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Bigel and its Applications in Topical Drug Delivery Systems: A Comprehensive Review

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ABSTRACT :

These hybrid formulations, named bigels, combine the general definitions of an organogel and a hydrogel. In the last few years, bigels have been noticed as advanced drug delivery systems especially suitable for topical applications. Bigels offer some unique advantages over the usual gel formulations because they provide an enhancement in drug release profiles, stability, and bioavailability. A review on critical aspects of bigel systems covering composition, structure, and mechanisms of drug release is presented here. Bigels can encapsulate a wide range of pharmaceutical and cosmetic formulations, including both hydrophilic and lipophilic drugs. The main thrust would be toward using bigels to deliver drugs topically within applications in dermatological treatments involving psoriasis, eczema, and fungal infections. Thus, there is only a controlled rate delivery of APIs combined with stability in various environmental conditions that makes bigels an ideal candidate for sustained-release formulations. Moreover, incorporation of surfactants, stabilizers, and other excipients enhances the performance of bigels. The possibility of bigels being incorporated with other delivery systems, including nanoparticles, liposomes, and micelles, holds great promise for the development of multifunctional drug delivery systems. However, a number of issues remain - formulation stability, issues with patient compliance, and regulatory hurdles that need to be overcome before this potential in pharmaceutical practice can be realized to its fullest. It has focused on very recent advances, formulation strategies, and the future outlook of bigels in the field of topical drug delivery.

Keywords: Bigels, topical drug delivery, controlled release, hydrogels, organogels, pharmaceutical applications, dermatological conditions, formulation stability, sustained release, drug encapsulation, excipients.

Introduction :

Bigels are complex drug delivery systems that will deliver a broad range of drugs, whether small molecules or biologics, through hydrophilic and lipophilic delivery from one formulation. This systematic structure, having hydrogels and organogels, started in the early 2000s with the recognition that these formulations could actually allow for the delivery of drugs through the skin. Since then, truly impressive developments have been reported in their synthesis. New areas of applications in dermatology, wound healing, and cosmetics were ushered into life [1,2].

With the pharmaceutical and personal care industries desiring more efficient and versatile drug delivery systems, development of bigels has been on the rise. Such dual-phase nature assures not only controlled release but also stability and bioavailability of drugs [3,4]. The treatments of chronic skin disorders, burns, and systemic drug delivery through transdermal administration are among the current applications of bigels. They are now ready to be incorporated into modern drug delivery systems, revolutionizing the way people are being treated topically because this will be shown in improving compliance by the patient and enhanced therapeutic results [5, 6].

As beneficial the bigels are, formulation and stability are still the challenges. Phase separation, solubility of active ingredients, and rheological properties need to be optimized as well so that the final product is effective. Despite these challenges, the versatility of bigels makes the subject particularly interesting to researchers and pharmaceutical companies alike [7,8].

2. Composition and Structure of Bigels

These are further categorized into two different phases: the hydrogel phase and organogel phase. The hydrogel phase usually comprises water-soluble polymers, such as carbomers, gellan, or xanthan gum. Organogel is prepared using a mixture of oils and lipophilic gelators, such as sorbitan monostearate or stearic acid [9,10]. The combination of the two phases produces a matrix that can steadily retain both hydrophilic and lipophilic drugs, which exhibit dual-mode drug release.

The choice of gelator dictates the mechanical properties, viscosity, and stability of the bigel system. Hydrophilic gelators allow for a gel to hold water, as in the case of carbomers and polyvinyl alcohol, while lipophilic gelators allow for the enhancement of the oil phase. Surfactants often aid in improving compatibility between two phases and thus ensures that the bigel is stable with minimal phase separation [11,12].

A major challenge in the preparation of bigels is that they have to consist of uniform and stable structures. Phase separation of the hydrophilic and lipophilic phases caused by interaction between them can adversely affect the performance. The stabilization of the bigel would be possible preventing

this interaction by the use of a surfactant for example, polysorbate 80 or lecithin. The addition of co-gelators would be helpful to increase the structural stability [13, 14].

