Conventional To Modern Approach on Ketoprofen Formulation: A Comprehensive Review

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Abstract
Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects by inhibition of prostaglandin biosynthesis. It undergoes metabolism in the liver via conjugation with glucoronic acid, hydroxylation of the benzoyl ring, and reduction of its keto group. Various forms of KP are available in the pharmaceutical market: coated tablets, capsules, gels for topical application, transdermal patches, liquid spray, and solutions for injection. It is important to note that their availability is subject to change. Such is the case with the topical application gel: once an over-the-counter medicine, it is now a prescription drug in many countries around the globe. This restriction is due to the fact that it has been established that topically applied KP can induce photosensitivity. It includes both phototoxic and photoallergic activity.1 In an experimental study, it was found that benzoyl radical is the key structure that provokes photosensitivity and the photo cross-reactivity of KP, suprofen and tiaprofenic acid. As that radical is common in benzophenone ultraviolet (UV) filters, cross-reactions are familiar with sunscreens containing mainly oxybenzone.3 However, the instability of KP under UV/visible light and the subsequent formation of degradation products are known to cause photosensitivity after topical application. It has been found that TiO2 inclusion in fabric backing can improve photostability, reduce photodegradation and increase photo safety of the drug in the KP-loaded patch. This study we mainly focus the technology used in the new formulation of ketoprofen to reduce the adverse effect of the conventional formulation and discuss the advantage of the neanotechnology used in the manufacturing of the new formulation
Keywords: Ketoprofen, photosensitivity, oxybenzone.

Introduction

Ketoprofen (KETO) is a traditional non-steroidal anti-inflammatory drug (NSAIDs) with good analgesic and antipyretic effects. However, as NASIDs, the toxicity of KETO towards gastrointestinal (GI) system might limit its clinical use. Since ketoprofen is low water-soluble, various techniques such as dry elixir, the solid dispersion, water-soluble prodrug or complexation have been applied for enhancement of the solubility. Further, frequent dosing of ketoprofen is required for therapeutic maintenance because of its fairly fast elimination from the body. Exposure of the stomach to high levels of ketoprofen can cause gastric damage such as ulceration or bleeding. To improve this disadvantage, sustained release or enteric-coating dosage forms have been developed, resulting in less frequent dosing and less gastrointestinal disturbance. The sustained release microspheres of ketoprofen have been developed using ethylcellulose (EC), which is often utilized as a matrix for preparation of prolonged release dosage forms

2. Latest Approaches of new formulation of ketoprofen

2.1. Novel transdermal ketoprofen formulation

Novel transdermal (TD) ketoprofen formulation was pursued to provide a convenient and pain-free route of administration. Previous this study has been employed on the animal (cattle) because Cattle may be subjected to painful procedures in the course of routine husbandry practice, such as dehorning, laparotomies, needle injections, spaying, and surgical and non-surgical castration of males. Topically applied non-steroidal anti-inflammatory drugs (NSAIDs) are becoming increasingly popular in human medicine, including ketoprofen (Derry et al., 2017; Serinken et al., 2016). Topical NSAIDs also offer a better risk-to-benefit ratio than NSAIDs administered by other routes, including oral administration. (Mills, et al., 2022).

2.2. Franz Diffusion Cell Approach for Pre-Formulation

In the development of innovative pharmaceutical products worldwide, suitable methods need to be established to evaluate the fundamental physicochemical parameters required in pre-formulation studies. Formulation studies are essential for drug effectiveness reliability, both in approved drugs and new pharmaceutical formulations. Simple methods must be

implemented for determining the main physicochemical parameters including solubility, partition coefficient and dissolution profiles (A Ashour, et al., 2016). In the case of topical formulations, for which the drug is released through the skin, evaluation of the permeation is critical to establish bioavailability and thereby make an approximation of the effectiveness. Additionally, for semi-solid dosage forms aimed for topical or transdermal application, methodologies to test and verify the performance in product pre-formulation stages are essential to avoid additional performance tests once the product is market-ready (Abdallah, Fathy, Tolba, El-Brashy, & Ibrahim, 2022).

