AN IN-DEPTH REVIEW ON RECENT DEVELOPMENTS IN ORAL KETOPROFEN DELIVERY: STRATEGIES FOR ENHANCED THERAPEUTIC PERFORMANCE

ABSTRACT

Ketoprofen, a widely prescribed non-steroidal anti-inflammatory drug (NSAID), suffers from limited oral bioavailability due to poor solubility and a short half-life, leading to frequent dosing and potential gastric irritation. This review examines recent advancements in oral Ketoprofen delivery, reporting clear findings in bioavailability improvement and gastric protection. Controlled-release systems—such as Zn-alginate beads, polysaccharide hydrogels, and monolithic osmotic tablets—demonstrated sustained drug release with reduced gastric side effects, extending anti-inflammatory action up to 7 hours. Oral-dissolving formulations, including fast-disintegrating tablets and electrospun fibers, showed enhanced dissolution rates and improved patient compliance, particularly benefiting individuals with swallowing difficulties. Complexation with polymers (e.g., polyacrylamide-grafted gum and sodium alginate) created pH-sensitive microbeads that released 83% of Ketoprofen at neutral pH, supporting gastro-protective effects. Lipid-based formulations, such as nanostructured lipid carriers and self-emulsifying systems, effectively improved solubility and permeability, enhancing Ketoprofen's absorption by up to 2.4 times. These findings underscore the potential of tailored delivery systems in optimizing Ketoprofen's therapeutic efficacy, safety, and patient adherence.

Key words: Oral Ketoprofen, Nsaid, Therapeutic Performance, Patients Diagnosed

INTRODUCTION:

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID), it is prescribed frequently for patients diagnosed with rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and other related disorders. Chemically, Ketoprofen is known as 2-(3-benzoylphenyl)-propionic acid and can be considered a weak acid, its structure includes a small hydrophilic carboxylic acid domain and a larger lipophilic domain (Figure 1). Ketoprofen is poorly soluble in water at neutral pH and its solubility increases at higher pH due to its acidic nature[1-2].

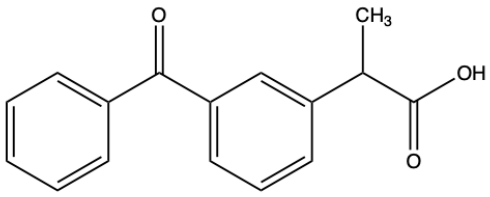

Figure 1: Ketoprofen Chemical Structure

Ketoprofen is classified as class II in the biopharmaceutical classification system (BSC), suggesting it has good permeability properties, but low water solubility resulting in poor oral absorption and bioavailability (Figure 2). Ketoprofen water solubility is estimated to be 10 mg/L at 22-24°C with a pKa value of around 4.45. In addition to its poor water solubility, Ketoprofen has a short half-life (1.5-4h) requiring high and frequent dosing to attain its therapeutic effect which is battled with its narrow therapeutic index (~2) and limited its use because of the severe adverse effect, especially gastric irritation, making Ketoprofen a subject of extensive studies to improve its oral bioavailability[1-3].

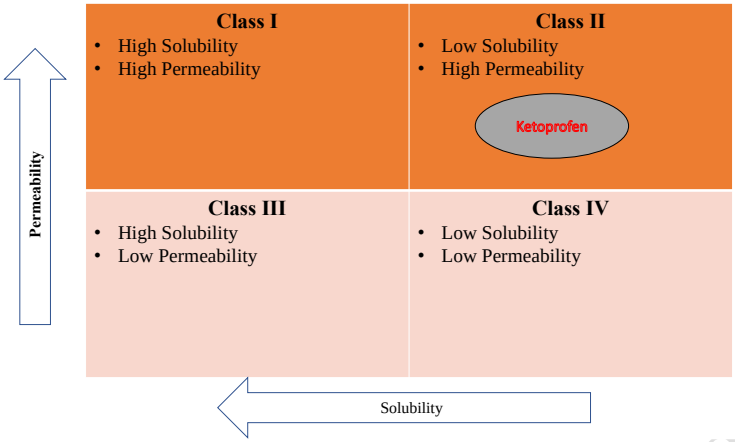

Figure 2: *Biopharmaceutical Classification System (BSC), Ketoprofen is Class II*

Ketoprofen acts primarily by blocking Cyclooxygenase-1 (COX 1), an enzyme responsible for producing prostaglandins with physiological purposes, and Cyclooxygenase-2 (COX 2), which is in charge of producing pro-inflammatory prostaglandins at the site of inflammation[4].

The easiest approach to providing medication is by oral dosing. However, oral NSAID delivery is constrained because of the significant first-pass impact and gastric damage[5]. The development of oral controlled and sustained release offers a potential benefit for NSAIDs. The justification for it is to allow medication release at a specified rate, provide sustained levels (requiring fewer doses), and minimize interaction with gastric mucosa (reduced gastric damage)[6].

Ketoprofen and other NSAIDs are desirable APIs for modification in their formulation to generate chronotherapeutic drug delivery systems that are helpful in treating early morning pathologies[7].

In 2020, the global market value of Ketoprofen was estimated to be around $34M, and it is projected to reach $39M by 2027[8,9]. Moreover, the estimated number of Ketoprofen prescriptions in the US in 2020 was around 15,950 prescriptions, indicating its widespread use among the American population[10]. In this review, we will be looking at the some of the advancements and

progress that were made to improve the oral delivery of Ketoprofen, its bioavailability, and minimizing its unwanted adverse effects.

1. Controlled-Release Formulation:

Controlled-release drug delivery systems are delivery systems that release a constant amount of the drug over a specific extended duration of time to maintain a constant drug-plasma levels, and reduce the frequency and the amount of dosing resulting in better patient compliance and minimize drug toxicity, and adverse effect[11]. The Controlled release of drugs can be achieved via various mechanisms such as diffusion, dissolution, chemical triggering, and solvent activation. Dissolution and diffusion mechanisms combined frequently to achieve controlled release[12].

Zn-alginate beads containing Ketoprofen were developed using prilling/ionotropic gelation, with a focus on optimizing particle size, shape, structure, drug loading, and release. The optimized beads demonstrated gastro-resistant properties, with delayed release in simulated intestinal fluid and sustained anti-inflammatory effects in vivo. The incorporation of Zn^{2+} as a cross-linker enhanced the beads' physicochemical properties and anti-inflammatory efficacy. The beads delayed Ketoprofen release for up to 7 hours and provided prolonged anti-inflammatory activity in rats, significantly reducing edema when administered 3 or 5 hours before induction, unlike pure Ketoprofen, which was effective only when given 0.5 hours before. Blank Zn-alginate beads showed no significant effect, confirming that the matrix itself does not interfere with the inflammatory process[13].

Ketoprofen-loaded alginate beads were formulated to control Ketoprofen release using the ionotropic gelation method. This technique, known for its simplicity, low cost, and high entrapment rates for poorly water-soluble drugs. Beads exhibited pH-sensitive release properties.

In acidic conditions (pH 1), the beads released only 10-15% of Ketoprofen over 4 hours, minimizing gastric mucosa irritation. In contrast, at a neutral pH (7.4), the beads released almost all of the Ketoprofen within 2 hours due to pH-sensitive swelling, which created a porous structure. The beads' swelling behavior was pH-dependent: at neutral pH, calcium ions were replaced by sodium and potassium ions, increasing electrostatic repulsion and water uptake, while in acidic conditions, protonation of carboxylate groups reduced swelling. The alginate beads also provided strong muco-protective effects compared to free Ketoprofen, making them advantageous for oral administration, especially for drugs sensitive to acidic environments or those causing gastrointestinal issues[14].

