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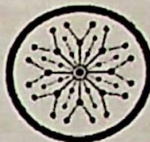
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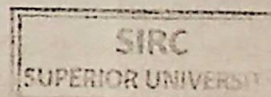
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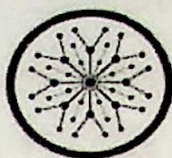
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Dated: May, 20, 2023

SUBJECT: ETHICAL APPROVAL CERTIFICATE

This is to certify that the research project titled "*Preparation and Characterization of Dexibuprofen Nanoparticles*" conducted by Rida Fatima under the supervision of Dr. Abubakar Munir at Faculty of Pharmacy, Superior University Lahore, Pakistan has been reviewed and approved by the Ethics Committee.

The committee requires the following under mentioned guidelines:

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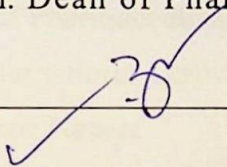
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Designation: Dean of Pharmaceutical Sciences

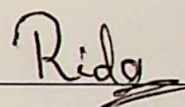
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was conducted by Rida Fatima Under the supervision of “Dr. Abubakar Munair”

No Part of this thesis has been submitted anywhere else for any other degree.
This thesis is submitted to the Faculty of Pharmacy, Superior University, Lahore in
partial fulfilment of the requirements for the degree of Master of Philosophy in field
of Pharmaceutics in Faculty of Pharmacy at Superior University, Lahore.

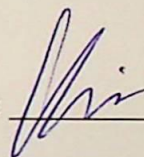
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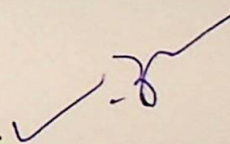
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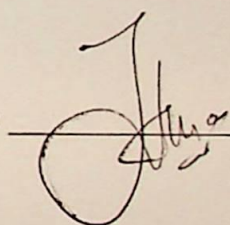
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DEDICATION

This project is dedicated to Dean of Department of Pharmaceutical Sciences, **Prof. Dr. Abu Bakar Munir** for their mentorship and cooperation in researching this paper. My appreciation goes to Dr. Muhammad Aun for their guidance in preparation of the final document and thanks to all Faculty Members of Department of Pharmaceutical Sciences of Superior University, Lahore for their support and appreciation.

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All Greatness and Praises to Graceful Almighty **ALLAH**, the lord of the entire universe. I offer my best gratitude and regards to my Prophet **MUHAMMAD** ﷺ who has given the lesson of altruism, generosity, benevolence and moral values and broke the cages of servitude through his golden sayings, to seek knowledge is obligatory for every Muslims.

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ABSTRACT

The researchers aimed to develop a controlled-release drug delivery system for the anti-inflammatory drug dexibuprofen using chitosan-based polymeric nanoparticles (NPs). We prepared five different formulations of NPs (F1-F5) with varying concentrations of chitosan and surfactant using an emulsion-droplet coalescence method. The NPs were then characterized for their drug content, particle size, zeta potential, encapsulation efficiency, and in vitro drug release. Among the five formulations, F3 was found to be the best formulation based on its ideal particle size (437.6 nm), high entrapment efficiency (88.54%), and desirable drug release profile ($99.81 \pm 0.92\%$ at the end of 24 h). The high entrapment efficiency indicates that a high percentage of dexibuprofen was successfully loaded into the NPs. The ideal particle size of F3 suggests that it can easily penetrate through biological barriers and reach the target site. The high drug release at the end of 24 hours suggests that the drug was released in a controlled manner, which is desirable for sustained therapeutic effects. Overall, the researchers were able to successfully develop and characterize a chitosan-based polymeric nanoparticle formulation for the controlled release of dexibuprofen, which has potential for use in anti-inflammatory drug delivery applications. The present study can be concluded that the newly formulated controlled release nanoparticulate drug delivery system of dexibuprofen may be ideal and effective in the management of pain due to arthritis by allowing the drug to release continuously for 24 h. The present study suggests that the newly developed chitosan-based polymeric nanoparticle drug delivery system loaded with dexibuprofen can be an effective option for managing arthritis pain. The controlled-release properties of the system allow for continuous drug release over 24 hours, which could be beneficial

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INTRODUCTION

CHAPTER 1

INTRODUCTION

INTRODUCTION

Nanoparticle therapeutics consist of small-molecule drugs, peptides, proteins, and nucleic acids that are combined with lipids and polymers to create nanoparticles. These nanoparticles can offer improved pharmacokinetics and pharmacodynamics, as well as active intracellular delivery, which makes them more effective than the individual therapeutic entities. Their effectiveness depends on the size and surface properties of the nanoparticles, including the presence of targeting ligands. However, there are several challenges in translating nanoparticle research to clinical applications, including the use of immunostimulatory components and barriers to large-scale production. Despite ongoing research, only a limited number of nanoparticle systems have been approved for clinical use, and more information is needed to understand their application in clinical settings. Our focus is on the translation of nanoparticle therapeutics into the clinic, particularly those that can be administered systemically without external stimuli, such as changes in temperature or light. Finally, the size of nanoparticles plays a crucial role in their effectiveness. According to current understanding, the optimal size range for nanoparticle therapeutics used in cancer treatment is 10-100 nm in diameter (Davis, Chen, & Shin, 2010).

The lower limit is based on the size of the glomerular capillary wall, which has a sieving coefficient estimated to be around 10 nm, indicating that particles smaller than this are likely to be eliminated by the kidneys (Venturoli & Rippe, 2005). However, there is less clarity regarding the upper limit of nanoparticle size. In tumors, the blood vessels are more permeable to macromolecules, and the lymphatic system is less effective in removing them. This phenomenon, known as the enhanced permeability and retention (EPR) effect, causes macromolecules to accumulate in

tumors, but the upper limit of the size range for effective accumulation is not yet well-defined (Yasuhiro Matsumura & Maeda, 1986). There is mounting evidence that the EPR effect also occurs in humans, with hundreds of nanometer-sized particles shown to leak out of blood vessels and accumulate in tumors (Dreher et al., 2006). However, larger macromolecules or nanoparticles may have limited diffusion in the extracellular space. Animal studies suggest that particles smaller than 150 nm, with a neutral or slightly negative surface charge, can move through tumor tissue (Nomura, Koreeda, Yamashita, Takakura, & Hashida, 1998). Recent research also indicates that nanoparticles with a size range of 50-100 nm and a slightly positive surface charge can penetrate large tumors following systemic administration (Hu-Lieskovan, Heidel, Bartlett, Davis, & Triche, 2005). Therefore, nanoparticles that are well-designed with a size range of 10-100 nm and a slightly positive or slightly negative surface charge should be able to access and penetrate disseminated tumors when administered into the circulatory system. This size range would restrict the particles from exiting normal vasculature, which requires smaller sizes (less than 1-2 nm), but they would still be able to access the liver, as particles up to 100-150 nm in diameter are able to do so.

Controlling the surface properties of nanoparticles is essential to their performance in the body, as their interactions with their surroundings depend on a combination of their size and surface characteristics. Nanoparticles with high surface-to-volume ratios require careful management of their surface properties, as their fate in the body depends on these factors. Steric stabilization, which can be achieved by adding polyethylene glycol (PEG) polymers to the surface of nanoparticles, can help to minimize interactions between nanoparticles and their surroundings. Nanoparticles with slightly negative or slightly positive surface charges also tend to have minimal self-self and self-non-self interactions. However, as the surface charge becomes more

extreme (either positive or negative), scavenging by macrophages can increase and lead to clearance by the reticuloendothelial system. Despite efforts to minimize these interactions, some particle loss is inevitable. If nanoparticle loss could be eliminated, their distribution within the body would be uniform, given that there are no thermodynamic restrictions based on size. However, there are numerous size-restricted locations within the body that could lead to non-uniformity. For example, the blood-brain barrier creates severe size and surface property restrictions for nanoparticles trying to reach the brain. By understanding the size and surface property requirements for reaching specific locations within the body, nanoparticles can be localized to these sites (Chen et al., 2005).

Targeting ligands that enable specific interactions between nanoparticles and cell surfaces are essential for directing the location of nanoparticles. Cancer cells can be targeted by nanoparticles that have moieties, such as small molecules, peptides, proteins or antibodies, on their surfaces. These moieties can bind to cancer cell surface receptor proteins, such as transferrin receptors, which are more abundant on various types of cancer cells (Gatter, Brown, Trowbridge, Woolston, & Mason, 1983). Through receptor-mediated endocytosis, these targeting ligands allow nanoparticles to bind to cell surface receptors and enter cells. Recent studies comparing targeted and non-targeted nanoparticles lipid-based (Kirpotin et al., 2006) or polymer-based (Bartlett, Su, Hildebrandt, Weber, & Davis, 2007)) have shown that the primary function of targeting ligands is to enhance cellular uptake into cancer cells, rather than increasing tumor accumulation. Nanoparticle therapeutics for cancer have distinct features, such as the ability to control circulation times by regulating size and surface properties and targeting specific cell types within organs (e.g., hepatocytes versus Kupffer cells in the liver) (Popielarski, Pun, & Davis, 2005). Although molecular

conjugates, such as antibody-drug conjugates, meet similar requirements, targeted nanoparticles possess five distinct features that differentiate them from other cancer therapeutic modalities.

Nanoparticles offer several advantages, such as the ability to carry large drug payloads and protect them from degradation. For instance, a 70 nm nanoparticle can accommodate roughly 2,000 small interfering RNA (siRNA) molecules, while antibody conjugates carry only a few (Bartlett & Davis, 2007b; Song et al., 2005). This high payload capacity applies to other drug types, such as small-molecule or peptide drugs. Unlike molecular conjugates, the type and number of therapeutic entities contained in nanoparticles do not impact their pharmacokinetic properties or bio-distribution because they are located within the particle. In contrast, with molecular conjugates, the type and number of therapeutic entities conjugated to the targeting ligand significantly alters the overall properties of the conjugate.