Franz Cells are a widely used methodology to evaluate in vitro drug permeation, which have advantages, such as (i) few handlings of tissues, (ii) no continuous sample collecting and (iii) low amount of drug required for analysis. With the rise of personalised medicine, it is necessary to develop various pharmaceutical dosage forms for the same active molecule allowing the variability of administration and dosage (Alshetaili, et al., 2016). Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) cover a range of indications and would require various dosages, formulations and administration forms as they are used for chronic as well as acute conditions such as in the treatment of chronic joint diseases (i.e., osteoarthritis and rheumatoid arthritis) and inflammatory diseases (i.e., acute fractures, sprains and sports injuries) (Belsey, et al., 2014). Some NSAIDs commonly used in medical practice include acetylsalicylic acid, ketoprofen (KTP), ibuprofen, naproxen, indomethacin and piroxicam. These drugs carry out their pharmacological action by decreasing inflammation, fever and pain processes. Despite the therapeutic benefits, these drugs have many adverse effects that affect gastrointestinal, renal and cardiovascular systems and the liver due to the unspecific blocking of the enzyme cyclooxygenase 1 (Chourasia, Kang, & Chan, 2011). Most NSAIDs are well absorbed when administered orally and are widely distributed throughout the body. In contrast, NSAID topical administration has a localised effect and a reduced risk of systemic adverse effects. This dosage form also avoids hepatic first-pass metabolism, allowing for sustained drug release, and is easy to apply and remove in the case of side effects (Salamanca, Barrera-Ocampo, Lasso, Camacho, & Yarce, 2018).

2.3. Enhancing drug photostability in topical application forms.

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) commonly used for its analgesic and anti-inflammatory properties, but it can degrade when exposed to light, leading to reduced potency and potential formation of harmful degradation products. To overcome, these strategies to enhance the photostability of ketoprofen in topical formulations Incorporating UV filters like octyl methoxycinnamate or benzophenone derivatives can protect the formulation from UV radiation. Adding antioxidants such as Vitamin E (tocopherol) or butylated hydroxytoluene (BHT) can help prevent oxidative degradation. Encapsulation Techniques: Liposomes, nanoparticles: Using nanoparticles, such as solid lipid nanoparticles (SLNs) or nanostructured lipid carriers (NLCs), can enhance photostability by shielding the drug from light. Microspheres: Encapsulation in polymeric microspheres can provide protection and controlled release. Formulation Adjustments: pH Adjustment: Adjusting the pH of the formulation to a more stable range for ketoprofen can reduce its degradation. Use of Opaque Packaging: Packaging the product in opaque or UV-blocking containers can significantly reduce light exposure. Viscosity Modifiers: Adding viscosity enhancers such as carbomers or hydroxypropyl methylcellulose (HPMC) can reduce the mobility of ketoprofen and its exposure to light. Chemical Stabilizers: Cyclodextrins: Inclusion of cyclodextrins can form inclusion complexes with ketoprofen, enhancing its stability. Stabilizing Agents: Incorporating stabilizing agents that can form a complex with ketoprofen and reduce its photodegradation. Optimization of Application Form Gels and Creams: Using gel or cream formulations can provide better protection compared to solutions. Emulsions: Oil-in-water or water-in-oil emulsions can provide a protective environment for ketoprofen Co-Formulation with Other Agents: Combination Therapy: Co-formulating ketoprofen with other agents that have photoprotective properties can enhance overall stability. Use of Light-Stabilizing Excipients: Titanium Dioxide or Zinc Oxide: These physical blockers can be included in the formulation to protect against UV radiation. Implementing these strategies can help improve the photostability of ketoprofen in topical formulations, thereby enhancing its therapeutic effectiveness and shelf life.

2.4. ketoprofen liquisolid compacts by Box-Behnken design.

The Box-Behnken design (BBD) is a statistical method used in the design of experiments, particularly for optimizing processes and formulations. It is a type of response surface methodology (RSM) that is efficient for exploring quadratic response surfaces and constructing second-order polynomial models without needing a full factorial experiment. Key Features of Box-Behnken Design, Rotatability and Efficiency: BBD is rotatable (or nearly rotatable), which means the design allows for uniform precision of the estimated response across the design space. It is more efficient than a full factorial design because it requires fewer experimental runs. Three-Level Design: Each factor is varied at three levels (low, medium, and high), typically coded as -1, 0, and +1. This helps in detecting curvature in the response surface. No Corner Points: The design avoids the extreme points (corners) of the factor space, which is useful when the extreme conditions are expensive or impractical to test. Balanced Design: It is a balanced design, meaning each factor appears at each level the same number of times.

2.5. Sustained release microsphere of ketoprofen

Ketoprofen, (RS) 2-(3-benzoylphenyl)-propionic acid is one of the propionic acid class of non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. It potently inhibits the enzyme cyclooxygenase resulting in prostaglandin synthesis inhibition. It also prevents formation of thromboxane A2 by platelet aggregation. Ketoprofen is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 0.5 – 2 h after a dose, but it

