ABSTRACT

The drugs with poor solubility result in delayed absorption which consequently affects the bioavailability. There are many drugs which are having good therapeutic value but not used commercially because of this reason. The permeation enhancers are therefore being utilized to counter this problem. There are many such synthetic and natural materials which have the ability to enhance the drug permeation rate. The essential oils, alcohols, terpenes, azoles and many other chemical derivatives have the capability to be used for permeation enhancer. The present review work suggested the role of permeation enhancer in the pharmaceutical world.

Keywords: Permeation enhancer, Essential oils, Drugs, Natural, Synthetic

INTRODUCTION

Nature has provided the humanities with the wide range of natural substances which can be used in a number of ways. In this context the pharmaceutical market and research too are in one way or the other dependent on nature. The herbal, as well as the biological products, can be utilized in this perspective. The numerous drugs are there which lack its usage and difficult to be formulated because of the poor permeability [1-8]. This hitch has confined the use of many drugs, which is potentially and therapeutically very active. To counter this problem the researchers have tried to incorporate the permeation enhancers. These permeation enhancers can be of natural origin or semi-synthetic or even synthetic too. The large numbers of researchers all over the globe are working hard to bring out the best permeation enhancer with wide compatibility [9-20]. The present work tries to focus on the natural permeation enhancer used in the pharmaceutical world.

Superlative properties of permeation enhancer [21]

1. Biocompatible with no toxicity induction properties (least or no chances of toxicity).
2. There should not be biocompatibility issues with incorporated medicaments.
3. Possesses good solvent properties with economical nature.
4. Must have sustainable, reproducible and rapid action.
5. Minimum adverse reaction with better therapeutic enhancement.
6. Should be physically and chemically inert with no organoleptic involvement with active ingredients and formulations.
7. Should not causes leakage of body fluid or endogenous material with unidirectional flow properties.
8. Must have the capacity to be tested in vitro for better results of final formulations.

Mechanism of permeation enhancers

The mechanism of action of permeation enhancer depends upon the technique through which it works. The permeation enhancers are operated though natural, drug vehicle based, chemical and physical. The natural permeation enhancers like terpenes and essential oils works through partition coefficient, diffusion coefficient, drug solubility, lipid extraction, molecular orientation and macroscopic barrier and perturbation [22, 23]. The drug vehicle-based technique is activated through enhancer’s interaction with the stratum corneum and initiate permeation.
In chemical permeation enhancers one among the three ways worked out like chemical interaction with intracellular protein, by improving partition of drug in stratum corneum, or by disruption of highly ordered lipids of stratum corneum. In case of the physical permeation enhancement technique the magnetic separation, physical separation and ultrasonic wave are utilized (iontophoresis, sonophoresis, magnatophoresis etc).

### Categories of permeation enhancers

| S. No. | Permeation enhancers category | Examples | Techniques of permeation enhancers |
|--------|------------------------------|----------|-----------------------------------|
| 1.     | Terpenes                     | • Neroliol  
• Farnesol  
• Carvone  
• Menthone  
• Linalool  
• Limonine | Natural Permeation enhancers |
| 2.     | Essential oils               | • Basil Oil  
• Neem Oil  
• Eucalyptus Oil  
• Soyabean Oil  
• Olive Oil  
• Groundnut Oil  
• Corn Oil  
• Jojoba Oil | Natural Permeation enhancers |
| 3.     | Sulfosoxides                 | • Dimethyl Sulfoxide  
• Dimethyl Acetamide | Chemical Enhancers |
| 4.     | Glycols                      | • Propylene Glycol  
• Polyethylene Glycol 400 | Chemical Enhancers |
| 5.     | Pyrrolidones                 | • 2-Pyrrolidone  
• 1-Lauryl-2-Pyrrolidone  
• N-Methyl-2-Pyrrolidone | Chemical Enhancers |
| 6.     | Alcohols                     | • Ethanol  
• 1-Hexanol  
• 1-Decanol  
• 1-Octanol  
• Lauryl Alcohol  
• Linolenyl Alcohol | Chemical Enhancers |
| 7.     | Azones                       | • 1-Alkyl-Cycloalkanones  | Chemical Enhancers |
| 8.     | Fatty acids and its esters   | • Oleic Acid  
• Lauric Acid  
• Capric Acid  
• Butyl Acetate  
• iso propyl Myristate  
• Cetyl Lactate | Chemical Enhancers |
| 9.     | Urea derivatives             | • Urea  
• 1-Dodecylurea  
• 1-Dodecyl-3-Methyl Urea  
• 1-Dodecyl-3-Methyl Thiourea | Chemical Enhancers |
| 10.    | Surfactants                  | • Cetyl Trimethyl Ammonium Bromide  
• Sorbiton Mono Palmitate | Chemical Enhancers |

