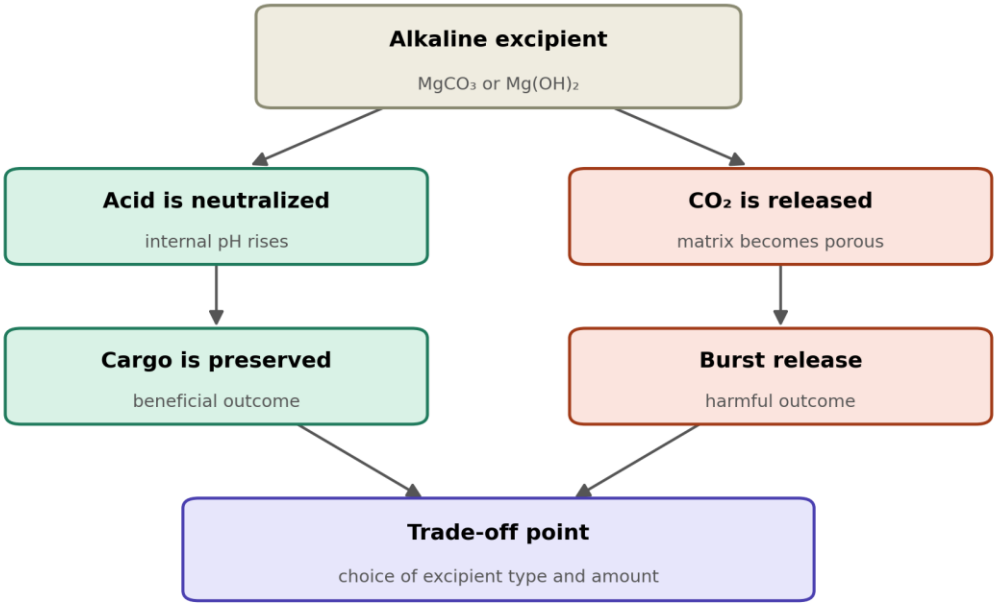

Figure 2. The dual effect of an alkaline excipient within the PLGA matrix (schematic)

Table 2. Comparative characteristics of alkaline excipients

Excipient	pH maintenance	Side effect	Suitable case
$Mg(OH)_2$	High, long-lasting	Releases no gas; low effect on morphology	Protein drugs; long-term systems
$MgCO_3$	High	Releases CO_2; increases porosity and burst release	When faster release is required
$ZnCO_3$	Moderate–high	Zn^{2+} coordinates with certain proteins	Requires caution
Basic phosphate buffers	Moderate; exhausted quickly	Enhances osmotic water uptake	Short-term systems
End-capped PLGA	Moderate; prophylactic	Slows degradation	An adjunct strategy to the excipient

In summary, no single excipient is universal. The choice should not be made according to a "strongest base" principle, but rather based on the risk category of the substance and the required duration of release.

3.5. Methodological heterogeneity

Across the publications reviewed, internal pH was measured by at least four different methods, incubation duration ranged from 3 days to 6 months, temperature ranged from 25–37°C, and the medium varied from distilled water to serum. In most studies internal pH was measured only once, at the final time point, which does not capture the kinetics of autocatalysis.

4. Discussion

The central conclusion of this analysis appears simple, yet its implications are far-reaching: the environment inside a PLGA nanoparticle functions as a chemical system independent of the external medium. Evaluating a formulation solely by external pH and the external release profile therefore leads to a systematic error. Many systems declared "stable" in the literature have been assessed as such only because the internal environment was never measured.

A second important aspect is the unity of acidification and the release profile. Any measure that increases matrix porosity produces two effects at once: the acid escapes to the exterior (beneficial) and

the substance is also released (harmful, if premature). The phenomenon of pore closing and opening described by Kang and Schwendeman is key to this process: matrix morphology is not static but changes throughout degradation. Fredenberg and co-authors likewise noted that the release mechanisms in PLGA systems are closely interrelated [15].

A third aspect is the contradiction inherent in particle size. Smaller particles are less prone to acidification because the diffusion path is shorter; however, because their specific surface area is larger, burst release and aggregation are intensified. In other words, the very decision that improves chemical stability can itself reduce colloidal stability.

A fourth aspect is the alternative route arising from the nature of the polymer itself. As shown in the work of Vokhidova and Rashidova, in polysaccharide-based systems stability is governed by synthesis conditions and stabilizer structure; here, the problem of ester hydrolysis and autocatalysis does not arise. At the same time, pH sensitivity and precipitation in neutral media remain a distinct problem for chitosan systems. Thus, replacing the polymer does not eliminate the stability problem but rather changes its nature.

4.1. Proposed minimal reporting standard

To ensure the comparability of publications, we propose the following mandatory set of indicators:

1) internal pH — measured at no fewer than three time points (baseline, around Phase II, and the endpoint), together with the measurement method and calibration conditions;

2) observation period — covering at least 50% of the full degradation period;

3) substance loss — the released fraction and the fraction remaining in the matrix reported separately, with a mass balance;

4) degradation products — identified at least qualitatively;

5) polymer characterization — lactide/glycolide ratio, Mw, and end-group type mandatorily reported.

4.2. Limitations of the study

This review is largely limited to publications in English; because negative results are rarely published, the stability figures reported in the literature may be more optimistic than the real-world situation; and the absence of a meta-analysis reduces the quantitative weight of the conclusions.

4.3. Directions for future research

Promising directions include: standardizing methods for measuring internal pH in real time and non-destructively; developing predictive mathematical models of autocatalysis kinetics; applying the quantum-chemical approach that Nurgaliyev and Rashidova used for chitosan [1] to PLGA–drug interactions; design-of-experiments (DoE) approaches that jointly optimize excipient and size parameters; and the development of dry, water-free-stored dosage forms.

5. Conclusion

Autocatalytic acidification in PLGA nanoparticles is not an accidental flaw but a consequence that follows logically from the mechanism of polymer degradation. It undermines the chemical stability of the encapsulated substance — proteins and peptides in particular — before it ever reaches the body.

The analysis leads to three main conclusions. First, because the internal environment is independent of the external environment, assessing stability solely on the basis of external pH is a systematic error. Second, alkaline excipients are effective but not universal: each one introduces its own trade-off in matrix morphology and release kinetics. Third, the weakest point in the field is the lack of standardization in internal-pH measurement; the proposed minimal reporting standard may partly resolve this problem.

The overall practical recommendation is this: rather than attempting to eliminate acidification altogether, it is more expedient to treat it as a controllable parameter that is accounted for from the earliest stage of formulation design.

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