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CHARACTERIZATION AND PHARMACOKINETIC ASSESSMENT OF NAPROXEN FORMULATIONS: DESIGN AND DEVELOPMENT INSIGHTS

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ABSTRACT

The study presents a comprehensive approach to the formulation, design, and pharmacokinetic assessment of naproxen formulations, focusing on their development and characterization for enhanced therapeutic efficacy. Naproxen, a widely used non-steroidal anti-inflammatory drug (NSAID), is often associated with gastrointestinal and other systemic side effects. The goal of this research was to design optimized naproxen formulations that improve drug release and bioavailability while minimizing side effects.

Various formulation techniques were explored, including solid dispersion, microencapsulation, and nanoformulations, aimed at enhancing the solubility and stability of naproxen. The characterization of these formulations involved a series of in-depth analyses, including drug release studies, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray diffraction (XRD), to assess the physical properties, morphology, and drug content uniformity.

In vitro pharmacokinetic assessments were carried out to evaluate the drug release profiles and to predict the absorption kinetics of the formulations. The formulations were subjected to dissolution studies, and the release data were analyzed using various models to understand the release mechanism. Additionally, the in vitro pharmacokinetics were used to estimate the bioavailability and potential improvements in the therapeutic action of the drug.

The results indicated significant improvements in drug release, solubility, and bioavailability for certain formulations, with enhanced stability and reduced risk of side effects. These findings suggest that advanced drug delivery strategies can offer substantial benefits for naproxen therapy, paving the way for the development of more effective NSAID formulations.

This research highlights the importance of innovative formulation techniques in improving the pharmacokinetics of naproxen, providing insights into how drug release and bioavailability can be optimized for better clinical outcomes.

I. INTRODUCTION

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II. LITERATURE SURVEY

Solubility Enhancement of NSAIDs: Several studies have highlighted the challenges associated with the poor aqueous solubility of NSAIDs like naproxen. Techniques such as solid dispersion (Chiou & Riegelman, 1971), inclusion complexation with cyclodextrins (Loftsson & Brewster, 2010), and nanoparticle engineering (Kumar et al., 2018) have been explored to enhance the solubility and dissolution rate of naproxen.

Advanced Formulation Techniques: Research into microencapsulation (Jain et al., 2015) and nanoemulsion systems (Sharma et al., 2020) has demonstrated the potential of these approaches to improve the controlled release and bioavailability of naproxen. Such methods also mitigate the gastrointestinal side effects commonly associated with NSAIDs.

Drug Delivery Systems: The development of sustained-release and controlled-release formulations of naproxen has been extensively studied. Techniques like matrix tablets (Korsmeyer et al., 1983) and hydrophilic polymers (Peppas et al., 1985) have been employed to regulate the release rate, prolong the drug's therapeutic action, and improve patient compliance.

Characterization Techniques: The application of advanced characterization

tools such as Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Scanning Electron Microscopy (SEM) is well-documented in the literature (Gupta et al., 2017). These techniques are crucial for understanding the physicochemical properties of drug formulations, including crystallinity, thermal stability, and surface morphology.

Pharmacokinetic Studies: Numerous studies have evaluated the pharmacokinetics of naproxen formulations to predict drug absorption, distribution, metabolism, and excretion (ADME). In vitro-in vivo correlation (IVIVC) models (Wagner et al., 1969) have been utilized to bridge the gap between laboratory data and clinical performance.

Enhancement of Bioavailability: Nanotechnology-based approaches, such as nanosuspensions and lipid-based carriers, have shown promise in enhancing the oral bioavailability of naproxen (Müller et al., 2000). These systems improve drug dissolution and permeability across biological membranes.

Gastrointestinal Safety of Naproxen: Studies have reported that conventional naproxen formulations often lead to gastrointestinal irritation due to direct mucosal exposure and systemic effects. Co-administration with proton pump inhibitors or the use of gastroprotective coatings (Singh et al., 2012) has been explored to reduce adverse effects.

Regulatory and Stability Considerations: Stability studies following ICH guidelines (Q1A) are critical for ensuring the safety and efficacy of naproxen formulations over their shelf life. Research by Patel et al. (2019) underscores the importance of stability testing in formulation development.

Emerging Delivery Systems: Recent innovations, such as transdermal patches and orally disintegrating films, have expanded the scope of naproxen delivery. These systems are designed for patient-centric applications, particularly for those with swallowing difficulties or requiring localized delivery (Basak et al., 2021).

This comprehensive review of existing literature underscores the diverse strategies and methodologies employed to enhance the formulation and therapeutic performance of naproxen. It also identifies gaps in current research, such as the limited exploration of hybrid delivery systems, providing a foundation for future studies.

