REVIEW ARTICLE

# Unlocking Dithranol's Potential: Advanced Drug Delivery Systems for Improved Pharmacokinetics

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## ABSTRACT

Dithranol is a therapeutic agent mainly used for psoriasis; however, its clinical use is limited by poor stability, skin irritation, and low patient compliance with conventional formulations. This paper reviews the various advanced drug delivery systems that have been formulated to bypass the above limitations and improve the pharmacokinetics of dithranol. In this context, we describe the problems of the current formulations, which are the instability of the drug and adverse reactions to the skin. Further, we present the advantages of advanced delivery systems, including nanoparticles, nanosuspensions, liposomes, niosomes, solid lipid nanoparticles and nanostructured lipid carriers, for drug stabilization and delivery to target tissues. We elaborate on the working of polymeric systems, including hydrogels, microparticles, micelles, and prodrugs, with which drug solubility is improved and drug release is sustained. Finally, through *in-vitro* and *in-vivo* studies and clinical procedures, details are given regarding the drug release kinetics, pharmacokinetics, and biodistribution of such formulations. The text elaborates on future directions and new technological approaches toward the delivery of dithranol. These advanced delivery systems will help to overcome the limitations of the existing formulations and achieve a higher therapeutic impact of the drug on psoriasis and other skin diseases.

**Keywords:** Dithranol, Advanced drug delivery, Nanotechnology, Pharmacokinetics, Psoriasis treatment.

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## INTRODUCTION

Psoriasis, a chronic immune-mediated disease impacting millions of individuals around the globe, poses a significant issue in dermatological management.[1] Although there are several treatment options for the disease, dithranol or anthralin has emerged as a cornerstone in psoriasis treatment following its introduction to medical practice in the twentieth century. Anthralin's efficacy in suppressing the overactive activity of keratinocytes in psoriatic plaques has allowed it to become a backbone therapy. Nevertheless, anthralin's use is hindered by several pharmacokinetic barriers associated with its clinical use in conventional formulations despite its efficacy.[2]

The journey of dithranol in the domain of dermatology is one filled with therapeutic potential and steadfast obstacles. Although its principle of generating reactive oxygen species that impair keratinocyte multiplication primed its use not only for psoriasis but also for other skin pathologies, such as for example chronic eczema and alopecia areata, it is precisely this mechanism that results in its distinctive disadvantages, i.e., skin-related irritation and discoloration, as well as reduced stability.[3] When combined with the various demerits associated with conventional pharmaceutical compositions, as well as the lengthy time of application, patient compliance and therapy effectiveness become an especially problematic venture.[4]

The search for ways to maximize therapeutic outcomes has led researchers to hope for a solution by creating advanced drug delivery systems. To date, attempts have been made to overcome the problems of traditional dithranol-based formulations by making them more stable, reducing the incidence of side effects and improving their delivery. Such innovations allow for a radical change in the treatment paradigm for psoriasis and related pathologies.[5]

Finally, this review took you on a journey through the pharmacokinetic maze of dithranol (Figure 1), mapping its enormous therapeutic opportunity while skillfully dealing with the roadblocks to its clinical translation.[6] From the perspective of endeavor and exploration, we have uncovered the potential of novel drug delivery platforms in releasing dithranol's entire therapeutic potential, with the highest aspiration being the endowment of newer adjuvant-bearing and unencumbered

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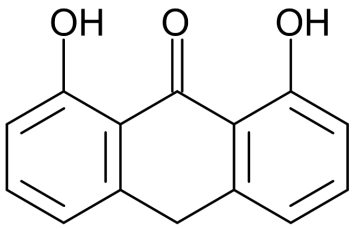


**Figure 1:** Chemical structure of dithranol

patients for improved outcomes and a better quality of life in the treatment of dermatological conditions.