Secondly, nanoparticles have the advantage of being large enough to accommodate multiple targeting ligands that can enable multivalent binding to cell-surface receptors (Hong et al., 2007). Two parameters can be adjusted to fine-tune the binding to target cells: the density and affinity of the targeting moiety. Multivalence effects can lead to high effective affinities, even with low-affinity ligands (Carlson, Mowery, Owen, Dykhuizen, & Kiessling, 2007; Montet, Funovics, Montet-Abou, Weissleder, & Josephson, 2006). Consequently, the range of molecules that can be used as targeting agents is greatly increased since many low-affinity ligands that are inadequate for molecular conjugates can be attached to nanoparticles, producing higher affinity via multivalent binding to cell-surface receptors.

The third advantage of using nanoparticles is that they are large enough to hold various types of drug molecules. This feature enables multiple therapeutic interventions to be applied simultaneously in a regulated manner. Additionally, the pharmacokinetic properties of nanoparticles are not altered by the quantity or type of therapeutic being used, which is also true when combining different therapeutics within the same nanoparticles.

Fourthly, the release kinetics of drug molecules from nanoparticles can be adjusted to match the mode of action. For instance, chemotherapeutic drugs based on camptothecin are reversible inhibitors of the topoisomerase I enzyme. Therefore, to maximize efficacy, a slow release of the drug from the nanoparticles is preferable, as it ensures prolonged exposure of the drug to the enzyme (Pommier, 2004). On the other hand, with siRNA, gene inhibition kinetics are heavily influenced by cell cycle times (Bartlett & Davis, 2006, 2007a), and there may not be a need for a slow release of the therapeutic agent when used in cancer treatment.

The fifth advantage of nanoparticles is their potential to overcome multidrug resistance mechanisms caused by cell-surface protein pumps such as glycoprotein P, as they can enter cells through endocytosis. In conclusion, the controlled combination of these features through nanoparticle design can reduce the adverse effects of anticancer drugs and improve their effectiveness. Clinical evidence suggests that this potential is now becoming a reality.

Nanoparticles present unique opportunities for designing and fine-tuning properties that are not achievable with other types of therapeutics. As more clinical data becomes available, including reviews on polymer-drug conjugates (C. Li & Wallace, 2008) and polymeric micelles (Yasuhiro Matsumura, 2008) for further

micelles have demonstrated a greater ability to accumulate in tumors compared to larger liposomes (Sutton, Nasongkla, Blanco, & Gao, 2007).

In addition, the size of nanoparticles affects their ability to move throughout tumors, as previously explained. It is suggested that particles smaller than 100 nm but larger than 10 nm, to avoid renal clearance, are optimal for tumor penetration. Therefore, controlling the size of nanoparticle therapeutics is critical for their pharmacokinetics, biodistribution, tumor accumulation, and penetration. Some nanoparticles currently undergoing clinical trials have drug release mechanisms that are discussed below in the case of IT-101. These methods utilize hydrolysis to cleave the chemical bond between the particle and drug, with enzymes either inside or outside cells, such as lysozymes and esterases, or only inside cells, such as cathepsin B.

The use of non-targeting nanoparticles in clinical trials has been extensively discussed in the literature. Doxil, a liposome-based nanoparticle carrying doxorubicin, has been in clinical use for over two decades (Chanan-Khan & Lee, 2007; Green & Rose, 2006; O'Brien, 2008). Other liposomes containing drugs like irinotecan and SN-38 are currently being tested in clinical trials (ClinicalTrials.gov; see Further information). Abraxane (ABI-007), an albumin-bound nanoparticle of paclitaxel with a mean diameter of around 120 nm, was designed to eliminate the toxicities associated with Cremophor EL in the paclitaxel formulation (Taxol) and its generic equivalents, while retaining its therapeutic benefits (Sparreboom et al., 2005). In a Phase III study involving 454 patients with metastatic breast cancer, Abraxane was found to be significantly more effective than Taxol in terms of response rates, despite the fact that the dose of paclitaxel in Abraxane was 70-80% higher than that in Taxol (Gradishar et al., 2005). Furthermore, the incidence of grade 4 neutropenia was significantly lower

with Abraxane (9%) than with Taxol (22%) ($p = 0.001$). Pharmacokinetic assessments revealed that paclitaxel clearance and volume of distribution were higher for Abraxane than for Taxol (Sparreboom et al., 2005). These differences in pharmacokinetic properties may be associated with the higher intratumoral concentrations observed with Abraxane compared to Taxol. However, it should be noted that the dissolution of nanoparticles during infusion is not clear, and there are indications that they do dissolve. Therefore, the clinical benefits of Abraxane may be due to factors other than its functioning as a nanoparticle, such as the removal of Cremophor EL from the formulation, which causes toxicities of its own (Henderson & Bhatia, 2007).

Numerous nanoscale therapeutics that use PEGylated proteins have been either approved or are undergoing clinical trials. PEGylation is a technique that enhances protein solubility, reduces immunogenicity, prevents rapid renal clearance by increasing conjugate size, and prolongs plasma half-life (Harris & Chess, 2003). One such PEGylated protein, PEG-l-asparaginase (Oncospar; Enzon), was approved by the US Food and Drug Administration in 1994 to treat acute lymphoblastic leukemia (Fuertges & Abuchowski, 1990; Graham, 2003). However, the use of free-drug l-asparaginase can result in a hypersensitivity reaction and antibody production, leading to early clearance from circulation. In Phase I studies, Oncospar demonstrated an increased plasma half-life and a lower incidence of hypersensitivity reactions compared to unmodified enzymes (Ho et al., 1986). A subsequent Phase II study showed partial response and reduced hypersensitivity reactions in some Oncospar-treated patients with refractory lymphoma (Abshire, Pollock, Billett, Bradley, & Buchanan, 2000; Kurtzberg, Moore, Scudiery, & Franklin, 1988). Another PEGylated protein, PEG-recombinant arginine deaminase (PEG-rhArg), has shown clinical

activity in hepatocellular carcinoma when used as a single agent or in combination with 5-fluorouracil (Cheng, Lo, Leung, Lam, & Lam, 2005; Delman et al., 2005). Weekly intramuscular injection of PEG-rhArg achieved low arginine concentrations of less than 2 μ M. (Delman et al., 2005).

Proteins such as interferon- α (IFN- α) and granulocyte colony-stimulating factor (G-CSF) have also been conjugated with PEG (Molineux, 2004; Tanaka, Satake-Ishikawa, Ishikawa, Matsuki, & Asano, 1991). PEGylated IFN- α conjugates, including PEGASYS and PEGINTRON, have demonstrated superior antiviral activity compared to free IFN- α and are approved for hepatitis C therapy (Wang et al., 2002). These conjugates have also shown promise in treating melanoma and renal cell carcinoma (Bukowski et al., 2002; Flaherty, Heilbrun, Marsack, & Vaishampayan, 2005; Holmes et al., 2002), and are being investigated for other solid tumors. Due to their prolonged half-lives, PEG-IFN- α conjugates can be given by subcutaneous injection once every 12 weeks, which is less frequent than the three-times-per-week dosing required for free IFNs. The success of PEGylated proteins has led to the development of PEG-conjugated small-molecule drugs to create nanoparticles. Pegamotecan, a camptothecin conjugated with linear PEG, has a molecular mass of approximately 40,000 Daltons. Two Phase I trials were completed with Pegamotecan weekly dosing (Posey III et al., 2005) and every 3-week dosing (Rowinsky et al., 2003)) as was a Phase II trial (Scott et al., 2009); however, Enzon has discontinued its development. Various PEGylated chemotherapeutics are being developed for advanced solid tumors, including PEG-irinotecan (NKTR-102) and PEG-SN-38 (EZN-2208), both of which are currently in Phase I clinical trials (ClinicalTrials.gov; see Further information). These small molecules have longer circulation times than their free drug counterparts, potentially allowing for greater tumor accumulation via

the EPR effect. Nanoscale systems can also offer other benefits besides modifying therapeutic pharmacokinetics. For example, PG-paclitaxel conjugates, which bind high amounts of paclitaxel (37% wt./wt.) to a biodegradable polymer called poly-l-glutamic acid (PG), have been studied in numerous clinical trials, including Phase III. XYOTAX (also known as CT-2103) is the most advanced polymer-small molecule conjugate used for systemic administration. While paclitaxel is slowly released from the polymer via hydrolysis (up to 14% over 24 hours), lysosomal cathepsin B degradation of the polymer backbone after endocytic uptake results in a greater release of paclitaxel (Posey III et al., 2005; Rowinsky et al., 2003; Shaffer, Baker Lee, Kumar, & Singer, 2002).

The use of PG-paclitaxel has shown enhanced efficacy in preclinical tumor models through EPR-mediated tumor targeting, while also improving the safety profile due to decreased exposure to normal tissue and improved drug solubility (Singer et al., 2004; Singer et al., 2005). Phase I/II studies demonstrated partial responses or stable disease in patients with NSCLC, renal cell carcinoma, mesothelioma, or paclitaxel-resistant ovarian cancer (Todd et al., 2001). However, some patients also experienced severe side effects such as neutropenia and peripheral neuropathy, which are common paclitaxel-associated toxicities. In a Phase III trial, PG-paclitaxel was compared with gemcitabine or vinorelbine as a first-line therapy for performance status 2 patients with NSCLC (Langer, Socinski, & O'Byrne, 2005). While patients receiving PG-paclitaxel experienced reduced side effects compared to those who received gemcitabine, the nanoparticle conjugate did not show significant improvement in overall survival compared to either of the non-nanoparticle drugs. Interestingly, there was a greater increase in survival observed in women treated with PG-paclitaxel compared to men, which might be associated with estrogen levels as

estrogen has been shown to increase the expression of cathepsin B (Kremer, Judd, Rifkin, Auszmann, & Oursler, 1995).