III. FORMULATION APPROACHES FOR COLON TARGETED DRUG DELIVERY

3.1. pH-Dependent Drug Delivery Systems

One potential targeted technique for colonic medication administration is the colon's comparatively higher pH than that of the upper GI tract. Therefore, pH-dependent polymers like cellulose acetate phthalates (CAP), hydroxypropyl methyl-cellulose phthalate (HPMCP) 50 and 55, and copolymers of methacrylic acid and methyl methacrylate (e.g., Eudragit® S 100, Eudragit® L, Eudragit® FS, and Eudragit® P4135 F) are used to design a colon-targeted drug delivery system [11,12]. The most popular synthetic copolymers for colonic drug administration, in particular, are Eudragit® polymers, which provide pH-dependent drug release and mucoadhesiveness [13,14]. The ideal polymer should be soluble in the terminal ileum and colon yet resistant to the low pH of the stomach and the proximal portion of the small intestine. In order to delay drug breakdown and

avoid premature drug release in the upper GI tract before reaching colonic locations, drug delivery systems coated with pH-dependent polymers with a dissolution threshold of pH 6.0–7.0 are anticipated to be effective [15]. However, because of the wide range of inter- and intra-subject variation in vital factors including pH, fluid volumes, GI transit durations, and motility, this pH-dependent device has shown notable variability in drug release and failure in vivo [16]. Additionally, microbial metabolism, water consumption, illness condition, and nutrition may all drastically change the pH ranges of the GI tract [17]. For instance, compared to healthy people, patients with ulcerative colitis have higher acidic intestinal pH, which results in partial medication release from enteric coated systems at the target location [16]. Therefore, the effectiveness of pH-dependent drug release systems may be diminished by the dynamic pH shift caused by several internal and external causes, which frequently results in poorly site-selective drug release. Due to either early drug release prior to the target location or disintegration failure at the target site, Ibekwe et al. [18] also found that the Eudragit® S coating was unsuitable for colon-targeted drug release. The absence of site-selective drug release of Eudragit® S coated tablets was verified in the ensuing human investigations by Ibekwe et al. [19], indicating that a number of physiological parameters, including as intestinal transit duration, feed status, and gastrointestinal pH, influence the breakdown of these tablets.

There have been attempts to employ pH-dependent delivery systems in conjunction with other delivery methods, such as time-dependent and enzyme-triggered systems, in order to get around this constraint. For instance, high-amylose maize starch and Eudragit® S were used to integrate colonic microbial degradation systems and pH-dependent systems [16,20].

In order to speed up drug dissolution at pH > 7, Liu et al. [21] used a dual coating technique, employing an organic solution of Eudragit® S for the outer layer and an alkaline aqueous solution of Eudragit® S with buffering agents for the inner layer. The in vivo performance of this dual coated method was next assessed in humans by Varum et al. [22], who showed that the dual coated tablets disintegrated more consistently, mostly in the lower digestive tract. For the colonic administration of prednisolone, Hashem et al. [23] created microspheres that combined pH-dependent and time-dependent mechanisms. They prevented premature drug release in the upper gut and increased colonic drug delivery by combining Eudragit® S with ethyl cellulose [23]. Another multi-unit technology that offers consistent, delayed medication release and targeted drug delivery to the colon is Eudracol®. The foundation of this technology is covering the pellet with Eudragit® RL/RS and Eudragit® FS 30D, which provides pH- and time-dependent colon-specific drug release [24]. Although more work has to be done, integrated systems of the various release-triggering mechanisms are generally more useful than pH-dependent systems alone in overcoming the pathophysiological unpredictability. Furthermore, nano-/micro-particles have a lot of promise for improving medication absorption and precisely targeting inflammatory colonic regions. As a result, many formulations have been created for colon-targeted drug delivery that combine a pH-dependent mechanism with particle size reduction.

3.1.1. Polymer-Based Nano-/Micro-Particles

pH-dependent polymeric nanoparticles have been shown in several studies to be efficient colonic drug delivery vehicles [25, 26]. Mutalik et al. [27] delivered curcumin nanoparticles to the colon using a new pH-sensitive hydrolysed polyacrylamide-grafted-xanthan gum (PAAm-g-XG). At pH 1.2 and 4.5, the PAAm-g-XG-modified nanoparticles released very little drug; at pH 7.2, however, the nanoparticles produced a greater and quicker amount of drug [27]. As a result, in IBD rat models, the nanoparticles effectively reduced intestinal inflammation and caused weight reduction. Moreover, the drug release rate may be regulated using the blended combination of two distinct pH-sensitive polymers. By combining Eudragit® L100 and Eudragit® S100, Sahu and Pandey [28] created HBsAg-loaded nanoparticles for efficient colonic immunisation, demonstrating both the enhanced immune response and the efficient dispersion of nanoparticles at the colon [28]. Budesonide-loaded pH-/time-dependent nanoparticles were created by Naeem et al. [29] to enhance the site-specificity to the colon for the efficient treatment of colitis. The oil-in-water emulsion solvent evaporation process was used to create these nanoparticles using Eudragit® FS30D and Eudragit® RS100. While Eudragit® RS100 is a time-dependent, controlled-release polymer with limited permeability, Eudragit® FS30D is a pH-dependent polymer that dissolves in an environment above pH 7.0. By combining these two polymers, sustained drug release was accomplished throughout the colon and premature drug release in the upper GI tract was successfully reduced. Additionally, these pH-/time-dependent nanoparticles more effectively transported medications to the inflammatory colonic regions in colitis mouse models. [29].

