

Review of Ointment Formulations in Modern Pharmaceutics

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Abstract

Ointment formulations refer to semisolid topical formulations of a certain consistency made by homogeneous mixing of the drug with a suitable base. Ointments made with an emulsion type base are called creams. Ointment agents since the aspects of liquid formulations mainly protect wounds, lubricate the skin and local treatment, etc., some drugs can have a local onset of action after transdermal absorption and can also produce systemic therapeutic effects. Therefore, ointment formulations have attracted much attention for their advantages of convenient use, stable properties, good dissolution properties, and are also one of the important directions in modern pharmaceutics research.

Keywords

Ointment; Pharmaceutics; Research Progress.

1. Introduction

Ointment formulations refer to a semisolid topical formulation made of a drug with an appropriate base that is applied to the skin, mucous membranes, or wounds. Ointments mainly play protective, lubricating, and topical therapeutic roles, and some drugs can also produce systemic therapeutic effects after transdermal absorption [1]. Ointment formulations have the characteristics of maintaining stable and long-lasting blood concentration, being safe and reliable, rapid in efficacy, convenient in administration, and easy to be popularized.

2. The Classification of Ointment Base

The base, which acts as an excipient for ointments and accounts for the vast majority of ointment composition, confers a certain physicochemical profile to the ointment and plays an important role for both its quality and drug efficacy. There are 3 categories of commonly used ointment bases: oily, emulsion type, and water-soluble.

The performance of ointment bases depends on the formulation choice, and commonly used water-soluble base include Carbomer, polyethylene glycol (PEG), etc. Emulsion type base can make drug easy transdermal absorption, and emulsion type base is further divided into W/O type, O/W type, W/O/W and so on, O/W type is more conducive to transdermal absorption [2]. Qiyuan Jing [6] determined the in vitro transdermal drug release rate of Tabazol and hydrocortisone from various ointments with different base, different main drug concentrations, and different permeation enhancers, and concluded that O/W type base was also found to be more favorable for the percutaneous permeation of Tabazol and hydrocortisone than W/O type base.

The inability of two mutually insoluble pure liquids to form a more stable emulsion necessitates that another emulsifier ingredient (surfactant) be added to play a stabilizing role [10]. The application of surfactants in ointments is more mature. In ointments of types O/W and W/O mainly as emulsifiers. At the same time, it can increase the water absorption, washability of the base. I.e. promoting drug dispersion but also drug penetration [3].

Oily base have good skin sealing properties, easily promote skin hydration, are able to protect and soften the skin, but affect the release penetration of drugs and are not suitable for skin diseases with exudates. Commonly used oily ointment base materials are petrolatum, liquid paraffin, lanoline, vegetable oils, etc., and petrolatum is the most commonly used.

3. Principles of Selection of Substrates

3.1. Effect of Base on Drug Transdermal Release

Transdermal drug delivery system is the main mode of administration of ointment agents, which can make the drug continuously diffuse through the skin, permeate, enter the blood circulation after absorption, maintain the blood concentration stable for a long time, avoid the liver and gastrointestinal tract enzymolysis of the drug, reduce the frequency of administration, reduce individual differences in absorption and metabolism, and improve the bioavailability of the drug [4]. In the use of base ointments for the treatment of skin, surface absorption by the skin is related to skin permeability, skin hydration degree, contact time, skin temperature, epidermal damage, skin acid base, as well as drug saturation [5]. Therefore, the transdermal permeation method is an *in vitro* assay for studying drug release from ointments to explore the effect of different matrices on the permeation rate of drugs from ointments. Franz diffusion cell experiment is one of the mainstream methods to evaluate the transdermal absorption, and Dufeng et al used the modified Franz diffusion cell method to determine the cumulative permeation amount of DHA and the *in vitro* transdermal rate using rat skin as the transdermal barrier. Previously used 20% ethanol physiological sodium chloride solution as receiver liquor to determine the transdermal rate of 5 kinds of DHA ointments: oil-soluble ointment, Carbopol water-soluble ointment, poloxamer water-soluble ointment, O/W type cream, and W/O type cream, which were 10.376, 25.67, 13.295, 12.637, 11.675 $\mu\text{g}/\text{h}\cdot\text{cm}^2$. Zhou Gang [8] et al modified Franz diffusion cell to determine the permeation absorption pattern of tacrolimus ointment, comparing the consistency of the test and reference 0.1% tacrolimus ointment transdermal effect.

3.2. Choice of Special Base

With the continuous development of ointment agents, it is difficult for traditional ointment base to meet the demand of special drugs. Some novel base drugs also appeared in recent years, exerting different therapeutic efficacy by improving the stability and transdermal efficiency of drugs to achieve different therapeutic effects.

Paller et al [9] prepared crisaborole ointment, a novel PDE-4 inhibitor, significantly reduced signs and symptoms of atopic dermatitis in children and adults in two phase III studies. Crisaborole, a leading nonsteroidal *in vitro* therapeutic, inhibits hyperactive PDE-4 in ad to reduce local inflammation that contributes to disease exacerbation. Has low systemic absorption, and is rapidly metabolized to its inactive metabolites, reducing the risk of systemic side effects, making it a promising therapeutic alternative to existing topical therapies.