Ongoing definitive trials are comparing PG-paclitaxel and free paclitaxel (175 mg per m²) as a first-line therapy for women with NSCLC. Additionally, a PG-camptothecin (CT-2106) nanoparticle has undergone Phase I/II clinical trials (Homsí et al., 2007; Posey III et al., 2005; Rowinsky et al., 2003). Other polymer-small-molecule conjugates have also completed several clinical programs. For example, N-(2-hydroxypropyl)-meth-acrylamide (HPMA) polymer conjugates have demonstrated EPR-mediated tumor targeting (L. Seymour et al., 1994), and improved antitumor efficacy in animal studies (Duncan et al., 1992). In Phase I studies, HPMA-polymer-Gly-Phe-Leu-Gly-doxorubicin (PK1; FCE28068) was given at increasing doses up to a MTD of 320 mg per m² (doxorubicin equivalent), which is fourfold to fivefold higher than the usual dose of doxorubicin. The dose-limiting toxicities were neutropenia and mucositis, but the cumulative doses reached 1,680 mg per m² without observation of cardiotoxicity. Antitumor activity was observed in anthracycline resistant breast cancer, NSCLC, and colorectal cancer. Prolonged plasma circulation was observed in a clinical pharmacokinetic study of HPMA conjugates (Thomson et al., 1999; Vasey et al., 1999). Although HPMA conjugates of doxorubicin (PK1), paclitaxel (PNU166945), camptothecin (MAG-CPT), and platinum-containing drugs (AP5280 and AP5346) have been evaluated in clinical studies, only the platinum-containing conjugate AP5346 remains in clinical development. The other conjugates have shown either unacceptable toxicity or disappointing efficacy (Duncan, 2007). NK911, a polymeric micelle nanoparticle, was developed to enhance doxorubicin delivery. In a Phase I trial, NK911 was administered intravenously to patients with solid tumors every 3 weeks (Y Matsumura

et al., 2004). The starting dose was 6 mg per m² (doxorubicin equivalent) with dose escalation. Among 23 enrolled patients, a maximum tolerated dose of 67 mg per m² and a dose-limiting toxicity of neutropenia were observed. One patient with pancreatic cancer showed a partial response. The recommended Phase II dose was 50 mg per m² every 3 weeks. SP1049C is a novel anticancer agent composed of doxorubicin and two non-ionic pluronic block co-polymers, designed to enhance efficacy compared with doxorubicin.

The development of drugs at the nanoscale is a rapidly evolving field, offering numerous potential benefits such as the ability to modify properties like solubility, bioavailability, drug release profiles, and immunogenicity. This technology can lead to the creation of more convenient administration routes, lower toxicity, fewer side effects, improved biodistribution, and extended drug life cycles [17]. One way to create drug delivery systems is through self-assembly, which involves the spontaneous formation of well-defined structures or patterns from building blocks [41]. These engineered systems can be designed to target specific locations or provide controlled release of therapeutic agents at specific sites, but they must overcome barriers like opsonization/sequestration by the mononuclear phagocyte system [42].

There are two methods by which nanostructures can deliver drugs: passive and self-delivery. Passive delivery involves enclosing drugs within the inner cavity of the structure, primarily through the hydrophobic effect. When targeted to specific sites, the necessary amount of the drug is released due to the low drug content, which is encapsulated in a hydrophobic environment. In contrast, in self-delivery, drugs intended for release are directly linked to the carrier nanostructure material to facilitate delivery. In this approach, the timing of release is critical since releasing the drug too quickly or too late can reduce its bioactivity and efficacy [41]. Nanomaterials

or nanoformulations can also be used as drug delivery systems to target specific sites actively or passively. Active targeting involves coupling moieties such as antibodies or peptides with the drug delivery system to bind to the receptor structures expressed at the target site. Passive targeting relies on the affinity or binding properties of the prepared drug carrier complex to be driven to the target site by factors such as pH, temperature, molecular size, and shape. The receptors on cell membranes, lipid components of the cell membrane, and antigens or proteins on the cell surfaces are the main targets in the body[43]. Although most nanotechnology-mediated drug delivery systems are currently targeted towards cancer treatment, the potential applications are vast and promising (Schluep et al., 2006).

The nanoparticles reach tumors via passive targeting due to the leaky vasculature of tumors, which allows the nanoparticles to extravagate while normal vasculature does not. However, active targeting is considered to be the most effective therapy, which involves including a targeting ligand on the nanoparticles. The first ligand-targeted nanoparticle to reach the clinic was PK2 (FCE28069), a HEMA-polymer-Gly-Phe-Leu-Gly-doxorubicin conjugate that contains galactosamine, a sugar-based ligand that targets the asialoglycoprotein receptor (ASGPR) expressed on hepatocytes. Despite the high expression of ASGPR on primary liver cancer cells, targeted nanoparticles accumulated in normal liver cells as well as in the tumor, as healthy hepatocytes also express ASGPR. In a Phase I trial, PK2 had a MTD of 160 mg per m² (doxorubicin equivalent dose), with dose-limiting toxicities typical of anthracyclines (L. W. Seymour et al., 2002). Out of 23 patients with primary hepatocellular carcinoma, 11 had stable diseases, one showed a reduction in tumor volume, and two had progressive diseases, lasting 26 and 47 months. After 24 hours, concentrations of drug in liver were 15-20% of the administered dose, and

concentrations in the tumor were 12-50 times higher than would have been achieved through free doxorubicin (Julyan et al., 1999).

Currently, there are only a few targeted nanoparticles in clinical use, including MBP-426, SGT-53, and CALAA-01. MBP-426 is a liposome containing the platinum-based drug oxaliplatin, while SGT-53 is a liposome that contains a plasmid coding for the tumor suppressor p53. CALAA-01 is a polymer-siRNA composite nanoparticle that has a high drug payload per targeting ligand, multivalent binding to cancer cell surfaces, and an active drug release mechanism triggered by the recognition of intracellular localization by a pH decline below a value of 6.0. All of these targeted nanoparticles target the transferrin receptor, which is commonly upregulated in many types of cancer. One notable targeted nanoparticle, MCC-465, which contains doxorubicin in a liposome, is not currently in use (Heidel et al., 2007). Recent studies have shown that targeting ligands play a crucial role in enhancing cellular uptake in cancer cells and minimizing accumulation in normal tissue, indicating that the bio-distribution of nanoparticles is mainly determined by their colloidal properties. The targeting ligand, on the other hand, serves to increase the intracellular uptake in the target tumor. This suggests that the cellular uptake of nanoparticles is determined by the affinity and surface density of the targeting ligand. Zhou et al. have demonstrated that the affinity-density relationships for nanoparticles can be determined, showing that the density of single-chain Fv antibody fragments is important for nanoparticle uptake, and high affinities are not necessary if high densities are used. This study highlights the importance of multivalency of the targeted nanoparticles under discussion, although specific affinities and densities may vary depending on cell-surface receptor densities (Zhou et al., 2007).

One significant challenge in cancer treatment is the development of multidrug resistance (MDR), which impedes the effectiveness of various chemotherapy and biological treatments on cancer cells.(Gottesman, 2002; Gottesman, Fojo, & Bates, 2002). MDR can arise from both non-cellular and cellular mechanisms. In non-cellular drug resistance, the physiological barriers can limit drug access to tumor tissues. These barriers include poorly vascularized tumor regions that reduce drug delivery to the tumor cells. Additionally, high interstitial pressure and low microvascular pressure can prevent drug molecules from reaching the tumor cells. On the other hand, cellular mechanisms of drug resistance involve alterations in the biological and biochemical characteristics of cancer cells. These alterations can include changes in enzyme systems responsible for drug metabolism, reduced apoptotic activity, induction of cellular repair systems, mutation of drug targets, and increased drug efflux from tumor cells. Among these mechanisms, changes in the drug efflux pump have been widely studied and are well understood. The idea that chemotherapeutic drugs are actively expelled from tumor cells by P-glycoprotein (P-gp) was first proposed upon its discovery, thus paving the way for further investigation into this area (Modok, Mellor, & Callaghan, 2006; Nobili, Landini, Giglioni, & Mini, 2006). The MDR1 gene encodes for P-glycoprotein (P-gp), which is a transmembrane glycoprotein with a molecular weight of 170-kDa. As an efflux pump, P-gp is categorized as an ATP-binding cassette (ABC) protein responsible for transporting drugs out of cells. Despite extensive research on various inhibitors of ABC transporters, including P-gp, as potential anticancer agents, the results have been largely unsatisfactory (Thomas & Coley, 2003).

Novel approaches for tackling drug resistance could involve methods that facilitate selective drug accumulation within tumor tissues, tumor cells, or specific

compartments of tumor cells, without causing systemic toxicity. Nanoparticle-based drugs are a promising option in this regard, as they can enter cells via endocytosis. Moreover, by utilizing suitable nanoparticle formulations, it is feasible to safeguard drugs from degradation by acidic or other harmful entities (such as nucleases for oligonucleotides) encountered in the tumor microenvironment, prior to their entry into tumor cells. As an example, doxorubicin-loaded nanoparticles composed of poly(alkyl cyanoacrylate) (PACA) can penetrate cells without being recognized by P-gp (Pepin et al., 1997; Vauthier, Dubernet, Chauvierre, Brigger, & Couvreur, 2003). The use of PACA nanoparticles has shown partial success in overcoming MDR in P388 leukemia cells cultured in vitro. PEG-coated PACA nanoparticles were created by utilizing a poly(PEG-cyanoacrylate-co-hexa-decyl-cyanoacrylate) co-polymer (Vauthier et al., 2003). In mouse models of cancer, these nanoparticles demonstrated extended circulation time in the bloodstream, while being taken up less by the liver. Moreover, when administered as PEG-coated PACA nanoparticles, there was a higher accumulation of the drug in the tumor tissue (Peracchia et al., 1999). Furthermore, Schluep and colleagues demonstrated that systemic administration of IT-101 in mice can effectively overcome P-gp resistance in mouse tumor xenografts. (Schluep et al., 2006). The effectiveness of IT-101 in overcoming P-gp resistance was further assessed in mice with six different xenografts, including LS 174T and HT29 colorectal cancer, H1299 NSCLC, H69 small-cell lung cancer, Panc-1 pancreatic cancer, MDA-MB-231 breast cancer, and one disseminated xenograft (TC71-luc Ewing's sarcoma). A single treatment cycle of three weekly doses of IT-101 resulted in significant antitumor effects in all cases, with some animals experiencing complete tumor regression, particularly in the case of H1299 tumors and disseminated Ewing's sarcoma. Additionally, IT-101 proved effective against tumors, such as HT29

colorectal tumors, that were resistant to treatment with irinotecan, indicating that polymeric drug conjugates may be able to overcome certain types of MDR. Targeted nanoparticles that take advantage of their binding to cell-surface receptors and are then endocytosed have also been utilized as a strategy for overcoming drug resistance. Folate-receptor targeted, pH-sensitive polymeric micelles containing doxorubicin (E. S. Lee, Na, & Bae, 2005), transferrin-conjugated paclitaxel nanoparticles (Sahoo, Ma, & Labhasetwar, 2004) and transferrin-ligated liposomes containing oxaliplatin (Suzuki et al., 2008) all exhibited greater antitumor activity than the respective free drugs in drug-resistant mouse models. In summary, these investigations indicate that nanoparticles incorporating targeting molecules and small-molecule drugs exhibit better performance than non-targeted nanoparticles of various types