3.1.2. Lipid-Based Formulations

Liposomes, which are made of double-layered phospholipids, are an effective drug delivery mechanism [10, 30, 31]. Drugs that are hydrophilic or lipophilic can be incorporated into liposomes since they are biodegradable and biocompatible [32, 33]. Liposomes' surface can be coated with ligands to increase site-specificity and pH-dependent polymers to prevent liposome destabilisation in acidic environments. For instance, Zhao et al. [34] coated the surface of anionic liposomes with pH-dependent Eudragit® S100 and glycol chitosan to create colon-targeted liposomal formulations for sorafenib. Rats' systemic exposure to sorafenib was improved by these liposomes' exceptional stability at both acidic and neutral pHs and their low drug leakage [34].

In terms of drug protection, entrapment effectiveness, and boosting the quantity of medication released at certain areas, solid lipid nanoparticles are also an excellent method [10,35,36]. Solid lipid nanoparticles' lipid matrix breaks down gradually, allowing for prolonged drug release [10].

When designing colon-targeted drug delivery systems, self-microemulsifying drug delivery systems (SMEDDS) have great promise for improving the oral bioavailability of a variety of hydrophobic medications [37–41]. Curcumin-containing folate-modified SMEDDS (FSMEDDS) were made by Zhang et al. [42] and put into soft capsules coated with Eudragit® S 100. Colon cancer cells' folate receptors were effectively bound by this curcumin-loaded FSMEDDS formulation. These findings showed that colon-targeted FSMEDDS capsules are a practical way to deliver curcumin to the colon [42].

3.1.3. Tablets and Capsules

Despite the limited number of commercially available products, film coated tablets or capsules can be used to provide colon focused medication administration [4,43]. A pH-sensitive polymer-coated drug delivery system's colonic drug release is depicted schematically in Figure 1. Both macromolecules and low molecular synthesised medicines can be used using this approach. Eudragit L100-coated tablets were recently created by Crowe et al. [44] to administer a new anti-tumor necrosis factor α domain antibody (V565) colonically. At pH > 6, this tablet showed sustained drug release; however, after two hours of incubation in acidic circumstances, there was no drug release. The prolonged release of V565 in the colon for the topical treatment of IBD was further validated by in vivo research conducted on monkeys [44]. Additionally, a mixture of copolymers with different ratios can be used to alter the drug release characteristics [44]. For colon-targeted medication administration, this combination method could be better than tablets coated with a single polymer. However, because the pH in the GI tract varies, tablets coated solely with pH-sensitive enteric polymers still have problems with premature drug release [45]. Furthermore, site-specific drug release from the pH-dependent system is impacted by variations in the GI fluid composition, eating status, and GI transit time [45]. As a result, ongoing attempts have been made to increase the targeting effectiveness by multi-unit formulations that integrate several mechanism-based systems with pH-dependent coating [46]. A bisacodyl-loaded multi-unit tablet, for instance, was made by Park et al. [46] by covering it with various mixtures of pH-dependent polymers (Eudragit S and L) and time-dependent polymers (Eudragit RS). In the simulated intestinal and stomach fluids, the optimised tablet's drug release was negligible, but in the colonic fluid, it was widespread [46]. A tablet core was successively coated with low-viscosity HPMC and Eudragit® L to create an efficient colonic delivery system of 5-aminosalicylic acid. Foppoli et al. [47] recently disclosed this method, which was based on a combination of time-dependent and pH-dependent techniques. Additionally, they verified that there was no early drug release before reaching the colon in both fed and fasted stages, based on a human γ-scintigraphy research [47].

Zein's resistance to low pH settings makes it a promising carrier for controlled-release solid dispersion systems that transport poorly water-soluble medications to the colon [48]. Using the biopolymer Zein in conjunction with Kollicoat® MAE 100P, a single-layer film coating of tablets has recently demonstrated great promise in preventing drug release in the upper gastrointestinal tract for delayed drug release in the colon [49]. The effectiveness of coated tablets for colonic medication administration is significantly influenced by the coating layer's thickness and the proportion of its constituent parts.