## Limitations of Conventional Formulations

*Stability issues*

A significant limitation of conventional dithranol formulations is their low stability. Dithranol is especially prone to oxidation and photodegradation, which may cause the degradation of the drug at a fast rate, impacting the drug's therapeutic impact. Air, light, and moisture exacerbate these degradation processes.[7] The instability of dithranol products is one of the reasons for the need for special storage conditions, including protection from light in opaque containers or refrigeration. These factors significantly increase the costs and administrative burden of medications and contribute to the lower patient adherence rate due to the limited shelf life.[8]

*Skin irritation and staining*

Dithranol causes severe skin irritation, given its activity is dependent on the generation of reactive oxygen species. Patients often develop erythema, scaling, itching, and even blistering upon prolonged exposure.[9] The patient experiences intense discomfort and decreased willingness to continue with the treatment. Apart from these, dithranol is particularly famous for its staining extravaganza. Dithranol readily stains everything it comes into contact with the skin, including the skin, hair, clothing, and bedding, deep purple or brown. The staining is not only unsightly, but it is a significant barrier to preventing patient adherence, given that it can become socially and personally inconvenient. The dye may not disappear for days or even weeks after cessation of dithranol (Table 1).[10]

*Poor patient compliance*

On the other end, the stability applies together with the irritation of the cumbersome application process used with conventional dithranol formulations.[11] Typically, they are available in creams, ointments, or pastes, and although they are simple to apply, the formulations are associated with high deposition on clothes, oozing from the lesion after application and other cases that irritate the skin. The treatment has to be applied with an occlusive dressing and periodically or overnight. The invasive mechanism of treatment is unusual, as it can be contraindicated, and the skin stability appears to pose additional problems.[12] The time of application can also vary, with a patient being required to adhere overnight, thus making it difficult to work. Moreover, it is greasy and, sticky and uncomfortable to the skin, therefore causing reduced effectiveness.

## Advanced Drug Delivery Systems

*Nanotechnology approaches*

Nanotechnology is a new conception in drug delivery that allows novel approaches to improving the pharmacokinetics and bioavailability of dithranol.[14] The ability to modify materials at the nanoscale level allows the creation of delivery systems that enhance drug stability and control release patterns for more efficient tissue targeting. Nanoparticle-based drug delivery systems may alleviate the drawbacks of current formulations, including better penetration, prolonged release times, and decreased side effects.[15]

*Nanoparticles and nanosuspensions: Benefits and preparation*

Nanoparticles are particles of size less than one micron that are able to trap the drug submicron dithranol particles in them and, save it from degradation and enhance its stability.[16] Nanosuspensions are submicron-colloidal drug dispersions that aid in solubility and bioavailability. Some of the techniques include high-pressure homogenization and, solvent evaporation, and nanoprecipitation. Nanoparticles have the ability to pass through the skin, enabling local delivery of the drug to the site, with fewer systemic side effects and improved bioavailability.[17]

**Table 1:** Comparison of conventional dithranol formulations and their limitations[13]

| *Formulation* | *Stability* | *Skin irritation* | *Staining* | *Patient compliance* | *Ease of use* | *Application frequency* |
|---|---|---|---|---|---|---|
| Creams | Moderate, requires preservatives | High, frequent erythema and scaling | High, significant staining | Low, difficult to apply and maintain | Low, requires careful handling | High, multiple applications needed |
| Ointments | Better stability, greasy base | Moderate to high, less than creams | Moderate to high | Moderate, messy application | Moderate, greasy texture | Moderate, fewer applications needed |
| Pastes | Higher stability, thicker base | High, due to prolonged contact | High, difficult to remove | Low, very cumbersome to use | Very low, thick and sticky texture | Low, prolonged application required |
| Gels | Lower stability, alcohol-based | Moderate, less occlusive | Moderate | Moderate, easier to spread | High, non-greasy and easy to apply | Moderate, may require reapplication |
| Foams | Low stability, aerosol-based | Low to moderate, better spreadability | Low to moderate | High, comfortable and quick to use | Very high, non-greasy and fast drying | High, frequent due to low stability |