To explore biologically active substances with functions to control the infection of pathogens associated with biofilm formation, selected phenolics such as cardanols, tannic acid, tea tannins, and lignin were chemically or physically modified. These structurally diverse phenols are converted into supramolecular nanostructures with variable shapes and sizes by self-assembly or hydrogel formation for ointment formulation [11]. Song et al [14] utilized a class of sulfobutyl ethers in supramolecular chemistry- β -Cyclodextrin inclusion with nimesulide improved the water solubility of hydrophobic drugs, increased bioavailability, and also reduced their toxic side effects.

3.3. Ratio of Stroma

The choice of the proportion of each ingredient in the base can have an important impact on the ointment's pharmacodynamic release, percutaneous absorption, and quality control. For the study of base formulation usually, orthogonal test or single factor experimental method was used to design experiments to explore the optimal base ratio.

Chunjuan Lei [12] used ointment appearance traits, centrifugation test, heat and cold tolerance test as evaluation standards to screen HLB value, emulsifier and oil phase dosage and optimize the ointment prescription. At a prescription optimal HLB value of 10.5, mixed emulsifier Tween 80 and glyceryl monostearate dosages of 6% and 4%, respectively, and oil phase white petrolatum and octadecanol dosages of 8% and 7%, respectively, a qualified compound gramab ointment could be prepared. Meliwei [13], the base formulations of sentinel Mandarin ointment with the best results were determined as follows: 10 g of stearic acid, 30 g of cetyl alcohol, 806 g of span-806-g, bht3-g, 5563-g as the oil phase; Glycerol 20 g, sorbic acid 1 g, laurdiazepoxide 10 g, triethanolamine 1 g, Tween-80 2 g and water 206 g.

3.4. Preparation Process of Ointment Base

Ointments are complex systems with multiple components constituting, in which each component is relatively combined to form an effective effect, and the preparation of an ointment agent should follow the appropriate dosage and clinical use. There are three methods commonly used to prepare ointments: investigational, melt, emulsification.

Investigational method: when the base (oily) is semi-solid, the grinding method can be directly adopted. At room temperature, the base was aliquoted with the drug and mixed well. This method is not intended for base insoluble drug preparation, nor for large scale production- Usually modulated with an ointment knife on a soft cyanine plate of ceramic or glass, also prepared in a mortar.

Melt method: the preparation of large amounts of oily base is commonly used. The general procedure is as follows: a high melting point substance in the base is first heated to melt, stirred and added to the remaining low melting point base, resulting in a homogeneously delicate mixed base. This is especially true for matrices containing solid ingredients, where the drug is insoluble in the base, it is then finely honed and added to the molten base to form a homogenous, fine, non granular paste like finished product.

Emulsification method: the common method is: the base that is oil bath in the prescription is heated to the molten state first, and then the water-soluble ingredients are heated after dissolving them in water. The aqueous phase is slowly added to the oily phase with constant agitation for a period of time, and finally to ingredients for which no water oil can be added with even stirring and ready condensation, which in mass production, will often be achieved using a continuous cream machine with a rotary heat exchanger.

Other methods: as the variety of ointment agents increases, the efficacy of drugs differs, and people use different preparation processes depending on the ointment characteristics. Research [15] proposed the preparation of polyethylene glycol based ointment by hot melt extrusion (HME) process. Lidocaine was used as a model drug. The process uses an improved screw design, and parameters such as feed speed, barrel temperature, and screw speed are optimized to obtain a homogeneous product. And compared the product characteristics with the same kind of ointments prepared by traditional fusion method. The rheological properties, drug release characteristics, and texture characteristics of the hot-melt extruded products were similar to those of conventionally prepared products, demonstrating the novel application of hot-melt extrusion process for local semi-solid manufacturing.

4. Methods for Quality Evaluation of Ointments

Transdermal test is an important means to evaluate the percutaneous absorption characteristics of drug formulations, and the way is mainly divided into ex vivo test and in vivo test. The diffusion cell test is the most common method to evaluate ex vivo skin permeability, and it is convenient, cost-effective, time-saving, and repeatable for use, as well as the first step to evaluate the percutaneous absorption of drugs. Jianming zhang¹⁶ took the prepared abdominal skin of rats fixed in a pre heated diffusion cell to conduct a transdermal experiment, and found that the permeation rates of three hydrocortisone topical ointment formulations through the skin of diabetic rats were statistically different when they were administered using O/W type ointment or water-soluble base, compared with normal rats. To promote the absorption of drugs, commonly used transdermal absorption agents include: laurazone, menthol, azone as colorless, non-toxic, non irritant highly effective transdermal absorption agents. Charing hong¹⁷ investigated and compared their effects and found that among the compound Asiatic gel, the best transdermal efficacy was achieved with laurazone 1.0%.

5. Conclusion

Ointment agents simultaneously offer several advantages such as ease of use, rapid efficacy, few side effects, plasticity of the base and characteristics of different materials that endow the ointment with different characteristics from other topical systems. The preparation process is simple, but due to part of the base oily, poor water absorption, and not easy to mix with the secretion fluid, combined with some drugs by themselves large molecular weight, the release and penetration ability of drugs is poor, so that the efficacy of drugs cannot be fully exerted, the utilization is lower, and then the efficacy affects. And for example petrolatum, which is not easy to remove after it is applied to the skin surface, also causes a lot of inconvenience to the patient.

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