To increase the targeting efficiency of pH-dependent delivery systems, novel coating technology has been intensively sought in recent years. ColoPulse technology, for instance, is a novel pH-responsive coating technique that uses a super-disintegrant in the coating matrix to hasten disintegration at the target location [50–52]. When a super-disintegrant is added in a non-percolating manner, the drug release becomes more dependable and pulsatile. ColoPulse pills allowed for site-specific distribution of the active ingredient to the ileo-colonic area in both healthy volunteers and Crohn's disease patients,

according to earlier research [50,51]. Additionally, the targeting effectiveness of ColoPulse delivery devices was unaffected by the type of meal consumed or the time it was consumed [51]. This technique was recently used by Gareb et al. [52] to create zero-order sustained-release budesonide tablets that target the ileo-colonic for the topical treatment of IBD. The findings showed that the produced tablet's medication release started in the simulated ileum and continued at a consistent pace throughout the duration of the simulated colon [52]. For the local treatment of ileo-colonic IBD, they also created and verified the manufacturing procedure for oral infliximab tablets coated with ColoPulse technology [53]. An further strategy for site-specific medication administration is the creation of capsule shells with inherent gastroresistance. Some possible benefits of these gastroresistant capsule shells include the ability to encapsulate a variety of medications, reduce research and development expenses, and be produced in large quantities using a standard high-speed capsule filler. A straightforward process for creating enteric capsule shells without the need for further coating stages was described by Barbosa et al. [54]. They used cellulose derivatives (HPMC AS-LF and HP-55) and acrylic/methacrylic acid derivatives (Eudragit® L100 and Eudragit® S100) to create distinct enteric capsule shells that target different GI tract regions. This may offer an additional alternative for targeted medication administration, even if the efficacy of premade enteric capsules for colonic drug delivery has not yet been fully assessed. Large manufacturing employing a standard high-speed capsule filler, encapsulating a variety of medications, and perhaps lowering R&D expenses (Pharmaceutics 2020, 12, x 5 of 19). A straightforward process for creating enteric capsule shells without the need for further coating stages was described by Barbosa et al. [54]. They used cellulose derivatives (HPMC ASLF and HP-55) and acrylic/methacrylic acid derivatives (Eudragit® L100 and Eudragit® S100) to create distinct enteric capsule shells that target different GI tract regions. Although a comprehensive evaluation of the efficacy of premade enteric capsules for colonic medication administration has not yet been conducted, this may

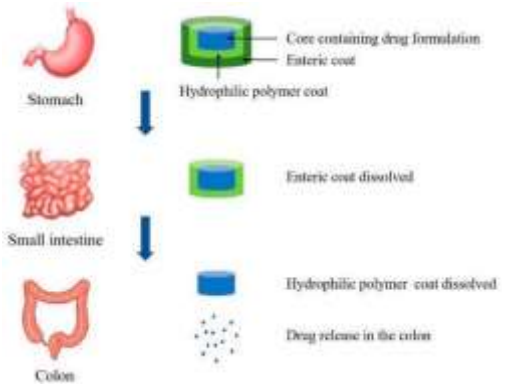

Figure 1. Drug release in the colon from pH-sensitive polymer-based system.

3.2. Enzyme-Sensitive Drug Delivery Systems

3.2.1. Polysaccharide-Based Systems

Because of the sudden rise in microbiota and the corresponding enzyme activity in the lower GI tract, microbiota-activated delivery methods have demonstrated promise in colon-targeted medication delivery. These systems rely on the polymers that colonic microorganisms may break down as well as the particular enzyme activity of the bacteria that live there. Because they may maintain their integrity throughout the upper gastrointestinal tract while being broken down by colonic bacteria to release the entrapped medication, polysaccharides including pectin, guar gum, inulin, and chitosan have been specifically employed in colon-targeted drug delivery systems

[55]. New polysaccharides, such as agave fructans and arabinoxylans, are being investigated recently for colonic drug delivery systems [56,57]. Moreover, polysaccharide derivatives or structural changes might enhance site specificity, stability, and drug release behaviour [58]. Through extended contact between the mucosal surface and drug delivery vehicles, polysaccharide mucoadhesiveness may promote drug absorption.

By combining polysaccharides and polymers, polysaccharide-based solutions can be created to address these problems and prevent early drug release in the upper gastrointestinal tract. For instance, a variety of polysaccharides are frequently employed in conjunction with water-insoluble polymers such ethyl cellulose and Eudragit RS to transfer drugs to the colon [62]. When it came to colon-specific medication delivery, using a blended combination of polysaccharides or other polymers seemed to be more successful overall than using just one polysaccharide [62]. The kind and concentration of polysaccharides in the mixed mixture determine the rate of medication release. For orthotopic colon cancer treatment, Song et al. [63] recently created an oral drug delivery device with magnetic resonance imaging capabilities and planned drug release. They chose chitosan (CS), an enzyme-sensitive moiety that may be broken down by β-glycosidase in the colon, and polyacrylic acid (PAA), a pH-responsive polymer, to be anchored on Gd3+-doped mesoporous hydroxyapatite nanoparticles (Gd-MHAp-NPs). Following oral delivery, CS and PAA may be able to stop early drug release and increased drug concentrations at the locations of colon tumours [63]. Additionally, a synergistic therapeutic effect was obtained by encapsulating both 5-fluorouracil and gefitinib in Gd-MHAp NPs, indicating that this innovative delivery system may be a potential therapy option for orthotopic colon cancer with programed drug release inside the colonic environment [63]. Table 1 displayed a few of the chosen instances for polysaccharide-based systems that combine polysaccharides and polymers.