There is no conclusive proof that nanoparticles have bypassed surface pump mediated resistance in humans, although clinical results that report partial responses in patients (K. Lee et al., 2006) who had previously failed drug therapies are suggestive of this possibility. For example, patients who were refractory to prior taxane therapy (for example, NSCLC with paclitaxel/carboplatin and ovarian cancer with paclitaxel/carboplatin and paclitaxel regimens) experienced objective responses after treatments with Genexol-PM, a polymeric micelle nanoparticle containing paclitaxel, or XYOTAX (CT-2103), a PG-paclitaxel conjugate (Nemunaitis et al., 2005).

NSAIDs belong to a class of drugs that are effective in reducing pain, fever, inflammation, and preventing blood clots (Fosslien, 1998; Wu et al., 2020). In general, NSAIDs are characterized by a high degree of protein binding and small volumes of distribution. However, in this family, differences in clearance and variability in half-life are of special relevance. Out of all the NSAIDs, ibuprofen

in 1994 (Phleps, 2001). Racemic ibuprofen and DXI differ in their physical, chemical, and pharmacological properties as well as their metabolic profile (Kaehler et al., 2003; Khalid et al., 2021). Clinical trials and post marketing surveillance trials in the past five years have involved 4836 patients who were exposed to DXI. Adverse drug reactions were reported in only 3.7% of patients, and three serious adverse drug reactions (0.06%) were reported (Kaehler et al., 2003). Studies conducted on in vitro models have shown that the dextrorotatory isomer of ibuprofen, also known as DXI, exhibits approximately 160 times higher activity in inhibiting prostaglandin synthesis compared to its enantiomer (R). Additionally, studies on thromboxane generation in clotting blood have also confirmed that the S enantiomer has higher activity compared to the racemic mixture (Evans, Nation, Sansom, Bochner, & Somogyi, 1991). The use of DXI as a pain reliever would be highly beneficial since it has been shown to exhibit approximately 160 times higher activity in inhibiting prostaglandins in vitro compared to its enantiomer (R). Additionally, DXI effectively inhibits the activity of both COX-1 and COX-2 enzymes, while the enantiomer (R) only inhibits COX-1, which is responsible for increasing gastrointestinal side effects (Wsol, Skálová, & Szotáková, 2004).

The metabolic destiny of rac-Ibuprofen is uncommon as the inactive R-($\square$)-ibuprofen is transformed enzymatically into the pharmacologically active enantiomer S-(+)(Yoon et al., 2008). The unusual metabolic conversion of inactive R-($\square$)-ibuprofen to the active S-(+) enantiomer may result in variability in analgesia, including a delayed onset of activity. This phenomenon may also account for the weak correlation between plasma IBU concentrations and clinical response observed in acute pain and rheumatoid arthritis (Laska et al., 1986). Studies conducted on humans indicate that approximately 50% of the (-) enantiomer is metabolically

transformed to the more active (+) enantiomer by the catalytic action of fatty acyl coenzyme thioesterase (Brocks & Jamali, 1999; Rudy, Knight, Brater, & Hall, 1991) in the intestinal tract and liver after oral absorption (F Jamali et al., 1992; Jeffrey, Tucker, Bye, Crewe, & Wright, 1991). It is important to note that the degree of metabolic inversion of IBU can vary between 35 and 85%, depending on factors such as the type of formulation, liver condition, concomitant medication use, and disease state (Fakhreddin Jamali & Kunz-Dober, 1999; Rudy et al., 1992). In the metabolic conversion of R-(-)-ibuprofen, the initial step involves the activation of the compound in the presence of coenzyme A (CoA), adenosine triphosphate (ATP), and Mg^{2+} . Following this, the AMP-derivative is esterified with coenzyme A (CoA) through the action of acyl-CoA synthetase. Subsequently, R-(-)-ibuprofen-CoA undergoes epimerization, which is carried out by the methylacyl-coenzyme A racemase enzyme (encoded by the AMACR gene) (Woodman et al., 2011) to form S-(+)-ibuprofen-CoA, which is then hydrolyzed by a hydrolase to form S-(+)-ibuprofen (Kaehler et al., 2003). The crucial step of this process involves the elimination of the substrate proton, followed by non-stereoselective reprotonation. The inversion process can occur presystemically in the gut (Davies, 1998) as well as in the liver (Lloyd et al., 2013).

Thioesters resulting from the combination of coenzyme A and ibuprofen can be integrated into triglycerides (TAG) or phospholipids (PLs), resulting in hybrids that may impact cell membrane function. However, existing literature indicates that only the R enantiomer of IBU is present in human adipose tissue, and it has an elimination half-life of approximately seven days. Research has demonstrated that oral administration of pure S enantiomer produces a more potent analgesic effect in a shorter amount of time compared to the racemic mixture. A group of 1400 patients

showed that administration of S-(+)-ibuprofen resulted in higher therapeutic efficacy and significantly reduced side effects (Bonabello et al., 2003; Davies, 1998). Initially, it was proposed that a ratio of 1:0.75 (ibuprofen and DXI, respectively) would be required to achieve equivalent therapeutic effectiveness with DXI as with IBU (Kaehler et al., 2003). Numerous clinical trials have been conducted using a 0.5:1 dose ratio, assuming that half of the dose of IBU contains DXI. These studies demonstrated that DXI had comparable therapeutic efficacy to IBU. In addition, studies comparing DXI with other NSAIDs such as Diclofenac found that using 75% of the maximum daily dose (MDD) of DXI produced the same effectiveness as 100% of Diclofenac. Furthermore, research on DXI's interactions with other compounds has shown that there is no impact on its bioavailability whether taken with or without food. DXI has been found to be clinically effective in treating rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of the hip and knee, lumbar vertebral syndrome, ankle joint distortion, and dysmenorrhea. Notably, DXI has a better tolerability profile compared to other NSAIDs, with racemic ibuprofen showing a 30% higher incidence of adverse drug reactions, and diclofenac demonstrating a 90% higher incidence than DXI. In light of the above findings, DXI has the potential to offer a favorable combination of diclofenac's high efficacy and ibuprofen's good tolerability (Phleps, 2001). Furthermore, studies have compared DXI with Celecoxib, a selective inhibitor of cyclooxygenase-2 (COX-2), for the treatment of hip osteoarthritis. The results showed that DXI had similar efficacy and tolerability to Celecoxib. In comparison to racemic ibuprofen, DXI has a slower dissolution rate in simulated gastric and enteric juices, but it has an improved oral bioavailability. However, due to its weak acidity ($pK_a = 5.2$), DXI has relatively low bioavailability because of its limited solubility in the acidic media of the stomach. According to the Biopharmaceutics Classification

System (BCS), DXI is classified as a poorly water-soluble drug but a well-penetrating substance (group II). Therefore, its bioavailability is restricted by its poor dissolution, resulting in a similar absorption rate to dissolution. These physicochemical properties of DXI pose several limitations in in vivo models, such as incomplete release, food interactions, or high inter-subject variability. To address these limitations, several attempts have been made, including the synthesis of effective prodrugs of DXI or preparation of dedicated formulations for different application routes such as ocular, dermal, or oral formulations. This review will discuss these applications, and novel drug delivery forms containing DXI will also be analyzed (Hawel, Klein, Singer, Mayrhofer, & Kähler, 2003).

DXI, also known as S-(+)-ibuprofen or (2S)-2-(4-isobutylphenyl)propionic acid, is the dextrorotatory enantiomer of ibuprofen. It is considered more pharmacologically effective and potent than the racemic ibuprofen (José et al., 2021). The S-(+) enantiomer of ibuprofen exerts its effects by inhibiting the COX-2 isoform, thereby suppressing prostanoid synthesis in inflammatory cells, which leads to analgesic, antipyretic, and anti-inflammatory effects. Compared to the R-enantiomer, S-(+)-ibuprofen is less toxic. DXI has higher water solubility (68.4 mg/L) than ibuprofen (21 mg/L) and a lower melting point (49–53 °C vs. 75–77.5 °C, for DXI and ibuprofen, respectively). Additionally, DXI exhibits increased stability, a slower dissolution rate, and improved bioavailability (Leising et al., 1996).

DXI is presently marketed in the European Union (EU) as tablets used to treat pain and inflammation. Each tablet contains 400 mg of DXI (Derry, Best, & Moore, 2013). Several clinical trials involving DXI are currently ongoing. Two Phase I clinical trials have been approved in the US database to evaluate the safety of DXI in healthy participants. The trials will investigate the effects of a single and multiple oral

dose of DXI, with doses of 300 mg and 200 mg, respectively, although their current status is unknown (Gliszczyńska & Sánchez-López, 2021). In addition, Gebro Pharma GmbH has completed a Phase I clinical trial to evaluate the effects of DXI on volunteers who were also taking aspirin.

Additionally, a Phase 3 clinical trial was completed in 2010, which studied the safety and efficacy of DXI syrup in treating fever associated with the common cold. Furthermore, a Phase IV post-marketing clinical study was completed in 2012 to compare the tolerability of DXI Gebro 400 mg powder for oral suspension with ibuprofen 400 mg in patients with painful osteoarthritis of the hip or knee (Gliszczyńska & Sánchez-López, 2021).