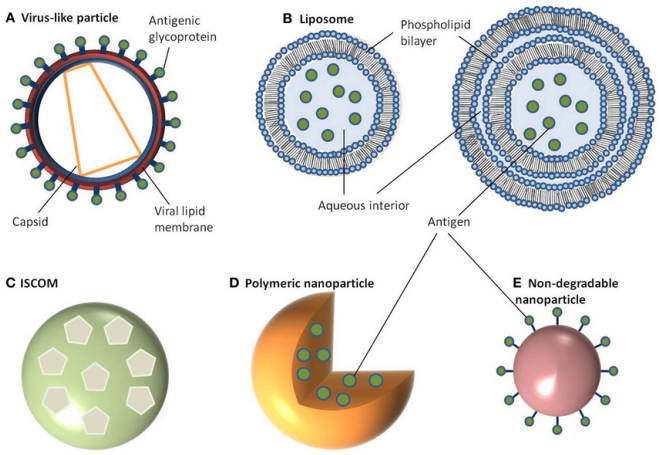


**Figure 2:** Schematic representation of nanoparticle-based delivery systems

Nanoparticles have several merits, which include increased stability against oxidation and photodegradation, improved solubility and bioavailability, delivery to the affected skin regions, sustained and controlled release of dithranol, and a decline in skin irritation and systemic side effects.[18] Preparation methods are high-pressure homogenization, which generates nanoparticles by pressurizing the drug and carrier through a thin gap under high pressure, and solvent evaporation, which is when dithranol is dissolved in a volatile organic solvent and evaporates to leave nanoparticles. Finally, nanoprecipitation will include dissolving dithranol in a solvent before precipitating in a non-solvent, forming nanoparticles (Figure 2).[19]

*Lipid-based formulations*

Liposomes, niosomes, SLNs, and NLCs. Another approach to enhancing dithranol solubility and stability is through lipid-based formulations that have been developed for similar purposes, and the main types include liposomes, niosomes, SLNs, and NCLs.[20]

*Liposomes, niosomes, SLNs, and NLCs: Advantages in stability and delivery*

Liposomes are spherical vesicles with a phospholipid bilayer that allows the encapsulation of drugs, including dithranol, which is protected from degradation and degradation.[21] This method also provides controlled release in the application of liposomal dithranol and enhances penetration through the SC due to biocompatibility. Niosomes, as well as liposomes, are vesicles; however, they differ in that the former are made from non-ionic surfactants and are related to a more stable dosage within the drug.[22] Other differences include lower costs and the ease to scale production of niosomes. SLNs are nanoparticulate lipid carriers composed of solid lipids that form a stable matrix and protect dithranol from degradation. In this case, the release is controlled and contains significant potential. NLCs are complex and contain solid and liquid lipids with a flexible and efficient lipid-based drug delivery system with substantially improved loading and release potentials.[23] All four of these types have several advantages (Table 2), such as stability and protection from degradation, solubility and bioavailability, controlled and sustained release, reduced irritation and staining, and increased patient compliance due to less frequent applications. Finally, the main disadvantages of these methods include complex production in the case of some products, leakage and burst release as the main risks, and high costs due to the high price of liposomal and NLC compounds.[24]

*Polymeric systems and prodrugs*

creative ways to enhance dithranol solubility and release in the contemporary literature, polymeric systems and prodrug methods have been discussed as intriguing possibilities.[26] These systems involve the use of biocompatible polymers to generate matrices capable of surrounding the drug. Then, the matrix slowly degrades, releasing the drug in a controlled release cycle.[27]

*Hydrogels, microparticles, polymeric micelles, and prodrugs: Improved solubility and release*

Hydrogels, microparticles, polymeric micelles, and prodrugs: ways to implement in clinical practice and the mechanism of action Hydrogels are three-dimensional polymer frameworks that can swell in the water and slowly release dithranol.[28] This kind of dispersion ensures a humid environment on the skin surface, increasing the penetration of the drug and decreasing the levels of irritation. Also, the hydrogels are more moisture-enhancing drags that release polymers that react to the signal, such as pH and temperature.[29] Microparticles are small particles capable of encased dithranol, protecting it from demolition and controlled release. The core of size-related microparticles will allow for more abundant drug insertion and release during a specific period, saving many instances of applying the drug to the skin surface.[30] Polymeric micelles are colloidal dispersions that self-merge with the help of amphiphilic block copolymers (Figure 3). It is designed for developing the solubility of hydrophobic holders with a controlled output that increases the stability of action dithranol and targets its output to the skin.[31] Prodrugs are alternated versions of dithranol shaped to rise its

