Pharmaceutical Sciences 2026;32(4):647-649
doi:10.34172/ps.43672
https://ps.tbzmed.ac.ir

Commentary

Beyond the Fallacy of Overgeneralization: A Perspective on Strategies for Reliable Comparative Studies of Nanocarriers

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Received: December 25, 2025, **Revised:** May 24, 2026, **Accepted:** May 25, 2026, **ePublished:** July 6, 2026

Nanocarriers have been widely applied to improve the delivery of different drugs. Due to the adaptability of the nanocarrier size, charge, and surface modification, they can improve the bioavailability, targeting, or controlled-release of drugs.[1,2]

The importance and frequency of utilization of nanocarriers in drug delivery attract the attention of researchers for the evaluation and optimization of their formulations. Many studies have investigated the optimal components, preparation method, and their ratio. [3,4] Many studies on nanocarriers include a comparison with another nanocarrier as a control to showcase their suitability. However, when such comparative studies are not carefully designed, they can potentially lead to unscientific and misleading generalizations. This paper discusses the fallacy of the unscientific generalization of comparative studies.

Generalization refers to the application of findings from a limited set of observations to broader or novel contexts. [5] It enhances research efficiency by enabling conclusions drawn from smaller samples to be extrapolated to larger populations.[6] Studies usually use laboratory-based or *in silico* models of real-world systems precisely to derive insights that can be applied more broadly. [7] However, comparative studies commonly falls into the fallacy of unscientific generalization, called overgeneralization. Overgeneralization is defined as extending a generalization beyond the scope for which it is valid. When a study demonstrates that a novel nanocarrier formulation has better properties compared to a control nanocarrier, an important question arises: "Wouldn't changing the control nanocarrier formulation reverse the outcome?" This inherent dependency limits the generalizability of the finding. Extending the results to the entire class of the control nanocarrier would constitute overgeneralization, unless the control nanocarrier was chosen with careful justification. For example, a study by Patel et al. has claimed that niosomes are generally better carriers for permeating, in comparison to ethosomes, only after comparing two sets of formulations.[8] Shah et al. prepared a single formulation for each of LeciPlex, invasomes, and liposomes and compared their impact on the penetrability of different loaded drugs; however, they overgeneralized the results to all the LeciPlexes, invasomes, and liposomes.[9] Mennini et al. prepared a single formulation for a nanostructured lipid carrier and liposomes and compared their transdermal delivery and claimed that the results confirmed the significantly better performance of the deformable liposomes than nanostructured lipid carrier in improving the permeation rate of the drug.[10]

The fallacy of overgeneralization can lead to two severe consequences. First, the non-generalizable findings waste the funding and time invested in the comparison. The earlier-mentioned studies, like many others, utilized research grants and valuable time to produce results that cannot meaningfully advance scientific understanding. However, the consequences extend beyond the mere non-usability of the result; they can also adversely affect subsequent studies that rely on the flawed comparison. For example, an entire class of nanocarriers might be wrongly abandoned based on published research that claims it is generally less potent than another, while a different formulation of that same nanocarrier could, in fact, be significantly more potent.

Although comparative studies are susceptible to this fallacy, three key strategies have been undertaken by researchers to overcome the overgeneralization problem. These strategies are classified and discussed as follows. Generalization through these strategies can extend the validation of the results to a wider range of situations.

1. Single distinguishing parameter: Factorial experiments test one variable at a time. [11] This means two samples can be validly compared if they differ solely in the variable of interest. For the same reason, nanocarriers can be compared to each other only if they share the same basal composition, differing in only one key component. Different classes of nanocarriers can be categorized into several types. Some of these share the same formulation, except for one single component. These classes typically have a primary structure, while their subclasses exhibit different modifications or moieties (such as conventional

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and hyaluronic acid-conjugated liposomes), a distinct or new component (like liposomes and porphysomes), or even different preparation methods (like niosomes and proniosomes). These nanocarriers can be compared through the evaluation of the distinguishing factor. As an example, ethosomes and transethosomes are directly comparable. They both contain phospholipids and a mixture of water and ethanol as the solvent. The key parameter distinguishing transethosomes from ethosomes is the presence of surfactants in their formulation. For instance, Ferrara et al. have evaluated ethosomal and transethosomal formulations of quercetin, using the same formulations, the same phosphatidylcholine amount, and the same ethanol concentration, with only the presence of Tween 80 differing. The valid claim and outcome of the research are the effect of Tween 80, in the applied concentration range, on the characteristics of the ethosome formulation. [12] However, this leads to a critical caveat, since transethosomes can have various types of surfactants; overgeneralizing the conclusion of this type of study to "the behavior of all transethosomes is a logical trap. The properties of transethosomes composed of other surfactants, such as sodium cholate and Span 60, are not guaranteed to be the same. In addition, other parameters like the basal ethosome formulation and the surfactant concentration might affect the impact of the surfactant on its properties.[13]

2. Representative formulations: Another option is to employ a control nanocarrier formulation that is widely recognized as a gold standard or representative of its class. Marketed formulation, as successful formulations can be potential representatives of a nanocarrier type. When the ultimate objective is a marketable product, comparing a novel formulation to an already marketed one represents a valid and pragmatic approach. For instance, Nehate et al. prepared doxorubicin-loaded polymersomes and compared the *in vivo* anticancer efficiency of the prepared vesicles with a marketed polymer-modified liposomal formulation (Doxil®).[14] However, using a commercially available formulation introduces a significant limitation. The industrial scale-up process can alter critical quality attributes, such as particle size distribution, and introduce batch-to-batch variability.[15] Therefore, the commercial product is a different entity from a carefully optimized laboratory-scale formulation. Hence, a direct comparison between the two is often inequitable.

3. Property-Specific Generalization: In addition to the previous strategies, which were based on experimental design, mechanistic justification can provide a more acceptable generalization. A comparison can be generalized if its outcome is conclusively tied to a difference in the fundamental characteristics of the two nanocarriers, where this difference is representative of their respective classes. Attia et al. suggested that the better drug dissolution rate from SBA-15, compared to MCM-41, was ascribed to its pore morphology. Since the pore morphology is a property inherent to SBA-15-type materials, the conclusion is generalizable. [16] Back to the Ferrara et al. study as another example, [12] from a mechanistic viewpoint, if the performance change in the presence of Tween 80 was claimed to be caused by a suggested mechanism that can be assumed to apply to a majority of different surfactants that have been applied for transfersomes, then it can be extrapolated that the transfersomes, in a general manner, would exhibit comparable behavior. However, the fundamental flaw in this type of comparison is that these studies often confirm a well-established, inherent property difference between the two nanocarrier classes.

Although these strategies each offer some positive progress in proper study design, all of them have limitations in generalization that should not be overlooked. Considering these limitations and generalization of the comparison results, within the limitations of each strategy, can lead to reliable and scientific generalizations.

In conclusion, comparative studies in nanocarrier development frequently fall into the fallacy of overgeneralization. Three commonly undertaken strategies to validate these generalizations are (1) using a control with a single distinguishing parameter, (2) comparing against marketed formulations, or (3) focusing on property-specific generalization. However, each of these approaches possesses inherent flaws that cannot be overlooked.

Acknowledgements

The author gratefully acknowledges support from Ferdowsi University of Mashhad.

Competing Interest

The author declares no financial or non-financial interest that could have appeared to affect the perspective reported in this paper.

Ethical Approval

Not applicable.

Funding

No funding or grant has been specified for this commentary paper.

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