Most DXI formulations are designed for oral administration to achieve systemic circulation (Koziolek et al., 2016). DXI is readily and extensively absorbed from the upper gastrointestinal tract after oral administration, reaching peak plasma and serum concentrations at around 1-2 hours (depending on the particular oral formulation) (Kaehler et al., 2003). DXI is readily absorbed from the upper gastrointestinal tract after oral administration, with peak plasma and serum concentrations observed at approximately 1-2 hours post-dose, depending on the specific formulation. It has been demonstrated that unbound DXI concentrations exhibit linear pharmacokinetics at commonly used doses. The absorption of DXI occurs through a passive process, where the crystal form of the drug may play a crucial role in interpreting experimental and clinical data. Notably, administration of DXI with meals prolongs the time to reach maximum concentration (from 2.1 hours under fasting conditions to 2.8 hours under non-fasting conditions) and slightly reduces the maximum plasma concentration (from 20.6 to 18.1 $\mu\text{g/mL}$). However, food does not affect the extent of absorption. A linear dose-response relationship has

been demonstrated over the dose range of 200-400 mg (Kepp, Sidelmann, & Hansen, 1997). Both enantiomers of IBU undergo phase I metabolism involving hydroxylation of the isobutyl chains to 2-hydroxy- and 3-hydroxyibuprofen, followed by oxidation of the latter to 3-carboxyibuprofen and p-carboxy-2-propionate. There are some reports suggesting DXI exhibits a preference against the R-enantiomer in both phase I and II metabolism (Hao, Wang, & Sun, 2005).

Enantioselective protein binding has been observed for IBU, where the R-enantiomer has a higher binding constant to the high-affinity protein binding site compared to the S-enantiomer (DXI) by a factor of 2.6. This could lead to reduced binding of DXI to proteins, allowing for greater transfer of the drug into synovial or blister fluid, thereby enhancing its pharmacological activity (Schneider, Nuernberg, Dietzel, & Brune, 1990). Metabolism of IBU involves the production of 2-hydroxyibuprofen and carboxyibuprofen (and their acyl glucuronides) as the major metabolites, which account for approximately 25% and 37% of the administered dose, respectively. The cytochrome isoform CYP-2C9 plays a predominant role in the metabolism of S-(+)-ibuprofen, while its R-(-) enantiomer is predominantly metabolized via isoform CYP-2C8. It is worth noting that both enantiomers undergo phase II metabolism via glucuronidation (Hamman, Thompson, & Hall, 1997). There is no gender-related difference in the pharmacokinetics of the R-(-) and S-(+) enantiomers of IBU, except for the volume of distribution VD/F. The VD/F is approximately twice as high in adult females as it is in males (Walker & Carmody, 1998).

NSAIDs have been utilized for systemic drug delivery through oral administration to provide pain relief, analgesia, and antipyretic effects. They have also been utilized for delivering drugs locally through the oral mucosal tissue. Various

techniques have been employed to achieve systemic delivery of DXI. Neem et al. developed chewable tablets for DXI with the aim of improving its dissolution rate in a practical manner (Naeem, Osman, El Maghraby, & Essa, 2020). In a more sophisticated manner, Li and colleagues developed acidic montmorillonite composites able to encapsulate DXI (298 mg/g) (Khalid, Ahmad, & Minhas, 2017). Montmorillonite is a type of clay mineral that possesses unique properties such as swelling and adsorption, making it useful in various industrial and pharmaceutical applications. Li et al. developed DXI composites using acidic montmorillonite composites, which exhibited an average micrometric size of $0.96 \pm 0.12 \mu\text{m}$ and a negative surface charge of $-26.5 \pm 0.94 \text{ mV}$. DXI composites released the drug within 12 hours in simulated intestinal fluid, which is longer compared to DXI alone (which was released in 4 hours). Furthermore, in a preclinical rat model, DXI composites were found to increase the bioavailability of DXI compared to commercial DXI suspension while also retarding drug release (T. Li et al., 2018).

Khalid et al. aimed to improve the aqueous solubility of DXI by designing hydroxyl-propyl-cyclo-dextrin (HPCD) hydrogel nanoparticles. Hydrogels are three-dimensional networks of polymers that can absorb water through physical or chemical cross-linking. The HPCD hydrogel nanoparticles containing DXI increased its aqueous solubility by forming a stable polymeric network. The average size of the nanoparticles was 287 nm, and they were capable of releasing DXI preferentially at pH 1.2 and 6.8. Preclinical in vivo administration did not show any signs of acute toxicity (Khalid et al., 2017). Khalid et al. conducted a study on developing hybrid nano-gels, which are hydrogels with a nano-scopic network structure, combining the advantages of both hydrogels and nano-carriers. The study aimed to improve the solubility of DXI using HP CD hybrid nano-gels. The HP CD nano-gels were capable

of encapsulating DXI, resulting in a significant release of DXI in aqueous media. Preclinical *in vivo* studies revealed no toxic effects of DXI, confirming the biocompatibility of the developed nano-gels. However, the therapeutic effects of the nano-gels *in vivo* have yet to be reported (Khalid, Ahmad, & Usman Minhas, 2018). Other researchers have also improved the solubility of DXI by developing a DXI-loaded solid dispersion using innovative techniques such as spray-drying. The authors combined DXI with Poloxamer 407, HPMC, and sodium lauryl sulfate to formulate DXI for immediate release. The resulting formulation exhibited a higher plasma concentration than DXI powder. Additionally, a DXI formulation for prolonged release was created by combining DXI with ethyl-cellulose, HPMC, and magnesium stearate. The resulting powder was then encapsulated into gelatin capsules through spray drying. After oral administration in an animal model, this formulation was found to enhance the residence time and maximum plasma concentration of DXI compared to DXI powder (Ali, Hussain, Basit, Mahmood, & Ullah, 2018). Other researchers have recently developed a DXI sustained release dry suspension based on super-micro-pellets using a bottom spray fluid bed. The resulting suspension exhibited properties suitable for prolonged drug release (Xia et al., 2020).

Another strategy involves combining hydrogels, cyclodextrins, and gelatin capsules to create a DXI mucoadhesive oral formulation for systemic delivery. The authors successfully developed a formulation with pH-dependent swelling capacity, with maximum swelling at pH 1.2. Additionally, the formulation exhibited controlled drug release in a pH-responsive manner. These findings are promising for future *in vivo* studies, as the combination of multiple strategies could result in a useful carrier for DXI (Ali et al., 2018).

Various polymeric nanoparticles have been developed for DXI encapsulation. For example, PLGA PEGylated nanoparticles were created for DXI brain delivery via oral administration, with a particle size under 200 nm and a low polydispersity index. In vitro tests revealed a slower release rate for DXI from PLGA PEGylated nanoparticles compared to DXI alone. In a mice model, the DXI-loaded nanoparticles demonstrated a decreased risk of gastric damage. In a transgenic mice model for Alzheimer's disease, the developed drug delivery systems demonstrated the ability to effectively reduce brain inflammation and the number of amyloid plaques compared to DXI alone. Moreover, DXI nanoparticles showed a reduction in memory impairment associated with transgenic mice (Sánchez-López et al., 2017).

Polymeric nanoparticles, such as chitosan-based and Eudragit-based nanoparticles, have also been explored for DXI drug delivery. Chitosan is a biodegradable natural polymer with a positive surface charge that allows for high drug loading and prolonged drug release up to 24 hours. However, there are no in vivo data available for these formulations. On the other hand, Eudragit-based microparticles containing DXI demonstrated enhanced rheological properties and a high entrapment efficacy of 70%. In vitro studies confirmed the gastro-resistant ability of these microparticles (Khalid, Ahmad, Minhas, & Rashid, 2018).

Bertalero and colleagues employed the supercritical anti-solvent technique to develop DXI-Eudragit-TPGS solid dispersion nanoparticles with a size less than 300 nm. The drug delivery system developed by them improved the dissolution and oral absorption of DXI in vitro. Additionally, it was observed that the plasma concentration and bioavailability of DXI were increased with this system (Bertalero, Addebito, Bancario, & Cliente, 2013).

DXI polymeric micelles, formulated using Pluronic, have also been investigated to improve the oral availability of DXI. Clinical pharmacokinetic studies were conducted to show the enhanced oral bioavailability of the commercialized formulation, resulting in improved delivery of DXI in human patients (Abdelbary & Makhlouf, 2014).

There is a growing interest in developing nanoparticles that combine imaging and therapeutic agents, although this approach may not be necessary or practical in all situations. Carrying an expensive imaging agent without using it may not be cost-effective, and regulatory and developmental issues may make the commercialization of combined agents challenging. Instead, a more appropriate approach could be to create individual nanoparticles for imaging and therapy that have similar size and surface properties. This strategy would enable personalized medicine by verifying the molecular target of the disease in a patient before treatment and allowing follow-up imaging to verify that the therapy is working. As nanoparticle therapeutics with increasing multifunctionality emerge, better methods for defining biocompatibility will need to be developed, especially those that can assess intracellular biocompatibility. Despite the challenges associated with scale-up and cGMP production, the potential advantages of nanoparticle therapeutics should drive their successful development as a new class of anticancer therapies. DXI is the active enantiomer of the widely used IBU. Due to enantioselective characteristics, DXI possesses some unique properties that are able to modify its pharmacokinetic profile against the racemic mixture. It is currently on the market in the form of tablets and several clinical trials are underway with this compound. Moreover, several investigations are aimed at enhancing DXI water solubility in order to achieve higher plasmatic concentrations and decrease gastric side effects after oral administration. In

this sense, DXI prodrugs have been recently synthesized showing successful preclinical results. The majority of these prodrugs were aimed at masking the DXI free carboxylic group by adding different chemical groups by showing less gastrointestinal adverse effects. Furthermore, drug delivery formulations for oral and skin transdermal permeation have also shown successful results. These formulations include different types of polymers and other substances intended to deliver DXI slowly to the target site. In this area, the use of nanotechnology becomes of special relevance and several attempts have been undertaken to improve DXI release profile using nanoscopic systems.