All things considered, polysaccharides are still widely employed in pharmaceutical applications despite the primary disadvantages and restrictions of polysaccharide-based delivery methods. Various attempts have been made to address these issues.

3.2.2. Phloral® Technology

A new colonic coating method that combined bacterially-triggered and pH-dependent systems into a single layer matrix film was described by Ibekwe et al. [20]. A combination of biodegradable polysaccharide and Eudragit S was used to film-coat the tablets. The continuous disintegration of these tablets in the colon, independent of food state, was validated by a gamma scintigraphy research conducted on human volunteers. This suggests that the dual-mechanism coating may improve colonic medication targeting and overcome the limitations of single trigger systems [20]. Then, under both healthy and pathological conditions, Phloral® (Figure 2) coating technology showed accurate and failsafe drug release in the colon [81]. This system is made up of a pH-dependent polymer and an enzyme-sensitive component (natural polysaccharide), and the pH and enzymatic triggers complement each other to promote site-specific release [81]. Enzymes released by intestinal microflora independently breakdown the enzyme-sensitive component, even if the pH-dependent polymer's dissolution threshold is not met. The drawbacks of traditional

pH-dependent systems are solved by this extra fail-safe mechanism. Clinical trials have confirmed the constant medication release and decreased intra-subject variability of this novel technology in both patients and healthy people [81,82]. It can also be used to deliver macromolecules like proteins, peptides, and vaccinations orally. Dodoo et al. [83] recently looked at the technology's suitability for probiotic delivery in the colon. Dual-trigger coating technology was used to encapsulate the commercial goods and an in-house strain of freeze-dried Lactobacillus acidophilus into capsules that were intended to be delivered to the colon or lower small intestines. While the unencapsulated probiotics shown low tolerance to the gastrointestinal environment, over 90% of the viabilities were sustained when these capsules were exposed to the stomach environment for two hours [83]. Additionally, Allegretti et al. [84] showed that faecal microbiota transplantation capsules covered with a combination of pH-responsive and enzyme-triggered polymers effectively targeted the colon based on a comparative cohort analysis in patients.

OpticoreTM, an innovative starch-based coating technique, stands for optimised colonic release. It uses both pH-triggered and enzymatic-triggered release, and it was created using the Phloral® technology. To guarantee steady medication release in the colon, this coating technique includes two trigger systems in the outer coating layer and an accelerator in the inner coating layer. [Medicine]

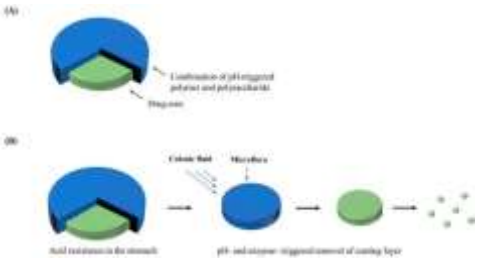

Figure 2. Schematic illustration of Phloral® tablet (A) and the drug release from Phloral® tablet (B).

3.3. Ligand/Receptor-Mediated Drug Delivery System

Targeting ligands on the carrier surface interact with particular receptors expressed at disease sites to enhance target specificity in ligand/receptor-mediated systems, which have been investigated for a more efficient local treatment of colonic disease with fewer harmful side effects (Figure 3). [85]. Different ligands (such as antibodies, peptides, folic acid, and hyaluronic acids) can be used to create ligand/receptor-mediated systems. These ligands are chosen based on the functional expression patterns of certain receptors/proteins at the target cells/organs. If necessary, it can also be used in conjunction with pH-dependent systems to optimise its GI stability and site specificity. The following describes some of the ligands utilised in colon-specific delivery. Figure 2. Phloral® tablet (A) and drug release from Phloral® tablet (B) are shown schematically. 2.3. Drug Delivery System Mediated by Ligand/Receptor Targeting ligands on the carrier surface interact with particular receptors expressed at disease sites to enhance target specificity in ligand/receptor-mediated systems, which have been investigated for a more efficient local treatment of colonic disease with fewer harmful side effects (Figure 3). [85]. Different ligands (such as antibodies, peptides, folic acid, and hyaluronic acids) can be used to create ligand/receptor-mediated systems. These ligands are chosen based on the functional expression patterns of certain receptors/proteins at the target cells/organs. If necessary, it can also be used in conjunction with pH-dependent

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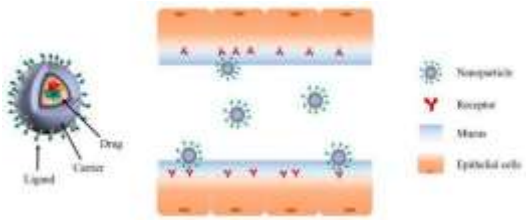

Figure 3. Schematic illustration of representative ligand/receptor-mediated drug delivery system.