Ketoprofen lysinate was successfully encapsulated in polysaccharides-based hydrogel using prilling techniques. Alginate and pectin were used as carriers and release-modifying agents, respectively. The best formulation was incorporated into an acid-resistant capsule, achieving delayed (90 min lag) and prolonged release (complete in 270 min). Beads were prepared with 2% alginate and 6% pectin, with varying drug-to-polymer ratios. Pectin-based beads showed superior encapsulation efficiency (81.8% to 93.7%) compared to alginate beads (39.0% to 49.7%), likely due to pectin’s lower molecular weight, which improved the gel matrix. SEM analysis revealed that pectin beads had a more compact inner structure. Alginate beads released Ketoprofen rapidly in acidic media, while pectin beads showed sustained release, with only 31.9-56.2% released after 120 minutes in acidic media and complete release was observed upon pH change within 1 hour. Increased drug content in pectin beads delayed drug release due to enhanced interactions between the drug and polymer, confirmed by DSC analysis[15].

Solid dispersions of Ketoprofen were formulated in monolithic osmotic tablets (MOT) to improve the solubility of Ketoprofen and provide a sustained release effect with improved therapeutic

efficacy and patient compliance. Ketoprofen solid dispersions were prepared using the solvent melt method with PEG 6000 as a hydrophilic carrier at various drug-to-carrier ratios. Characterization using DSC, TGA, and PXRD confirmed the amorphous state of Ketoprofen in the dispersions. The tablet core included Polyox N80 as a suspending agent, sodium chloride as an osmotic agent, and was coated with cellulose acetate. Solid dispersions significantly improved the dissolution rate compared to pure Ketoprofen and physical mixtures. The optimized MOT formulation exhibited zero-order release kinetics, achieving over 95% cumulative drug release, independent of environmental conditions and agitation speed. Drug release was primarily controlled by osmotic pressure, the suspending agent, and the solubility of Ketoprofen in the solid dispersion, offering a sustained and predictable release profile[16].

An oral press-coated tablet of Ketoprofen was prepared to deliver the drug in a time-controlled manner with a distinct predetermined lag time. The tablet was made by direct compression with Ketoprofen in the inner core and an outer shell composed of hydroxypropyl methyl cellulose (HPMC) and ethyl cellulose (EC). The release profile featured a lag time followed by a rapid release phase. Increasing the viscosity and concentration of HPMC extended the lag time, but EC had a more significant impact on delaying the release. The time-controlled release was influenced by the splitting of the outer shell, hydration, dissolution, and erosion of the polymers. EC alone provided a longer delay due to its slower medium penetration and hydrophobic nature. Optimizing the weight ratio of EC to HPMC can balance the lag time and release profile, with HPMC enhancing medium permeability and reducing lag time[17].

Neem gum was utilized to create a sustained-release matrix tablet for Ketoprofen, using concentrations from 10% to 40% in a wet granulation process. The study found that neem gum effectively retarded Ketoprofen release, with all tablet physical attributes meeting practical and

pharmacopeial standards. The formulation with 30% neem gum released 98.2% of Ketoprofen over 12 hours and was identified as the optimized formula. This formulation exhibited zero-order kinetics and followed an erosion and Fickian diffusion case-II transport mechanism for drug release[18].

HPMC-based oral matrices for Ketoprofen were analyzed to assess the effects of processing methods, filler types, and compression forces on drug release. The study found that formulations with dibasic calcium diphosphate, prepared by wet granulation and compressed with high force, sustained drug release for over 12 hours. In contrast, other formulations released the drug for only 6 hours. The T50% values, representing the time required for 50% of the drug to be released, varied significantly from 30 to 624 minutes, indicating considerable differences in release profiles across the formulations[19]. Another study examined the impact of partially and fully pregelatinized starch on the physical and sustained-release properties of HPMC-based Ketoprofen oral matrices. It was found that fully pregelatinized starch resulted in better sustained-release behavior, with less than 60% of the drug being released over 14 hours. In contrast, matrices with partially pregelatinized starch released approximately 90% of the drug within 2 hours. The study concludes that fully pregelatinized starch is more effective for sustained-release formulations[20].

2. Oral-Dissolving Formulations:

Oral-dissolving dosage forms are novel formulations that dissolve in the mouth saliva after a few seconds from administration, and they don't require drinking water with them[21]. They can be found in different forms such as oral dissolving granules (ODG), oral-dissolving tablets (ODT), oral-dissolving films (ODF), and oral lyophilizate (OL)[22]. They are presenting a suitable solution for

patients with swallowing difficulties and for pediatric use, preventing dysphagia and improving patient compliance[23,22].

A fast-disintegrating Ketoprofen tablet was developed to address swallowing difficulties and improve patient compliance. Tablets were made using a physical mixture and a solid dispersion with poloxamer 188 via the melt fusion technique. The 1:4 ratio formulation provided the best dissolution rate due to its rapid breakdown and drug absorption. Superdisintegrants and effervescent agents were tested, with effectiveness ranked as Crospovidone > Citric acid + Sodium bicarbonate > Sodium starch glycolate > Ac-Di-Sol. Transforming Ketoprofen into a solid dispersion increased its solubility 20 to 50-fold by converting it from crystalline to amorphous form. This enhanced water solubility was due to the interaction between poloxamer 188 and Ketoprofen, facilitating rapid hydration and solubilization[24].

Poly(vinylpyrrolidone) electrospun fibers that contain Ketoprofen were prepared as a fast-dissolving oral drug delivery system. The fibers were smooth, cylindrical, and contained amorphous solid dispersions of Ketoprofen, achieving nearly perfect encapsulation efficiency (100%). At low drug loading (9.09% w/w), the fibers disintegrated rapidly, enhancing dissolution, while at higher loading (23.08% w/w), this effect diminished, indicating a maximum effective drug loading capacity. All formulations remained stable under storage conditions (19-21ºC, RH 30-40%) for 4 weeks without changes in release profile, and performance was consistent across different throughput rates, supporting large-scale production feasibility. XRD and DSC confirmed the amorphous state of the drug, and UV spectroscopy showed that Ketoprofen loading matched theoretical values, indicating minimal loss during electrospinning[25].