### Advancement in permeation enhancers

Omar et al., 2019 developed the topical gel containing lignocaine for substituting the painful parenteral route. Transfersomal lignocaine was being prepared using PAMAM G3 dendrimer as permeation enhancer. The final formulation showed the enhancement in the local anesthetic activity by 1.62 folds [25].

Loganathan et al., 2001 studied the effect of permeation enhancers on the release of flurbiprofen from gel formulation. The DSMO and SLS were used as the permeation enhancers in different concentration. The 15% DSMO containing formulation showed the best results in vitro studied, while the anti inflammatory activity was too enhanced significantly as revealed through in vivo studies [26].

Rajan and Vasudevan 2012 studied the effect of permeation enhancers (Eucalyptus oil) on penetration of ketoconazole in the form of transfersomal gel. The results suggested the better in vitro release in comparison to conventional forms [27].

Gupta et al., 2012 provided evidence through the study that the permeation enhancers provide the better alternate to the conformist forms. The study also revealed the poorly soluble drug sertraline can be easily delivered transdermally using natural permeation enhancers [28].

Tawfeek et al., 2020 formulated the Lornoxicam transfersomes containing sodium deoxycholate. The drug belongs to the family of anti-inflammatory drugs and showed poor permeability. The results concluded that the encapsulated formulation showed better permeation along with higher flux and apparent permeability coefficient and superior anti-inflammatory activity compared to non-transfersomal LOR hydrogel and indomethacin gel as a standard NSAID [29].

Aggarwal et al., 2012 carried out the development of transdermal delivery system of olanzapine utilizing natural oils as permeation enhancers. Penetration enhancing the potential of groundnut oil, corn oil and jojoba oil in vitro permeation of olanzapine across rat skin was studied. The results suggested relative bioavailability of TDDS was 113.6 % as compared to oral administration of olanzapine [30].

Patil and Saragoi 2014 carried out the study of natural products as permeation enhancers. The permeation enhancer proves to be safe,
non-toxic, pharmaceutically inert, non-irritating, and non-allergic. Moreover, the SAR studies on the used permeation enhancers provided the results of better bioavailability and significantly enhanced activity [31].

Sharma et al., 2010 designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of olanzapine using blends of two different polymeric combinations, polyvinylpyrrolidone (PVP) and ethylcellulose (EC). Vegetable oils (soybean oil, olive oil, eucalyptus oil) were employed as permeation enhancers. In vitro skin permeation study was also conducted in a modified Franz’s diffusion cell which shows that the maximum permeation was with the formulation C3 and it was 768.64µg/cm² after 48 h. Optimized formulations were found to be suitable for formulating in terms of physicochemical characteristics and there was no significant interaction noticed between the drug and polymers used [32].

Nan et al., 2018 investigated the enhancement effects of natural transdermal permeation enhancers from Lardum palustre L. var. angustum N. Busch. The outcomes of research recommended that the effectiveness and safety of the natural transdermal permeation enhancers could be improved by understanding their composition and the enhancement mechanisms [33].

CONCLUSION

From the current review work, the critical roles of the permeation enhancers are being accessible. The permeation enhancers are being available in wide varieties and so many options that the researchers can modify the formulations. The recent advancements in the utilization of the enhancers also suggested the commercial role and the marketed value. Further, the future prospective as the penetration enhancers is still not clear and needs more research to strengthen its economical and marketable value.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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