3.3.1. Antibodies

Anti-transferrin receptor antibody-conjugated liposomes were created by Harel et al. [86], who showed that the conjugated liposomes internalised more readily in cells than unconjugated liposomes. Additionally, compared to the normal mucosa, the accumulation at the site of inflammation was more than four times higher due to the preferential distribution of anti-transferrin receptor antibody-conjugated liposomes to the inflammatory mucosa rather than the normal mucosa. For the treatment of IBD, Xiao et al. [87] also created nanoparticles that were scCD98-functionalized, or made with single-chain CD98 antibodies on their surface. In animals with colitis, intestinal macrophages and colonic epithelial cells overexpress the heterodimeric neutral amino acid transporter CD98. High affinity for CD98-overexpressed cells was demonstrated by scCD98-functionalized nanoparticles [87]. The expression levels of CD98 and the severity of colitis in mice were decreased by scCD98-functionalized nanoparticles carrying CD98 siRNA (siCD98).

3.3.2. Folic Acid

Since many malignancies overexpress the folate receptor, folic acid, a water-soluble vitamin, acts as a tumor-selective targeting ligand [88]. Folic acid-decorated nanoparticles have been shown in several studies to promote tumor-selective medication absorption. Folic acid-conjugated liposomes, for instance, enhanced the anti-cancer efficacy of daunorubicin by promoting folate receptor-mediated drug absorption, according to Xiong et al. [89]. Additionally, folic acid (FA)-conjugated liposomes containing 5-fluorouracil (5-FU) were created by Handali et al. [90]. 5-FU loaded FA-liposomes showed a substantial decrease in tumour volume and increased cytotoxicity in comparison to the free medication. These findings suggest that folic acid-targeted liposomes might be a useful medication delivery system that improves the administration of certain drugs to cancer cells. A folate-modified self-microemulsifying drug delivery system (FSMEDDS) including curcumin was previously studied by Zhang et al. [42] as a way to enhance drug solubility and delivery to the colon. Their findings demonstrated that an FSMEDDS may effectively enter the colon and quickly release its medication payload [42]. Additionally, the formulation of FSMEDDS may actively target tumour cells that overexpress folate receptors, suggesting that FSMEDDS might be a potential carrier for curcumin administration in the colon.

3.3.3. Hyaluronic Acid

The natural polymer hyaluronic acid (HA) is made up of N-acetyl-d-glucosamine and d-glucuronic acid disaccharide units. HA-conjugated drug delivery systems have been investigated for target-selective drug administration because of HA's strong affinity for the CD44 receptor, which is overexpressed in a number of malignancies [91]. For instance, the efficiency of HA-modified mesoporous silica nanoparticles in targeting CD44-

overexpressing cancer cells has been investigated in earlier research [91,92]. In order to address the inflammatory intestinal mucosa, Vafaei et al. [93] created self-assembled HA nanoparticles as colonic carriers of budesonide. In an inflammatory cell model, budesonide-loaded HA nanoparticles showed increased uptake in cells that overexpressed CD44 receptors, which resulted in a reduction in the release of TNF-α and IL-8 [93]. For the treatment of IBD, HA-conjugated nanoparticles seem to be a viable targeted medication delivery method.

In order to develop a targeted, synergistic drug delivery method for colon cancer treatment, Xiao et al. [94] looked into a combination chemotherapy based on HA nanoparticles. They created HA-functionalized camptothecin (CPT)/curcumin (CUR)-loaded polymeric nanoparticles (HA-CPT/CUR-NPs), which have a negative zeta potential and are around 289 nm in size. Significant cancer-targeting capacity was demonstrated by HA-CPT/CUR-NPs against Colon-26 cells [94]. They also looked at a technique that uses hyaluronic acid (HA)-functionalized polymeric nanoparticles to deliver curcumin (CUR) and CD98 siRNA (siCD98) simultaneously [95]. via shielding the mucosal barrier and reducing inflammation, the co-delivery of siCD98 and CUR via HA-functionalized nanoparticles demonstrated an improved therapeutic impact against ulcerative colitis in comparison to the single drug-based monotherapy [95]. HA-functionalized polymeric nanoparticles might therefore be a useful colonic delivery system for combination medication treatment. Gemcitabine-containing HA-conjugated PEGylated multi-walled carbon nanotubes (GEM/HA-PEG-MWCNTs) were recently created by Prajapati et al. [96] to target colon cancer. The surface of PEGylated multi-walled carbon nanotubes (MWCNTs) was conjugated with HA. Improved pharmacokinetic behaviours and anti-proliferative efficacy were among the encouraging outcomes of this formulation's successful colon cancer targeting. [96].