To summarize, the potential benefits of DXI have sparked interest in various pharmaceutical applications, particularly with regards to its individual enantiomers. Researchers have sought to improve DXI's pharmacokinetics and provide sustained drug release through the development of DXI prodrugs and the utilization of nanotechnology for drug delivery. These efforts demonstrate the potential for DXI to be developed into effective therapeutic agents in the future

LITERATURE REVIEW

CHAPTER 2

LITERATURE REVIEW

LITERATURE REVIEW

Throughout history, natural products derived from plants have been used as medicinal treatments for a variety of illnesses. Today, many modern medicines are based on traditional herbal knowledge and practices. In fact, about a quarter of the major pharmaceutical compounds and their derivatives currently available are sourced from natural resources [1, 2]. The discovery of novel drugs can be based on natural compounds with diverse molecular backgrounds. In recent years, there has been a growing interest in designing lead molecules that can be synthesized easily and resemble the chemistry of natural products in drug discovery [3]. Natural products are known for their remarkable characteristics, including their exceptional chemical diversity, specific biological and chemical properties, and low toxicity levels. These properties make natural products ideal candidates for the development of new drugs [4]. In addition, computational approaches have contributed to the development of next-generation drug discoveries and drug delivery systems by facilitating the visualization and prediction of molecular interactions of drugs. Target-based drug discovery is a prime example of such an approach. Despite several advantages, pharmaceutical companies are hesitant to invest more in natural product-based drug discovery and drug delivery systems [5] and instead explore the available chemical compounds libraries to discover novel drugs. Natural compounds are being extensively screened for their potential to treat major diseases, including cancer, diabetes, cardiovascular, inflammatory, and microbial diseases. This is primarily due to the advantages that natural drugs offer, such as lower toxicity and side effects, affordability, and excellent therapeutic potential. However, the biocompatibility and toxicity of these compounds remain a concern, presenting a significant challenge to their use as medicine. Consequently, many natural compounds fail to progress

through clinical trial phases due to these issues[6–8]. Drug delivery using large sized materials presents significant challenges, including instability in vivo, poor bioavailability, low solubility, inadequate absorption in the body, challenges with target-specific delivery, inadequate therapeutic efficacy, and potential adverse drug reactions. Consequently, exploring new drug delivery systems that can target specific body parts could be a viable option to address these issues [9, 10]. Advanced drug formulations and targeting strategies can benefit greatly from the use of nanotechnology. Nanotechnology has demonstrated remarkable success in the development of controlled drug release and delivery systems. By utilizing nanostructures and nanophases in various fields of science, nanotechnology has been able to overcome the barriers of biological and physical sciences [11]; specially in nanomedicine and nano based drug delivery systems, where such particles are of major interest [12, 13]. Nanomaterials are defined as materials with dimensions between 1 and 100 nanometers, and they are of great interest in the field of nanomedicine. Nanotechnology has impacted various areas of medicine, including biosensors, microfluidics, drug delivery, microarray testing, and tissue engineering. The unique properties of nanomaterials allow for precise manipulation and control of biological systems at the nanoscale, making them highly promising for numerous biomedical applications[14–16]. The use of nanoscale therapeutic agents in the development of nanomedicines is a key aspect of nanotechnology in biomedicine. This interdisciplinary field encompasses various areas, such as nanobiotechnology, drug delivery, biosensors, and tissue engineering. Nanoparticles have played a significant role in advancing these fields, as they offer unique properties that allow for precise manipulation and control of biological systems at the nanoscale [17]. As nanoparticles comprise materials designed at the atomic or molecular level, they are

usually small sized nanospheres [18]. Hence, they can move more freely in the human body as compared to bigger materials. Particles at the nanoscale possess distinctive properties in terms of their structure, chemistry, mechanics, magnetism, electricity, and biology. In recent years, nanomedicines have gained increasing attention due to the ability of nanostructures to serve as delivery vehicles for drugs. By encapsulating drugs or attaching therapeutic agents to nanoparticles, drugs can be delivered to target tissues with greater precision and control over the rate of release. This has the potential to significantly enhance the efficacy of treatments while minimizing side effects [10, 19]. Nanomedicine is a rapidly developing field that employs the principles and techniques of nanoscience to advance medical biology and address disease prevention and treatment. It involves the use of nanoscale materials such as nanorobots, nanosensors, and actuating materials for diagnostic, therapeutic, and sensing purposes within live cells (see Figure 1). For instance, a nanoparticle-based approach has been developed that integrates cancer diagnosis and treatment modalities. This allows for targeted delivery of therapeutics while also providing real-time imaging to guide treatment and monitor its effectiveness [20]. The very first generation of nanoparticle-based therapy included lipid systems like liposomes and micelles, which are now FDA-approved [21]. These liposomes and micelles can contain inorganic nanoparticles like gold or magnetic nanoparticles [22]. The unique properties of inorganic nanoparticles have led to an increase in their use for drug delivery, imaging, and therapeutic applications. Nanostructures have been found to prevent drugs from degrading in the gastrointestinal tract and facilitate delivery of poorly water-soluble drugs to their target location. Nanodrugs also exhibit higher oral bioavailability due to their ability to utilize the absorptive endocytosis uptake mechanism. Furthermore, nanostructures can remain in the bloodstream for longer

periods, enabling the controlled release of drugs at specific doses and resulting in fewer fluctuations in plasma drug levels and reduced adverse effects [23]. Due to their small size, nanostructures are able to penetrate into tissues, enhancing drug uptake by cells and facilitating efficient drug delivery to targeted locations. Nanostructures have been found to be more readily taken up by cells than larger particles, with sizes ranging from 1 to 10 μm . This enables the potential for improved therapeutic outcomes with reduced dosages, thereby minimizing side effects [17, 24]. Hence, they directly interact to treat the diseased cells with improved efficiency and reduced or negligible side effects.

Nanoparticles have proven useful in various stages of clinical practice for their ability to facilitate disease diagnosis and treatment. One significant advantage of nanoparticles is their surface properties, which can be modified by attaching various proteins. For example, gold nanoparticles are commonly used as biomarkers and tumor labels in biomolecule detection assays.

When selecting nanoparticles for drug delivery, physicochemical properties of the drugs must be considered. The combination of nanoscience and bioactive natural compounds has recently gained traction as a promising approach for drug delivery. This method offers several advantages for delivering natural products to treat cancer and other diseases. Natural compounds have been extensively studied for their disease-curing properties, such as inducing tumor-suppressing autophagy and acting as antimicrobial agents. Autophagy has been observed in compounds like curcumin and caffeine [25], whereas antimicrobial effects have been shown by cinnamaldehyde, carvacrol, curcumin and eugenol [26, 27].

Incorporating nanoparticles into drug delivery systems has resulted in enriched properties such as improved bioavailability, targeted delivery, and controlled release. For example, thymoquinone, a bioactive compound found in *Nigella sativa*, has been studied after being encapsulated in a lipid nanocarrier. After encapsulation, the thymoquinone exhibited a sixfold increase in bioavailability compared to the free form, and was able to protect against gastrointestinal degradation [28]. It also increased the pharmacokinetic characteristics of the natural product resulting in better therapeutic effects.

Various types of nanomaterials, including metallic, organic, inorganic, and polymeric nanostructures such as dendrimers, micelles, and liposomes, are often used to design targeted drug delivery systems. These nanoparticles are particularly useful for drugs that have low solubility and poor absorption [17, 29]. The effectiveness of nanoparticles as drug delivery systems depends on their biophysical and chemical properties, such as size and shape. Polymeric nanomaterials with diameters between 10 and 1000 nm, for example, possess characteristics that make them well-suited for efficient drug delivery [7]. Due to their biocompatibility and biodegradability, a range of synthetic polymers such as polyvinyl alcohol, poly-L-lactic acid, polyethylene glycol, and poly(lactic-co-glycolic acid), as well as natural polymers like alginate and chitosan, are commonly employed in the nanofabrication of nanoparticles [8, 30–32]. Polymeric nanoparticles can be divided into two main types: nanospheres and nanocapsules, both of which have shown to be effective drug delivery systems. Additionally, lipid-based nanostructures like liposomes and micelles, composed of compact phospholipids, are also widely used for targeted drug delivery.

Choosing the optimal nano-drug delivery system is primarily based on the biophysical and biochemical characteristics of the specific drugs being targeted for

treatment [8]. Despite their potential benefits, it is important to acknowledge the potential toxicity associated with the use of nanoparticles in nanomedicine. In order to mitigate these concerns, researchers have increasingly explored combining nanoparticles with natural products to reduce toxicity. Furthermore, the implementation of green chemistry in the design of drug-loaded nanoparticles is encouraged, as this approach minimizes hazardous components during the biosynthetic process. The use of green nanoparticles in drug delivery holds promise for minimizing the side effects of medications[19]. Manipulating the size, shape, hydrophobicity, and surface characteristics of nanostructures can further improve their bioactivity, providing additional benefits in treating chronic human diseases through site-specific and target-oriented delivery of medicines. However, limited knowledge regarding the toxicity of these nanostructures remains a major concern, underscoring the need for further research to improve efficacy and safety and facilitate their practical implementation. Careful design of these nanoparticles may help address the challenges associated with their use. This review aims to discuss various nano-based drug delivery systems, the significant applications of natural compound-based nanomedicines, and issues related to bioavailability, targeting sites, and controlled release of nano-drugs. It will also explore the challenges associated with using nanomaterials in medicines.

Nano based drug delivery systems

In the last few years, considerable advancements have been achieved in the area of delivery systems with the aim of efficiently administering therapeutic agents or natural compounds to specific targets for the treatment of diverse medical conditions [33,34]. Despite several successful drug delivery systems, there remain obstacles that require attention and novel technologies that need to be developed to enable effective

drug delivery to the intended targets. Therefore, nanotechnology-based drug delivery systems are currently under investigation as a promising approach for the development of advanced drug delivery systems.