3. Mechanisms of Drug Release from Bigels

The major mechanism of drug release in bigels is found to be mainly due to diffusion, partitioning, and swelling. Hydrogel acts as the main route of diffusion for hydrophilic drugs, while the primary route of lipophilic compounds involves the organogel phase. Intermolecular drug interactions with the gel matrix, along with drug solubility, alter the rate of drug release, and the viscosity of the gel.

Generally, drugs released from bigels provide a pattern for controlled release that lasts for a relatively long duration because the mechanism of releasing the drug from the gel matrix can be sustained over time. Temperature, pH, and ionic strength have also been shown to influence drug release rates from bigels [15,16]. For example, gel viscosity decreases with the increase in temperature; hence, drug release rates increase.

It has emphasized the impact that different formulation parameters have on the drug release profile. The drugs, if they are lipophilic, are seen to be incorporated into the organogel phase in general with slower release rates than hydrophilic drugs in the hydrogel phase. For some applications-bigels with optimally tuned release characteristics have been developed, such as for wound healing or transdermal drug delivery [17,18].

4. Applications of Bigels in Topical Drug Delivery

Bigels have been developed into a wide-range application field, mainly in the fields of dermatology and wound healing. Due to the fact that bigel systems are capable of delivering hydrophilic as well as lipophilic drugs from one formulation, they are highly recommended for chronic skin conditions, including psoriasis, eczema, and acne [19,20]. Moreover, bigels have also found increased usage in the treatment of acute wounds, burns, and ulcers, wherein controlled release of therapeutic agents improves healing and reduces infections.

Bigels are being investigated for their use in dermatology as delivery systems for corticosteroids, antifungals, and antibiotics. Thus, in this regard, bigels are allowing for localized treatment with a minimal amount of systemic absorption of therapeutic drugs. A bigel formulation with hydrocortisone and clotrimazole further indicated an enormous potential in the treatment of fungal infections when it manifested therapeutic efficacy with anti-inflammatory benefits [21, 22]. Similarly, ibuprofen loaded bigels have been investigated for their topical anti-inflammatory and analgesic applications with promising results compared with the conventional creams and gels [23,24].

Cosmetics form: Bigels have also proven to be useful in cosmetic formulations, serving as delivery systems for active ingredients such as antioxidants, moisturizers, or anti-aging agents. Bigels offer tremendous versatility toward developing multi-tasking products that can address several skin-related issues simultaneously. For example, a bigel formulation with vitamin C and hyaluronic acid has been shown to enhance skin hydration with considerable potential to act as an anti-wrinkle and anti-line formulation [25,26].

5. Challenges in Formulation and Stability of Bigels

Although the bigels have many advantages, their preparation and formulation process is complex and usually contains significant technical challenges. The stability of the dual-phase system may be one of the key concerns. Phase separation can take place in an unfavorable interaction between hydrophilic and lipophilic components, which eventually causes loss of efficacy. This can be avoided by ensuring that the gelator and surfactant ratios are precise, while the formulation is adequately stability tested under different environmental conditions, which can range from temperature variations to pH changes [27, 28].

Another problem of bigel preparation is solubility of active pharmaceutical ingredients. Some drugs do not dissolve well in aqueous or oily phase, thus the loading efficiency would be poor. For better solubility, co-solvents could be applied or the formulation would be adjusted accordingly [29,30]. Viscosity of the gel is also very important in the release profile of the drug. It can slow down release if it is highly viscous, and vice versa, low viscosity may lead even to not being retained enough by the drug.

In addition, shelf life is lost through microbial contamination, especially when the formulation is for application on compromised skin or open wounds. Thus, preservation systems and antimicrobial agents must be included in bigels in order that their application safety and efficacy can be ensured over time [31,32].

6. Physicochemical Properties of Bigels

The physicochemical properties of bigels-viscosity, pH, solubility, and mechanical properties- control the efficiency in drug delivery applications. The extension of the spreading properties makes them critical in the development of bigel-based systems for topical application, which should provide uniform release of the drug onto the skin surface. A more viscous formulation will adhere better to the skin; therefore, the contact time is prolonged with sustained release of the active ingredient [33]. High viscosity may make the product become too thick for application or even irritating to use, hence putting a limit on its acceptability for continuous usage.