causes a certain irritation in the gastrointestinal mucous membrane and possesses a bitter taste and aftertaste. This makes ketoprofen a very good candidate for the formulation of controlled release dosage forms. Ketoprofen microspheres help to protect the gastric mucous membrane from drug irritation and to mask its taste**.** Simple ketoprofen microspheres (MS) were prepared using EC and ketoprofen by the dry-in-oil method as follows: EC (1.5 g) and ketoprofen (0.9, 1.5 or 2.25 g) were dissolved in 25 ml of acetone. The solution was added drop-wise to 250 ml of liquid paran containing SS-30 at 2 **%**(w/v) and stirred at 600 rpm and 20°C. The emulsion was stirred at room temperature for 1 h, then at 35°C for 5 h and inally at 57°C for 1 h. One hundred ml of n-hexane warmed at 55°C was added to the mixture, and ˆltered using a membrane with a pore diameter of 0.45 mm. The residue was washed with n-hexane warmed at 55°C to yield MS. Ketoprofen microspheres with PEG (MS-P) were prepared as follows: PEG (0.075, 0.15 or 0.3 g) was dissolved in 25 ml of acetone warmed at 35°C. After cooling the solution at 20°C, 1.5 g of ketoprofen and 1.5 g of EC were added. The subsequent procedures were the same as those described for MS. Ketoprofen microspheres with HPC (MS-H) were produced as follows: HPC (0.075, 0.15 or 0.3 g) was added to 25 ml of acetone at 20°C, and stirred vigorously at 14000 rpm for 1 min. Then, 1.5 g of ketoprofen and 1.5 g of EC were added to the suspension, and dissolved. The subsequent procedures were the same as those described for MS. Chitosan-coated ketoprofen microparticles (Chi-MP) were prepared by coating MS with FTCChi as shown in Fig. 1A. MS prepared from the solution of EC (1.5 g) and ketoprofen (1.5 g) in 25 ml of acetone was used. FTC-Chi (100 mg) was dissolved in 5 ml of 2**%**(v/v) acetic acid aqueous solution. MS (100 mg) was suspended in the solution, and added drop-wise to 20 ml of liquid para‹n containing SO-15 at 1**%**(w/v) and stirred at 600 rpm. The suspension was added drop-wise to 500 ml of double solvent layers of n-hexane/1 M NaOH (2 : 3, v/v) and stirred at 300 rpm. One min later after end of dropping, the particles precipitated in 1 M NaOH aqueous layer were collected by ˆltration using mesh (opening 150 mm), washed with 500 ml of water, and dried in a desiccator in vacuo at room temperature to produce Chi-MP.

2.6. Nano emulsion for topical delivery.

2.6.1. Transdermal drug delivery system

Transdermal drug delivery system (TDDS) is one of the most exciting parenteral drug delivery systems in the pharmaceutical field.1) TDDS confers several advantages such as decreasing dosing frequency, reducing side effects, and avoiding hepatic first-pass metabolism.2,3) Despite these advantages, TDDS often has difficulty in drug permeation ability because the skin's hydrophobic stratum corneum acts as an effective barrier. TDDS using a therapeutic deep eutectic solvent (DES) has attracted much attention recently. DES is a liquid consisting of two or more solid compounds of hydrogen donor and acceptor and has lower melting point than room temperature.4,5) It offers several advantages such as increasing solubility and circumventing polymorphism. In addition, DES could be used for transdermal formulation of drugs without vehicle, with efficient transdermal drug permeation.6) Therefore liquid formulation consisting of the compounds themselves would beuseful for TDDS. Supercooled liquid (SCL) is a liquid state at temperatures below the melting point.7) While amorphous compounds have glass transition temperature (Tg) above a certain temperature, SCL presents Tg below that temperature. Therefore, compounds with Tg below room temperature could form liquid state at that temperature and be useful for TDDS as well as DES. In addition, it would be applicable for drug–drug or drug–excipient combinations with melting points above room temperature, because Tgs of compounds are lower than melting temperatures. However, the potential of SCL for TDDS remains unclear. Because SCL is a more thermodynamically unstable state than amorphous state8) it is likely to crystallize whereas DES is thermodynamically stable state and does not crystallize. A co-amorphous system defined as an amorphous solid state comprising two or more low molecular compounds recently has been gathering much attention. In the coamorphous system, drug–drug or drug–excipient interacts with each other and inhibits crystallization at the amorphous state.9,10) Several researchers have shown that a co-amorphous system improved stability of the amorphous state compared with that of single compound.11,12) Hence SCL based on the co-amorphous approach, which stabilizes the thermodynamically unstable state by intermolecular interactions, should also improve the stability of the SCL state. The purpose of the present study was to explore the possibility of TDDS using SCL and to improve the stability of SCL using co-amorphous approach. Ketoprofen (KET) and ethenzamide (ETH) were employed as the binary SCL component. Formation of KET SCL and KET–ETH SCL was evaluated by thermal analysis. The interactions between KET and ETH in the binary SCL were evaluated by Fourier transform (FT)-IR spectra. The stability of SCLs was evaluated and transdermal permeation of drugs from the SCLs was also examined.