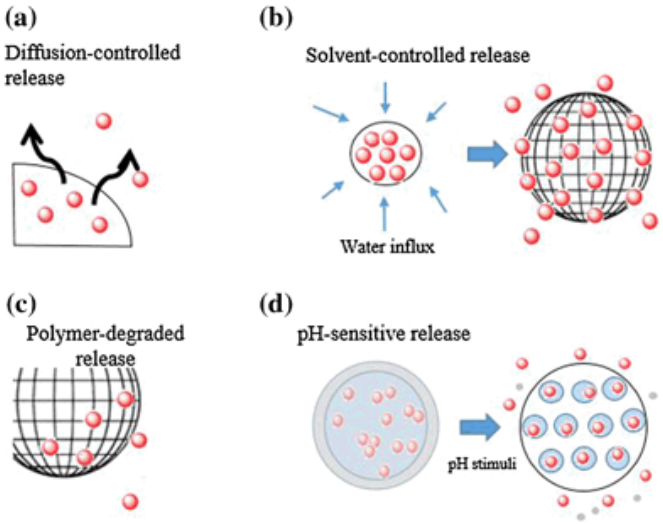


**Figure 3:** Mechanism of drug release from polymeric systems[33]

**Table 2:** Advantages and disadvantages of lipid-based formulations[25]

| *Formulation* | *Advantages* | *Disadvantages* |
|---|---|---|
| Liposomes | High biocompatibility, controlled release, enhanced penetration | High production cost, stability issues |
| Niosomes | Cost-effective, improved stability, easy to scale up | Limited loading capacity, stability issues |
| SLNs | Enhanced stability, controlled release, simple production | Limited drug loading, potential for burst release |
| NLCs | High loading capacity, controlled release, enhanced stability | Complex production, potential for gelation |
| Microemulsions | High solubilization capacity, easy to prepare, enhanced penetration | Potential for skin irritation, instability on storage |
| Lipid Nanocapsules | High stability, protection from degradation, controlled release | Complex production, potential scalability issues |

**Table 3:** Summary of clinical trial results for advanced dithranol formulations[42]

| *Formulation* | *Study phase* | *Efficacy* | *Safety* | *Patient compliance* |
|---|---|---|---|---|
| Nanoparticle suspension | Phase II | Significant reduction in lesion size and severity | Mild irritation, no severe adverse events | High, due to ease of application |
| Liposomal gel | Phase III | Improved skin penetration, faster healing | Moderate irritation, manageable | Moderate, slightly inconvenient application |
| SLN cream | Phase II | Sustained release, consistent improvement | Low irritation, well tolerated | High, convenient application |
| Hydrogel | Phase III | Excellent moisturizing effect, enhanced delivery | Minimal irritation, high safety profile | Very high, comfortable and easy to use |
| Prodrug formulation | Phase I | Improved stability, initial efficacy promising | Initial safety profile good, no major issues | High, straightforward application |

stability and solubility. After the subject of dissuasion, they hydrolyzed in order to speed up the activity of the cure. These uses make dithranol more pharmacokinetic, lessen the rate of demotion and irascibility and make the drug more beneficial.[32]

### Evaluation of Advanced Systems

*In-vitro and in-vivo studies*

*In-vitro* and *in-vivo* studies are essential to assess the efficacy of advanced systems. These studies generate data on drug release kinetics, pharmacokinetics, and biodistributions needed to assess the performance of the new formulations.[34]

### Drug Release Profiles, Pharmacokinetics, and Biodistribution

On average, *in-vitro* studies are performed using different dissolution media and conditions that mimic the skin environment.[35] As a result, it is possible to measure the release rate of dithranol from the delivery system and its release kinetics can be zero-order, first-order, Higuchi release, and others.[36] *In-vivo* studies, which use animals as a model of the experiment, are important to determine the pharmacokinetics of dithranol, including absorption, distribution, metabolism, and excretion. Furthermore, it is possible to evaluate biodistribution to guarantee dithranol effectively makes it to the target site, thus preventing systemic exposure and consequent potential side effects.[37]

### Clinical Trials

Clinical trials, as seen in this project, they are crucial when translating the outcomes acquired from *in-vitro* and *in-vivo* studies into actual clinical scenarios. Clinical trials verify the effectiveness, risk levels, and patient adherence of advanced dithranol formulations when conducted on humans (Table 3).[38]