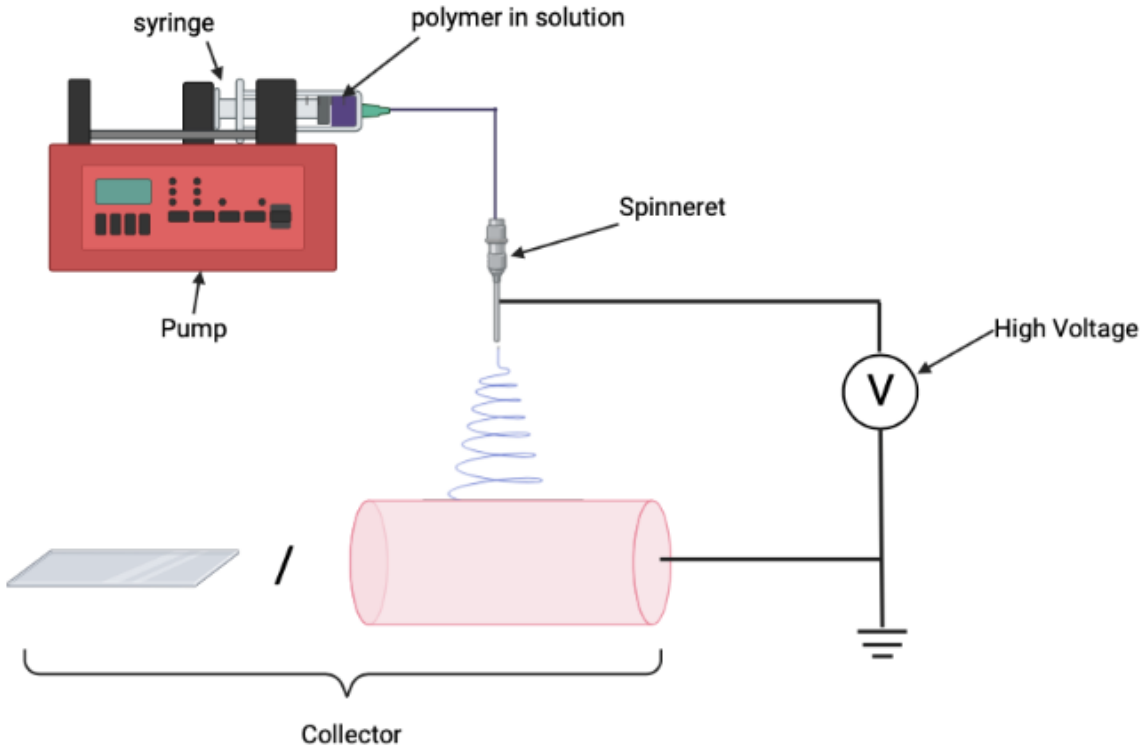

Figure 3: Schematic Image for the electrospinning process

Lactose-free orodispersible tablets containing Ketoprofen were developed using two methods: wet granulation followed by compression and freeze-drying from suspension. Both methods used three superdisintegrants: croscarmellose, crospovidone, and starch glycolate. The wet granulation and compression method yielded tablets with shorter disintegration times, faster dissolution, and better content uniformity compared to freeze-dried tablets, which had higher friability and longer disintegration times. Croscarmellose resulted in the lowest disintegration time but slower dissolution compared to crospovidone and starch glycolate. The compression method proved more reproducible, especially with 19.34% superdisintegrant and 1% sodium lauryl sulfate to enhance Ketoprofen solubility[26].

A mouth-dissolving tablet (MDT) of Ketoprofen was developed using three superdisintegrants: crospovidone (CP), croscarmellose sodium (CCS), and sodium starch glycolate (SSG). Various formulations were evaluated for pre- and post-compression properties. One formulation with optimal performance had a dispersion time of 14 seconds and achieved 99.9% drug release within 5 minutes. The effectiveness of disintegrants was ranked as CCS > CP > SSG, increasing concentrations of disintegrants resulted in shorter dispersion time. The type and concentration of superdisintegrant significantly influenced the drug release profile from the MDT, highlighting their critical role in enhancing tablet performance[27].

Similarly, the oral dissolving film (ODF) of Ketoprofen was prepared using both natural and synthetic film-forming polymers and utilizing the solvent-casting method. The films demonstrated satisfactory physical and mechanical properties, meeting all required standards. FTIR analysis confirmed compatibility between Ketoprofen and all polymers and excipients used. Disintegration times ranged from 19 to 36 seconds, with most formulations meeting the FDA-recommended limit of 5-30 seconds, except one. Films containing pectin disintegrated the fastest at 19 seconds. Most formulations released over 80% of Ketoprofen within 4 minutes in a phosphate buffer (pH 6.8). The films were 2x2 cm in size, each containing 13 mg of Ketoprofen[28].

An orally disintegrating tablet of Ketoprofen was prepared using the direct compression technique, evaluating the effects of different types and concentrations of superdisintegrants: croscarmellose, crospovidone, and sodium starch glycolate at 5%, 10%, and 15%. The optimal formulation with 10% crospovidone demonstrated the best physicochemical performance, showing rapid disintegration and improved wetting times, enhancing absorption, bioavailability, and patient compliance. Increasing the concentration of superdisintegrants beyond the optimal level increased disintegration time due to viscous gel layer formation, which hindered water penetration, except

in the case of crospovidone due to its lower gel-forming tendency. Superdisintegrant efficiency ranked as crospovidone > sodium starch glycolate > croscarmellose, with 10% identified as the optimal concentration for effective disintegration[29].

3. Complexation with polysaccharides and polymers:

A pH-sensitive interpenetrating polymer network (IPN) microbeads were developed for controlled and gastro-protective delivery of Ketoprofen using polyacrylamide-grafted-gum ghatti (PAAm-g-GG) and sodium alginate (SA) (Figure 4). These microbeads were synthesized using dual crosslinking and exhibited a spherical shape, with sizes ranging from 820-931 µm. Larger microbeads formed with increased amounts of PAAm-g-GG and Ketoprofen due to higher viscosity, while higher calcium ion concentrations resulted in smaller microbeads. Drug entrapment efficiency (DEE) ranged from 78.87% to 90.77% and improved with increased calcium ion concentrations, leading to stiffer microbeads with reduced drug leakage. DSC and XRD analysis confirmed the amorphous dispersion of Ketoprofen in the IPN microbeads. The microbeads showed pH-sensitive swelling behavior, with significant size increases at pH 7.4 compared to pH 1.2. Drug release studies demonstrated a controlled release pattern over 12 hours, with 17% of the drug released at pH 1.2 and 83% at pH 7.4. The release mechanism followed case II transport at pH 1.2 and anomalous transport at pH 7.4, attributed to the presence of carboxylate groups and the mechanical strength of the IPN structure. In vivo studies in Wistar rats showed that IPN microbeads delayed Ketoprofen release in the stomach, reducing ulceration, mucosal erosion, and hemorrhage compared to pristine Ketoprofen. Pharmacokinetic analysis revealed that IPN microbeads extended the drug's absorption time (t_{max} of 6 hours) compared to pristine Ketoprofen (t_{max} of 1 hour), with a lower peak concentration but higher overall exposure (AUC). The anti-inflammatory effect was sustained and delayed, with reduced ulcer severity (0.15 ± 0.64 mm)

compared to pristine Ketoprofen (1.97 ± 0.72 mm). These findings suggest that IPN microbeads provide a gastro-protective, controlled-release system for Ketoprofen, enhancing therapeutic efficacy and safety[30].

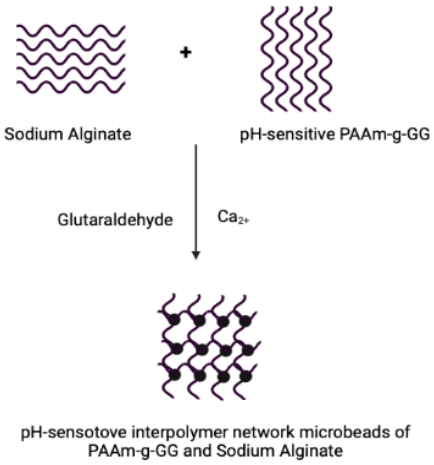

Figure 4: Preparation of the pH-sensitive Interpolymer network microbeads

Two types of Ketoprofen enteric beads were developed using alginate: calcium alginate for rapid release and chitosan-alginate for sustained release. Calcium alginate beads released less than 10% of Ketoprofen in acidic conditions but 95% at pH 6.8 within 45 minutes. Chitosan-alginate beads released less than 5% in acidic conditions and about 50% over 6 hours, reaching 95% after 12 hours at pH 6.8. Calcium alginate beads followed the Korsmeyer-Peppas model with a case-II transport mechanism, while chitosan-alginate beads showed a non-fickian mechanism combining diffusion and polymer relaxation. The addition of chitosan effectively controlled Ketoprofen release. Furthermore, higher molecular weight sodium alginate enhanced drug loading, entrapment efficiency, and viscosity of chitosan-alginate beads, particularly at lower alginate concentrations[31].