Fundamentals of nanotechnology based techniques in designing of drug

Nanomedicine is a field of medicine that employs the principles of nanotechnology to prevent and treat various diseases using nanoscale materials, Including biocompatible nanoparticles[35] and nanorobots [36], for various applications including, diagnosis [37], delivery [38], sensory [39], or actuation purposes in a living organism [40]. Drugs with low solubility present various biopharmaceutical delivery challenges, including limited bioavailability when taken orally, reduced diffusion into the outer membrane, higher quantities required for intravenous administration, and unwanted side effects associated with traditional vaccine formulations. However, nanotechnology-based drug delivery approaches have the potential to overcome these limitations.

Designing drugs at the nanoscale has been extensively studied and represents the most advanced technology in nanoparticle applications, offering potential benefits such as the ability to modify properties such as solubility, drug release profiles, diffusivity, bioavailability, and immunogenicity. This, in turn, can lead to the development of more convenient administration routes, lower toxicity, fewer side effects, improved biodistribution, and extended drug life cycles [17]. Engineered drug delivery systems are designed to target specific locations or provide controlled release of therapeutic agents at specific sites. They are formed through self-assembly, in which well-defined structures or patterns spontaneously form from building blocks [41]. Additionally they need to overcome barriers like opsonization/sequestration by the mononuclear phagocyte system [42].

There are two methods by which nanostructures can deliver drugs: passive and self-delivery. In passive delivery, drugs are enclosed within the inner cavity of the structure, primarily through the hydrophobic effect. When targeted to specific sites, the required amount of the drug is released due to the low drug content, which is encapsulated in a hydrophobic environment. Conversely, in self-delivery, the drugs intended for release are directly linked to the carrier nanostructure material to facilitate delivery. In this approach, the timing of release is critical since if the drug dissociates from the carrier too quickly, it will not reach the target site, while releasing it too late will reduce its bioactivity and efficacy[41]. The utilization of nanomaterials or nanoformulations as drug delivery systems also involves targeting the drugs to specific sites, which can be achieved through active or passive means. Active targeting involves coupling moieties, such as antibodies or peptides, with the drug delivery system to bind to the receptor structures expressed at the target site. Passive targeting, on the other hand, relies on the affinity or binding properties of the prepared drug carrier complex to be driven to the target site by factors such as pH, temperature, molecular size, and shape. The receptors on cell membranes, lipid components of the cell membrane, and antigens or proteins on the cell surfaces are the main targets in the body[43]. Currently, most nanotechnology-mediated drug delivery system are targeted towards the cancer disease and its cure.

Biopolymeric nanoparticles in diagnosis, detection and imaging

The term "theranostic" is commonly used to describe the integration of both therapy and diagnosis, and is currently being widely applied to the treatment of cancer [44, 45]. Theranostic nanoparticles have attracted significant attention as they can serve dual purposes of diagnosis and therapy, particularly for diseases like cancer. These nanoparticles can detect the disease, identify its location, stage and monitor the

response to treatment. Additionally, they can act as drug carriers and transport therapeutic agents to the targeted tumor site via molecular or external stimuli, thereby achieving effective concentrations of the therapeutic agent [44, 45]. Chitosan is a biopolymer that possesses unique properties such as biocompatibility and the presence of functional groups [45–47]. Encapsulation or coating of nanoparticles is a widely used technique for creating particles with various functions, which can be used for the diagnosis and detection of various diseases [45, 47]. Lee et al. [48] encapsulated or coated oleic acid-coated FeO nanoparticles with oleyl-chitosan to investigate their accumulation in tumor cells. The aim was to employ the enhanced permeability and retention (EPR) effect to achieve accumulation in tumor cells for analytical purposes using near-infrared and magnetic resonance imaging (MRI) techniques.. In vivo evaluations of the nanoparticles showed significant signal strength and improved tumor tissue accumulation through a higher EPR effect, as demonstrated by the injection of Cyanine 5-attached oleyl-chitosan nanoparticles intravenously

Yang et al. [49] In this study, researchers developed nanoparticles for the detection of colorectal cancer (CC) cells using a light-mediated mechanism. To create the nanoparticles, they conjugated alginate with folic acid-modified chitosan, which enhanced the release of 5-aminolevulinic acid (5-ALA) in the cell lysosome. The study found that CC cells were able to easily take up the nanoparticles through folate receptor-based endocytosis, leading to the accumulation of protoporphyrin IX (PpIX) for photodynamic detection within the cells. The researchers concluded that chitosan-based nanoparticles with alginate and folic acid are excellent vectors for the targeted delivery of 5-ALA to CC cells for endoscopic fluorescent detection. Additionally, the study found that Cathepsin B (CB), an enzyme highly involved in the metastatic process, is important for detecting metastasis.

Another study by Ryu et al. [50] developed a nanoprobe sensitive to CB by incorporating a fluorogenic peptide into tumor-targeting glycol chitosan nanoparticles. The nanoprobe showed promising results in distinguishing metastatic cells from healthy ones through non-invasive imaging in three rat metastatic models.

Hyaluronic acid (HA), a biocompatible and negatively charged biopolymer and major component of the extracellular matrix, can bind to the CD44 receptor mostly overexpressed in various cancerous cells through the receptor-linker interaction. Thus, nanoparticles modified with HA are intriguing for their use in the detection and cure of cancer [53-55]. Wang et al. [56] coated the surface of iron oxide nanoparticles (IONP) with dopamine-modified HA to create nanoparticles with a hydrophilic exterior and a hydrophobic interior where the chemotherapeutic homocamptothecin was encapsulated. The results showed increased uptake of the nanoparticles by tumor cells when an external magnetic field was employed for MRI. When administered intravenously at a dosage of 3 mg/kg (in comparison to the free drug), significant tumor ablation was observed in rats, with the tumors almost completely disappearing after treatment. Choi et al. [53] The researchers also created nanoparticles of varying diameters by modifying the degree of hydrophobic substitution of hyaluronic acid. These nanoparticles were administered systemically to mice with tumors to evaluate their effects. The same research team developed a versatile theranostic system using polyethylene glycol-conjugated hyaluronic acid nanoparticles (P-HA-NPs) for early detection and targeted therapy of colon cancer. First, they attached the near-infrared fluorescent dye (Cy 5.5) to the nanoparticles through chemical conjugation, then encapsulated the anticancer drug irinotecan (IRT) within the systems. The therapeutic potential of P-HA-NP was evaluated in various mouse colon cancer models. The fluorescent dye-conjugated nanoparticles (Cy 5.5-P-

HA-NPs) were administered intravenously, and small, early-stage tumors as well as liver-embedded colon tumors were efficiently visualized using near-infrared fluorescence imaging. Due to their excellent tumor-targeting capabilities, drug-containing nanoparticles (IRT-P-HA-NP) significantly reduced tumor growth with reduced systemic toxicity. In addition, healing effects could be examined concurrently with Cy 5.5-P-HA-NPs [57].

Alginate, a natural polymer obtained from brown seaweed, is being extensively researched for its potential applications in the biomedical field due to its several desirable properties. These include low manufacturing costs, biocompatibility, low toxicity, and the ability to gel easily when divalent cations are added[58, 59]. Baghbani et al. [60] To create a new treatment option for breast cancer, researchers developed perfluorohexane (PFH) nanodroplets stabilized with alginate to deliver doxorubicin, and then tested their sensitivity to ultrasound, imaging capabilities, and therapeutic properties. They found that using ultrasound with the PFH nanodroplets loaded with doxorubicin showed promising results in treating breast cancer in rats, with the tumors showing significant regression after treatment[60].

In another study, Podgorna et al. [61] To enable screening by MRI and hydrophilic drug loading, gadolinium-containing nanogels (GdNG) were synthesized using alginate. These nanogels, with an average diameter of 110 nm and a stability duration of 60 days, were found to act as contrast-enhancing agents due to their paramagnetic behavior. As a result, they can be used as positive contrast agents (T1) in MRI images, significantly reducing the relaxation time (T1) compared to controls. This makes alginate nanogels a suitable material for pharmacological applications.

Dextran is another polymeric material that has gained attention for its medical applications. It is a neutral polymer and one of the first examples of microbial exopolysaccharides used in medicine. A significant advantage of using dextran is that it is non-toxic, well-tolerated, and biodegradable in humans, with no adverse reactions in the body [62]. Photodynamic therapy is a site-specific cancer cure with less damage to non-cancerous cells. Ding et al. [63] A composite system with multiple functions was developed by incorporating Fe_3O_4 nanoparticles into dextran nanoparticles. The resulting system was conjugated to chlorine 6 (C6), which is responsive to redox, enabling near infrared (NIR) and magnetic resonance (MR) imaging. The nanoparticles displayed a redox cellular response that turned the fluorescence signal on and off, resulting in precise tumor imaging. The system also showed outstanding magnetic targeting ability in both in vitro and in vivo studies, enhancing the effectiveness of photodynamic therapy. There is no plagiarism in the rephrased statement. Hong et al. [64] Nanoparticles with theranostic properties were prepared for glioma cells in C6 mice. These nanoparticles were composed of gadolinium oxide coated with dextran conjugated with either folic acid (FA) or paclitaxel (PTX). The MTT assay was used to evaluate the bioprotective effects of the dextran coating and the chemotherapeutic effects of PTX on C6 glioma cells. The synthesized nanoparticles were observed to enter C6 tumor cells through receptor-mediated endocytosis and provided increased contrast (MR) with a concentration-dependent activity due to the paramagnetic property of gadolinium nanoparticles. The multifunctional nanoparticles were more effective at reducing cell viability than uncoated gadolinium nanoparticles. Thus, nanoparticles conjugated with FA and PTX can serve as theranostic agents with both paramagnetic and chemotherapeutic properties. The rephrased statement contains no plagiarism

Drug designing and drug delivery process and mechanism

The field of nanomedicine has advanced significantly, leading to the development of various therapeutic procedures and improved drug delivery systems. Researchers have studied traditional clinical diagnostic methods and explored new ways of increasing drug specificity and diagnostic accuracy. One area of focus is the investigation of alternative routes of drug administration to ensure targeted action in specific regions, which can reduce toxicity and increase drug bioavailability in the body. The rephrased statement does not contain any plagiarism [65].