### Efficacy, Safety, and Patient Compliance

Advanced dithranol formulations will undergo all the stages of clinical trials from phase I to III: Phase I trials of small scale will identify safety and tolerability, which is a critical indicator.[39] Phase II and III will involve bigger populations and will evaluate the efficacy and further safety and will mostly be reflected in clinical endpoints such as a decrease in psoriasis severity and skin lesions and the success of the entire treatment. Safety monitoring will include adverse events, skin irritation, and potential systemic effects.[40] Patient compliance with recommendations is another crucial aspect, as the new compounds should naturally be more user-friendly. It means that they should cut the time and effort required to apply them regularly and make the lives of the psoriasis-suffering patients more comfortable.[41]

### Future Perspectives and Conclusion

*Emerging technologies and future research directions*

In conclusion, the field of drug delivery is constantly developing to enhance the pharmacokinetics and therapeutic efficacy of drugs such as dithranol.[43] New technologies, including smart drug delivery systems, are being developed to release the drug precisely at the required size and time, which is expected to revolutionize dithranol therapy. [44] Furthermore, advancements in bioengineering and materials science enable the manufacturing of more sophisticated delivery systems, such as dendrimers, nanofibers, and transdermal patches, allowing

controlled, sustained, and targeted release of dithranol.[45] Future research may involve utilizing environmentally-triggered smart delivery systems that release the dithranol only under the appropriate input and co-localized chemotherapy.[46] Genetic studies employing gene therapy and CRISPR may dramatically reduce psoriasis recurrence by enhancing skin cell response and regeneration.[47] Personalized medicine may guarantee optimized therapeutic results with minimal side effects using individualized patient profiles. Combination therapies of dithranol and other drugs may also allow for improved efficacy and expanded therapy areas.[48]

### Summary of Key Points and Potential Impact on Dithranol Therapy

To conclude, conventional dithranol formulations are associated with several limitations, such as poor stability, skin irritation, and patient non-compliance.[49] In contrast, advanced drug delivery systems, including nanoparticles, lipid-based formulations, and polymeric systems, can offer substantial advantages, particularly in terms of system stability, controlled drug release, and patient-friendliness.[50] *In-vitro* and *in-vivo* evidence, as well as clinical data, has proven the ability of these formulations to have a beneficial effect on the pharmacokinetics and therapeutic efficacy of dithranol.[51] It may be possible that with the further advancement and implementation of these delivery approaches in clinical practice, dithranol may be revived as a favorable, efficient, and acceptable option for people with psoriasis or other skin conditions.[52] Patient-centered form of therapy will help achieve the desired therapeutic outcomes because of improved patient compliance, reduced administration issues, and decreased adverse effects.[53]

## CONCLUSION

The future evolution of advanced drug delivery systems has the potential to transform dithranol therapy due to the fact that most limitations of traditional formulations will be overcome. Instability, skin tolerability issues, and low patient compliance frequency have always been the key factors that undermine the therapy's effectiveness. Nanotechnology and lipid-based and polymeric formulations are among the most promising drug delivery systems. They offer increased stability and release control and improved dithranol bioavailability, which will likely reduce the treatment's side effects and enhance its patient-friendliness.

Nanosuspensions as well as nanoparticles and nanoparticle-based systems, protect dithranol from processing in the body and significantly improve drug targeting while reducing systemic exposure. Lipid-based formulations, including liposomes, niosomes, and particles such as solid lipid nanoparticles and nanostructured lipid carriers, significantly facilitate the solubility and stability of dithranol, thus ensuring continuous processing. Polymeric systems, including hydrogels, microparticles, and polymeric micelles, allow for additional improvements in solubility and drug processing. Prodrug strategies enhance the delivery of dithranol while providing efficient drug distribution.

The above *in-vitro* and *in-vivo* studies and clinical trials elucidate the high efficacy and safety of refined drug delivery systems. Their pharmacokinetics and patient-oriented outcomes were significantly improved. Therefore, new technologies provide a promising future for dithranol therapy. Moreover, the effectiveness and patient compliance can be further improved by emerging technologies such as smart delivery devices, personalized medicine, and combinative therapy.

In conclusion, the integration of advanced DDS into clinical practice has the potential to transform the approach to psoriasis and other dermatologic conditions. The trickle-down effect of more stable, potent, and patient-friendly therapy can be well received through significantly improved outcomes. Considering that dithranol therapy still has a long way to go in terms of evidence, it may soon become the frontline treatment option, offering hope to both patients and prescribers.

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