A nanogel carrier system for gastro-protective delivery of Ketoprofen was developed using Carbopol, methacrylic acid (MAA) for polymer grafting, and Methyl bisacrylamide (MBA) as a cross-linking agent. The system demonstrated pH-sensitive drug release, with maximum release at pH 7.4 and minimal release at pH 1.2, indicating its potential to bypass stomach acid. PXRD data revealed that the drug was in an amorphous state within the formulation, despite the crystallinity of its components. This formulation enhances drug bioavailability and minimizes gastric irritation, making Carbopol-g-methacrylic acid nanogels a promising tool for gastro-protective delivery of irritant drugs like Ketoprofen[32].

The complexation of Ketoprofen with β-CD led to the enhancement of the new complex product and resulted in a higher bioavailability than that of pure Ketoprofen. Also, the anti-inflammatory activity of Ketoprofen/β-CD complex was higher than that of Ketoprofen alone in two models of experimentally induced acute inflammation in rate by intraplantar administration of 10% aqueous kaolin suspension and intraperitoneal administration of 1% sodium thioglycolate solution. Both the anti-inflammatory and the analgesic activity of the Ketoprofen/β-CD complex were significantly higher and faster in onset than Ketoprofen alone, even at low dose rates[33]. Similar results were observed with the complexation of other NSAIDs with β-CD, which has enhanced therapeutic effect, better API stability, and less GI irritation[34-38].

Interpolymer complexes (IPCs) of chitosan with sodium alginate, sodium carboxymethylcellulose, and pectin were investigated for oral controlled drug delivery. The chitosan-sodium carboxymethylcellulose IPC showed superior control over drug release compared to chitosan-sodium alginate and chitosan-pectin IPCs. Physical mixtures of chitosan with these polymers were also studied, revealing that dissolution rates depended on the interaction between chitosan and the

anionic polymers, the ratio of chitosan to the anionic polymer, and the pH of the dissolution medium. In vivo tests with albino rabbits indicated that tablets with a 1:1 chitosan-sodium carboxymethylcellulose physical mixture had lower peak plasma concentrations and prolonged drug release compared to the IPC formulation. This study highlights the importance of selecting the right IPC or polymer ratios to achieve controlled drug delivery at specific locations within the GIT[39].

4. Microcarriers:

Microcarriers are drug delivery systems that are capable of carrying and releasing the drug on demand, they can control drug plasma levels and improve drug pharmacokinetics by extending/sustaining drug release resulting in enhanced oral bioavailability[40]. Several polymers have been used to prepare microcarriers such as chitosan, cellulose, sodium alginate, collagen, polycaprolactone, gelatin, and poly(D/L-lactide-co-glycolide)[41-44], and several methods were implemented to create microcarriers like spray drying, ultrasonic crushing, emulsifying solvent evaporation, and high-pressure homogenization[41].

A Ketoprofen-loaded microparticles was developed using a solvent-free technology, specifically VarioSol® with dense CO_2 and stearic acid with methacrylic polymers. This single-step process yielded uniform microparticles with 40% drug content and favorable powder characteristics. In vitro studies showed rapid drug release at pH 6.8, but the microparticles could delay drug release in acidic conditions, though not fully meeting EMA standards for gastro-resistance (≤10% release after 1 hour at pH 1.0). Despite not achieving full gastro-resistance, the results offer a promising basis for future delayed-release formulations[45].

In another study, a core-shell devices were developed for the sustained-release of Ketoprofen Lysinate using electrofluidodynamics and layer-by-layer techniques. Cellulose acetate microparticles were first created via electrohydrodynamic atomization. A chitosan layer was then applied to form a core-shell structure, with cellulose acetate providing gastro-resistance and chitosan enhancing drug encapsulation and water retention. This structure delays drug release in the stomach and promotes release in the intestines. The devices released over 80% of the drug along the gastrointestinal tract, with a significant delay in release (up to 3 hours) and sustained release for about 6 hours[46].

Nikam et al. developed a controlled-release microsphere for Ketoprofen using biodegradable waxes (beeswax and ceresin wax) combined with a wetting agent. Scanning electron microscopy confirmed the microspheres were spherical and smooth, while FTIR analysis ensured stability and compatibility. The in vitro release study showed an initial burst followed by sustained release over 24 hours. The microspheres, especially those with higher beeswax concentration, maintained effective drug levels longer, releasing about 92% of the drug within 24 hours. This sustained release could help reduce Ketoprofen's side effects compared to conventional dosage forms[47].

Another controlled-release Ketoprofen microspheres was developed using Eudragit® RS 100 and the solvent evaporation technique. They explored various process variables, including drug-to-polymer ratio, stirring rate, and emulsifier concentration. The microspheres demonstrated prolonged and controlled drug release, with lower C_{max} and higher T_{max} values compared to controls. Bioavailability studies in rabbits indicated that Ketoprofen-loaded microspheres had superior bioavailability compared to commercially available formulations and the unmodified drug. The study suggests that Eudragit® RS 100 is effective for achieving sustained drug release and enhancing Ketoprofen's bioavailability[48].

A similar study was conducted using the same technique for the preparation of a Ketoprofen-loaded microsphere using a different type of Eudragit polymer. Baig et al used water-insoluble polymers, such as Eudragit RS and Eudragit RL, as carriers for oral administration to achieve oral controlled release of Ketoprofen and to protect the gastric mucous membrane. All preparations had good entrapment efficiency, but the combined polymer formulation had the best efficiency. The particle size rises with increasing polymer concentration. The combined polymer microspheres had larger particle diameters than the separate polymers. The formulation's in-vitro release corresponded most closely to the Zero-order kinetics. According to the stability studies, 25°C is the ideal temperature for storing Ketoprofen Eudragit microspheres[49].

Another biodegradable water-insoluble polymer Acrycoat S100 was used to fabricate a controlled-release microsphere to limit the disadvantages of Ketoprofen. The emulsion solvent evaporation process was used to successfully create Ketoprofen microspheres. The polymer-drug ratio affects both the particle size and the microsphere's ability to release drugs. All formulations sustained in vitro drug release was seen during 12 hours. In light of this, it can be said that Ketoprofen-loaded Acrycoat S100 microsphere may be effective to achieve a prolonged drug release profile suitable for oral administration to reduce GI adverse effects[50].

Moreover, a novel microcontainer-based oral drug delivery system was developed featuring detachable microcontainers (D-MCs) for Ketoprofen. These D-MCs, created on a sacrificial layer for easier handling, were filled with Ketoprofen using supercritical carbon dioxide (scCO2) and coated with the pH-sensitive polymer Eudragit® L100 to ensure drug release only in the intestine. This approach kept Ketoprofen in an amorphous state, enhancing its absorption. Compared to traditional capsules, D-MCs increased the drug's absorption rate by 2.4 times and oral

bioavailability by 180% within 4 hours. Both in vivo and ex vivo studies validated the effectiveness of this delivery system[51].