One other important factor concerning stability is that of the bigel's pH. The pH can impact both the formulation as well as the drug itself, in regards to stability. Most drugs are pH-dependent and should be kept within an appropriate pH range for therapeutic integrity and activity. This pH shift could affect the solubility as well as the release rate of the drug and may lead to degradation or even suboptimal performance [34,35]. Thus, usually, bigel formulations encompass pH control in the system to ensure stability of the active pharmaceutical ingredient over the shelf life.

Another critical physicochemical parameter of bigel formulations is drug solubility. Drugs must be solubilized in the hydrogel or organogel phase of the bigel for being effectively delivered through the skin. The poor solubility results in grave limitations to the bioavailability of the drug; co-solvents or solubilizing agents are used sometimes to improve drug solubility and thus ensure better release profiles [36].

Different physicochemical properties of the bigels can be characterized using various techniques, which range from rheological measurements to DSC, SEM. The former would give the structure of the gel with regard to the drug distribution and morphology of the formulation. It optimizes the drug release profile and makes sure of the overall stability and safety of the bigel formulation [37].

7. Bigels in Combination with Other Drug Delivery Systems

There are also bigels that might be combined with other advanced drug delivery systems. Perhaps one of the most important combinations is association with liposomes, which are spherical vesicles that may encapsulate both hydrophilic and lipophilic drugs. When the liposomes combine with bigel, this system benefits from both sustaining release properties of the bigel matrix and from enhanced penetration capabilities of liposomes [38].

Bigels were combined with microemulsions-a thermodynamically stable mix of oil, water, and surfactants. Microemulsions have an ability to solubilize poor water-solubility drugs, which then improves the bioavailability of the drugs. The combination of bigels with microemulsions provides a peculiar delivery system that can handle a wide range of drugs having different solubility profiles [39]. This combination can offer targeted, sustained, and controlled release that enhances the therapeutic effect.

Another possible combination is bigels with SLNs. SLNs are nanosized solid lipid particles produced from solid lipids. They have been successful as drug carriers for drugs exhibiting lipophilic behavior. If SLNs are manufactured in combination with bigels, then the stability and bioavailability of lipophilic drugs can be significantly improved, with an added advantage of bigel's dual phase delivery mechanism [40]. This type of hybrid system does promise augmented topical drug delivery especially in chronic diseases and local skin diseases.

8. Patient-Centric Considerations in Topical Drug Delivery with Bigels

Acceptability of the patient is one of the most significant factors ruling the success of a topical drug delivery system. In this regard, bigels have several advantages; it is easy to apply, has no greasiness, and appears transparent, qualities that are appealing to patients. The nongreasy finish and smooth feel after application of bigels attract them more than traditional ointments, which are perceived as oily and uncomfortable in nature [41]. On the other hand, cosmetics usage as well as dermatological purposes have become increased because the formulation with bigels has been under a clear or transparent form, thus enhancing cosmetic values [42].

Comfort in the long term is another important issue concerning the acceptability of a patient to a formulation. Bigels are less greasy and more readily absorbed than traditional ointments, meaning irritation or discomfort from skin adhesions is less likely to arise for topical systems that may have the potential to relate problems with other systems of topical usage. This makes the feature particularly important in chronic diseases or conditions that require long-term treatment such as psoriasis, eczema, or acne, where patient compliance is critical [43].

Additionally, staining of clothing or bedding is one of the concerns about the patient. Because bigels are translucent and non-greasy, they will not stain more than ointment or creams and are hence more acceptable. Of utmost importance is ease of removal coupled with layering of a thin layer over the affected area with no mess and residue benefiting the patient's convenience and comfort [44].

9. Comparative Analysis of Bigels with Other Drug Delivery Systems

Bigels have been compared to emulsions, liposomes, microemulsions, as well as transdermal patches in order to outline their advantages and disadvantages. Unlike conventional emulsions that have a water phase and an oil phase, bigels establish a more stable and homogenous matrix that improves the controlled release of drugs within more time [45]. Though emulsions are generally susceptible to the effects of phase separation and instability, bigels are not due to their novel two-phase structure, supporting the longer stability of the formulation [46].