2.6.2. SPRC and KETO co-loaded PLGA microsphere

SPRC and KETO co-loaded PLGA microspheres (SK@MS) were prepared via the double emulsion solvent evaporation method with little modification.[47] Briefly, 200 mg of SPRC was firstly dissolved in 2000 μL of distilled water to form the inner water phase (W1). The oil phase (O) was prepared through dissolving 1000 mg of PLGA and 45 mg of KETO in 20 mL of DCM, and the W1 was then dropwise added to the O. Next, the mixture was emulsified with homogenizer at 7000 rpm for 2 min in an ice bath. The obtained primary emulsion (W1/O) was then added into 2500 mL of 0.5% (w/v) PVA solution and further emulsified by a homogenizer at 7000 rpm for 4 min to prepare the W1/O/W2 emulsion, and this W1/O/W2 emulsion was hardened under magnetic stirring (400 rpm) for 5 h. The obtained particles were collected through centrifugation, washed 3 times with distilled water and lyophilized. Finally, the lyophilized particles within the range from 20 to 30 micron were selected through sieve and named as SK@MS. Chronic administration of high doses of SPRC generally leads to side effects such as organ injury, which might be caused via the persistent high H2S concentration

in vivo, and a long-term exposure to H2S could harm organism.59,60 To evaluate the potential harm of supplementations to body, the heart, liver, spleen, kidneys, and lungs were resected from rats and examined by H&E staining

2.7. Ketoprofen-induced photoallergic dermatitis

Drug-induced photosensitivity reactions are significant adverse effects. Ketoprofen is one of the most common drugs that can cause skin rash in sun-exposed areas. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ketoprofen, are often used for a variety of symptoms, including pain and fever. An understanding of the presentation and clinical course of ketoprofen-induced photosensitivity is necessary to correctly diagnose and manage this condition. Ketoprofen-induced photosensitivity reactions usually present as photoallergic dermatitis, which is a cell-mediated immune process. The benzophenone moiety in ketoprofen plays a major role in ketoprofen's ability to act as a photosensitizer. Several agents, such as fenofibrate and octocrylene have been found to be associated with aggravation of ketoprofen-induced photoallergic dermatitis or cross-photosensitization, and these reactions result from structural similarities with ketoprofen. Treatment of ketoprofen-induced photoallergic dermatitis includes discontinuation of ketoprofen, topical or systemic corticosteroids and avoidance of sun exposure and agents known to exacerbate dermatitis. In conclusion, photoallergic dermatitis is a significant adverse effect of ketoprofen. Some agents known to worsen dermatitis may be found in sun protection products (notably, octocrylene in sunscreen). Educating the patient to avoid these products is critical to treatment. Since NSAIDs, such as ketoprofen, are used commonly for a variety of illnesses, drug-induced photoallergic dermatitis should be high on the differential in individuals using these medications who present with acute onset of a rash in sun-exposed areas.

Conclusion:

The transition from conventional to modern approaches in ketoprofen formulation reflects advancements in drug delivery systems aimed at improving efficacy, safety, and patient compliance. Here's a conclusion summarizing these advancements. The evolution from conventional to modern ketoprofen formulations underscores significant progress in pharmaceutical technology. Conventional formulations, such as oral tablets and capsules, often posed challenges including gastrointestinal irritation, first-pass metabolism, and inconsistent plasma drug levels. These limitations necessitated the exploration of novel delivery systems. Modern approaches have successfully addressed many of these issues, enhancing the therapeutic profile of ketoprofen. These advancements include: Transdermal Delivery Systems: Patches and gels allow for controlled, sustained release of ketoprofen, reducing gastrointestinal side effects and improving patient compliance by providing a non-invasive route of administration. Nanotechnology: Nano formulations, such as nanoparticles and nanogels, have improved the bioavailability and targeted delivery of ketoprofen. These systems enhance drug solubility, stability, and penetration to specific sites, thereby increasing therapeutic efficacy and minimizing adverse effects. Microspheres and Liposomes: These carrier systems have facilitated prolonged drug release and targeted delivery, reduced the dosing frequency and side effects while enhanced patient adherence to the treatment regimen. Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs): These lipid-based formulations offer improved drug stability, controlled release, and enhanced bioavailability, addressing the solubility issues associated with conventional formulations. Polymeric Systems: The development of hydrogels and polymeric nanoparticles has provided innovative platforms for the sustained and controlled release of ketoprofen, improving its therapeutic index. In conclusion, modern ketoprofen formulations represent a significant leap forward from their conventional counterparts. These advancements not only enhance the drug's therapeutic efficacy and safety profile but also improve patient adherence and overall treatment outcomes. The continuous development of innovative delivery systems holds promise for further improving the clinical use of ketoprofen and other nonsteroidal anti-inflammatory drugs (NSAIDs).

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