Marizza et al. proposed a method combining inkjet printing and supercritical technologies for loading Ketoprofen into poly(vinylpyrrolidone) (PVP) K10 microcontainers to improve oral bioavailability. They replaced inkjet printing with manual powder pressing into the microcontainers to simplify and speed up the process. The powder-filled containers were then subjected to supercritical CO2 (scCO2) impregnation. This approach allowed for repeatable direct printing of up to 20% polymer in aqueous solution and ensured that the drug remained in an amorphous state. The improved technique significantly reduced sample preparation time and facilitated a more detailed investigation of the effects of temperature, pressure, and impregnation time on drug loading, resulting in increased throughput while maintaining precision and reproducibility[52].

A safe, effective and targeted delivery system for Ketoprofen in the form of pH-sensitive oral hydrogel based on Cellulose Acetate Phthalate (CAP) and Hydroxyethyl methacrylate (HEMA) free radicle polymerization for colon targeting developed. The hydrogel, in the form of artificial microgels, showed regulated Ketoprofen release depending on pH: least at pH 1.2 and most at pH 7.4. The microgels' enhanced diffusion properties were confirmed by SEM and XRD. Cytotoxicity tests with the MTT assay showed no toxicity, suggesting that these synthetic microgels are effective for Ketoprofen encapsulation and could be useful for pain treatment[53].

A floating microsphere was also developed to prolong the stomach residency time of Ketoprofen while minimizing direct contact with the gastric mucosa. The emulsion solvent evaporation method was used to prepare the floating microsphere with Ethyl cellulose and Hydroxypropyl

methyl cellulose (HPMC) in a ratio of 1:1. Ketoprofen microspheres that had been manufactured demonstrated longer drug release times and improved encapsulation efficiencies. The microspheres showed excellent flotational properties and can stay in the stomach for 4 hours. Therefore, it may turn out that these floating microspheres are suitable for gastro retentive dose methods[54].

Aerogel microspheres was investigated as carriers for Ketoprofen using starch, alginate, and pectin polysaccharides. Prepared via an emulsion-gelation method and supercritical drying, these microspheres displayed amorphous drug loading ranging from 11–24 % (w/w) with stable storage due to their dry format. In vitro release studies revealed pH-sensitive behavior for alginate and pectin microspheres, following the Gallagher-Corrigan release model. Starch microspheres, due to their rigid structure, exhibited release driven by dissolution and conformed to first-order kinetics. This variability in drug release profiles indicates that polysaccharide-based aerogels can be tailored for customized oral drug delivery systems[55].

Cross-linking technique was used to develop an alginate microsphere for sustained delivery of Ketoprofen using calcium chloride. Depending on the composition of the various microspheres, formulations showed good encapsulation efficiencies ranging from 70.88% to 96.12%. Ketoprofen's delayed release for up to 8 hours in all formulations in an in vitro experiment using phosphate buffer as the release medium. As the polymer concentration increased, a slower drug release was seen. Making alginate-based microspheres that could maintain Ketoprofen and sustain release for a long time was possible[56].

Finally, Ketoprofen microspheres was developed using biodegradable polymers, polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA), via an oil-in-water solvent evaporation method.

The drug entrapment efficiency ranged from 71.62% to 86.40%, with PLGA-based microspheres showing higher efficiency than PLA-based ones. Drug release was sustained for 24 hours in phosphate buffer but was lower in acidic conditions. These polymeric microspheres show promise for safe and efficient sustained drug delivery, potentially mitigating Ketoprofen's side effects[57].

5. Nanoparticles:

Nanoparticles (NP) are considered a type of colloidal drug delivery system that is made of particles with a size range from 10-1000 nm in diameter. Nanoparticles are believed to improve the bioavailability of drugs simply by enhancing drug solubility, they also increase the residence time of drugs within the body by increasing the clearance half-life of drugs, and finally, they can be used to deliver medication to a specific location of the body, thus, reducing the drug dosage and off-site adverse effect. There are several types of nanoparticles formulation in the literature, with various sizes, shapes, and materials, among those types, are fullerenes, solid lipid nanoparticles (SLN), liposomes, nanostructured lipid carriers (NLC), nanoshells, quantum dots (QD), superparamagnetic nanoparticles, dendrimers and nanofibers[58]. Because of its poor water solubility and its irritant activity on the Gastrointestinal (GI) tract, Ketoprofen was the subject of several attempts to be incorporated into nanoformulations.

5.1. Solid lipid nanoparticles:

Ketoprofen solid lipid nanoparticles (KSLN) was utilized as a drug carrier. KSLNs were prepared using a solvent injection technique, dissolving Ketoprofen and glyceryl monostearate in isopropyl alcohol, then adding it to an aqueous poloxamer 407 solution and adjusting the pH with 0.1N HCl. The optimized KSLNs had particle sizes ranging from 101.8 to 427.0 nm and entrapment efficiencies of 60.55% to 92.70%, which increased with higher glyceryl monostearate

concentrations. The drug release showed a biphasic profile: an initial burst followed by sustained release due to lipid content. Encapsulation in cellulose acetate-coated capsules reduced Ketoprofen release to 57% over 12 hours in simulated gastrointestinal fluid, potentially minimizing gastrointestinal side effects by shortening drug residence time in the stomach[59].

5.2. Polymeric Nano-particles:

An orodispersible film loaded with Ketoprofen nanoparticles (KTF-NP-ODFs) was developed using anti-solvent precipitation, incorporating HPMC EC1 and PEG 400 to create a viscous nanosuspension cast into thin films. Optimization using the Box-Behnken design showed a fourfold increase in permeability compared to pure Ketoprofen, attributed to enhanced solubility from nanonization. X-ray diffraction and modulated DSC confirmed the transformation of Ketoprofen into an amorphous form, which improved the drug's long-term stability. Dissolution studies revealed that 95% of Ketoprofen was released from KTF-NP-ODFs within 60 minutes at pH 1.2, compared to only 29% from pure Ketoprofen. The improved dissolution rate is due to the combined effects of nanonization and amorphization, which provide a larger surface area, higher surface free energy, and increased surface-to-volume ratio, enhancing the release of Ketoprofen even under acidic conditions[60].

5.3. Nanofibers:

Ketoprofen-loaded nanofibers were prepared using electrospinning with polyvinylpyrrolidone (PVP) as the filament-forming polymer. Two formulations were tested: one without Ketoprofen (F0) and one with 10% Ketoprofen (F1). Characterization via DSC, XRD, SEM, and FTIR confirmed that Ketoprofen existed in an amorphous solid dispersion state within the polymer, facilitated by hydrogen bonding between Ketoprofen and PVP (Figure 5). Dissolution studies

showed a dramatic improvement: 76.8% of Ketoprofen dissolved within 10 seconds and 100% within 30 seconds from the nanofibers, compared to only 1.3% and 3.4% dissolution from the pure drug and physical mixture (PM), respectively. This enhancement is attributed to the high surface area, wettability, porous structure of the nanofibers, and the amorphous state of Ketoprofen, eliminating the need for crystal lattice breakage. The PM also showed improved dissolution due to partial conversion of Ketoprofen crystals into the amorphous form[61].