While bigels have a higher mechanical stability and are more easily formulated as compared to other popular carriers, such as liposomes and microemulsions, the latter has seen much popularity based on their ability to carry hydrophilic and lipophilic drugs. Liposomes and microemulsions suffer from instability, handling issues, and high formulation costs despite their efficiency in drug delivery. Bigels prove to be of greater practical use for a lot of topical applications due to their more simple composition and high stability [47].

Another delivery alternative of great importance is the transdermal patch, which also has its own set of challenges, like lower drug loading capacity and dependency on specifically formulated materials for facilitation of skin penetration. Although there are several advantages to delivering drugs through transdermal patches in controlled release for long periods, bigels are more flexible than patches with a very wide range of drugs that can be delivered without the need to use specific skin penetration enhancers [48]. Hence, bigels have many advantages pertaining to ease of application, comfort for the patient, and flexibility in formulation.

10. Economic Considerations and Market Trends for Bigels

Bigels are likely to weigh in the economic considerations with the growing need for drug delivery systems that are effective and patient-friendly. Bigels are, relatively speaking, a cost-effective alternative to more complex drug delivery systems such as liposomes and microemulsions, whose formulation does not require expensive raw materials and complicated manufacturing processes [49]. Moreover, the ready production and scalable nature of bigels make them a product that could appeal to pharmaceutical companies looking to reduce their costs without compromising efficacy [50].

For example, there is an expansion potential in the market for bigel-based products due to the developments taking place in drug formulation technology and rising need for efficient topical formulations. In contrast, the use of bigels also increases in the therapy of chronic skin diseases, for selected pain applications, and in wound management. All that would be helpful to bring prices down and thus bigel-based products to more people: cutting costs involved in production, such as finding cheap gelators or scaling up production [51].

There is also a trend toward combination products, which administer several drugs simultaneously. Bigels can accommodate both hydrophilic as well as lipophilic drugs; thus bigels are well suited for combination therapies that attempt to treat multiple symptoms or conditions under one stroke [52].

11. Environmental Impact of Bigels and Sustainability

The growth in emphasis on sustainability in pharmaceutical product development is also highlighting attention to the environmental impact of bigels. For instance, synthetic polymers and non-biodegradable surfactants used in some bigels have a potential contribution toward environmental pollution. However, lately, it has become the focus of many studies on developing eco-friendly bigels based on biodegradable and renewable sources [53].

These developments involve more recent studies on natural polymers like chitosan or alginate as biodegradable surfactants added to make bigels more environmentally friendly. Bigel formulations can be designed more with plant-based gelators, while the functional properties for drug delivery are maintained [54]. In other words, such key discoveries represent a significant milestone in finding ways to create much more sustainable pharmaceutical formulations that reduce their ecological footprint significantly.

Another approach is through energy savings in the production process of the product. Formulation optimization and implementation of a more energy-effective production process may allow for energy saving and waste minimization; thereby it is a greener product manufacturing process [55].

12. Future Trends and Innovations in Bigel Formulations

Bigels have exciting futures in drug delivery systems, with many innovations along the way. Researchers focus on novel materials that are advanced materials, such as nanomaterials and stimulus responsive systems, for improving functionality of bigels. Nanoparticles of solid lipid nanoparticles and dendrimers can be encapsulated in bigels to enhance drug solubility, stability, and bioavailability [56]. These nanomaterials could significantly improve drug delivery and enhance therapeutic efficacy of bigels.

Another interesting breakthrough is stimuli-responsive bigels, wherein the drugs elute in response to some external stimuli, such as temperature, pH, or light. This would ensure that the drug reaches the target location only when required. Hence, such systems could have a significant potential for personalized medicine and improved patient outcomes [57].

13. Conclusion

Bigels are an innovative promising drug delivery system, which may revolutionize the topical treatments of many diseases. Its structure is unique because it bears the properties of both gels and emulsions: it retains the ability of self-emulsifying in situ and yet allows controlled release of a drug and stability. When used in combination with advanced drug delivery systems, bigels provide improved therapeutic benefits in skin-related diseases as well.

The increased focus on patient-centric care, along with the improvements in the stability, physicochemical properties, and sustainability of bigels, are more likely to continue dictating the pathway of the evolution of this delivery system. Further breakthroughs in the formulation and combination of bigels with other systems will make them even more vital for the delivery of personalized and targeted medicine.

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