3.3.4. Peptides Peptide

attracts a lot of interest as a possible ligand for tailored medication delivery. Biocompatibility, cost-effectiveness, chemical variety, and stimulus responsiveness are only a few of the many benefits that peptides provide [97,98]. Furthermore, because of their wide binding surfaces with receptors, peptide ligands have significantly greater binding affinities and specificities than small molecule ligands [99,100]. The availability of high-throughput screening and the simplicity of synthesis utilising automated solid-phase peptide synthesis equipment are other benefits of peptide ligands. Additionally, by altering the peptide sequences, the metabolic instability caused by proteases may be addressed, encouraging the use of peptide ligands in certain drug delivery systems. Peptide-conjugated drug delivery systems are specifically investigated as a potential method for tumor-targeted medication administration. For instance, the use of synthetic 12-residue peptide (TWYKIAFQRNRK, TK peptide) for colon-specific anticancer medication delivery was examined by Ren et al. [101]. The integrin α6β1 subtype, which is increased in human colon cancer cells, is highly affinitized by TK. As a result, TK peptide was coupled as a targeting ligand to PEG-PLA micelles loaded with doxorubicin. The TK peptide appears to be a potential targeting ligand for colon-targeted treatment, as evidenced by the TK-conjugated micelles' much higher

cytotoxicity and improved penetration of the tumour spheroids [101]. To increase the oral bioavailability of insulin, Guo et al. [102] created colon-specific nanoparticles that were co-modified with cell penetration peptide (CPP) and amphipathic chitosan derivatives (ACS). ACS modification might accomplish colon-specific medication delivery and shield CPPs from deterioration in the upper GI tract. ACSs on the CS-CPP NPs' surface were progressively broken down after they arrived in the colon, and the exposed CPPs made it easier for the medication to pass through the colonic epithelium [102]. According to the findings of the in vitro and in vivo assessment, CS-CPP NPs might be a useful colon-specific drug delivery method to enhance the oral absorption of peptides and proteins.

3.4. Magnetically-Driven Drug Delivery System

Emerging new formulations for targeted and regulated drug administration include magnetic microcarriers, such as magnetic emulsions, magnetic liposomes, magnetic nanoparticles, and magnetic microspheres (Figure 4). In order to enhance the targeted treatment of colorectal cancer using mAb198.3 (a FAT1-specific monoclonal antibody), Grifantini et al. [103] created two distinct novel drug delivery systems with magnetic properties. These systems included mAb198.3 being embedded into human erythrocyte-based magnetised carriers or directly bound to super-paramagnetic nanoparticles. in much lower antibody levels, they found that both approaches were highly successful in identifying colon cancer cells and preventing the spread of the disease [103]. This work opened a new path for colon-targeted medication administration by demonstrating the potential of magnetically-driven drug delivery devices to increase the bioavailability and target specificity of anti-FAT mAb198.3 [103]. A magnetic belt was used in another earlier investigation to increase the effectiveness of hydrocortisone in rats [104]. Hydrocortisone-loaded magnetic mesoporous silica microparticles made up this nanodevice. A large azo derivative containing urea moieties was used to functionalise the drug-loaded nanoparticles' exterior surface. Because sodium dithionite decreased the azo bonds in the capping joint, a discernible payload release was place even though the nanodevices stayed capped at neutral pHs [104]. Additionally, they noticed that rats wearing magnetic belts were more successful, especially when an external magnetic field was used to increase the retention duration in the areas of interest [104]. This study showed that because magnetic belts lengthen the duration that medications are retained in the colon, they are more effective in treating IBD. By introducing plasmid DNA (pDNA) and superparamagnetic iron oxide nanoparticles (SPIONs) into RAW264 murine macrophage-like cells, Kono et al. [105] have created magnetically-directed cell delivery systems. Additionally, they showed that this magnetic cell delivery technology might improve macrophage colonic delivery in mice. [Pharmaceutics 2020, Volume 12, Issue 11, Page 105].

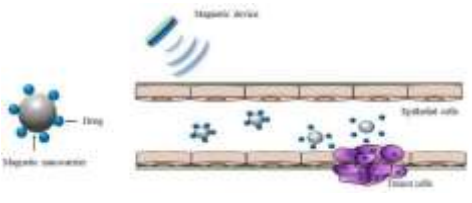

Figure 4. Schematic illustration of magnetic nanocarrier drug delivery system.

IV. COMPLEMENTARY TOOLS FOR DESIGNING THE EFFECTIVE

COLONIC DRUG DELIVERY SYSTEMS

Traditional approaches to medication formulation optimisation involve a number of trials, including different in vitro and in vivo testing, which are frequently laborious, expensive, and time-consuming [106]. Moreover, a lot of drug delivery methods show promise in vitro but frequently fall short in vivo, mostly because of a lack of mechanistic understanding from trial-and-error research [107]. To speed up the rational formulation design, computer techniques like data mining, molecular modelling and simulation, and artificial intelligence are helpful. By determining the crucial elements for formulation optimisation and choosing the most promising candidates for additional experimental validation, it can significantly reduce the time and effort required for experiments. The combined use of multiple chemo/bio informatics and statistical tools, for instance, has been shown by Metwally and Hathout [106] to accurately predict the loading efficiency of drugs in a carrier and to clarify the impact of specific drug molecular descriptors on their docked binding energies on carriers [106]. This would eliminate the need for time-consuming laboratory testing to accurately estimate loading capacity and entrapment efficiency in drug delivery systems.