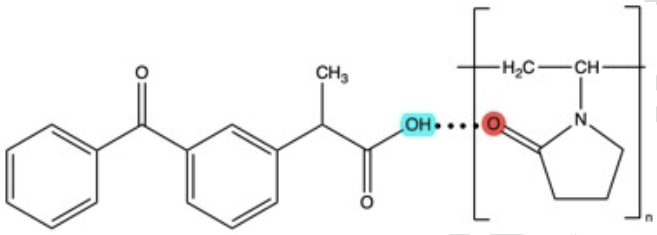

Figure 5: Hydrogen Bonding Ketoprofen-PVP

Ketoprofen-loaded chitosan/polyaniline hybrid nanofibers were developed as pH-responsive carriers for sustained drug release. The release of Ketoprofen was pH-dependent, increasing with higher pH, following Higuchi model kinetics and non-Fickian diffusion. The hybrid showed increased swelling at lower pH (63% at pH 2.0) due to protonation of amino and imino groups, enhancing hydrophilicity. In neutral pH, deprotonation led to a compact structure, reducing hydrophilicity. Ketoprofen release was 90% at pH 6.7 and 95% at pH 7.4 over 90 hours, compared to 70% at pH 2.0, due to reduced electrostatic interactions and higher solubility at neutral pH. The nanofibers sustained drug release effectively, with 65% released after 24 hours and 98% after 70 hours, highlighting their potential for controlled Ketoprofen delivery[62].

A Pickering nano-emulsions stabilized by Eudragit RL100 nanoparticles (NPs) were developed for oral Ketoprofen delivery. Eudragit RL100, known for its stability under gastrointestinal

conditions, was used to form NPs of 40 nm via nanoprecipitation. These NPs were then employed to create oil-in-water nano-emulsions using Labrafac® WL1349 as the oil phase, resulting in 220 nm emulsions with a polydispersity index of 0.184. Morphological analysis showed NPs as round spheres and nano-emulsions as larger particles. The NPs effectively stabilized the nano-emulsions, forming a rigid film that prevented flocculation and coalescence, thus enhancing stability. The Pickering nano-emulsions demonstrated prolonged Ketoprofen release compared to a control emulsion of Ketoprofen in Labrafac® WL1349. While the control released 100% of the drug within 1 hour, the Pickering nano-emulsions released only 30% in the first hour and 82% after 6 hours. This highlights the potential of Eudragit RL100 NPs in stabilizing nano-emulsions and designing novel controlled-release dosage forms for oral drug delivery[63].

5.4. Liposomes:

Liposomes are a highly explored type of nanoparticles, they are self-assembled lipid-based drug carriers that can form a bilayer and sometimes a centered series of multiple bilayers surrounding a central aqueous compartment. Their size can range from 30 nm to a micrometer in diameter. Liposomes can provide protection for the encapsulated drug from enzymatic attacks, and just like all nanoparticles they can extend drugs' half-life and target specific sites within the body[64].

A proliposomal powder of Ketoprofen was developed using the solvent evaporation method with various ratios of hydrogenated soy phosphatidylcholine (HSPC) and cholesterol to enhance dissolution rate, gastric absorption, and tolerance. The proliposomal powders showed significantly improved dissolution compared to pure Ketoprofen, with the best performance seen in formulations using equimolar ratios of HSPC and cholesterol loaded on Pearlitol SD 200, selected for its favorable flow characteristics and product consistency. The enhanced dissolution was

attributed to the transformation of crystalline Ketoprofen into an amorphous form, confirmed by solid-state characterization[65].

The encapsulation of Ketoprofen in liposomes stabilized with chitosan resulted in a sustained release of the drug, as indicated by prolonged antinociceptive activity in animal models. The liposomes were prepared using L-α-phosphatidylcholine, giving the vesicles a net positive charge and an average diameter of 1.287 µm. The Ketoprofen liposome formulation showed significant antinociceptive effects beginning at 90 minutes, with peak intensity between 2 to 8 hours and effects lasting up to 10 hours. The encapsulation efficiency was approximately 95%, confirmed by UV-Vis monitoring. The chitosan-stabilized liposomes released Ketoprofen more slowly than the pure drug, with a tmax of 1.5 hours compared to 0.5 hours for pure Ketoprofen, demonstrating the sustained release effect of the liposomal formulation[66].

6. Pharmacosomes:

Pharmacosomes are another lipid-based drug delivery system, it is a colloidal dispersion of drugs that bound covalently to lipids, they are neutral molecules that contain both positive and negative charge (zwitterionic), and possess both hydrophilic and lipophilic (amphiphilic) characteristics[67-68].

Despite the structural similarity between pharmacosomes and liposomes, the most significant difference between the two lipid-based delivery systems is the covalent bonding between the drug and the lipid in pharmacosomes, making the physicochemical properties of the formulation dependent on both the drug and the lipid, where in liposomes it is completely depending on the lipid used[67].

Ketoprofen pharmacosomes were prepared by complexing the drug with phosphatidyl using the solvent evaporation method. The pharmacosomes were in a disc shape and have a rough surface as shown in scanning electron microscopy. The solubility of the formulated pharmacosomes was enhanced significantly compared to the drug, which can be attributed to the wetting and dispersion mechanism. The enhanced solubility of Ketoprofen can be attributed to the solubilization that occurred due to the formation of micelles in the media and by the conversion of the crystalline Ketoprofen to the amorphous state due to complexation with the lecithin phospholipids. Drug content was found to be satisfactory in the range of 98-99% with high drug loading. Data showed that the release of Ketoprofen from the complex was sustained, following first-order kinetics, and diffusion was a non-fickian diffusion. Also, it was found that pharmacosomes were stable for two months in refrigerated conditions[69].

CONCLUSION:

The development of effective oral delivery systems for Ketoprofen is crucial for improving patient outcomes and minimizing the limitations associated with its physicochemical properties. This review has highlighted significant advancements in this field, showcasing various innovative approaches. Controlled-release formulations, including Zn-alginate beads, polysaccharide-based hydrogels, and monolithic osmotic tablets, demonstrate promising results in prolonging drug release, reducing dosing frequency, and minimizing gastrointestinal side effects. Oral-dissolving formulations, such as fast-disintegrating tablets, electrospun fibers, and orally disintegrating films, offer improved patient compliance and convenience, particularly for individuals with swallowing difficulties. Complexation techniques using polysaccharides and polymers provide gastro-protective controlled release, further enhancing the therapeutic profile of Ketoprofen. Lipid-based formulations, including self-emulsifying drug delivery systems and nanostructured lipid carriers,

effectively address the challenges posed by Ketoprofen's low solubility, leading to enhanced absorption and bioavailability.

The research efforts discussed in this review underscore the continuous pursuit of optimizing Ketoprofen therapy. While significant progress has been made, further research is warranted to explore novel biomaterials, optimize formulation parameters, and conduct comprehensive in vivo evaluations to translate these advancements into clinically viable solutions. The development of patient-centric oral delivery systems for Ketoprofen holds immense potential for improving treatment efficacy, reducing side effects, and ultimately enhancing the quality of life for patients suffering from inflammatory conditions.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

1. Mazumder K, Hossain ME, Aktar A, Mohiuddin M, Sarkar KK, Biswas B, et al. In silico analysis and experimental evaluation of ester prodrugs of Ketoprofen for oral delivery: with a view to reduce toxicity. Processes. 2021;9(12):2221.

2. Park S, Lee S-E, Lee J-K, Kim T-H, Jang WS, Park J-S. Preparation and physicochemical characterization of Ketoprofen-loaded emulsions. Journal of Pharmaceutical Investigation. 2016;46:487-93.

3. Das SK, Chakraborty S, Bose A, Rajabalaya R, Khanam J. Effects of the preparation technique on the physicochemical characteristics and dissolution improvement of Ketoprofen-SBE7-β-CD binary inclusion complexes. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2021;611:125775.

4. Patrignani P, Patrono C. Cyclooxygenase inhibitors: from pharmacology to clinical read-outs. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2015;1851(4):422-32.

5. Auriemma G, Cerciello A, Aquino RP. NSAIDS: design and development of innovative oral delivery systems. Nonsteroidal Anti-Inflammatory Drugs. 2017;33(10.5772).

6. Reis CP, Ferreira JP, Candeias S, Fernandes C, Martinho N, Aniceto N, et al. Ibuprofen nanoparticles for oral delivery: proof of concept. Journal of Nanomedicine & Biotherapeutic Discovery. 2014;4(1):1.

7. Bellomo RG, Carmignano SM, Palermo T, Cosenza L, Saggini A, Saggini R. Nonsteroidal anti-inflammatory drugs: integrated approach to physical medicine and rehabilitation. Nonsteroidal Anti-Inflammatory Drugs. 2017;67.

8. Szymański K, Gryta M, Darowna D, Mozia S. A new submerged photocatalytic membrane reactor based on membrane distillation for Ketoprofen removal from various aqueous matrices. Chemical Engineering Journal. 2022;435:134872.

9. Global Ketoprofen Market Report, history and forecast 2016-2027, Breakdown Data by manufacturers, key regions, types and application [Internet]. Precision Reports; 2021 [cited 2024 Sept 17]. Available from: http://www.precisionreports.co/global-Ketoprofen-market-18819328.

10. Kane S. Ketoprofen: ClinCalc; 2024 [Available from: https://clincalc.com/DrugStats/Drugs/Ketoprofen.

11. Adepu S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. Molecules. 2021;26(19):5905.

12. Bermejo M, Sanchez-Dengra B, Gonzalez-Alvarez M, Gonzalez-Alvarez I. Oral controlled release dosage forms: dissolution versus diffusion. Expert Opinion on Drug Delivery. 2020;17(6):791-803.

13. Cerciello A, Auriemma G, Morello S, Pinto A, Del Gaudio P, Russo P, et al. Design and in vivo anti-inflammatory effect of Ketoprofen delayed delivery systems. Journal of pharmaceutical sciences. 2015;104(10):3451-8.

14. Tous S, Fathy M, Fetih G, Gad SF. Preparation and evaluation of Ketoprofen-loaded calcium alginate beads. Int J PharmTech Res. 2014;6(3):1100-12.

15. Cerciello A, Auriemma G, Del Gaudio P, Cantarini M, Aquino RP. Natural polysaccharides platforms for oral controlled release of Ketoprofen lysine salt. Drug development and industrial pharmacy. 2016;42(12):2063-9.

16. Kaushik S, PATHAK K. Development and evaluation of monolithic osmotic tablet of Ketoprofen: Using solid dispersion technique. Int J Pharm Pharm Sci. 2016;8(12):41-7.

17. Patel J, Patel M, Bhandari A. Development and evaluation of time controlled pulsatile drug delivery system of Ketoprofen. Int J Curr Res Chem Pharma Sci. 2015;2(1):46-50.

18. Harsha MV, Baratam SR, Kishore AK. Development and evaluation of Ketoprofen sustained delivery system using Neem Gum. Research Journal of Pharmacy and Technology. 2021;14(2):817-22.

19. Nur AO, Elballa W, Osman ZA, Abdeen M. INFLUENCES OF PROCESSING METHOD, FILLER TYPE AND APPLIED COMPRESSION FORCE ON PHARMACEUTICAL PROPERTIES OF KETOPROFEN ORAL MATRICES. 2015;14(8):29-34

20. ELBALLA W, SALIH M. INFLUENCE OF PARTIALLY AND FULLY PREGELATINIZED STARCH ON THE PHYSICAL AND SUSTAINED-RELEASE PROPERTIES OF HPMC-BASED KETOPROFEN ORAL MATRICES. Int J Pharm Pharm Sci. 2022:29-34.

21. Almukainzi M, Araujo GL, Löbenberg R. Orally disintegrating dosage forms. Journal of Pharmaceutical Investigation. 2019;49:229-43.

22. Cornilă A, Iurian S, Tomuță I, Porfire A. Orally dispersible dosage forms for paediatric use: current knowledge and development of nanostructure-based formulations. Pharmaceutics. 2022;14(8):1621.

23. Hannan P, Khan J, Khan A, Safiullah S. Oral dispersible system: A new approach in drug delivery system. Indian journal of pharmaceutical sciences. 2016;78(1):2.

24. Sisodiya R. Formulation of fast dissolving Ketoprofen tablet by solid dispersion technique. Journal of Drug Delivery and Therapeutics. 2018;8(6-A):85-92.

25. Geng Y, Zhou F, Williams GR. Developing and scaling up fast-dissolving electrospun formulations based on poly (vinylpyrrolidone) and Ketoprofen. Journal of Drug Delivery Science and Technology. 2021;61:102138.

26. Oliveira LJ, Veiga A, Stofella NC, Cunha AC, da Graça T Toledo M, Andreazza IF, et al. Development and evaluation of orodispersible tablets containing Ketoprofen. Current Drug Delivery. 2020;17(4):348-60.

27. Venkateswarlu K. Formulation and in-vitro Evaluation of Mouth Dissolving Tablets of Ketoprofen: Effect of Disintegrants on Drug Release. PharmaTutor. 2017;5(6):17-24.

28. Sairam RJ, Thouseef M. DESIGN & DEVELOPMENT OF FAST DISSOLVING ORAL FILMS OF KETOPROFEN. 2018.

29. Nasser SJ, Sameen LH, Ghareeb MM. Preparation and Evaluation of Oral Disintegrating Tablets of Ketoprofen by Dirct Compression. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2012;21(2):63-8.

30. Boppana R, Mohan GK, Nayak U, Mutalik S, Sa B, Kulkarni RV. Novel pH-sensitive IPNs of polyacrylamide-g-gum ghatti and sodium alginate for gastro-protective drug delivery. International journal of biological macromolecules. 2015;75:133-43.

31. Cheng B, Li D, Huo Q, Zhao Q, Lan Q, Cui M, et al. Two kinds of Ketoprofen enteric gel beads (CA and CS-SA) using biopolymer alginate. asian journal of pharmaceutical sciences. 2018;13(2):120-30.

32. Sarfraz RM, Khan MU, Mahmood A, Akram MR, Minhas MU, Qaisar MN, et al. Synthesis of co-polymeric network of carbopol-g-methacrylic acid nanogels drug carrier system for gastro-protective delivery of Ketoprofen and its evaluation. Polymer-Plastics Technology and Materials. 2020;59(10):1109-23.

33. Grecu M, Năstasă V, Ilie C, Miron L, Mareş M. Comparative assessment of effectiveness of Ketoprofen and Ketoprofen/beta-cyclodextrin complex in two experimental models of inflammation in rats. Laboratory animals. 2014;48(1):20-6.

34. Loftsson T, Duchene D. Cyclodextrins and their pharmaceutical applications. International journal of pharmaceutics. 2007;329(1-2):1-11.

35. Lu W-L, Zhang Q, Zheng L, Wang H, Li R-Y, Zhang L-F, et al. Antipyretic, analgesic and anti-inflammatory activities of Ketoprofen β-cyclodextrin inclusion complexes in animals. Biological and Pharmaceutical Bulletin. 2004;27(10):1515-20.

36. Baboota S, Dhaliwal M, Kohli K. Physicochemical characterization, in vitro dissolution behavior, and pharmacodynamic studies of rofecoxib-cyclodextrin inclusion compounds. Preparation and properties of rofecoxib hydroxypropyl β-cyclodextrin inclusion complex: A technical note. AAPS PharmSciTech. 2005;6:E83-E90.