Generally speaking, computer modelling techniques enable the identification of crucial variables for formulation optimisation and offer comprehensive details on matters such as stability, drug release behaviour, entrapment efficiency, drug distribution/localization in delivery systems, and molecular interactions between the drug and its carrier [107]. As a result, these computational techniques can support more logical formulation design and optimisation while also enhancing trials. Furthermore, a new age of revolutionary drug delivery systems, including electronic and radiofrequency drug delivery devices, has been ushered in by the integration of such computational tools with other technologies for targeted drug administration. The next section discusses a few chosen instances of how computational and device-based methods may be used to support the formulation design of a colon.

4.1. Computer-Assisted Formulation Design

Statistical techniques and chemo/bio-informatics tools can support and enhance studies and help with the logical formulation design. The performance of drug delivery systems and the impact of several environmental factors, including as pH, temperature, salt content, external stimuli, and interactions with other biomolecules in the body, may also be investigated using the computational method. Patra et al. [108] created a luminous gel based on biopolymeric glycogen for the colon-specific administration of ciprofloxacin and metronidazole. They conducted an ab initio molecular dynamics investigation in addition to the experimental assessment to look into the likely molecular level interactions between medicines and hydrogel. In order to examine the pH-responsive swelling and drug release from the created hydrogel, they also carried out simulations using quantum mechanical and molecular mechanics [108]. In line with the experimental findings, the results demonstrated the physical contact between the drug molecules and the hydrogel during its swelling and validated the pH-dependent drug release patterns [106]. A new phospholipid (PL)-based prodrug strategy for colon-specific drug

administration is proposed by Markovic et al. [109]. This technique targets the phospholipase A2 (PLA2), an enzyme that is overexpressed in the tissues of the inflamed colon. They created PL-Fmoc conjugates with varying linker lengths between the PL and the drug moiety after first choosing Fmoc (fluorenylmethyloxycarbonyl) as a model molecule. The PLA2-mediated activation of the PL-Fmoc conjugates was then experimentally assessed. To find the ideal linker length for the therapeutically important medication in ulcerative colitis, such methotrexate, they also performed a unique molecular dynamics simulation of the transition state of the conjugate in the PLA2 enzyme complex. According to the simulation results, the rate of PLA2-mediated activation was determined by the free energy of the PL-prodrug binding to the enzyme's transition state geometry. A linker length of six should be ideal for the maximum level of PLA2-mediated activation, whereas shorter linkers activated to a lesser degree. According to this study, these extremely dependable computational techniques enable the optimisation of the molecular linker's chemical structure between the PL and drug moiety and also lessen the quantity of chemical synthesis required to create efficient prodrugs for colon-specific delivery [109].

4.2. Electronic Device-Assisted Formulation Design

medication absorption throughout the GI tract must be characterised in vivo for colon-specific medication delivery devices to be developed successfully. In order to ascertain if the tested formulation is appropriate for modified drug release, there is a pressing need for a rapid and easy method to accurately and consistently evaluate the drug release characteristics throughout the GI tract. In this way, integrating data from many sources is made easier by the use of electronics. The first intelligent electronic medication delivery and monitoring device in the world, IntelliCap®, combines real-time wireless communication, patient monitoring, and controlled drug release [111,112]. Caretakers may be able to track the capsule's passage through the gastrointestinal tract thanks to this electronic capsule's real-time wireless data recording capabilities. Additionally, in vivo data is accessible for formulation design when pH and transit are measured simultaneously and drug distribution is precisely targeted [111,112]. As a result, IntelliCap® technology offers a quick and practical instrument for the regulated delivery of drugs to certain GI tract locations. The ileo-colonic drug release of ColoPulse tablets in humans was verified by Maurer et al. [50,51] utilising the Intellicap® system, confirming that the ColoPulse system is a promising colonic drug delivery technology.

V. CONCLUSION

The study on the formulation, design, development, and in vitro pharmacokinetics of naproxen highlights the significant advancements in addressing its therapeutic challenges. Naproxen, a widely used NSAID, faces limitations such as poor solubility, gastrointestinal side effects, and suboptimal bioavailability. Through innovative formulation strategies, including solid dispersion, microencapsulation, and nanoparticle-based systems, this research demonstrates potential solutions to overcome these barriers.

The findings confirm that advanced techniques such as nanoformulations and

controlled-release systems can significantly improve naproxen's solubility, dissolution rate, and bioavailability. Furthermore, the use of comprehensive characterization methods, including DSC, XRD, and SEM, has provided valuable insights into the physicochemical and structural properties of the developed formulations.

Pharmacokinetic evaluations reveal that optimized formulations offer better drug release profiles and predictable absorption kinetics, paving the way for enhanced therapeutic efficacy and patient compliance. Moreover, addressing gastrointestinal safety through gastroprotective coatings and innovative delivery systems has further improved the usability of naproxen formulations.

In conclusion, this study underscores the potential of advanced drug delivery systems and formulation strategies to overcome the limitations of conventional naproxen therapies. It provides a foundation for future research to refine these methods and explore clinical applications, ensuring safer and more effective treatment options for patients.

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