37. Tayade P, Vavia P. Inclusion complexes of Ketoprofen with?-cyclodextrins: Oral pharmacokinetics of Ketoprofen in human. Indian journal of pharmaceutical sciences. 2006;68(2).

38. Maestrelli F, Zerrouk N, Cirri M, Mennini N, Mura P. Microspheres for colonic delivery of Ketoprofen-hydroxypropyl-β-cyclodextrin complex. european journal of pharmaceutical sciences. 2008;34(1):1-11.

39. El-Gawad A, El-Gawad A, Ramadan EM, Soliman OA, Yusif RM. Formulation and in-vivo study of Ketoprofen tablets prepared using chitosan interpolymer complexes. Bulletin of Pharmaceutical Sciences Assiut University. 2012;35(1):1-16.

40. Cai L, Li N, Zhang Y, Gu H, Zhu Y. Microfluidics-derived microcarrier systems for oral delivery. Biomedical Technology. 2023;1:30-8.

41. Liu Y, Huang Q, Wang J, Fu F, Ren J, Zhao Y. Microfluidic generation of egg-derived protein microcarriers for 3D cell culture and drug delivery. Science bulletin. 2017;62(18):1283-90.

42. Wan J. Microfluidic-based synthesis of hydrogel particles for cell microencapsulation and cell-based drug delivery. Polymers. 2012;4(2):1084-108.

43. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. Chemical reviews. 2016;116(4):2602-63.

44. Cheng CJ, Tietjen GT, Saucier-Sawyer JK, Saltzman WM. A holistic approach to targeting disease with polymeric nanoparticles. Nature reviews Drug discovery. 2015;14(4):239-47.

45. Segale L, Mannina P, Giovannelli L, Danan H, Esposito P, Galli L, et al. A novel dense CO2 supercritical fluid technology for the development of microparticulate delivery systems containing Ketoprofen. European journal of pharmaceutics and biopharmaceutics. 2012;82(3):491-7.

46. Guarino V, Caputo T, Calcagnile P, Altobelli R, Demitri C, Ambrosio L. Core/shell cellulose-based microspheres for oral administration of Ketoprofen Lysinate. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2018;106(7):2636-44.

47. Nikam V, Gudsoorkar V, Derle D. Development and evaluation of Ketoprofen loaded lipid microspheres for controlled release drug delivery. IJAPBC Int J Adv Pharm Biol Chemistry. 2015;4(2):287-93.

48. Abdallah MH, Sammour OA, El-Ghamry HA, El-Nahas HM, Barakat W. Development and characterization of controlled release Ketoprofen microspheres. Journal of Applied Pharmaceutical Science. 2012(Issue):60-7.

49. Fazil B, Mohammed G. Formulation and evaluation of controlled release Ketoprofen microspheres. International journal of research in pharmaceutical and biomedical sciences. 2012;3(3):1167-72.

50. Prajapati CV, Patel RP, Prajapati BG. Formulation, optimization and evaluation of sustained release microsphere of Ketoprofen. Journal of Pharmacy and Bioallied Sciences. 2012;4(Suppl 1):S101-S3.

51. Mazzoni C, Tentor F, Strindberg SA, Nielsen LH, Keller SS, Alstrøm TS, et al. From concept to in vivo testing: Microcontainers for oral drug delivery. Journal of Controlled Release. 2017;268:343-51.

52. Marizza P, Pontoni L, Rindzevicius T, Alopaeus J, Su K, Zeitler J, et al. Supercritical impregnation of polymer matrices spatially confined in microcontainers for oral drug delivery: Effect of temperature, pressure and time. The Journal of Supercritical Fluids. 2016;107:145-52.

53. Zia MA, Sohail M, Minhas MU, Sarfraz RM, Khan S, de Matas M, et al. HEMA based pH-sensitive semi IPN microgels for oral delivery; a rationale approach for Ketoprofen. Drug Development and Industrial Pharmacy. 2020;46(2):272-82.

54. Hafeez A, Maurya A, Singh J, Rana L. In-vitro evaluation of floating microspheres of Ketoprofen. Journal of Scientific and Innovative Research. 2013;2(3):714-22.

55. García-González CA, Jin M, Gerth J, Alvarez-Lorenzo C, Smirnova I. Polysaccharide-based aerogel microspheres for oral drug delivery. Carbohydrate polymers. 2015;117:797-806.

56. Al-Tahami K. Preparation, characterization, and in vitro release of Ketoprofen loaded alginate microspheres. Int J Appl Pharm. 2014;6(3):9-12.

57. Al-Nasi AA, Al-Tahami KA. Preparation, characterization, and in vitro release of Ketoprofen loaded polymeric microspheres. Int J PharmTech Res. 2016;9:313-21.

58. Mudshinge SR, Deore AB, Patil S, Bhalgat CM. Nanoparticles: Emerging carriers for drug delivery. Saudi pharmaceutical journal. 2011;19(3):129-41.

59. Srivastava A, Kumar S, Kushwaha P, Maddheshiya P, Srivastava M. Formulation and Optimization of Ketoprofen Loaded Solid Lipid Nanoparticles Using Central Composite Design. Pharmaceutical and Biosciences Journal. 2019:10-9.

60. Shah HG, Rathod V, Basim P, Gajera B, Dave RH. Understanding the impact of multi-factorial composition on efficient loading of the stable Ketoprofen nanoparticles on orodispersible films using Box-Behnken Design. Journal of Pharmaceutical Sciences. 2022;111(5):1451-62.

61. Yu D-G, Branford-White C, Shen X-X, Zhang X-F, Zhu L-M. Solid dispersions of Ketoprofen in drug-loaded electrospun nanofibers. Journal of Dispersion Science and Technology. 2010;31(7):902-8.

62. Minisy IM, Salahuddin NA, Ayad MM. In vitro release study of Ketoprofen-loaded chitosan/polyaniline nanofibers. Polymer Bulletin. 2021;78(10):5609-22.

63. Dieng SM, Omran Z, Anton N, Thioune O, Djiboune AR, Sy PM, et al. Pickering nano-emulsions stabilized by Eudragit RL100 nanoparticles as oral drug delivery system for poorly soluble drugs. Colloids and Surfaces B: Biointerfaces. 2020;191:111010.

64. Liu P, Chen G, Zhang J. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. Molecules. 2022;27(4):1372.

65. Gangishetty H, Eedara BB, Bandari S. Development of Ketoprofen loaded proliposomal powders for improved gastric absorption and gastric tolerance: in vitro and in situ evaluation. Pharmaceutical development and technology. 2015;20(6):641-51.

66. Tarţău L, Cazacu A, Melnig V. Ketoprofen-liposomes formulation for clinical therapy. Journal of Materials Science: Materials in Medicine. 2012;23:2499-507.

67. Semalty A, Semalty M, Rawat BS, Singh D, Rawat M. Pharmacosomes: the lipid-based new drug delivery system. Expert opinion on drug delivery. 2009;6(6):599-612.

68. Pandita A, Sharma P. Pharmacosomes: an emerging novel vesicular drug delivery system for poorly soluble synthetic and herbal drugs. International Scholarly Research Notices. 2013;2013(1):348186.

69. Kaur A, Sharma N, Harikumar S. Design and development of Ketoprofen Pharmacosomes for oral delivery. Pharmacophore. 2013;4(4-2013):111-9.