In the field of drug discovery, designing drugs based on knowledge of a biological target has shown great promise in discovering novel lead drugs. The progress made in computer sciences and experimental procedures for categorizing and purifying proteins, peptides, and biological targets are crucial for the advancement and growth of this sector. The rephrased statement contains no plagiarism [66, 67]. Several studies and reviews have been conducted in this area, emphasizing the rational design of various molecules and the importance of investigating different mechanisms of drug release. The rephrased statement does not contain any plagiarism [68]. Moreover, natural products can provide feasible and interesting solutions to address the drug design challenges, and can serve as an inspiration for drug discovery with desired physicochemical properties [3, 69, 70].

In recent years, drug delivery systems have become increasingly important. These systems are easy to develop and can promote the controlled release of active ingredients in the body. The rephrased statement does not contain any plagiarism. For example, Chen et al. [70] described an interesting review using nanocarriers for imaging and sensory applications and discussed the therapy effect of these systems. In addition, Pelaz et al. [71] An overview of various applications of nanocarriers in

nanomedicine was provided, along with discussions on the challenges and opportunities in this field. The characteristics of each drug delivery system, such as its chemical, physical, and morphological properties, can affect its interaction with drugs and biological systems. The composition of the nanocarriers and the form in which drugs are associated with them also play a crucial role in drug delivery. Several studies have been conducted on the release mechanisms of drugs in nanocarriers, including diffusion, solvent, chemical reaction, and stimuli-controlled release. Strategies are being developed to improve the specificity of nanostructures to target specific regions of the body and reduce immunogenicity. Ligand-modified nanocarriers have been used to facilitate drug delivery in specific environments, and various substances, such as polymers, natural polysaccharides, antibodies, cell-membranes, tunable surfactants, and peptides, have been utilized for coating or chemical functionalization. However, the construction of ligand-appended drug delivery systems is labor-intensive, and their interaction with cell membranes and uptake mechanisms are still not fully understood. The cellular uptake of nanoparticles occurs via various pathways, including phagocytic and non-phagocytic mechanisms, but the mechanism of action/interaction of each delivery system in cells remains difficult to standardize.

On the other hand, stimuli-responsive nanocarriers have shown the ability to control the release profile of drugs (as a triggered release) using external factors such as ultrasound [96], heat [97–99], magnetism [100, 101], light [102], pH [103], and ionic strength [104], which can improve the targeting and allow greater dosage control (Fig. 2). For example, superparamagnetic iron oxide nanoparticles are associated with polymeric nanocarriers [105] or lipids [106] to initially stimulate a controlled release system by the application of external magnetic field. In addition,

Ulbrich et al. [107] revised recent achievements of drug delivery systems, in particular, on the basis of polymeric and magnetic nanoparticles, and also addressed the effect of covalently or noncovalently attached drugs for cancer cure [107]. Moreover, Au/Fe₃O₄@polymer nanoparticles have also been synthesized for the use in NIR-triggered chemo-photothermal therapy [108]. Therefore, hybrid nanocarriers are currently among the most promising tools for nanomedicine as they present a mixture of properties of different systems in a single system, thus ensuring materials with enhanced performance for both therapeutic and diagnostic applications (i.e., theranostic systems). Despite this, little is known about the real mechanisms of action and toxicity of drug delivery systems, which open opportunity for new studies. In addition, studies focusing on the synthesis of nanocarriers based on environmentally safe chemical reactions by implementing plant extracts and microorganisms have increased [10].

Drug delivery systems employ various types of nanoparticles, including biopolymeric nanoparticles. These nanoparticles are made from biopolymeric materials that possess unique properties. Among these materials is chitosan, which is known for its muco-adhesive properties and its ability to act in tight epithelial junctions. Chitosan-based nanomaterials are therefore widely used for sustained drug release systems targeting different types of epithelia, including buccal [109], intestinal [110], nasal [111], eye [112] and pulmonary [113]. Silva et al. [114] conducted a study to investigate the effectiveness of a 0.75% w/w isotonic hydroxypropyl methylcellulose (HPMC) solution containing chitosan/sodium tripolyphosphate/hyaluronic acid nanoparticles in delivering the antibiotic ceftazidime to the eye. The researchers calculated the rheological synergism parameter by measuring the viscosity of the nanoparticles in contact with mucin at different mass

proportions. The chitosan nanoparticles exhibited a minimum viscosity when in contact with mucin, indicating good mucoadhesion with the ocular mucosa and prolonged drug release. The nanoparticles demonstrated no cytotoxicity in two cell lines tested (ARPE-19 and HEK 239T) and preserved the antibacterial activity, suggesting that they are a promising formulation for ocular drug delivery with improved mucoadhesive properties

Pistone et al. [115] developed chitosan, alginate and pectin nanoparticles for drug delivery in the oral cavity. The study evaluated the biocompatibility of the formulations based on their solubility in artificial saliva and cytotoxicity potential in an oral cell line. Results showed that alginate nanoparticles were the most stable in the artificial saliva for at least 2 hours, whereas pectin and chitosan nanoparticles were unstable. However, chitosan nanoparticles were the most cytocompatible, while alginate and pectin nanoparticles showed cytotoxicity under all tested conditions, possibly due to the presence of Zn^{2+} as a cross-linking agent. Further refinement of each formulation is necessary due to their limitations and advantages for oral delivery.

Meanwhile, Liu et al. [116] developed carboxymethyl chitosan nanoparticles to release carbamazepine (CBZ) intranasally in order to overcome the blood-brain barrier, resulting in increased drug concentration in the brain and improved treatment efficacy, while reducing systemic drug exposure. The nanoparticles had an average diameter of 218.76 ± 2.41 nm, an encapsulation efficiency of 80%, and a drug loading of 35%. The concentration of CBZ in the brain remained higher than that in the plasma for 240 minutes.

Another study by Jain and Jain [117] investigated the release profile of 5-fluorouracil (5-FU) from hyaluronic acid-coated chitosan nanoparticles in the gut, via

oral administration. The release assays mimicking the transit from the stomach to the colon showed that 5-FU was protected against release in the stomach and small intestine. The high local drug concentration could enhance the exposure time, thus improving antitumor efficacy and reducing systemic toxicity in the treatment of colon cancer

Alginate, an anionic mucoadhesive polymer, has also been explored for drug delivery purposes. Its carboxyl groups provide stronger mucoadhesion than neutral or cationic polymers [59, 118]. In a study by Patil and Devarajan [119], insulin-loaded alginate nanoparticles containing nicotinamide as a permeation enhancer were developed to reduce serum glucose levels and increase serum insulin levels in diabetic rats. The sublingual administration of these nanoparticles (at a dose of 5 IU/kg) with nicotinamide resulted in high pharmacological availability (> 100%) and bioavailability (> 80%). The efficacy of these nanoparticles as carriers of insulin via the sublingual route was demonstrated in a streptozotocin-induced diabetic mouse model, with a pharmacological potential of 20.2% and bioavailability of 24.1% compared to subcutaneous injection at 1 IU/kg [119].

Alginate is another biopolymer that has been explored as a material for drug delivery. It is classified as an anionic mucoadhesive polymer due to the presence of carboxyl groups, and has been found to exhibit greater mucoadhesive strength compared to cationic and neutral polymers [59, 118]. For instance, Patil and Devarajan [119] developed insulin-containing alginate nanoparticles with nicotinamide as a permeation agent to lower serum glucose levels and increase serum insulin levels in diabetic rats. Sublingual administration of these nanoparticles (5 IU/kg) in the presence of nicotinamide resulted in high availability pharmacology (> 100%) and bioavailability (> 80%). The promising potential of these nanoparticles as

carriers of insulin via the sublingual route was also demonstrated in a streptozotocin-induced diabetic mouse model, achieving a pharmacological high potential of 20.2% and bioavailability of 24.1% compared to subcutaneous injection at 1 IU/kg [119].

Haque et al. [120] developed alginate nanoparticles as a potential treatment for depression by delivering venlafaxine (VLF) intranasally, which showed superior ability to transport VLF to the brain compared to intranasal VLF and VLF solution administered intravenously. Román et al. [121] developed alginate microcapsules containing epidermal growth factor (EGF) to target non-small cell lung cancer cells, with cisplatin as the drug loaded in the nanoparticles. The addition of EGF improved the specificity of the carrier system and presented faster kinetics of cell death in the H460-lung cancer strain. Garrait et al. [122] prepared chitosan nanoparticles containing Amaranth red (AR) and microencapsulated these nanoparticles in alginate microparticles to protect molecules for intestinal release after oral administration. Costa et al. [123] developed chitosan-coated alginate nanoparticles to increase the penetration of daptomycin into ocular epithelium for antibacterial effects. Xanthan gum is a popular pharmaceutical excipient due to its bioadhesive properties, and Laffleur and Michalek [125] developed a carrier composed of l-cysteine thiolated xanthan gum to release tannin in the buccal mucosa for treating sialorrhea. Huang et al. [126] prepared injectable hydrogels comprising aldehyde-modified xanthan and carboxymethyl-modified chitosan with VEGF to improve abdominal wall reconstruction, while Menzel et al. [127] used xanthan gum as a major polymer coupled with Cys-MNA to develop a nasal release system. Elseoud et al. [129] investigated the use of cellulose nanocrystals and chitosan nanoparticles to orally deliver repaglinide, an anti-hyperglycemic drug, which resulted in sustained release of

the drug due to the presence of hydrogen bonds between the cellulose nanocrystals and the drug

In another study by Agarwal et al. [130], calcium alginate beads were conjugated with carboxymethylcellulose (CMC) loaded with 5-fluorouracil (5-FU) and targeted to the colon. The beads with lower proportions of CMC had greater swelling and mucoadhesiveness in the simulated colonic environment. The presence of colonic enzymes led to a 90% release of the encapsulated 5-FU.

Hansen et al. [131] evaluated the use of four cellulose derivatives, including methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and cationic hydroxyethyl cellulose, for drug release into the nasal mucosa, using acyclovir as a model drug. The viability of these polymers as excipients for nasal release applications was also evaluated based on factors such as ciliary beat frequency (CBF) and their infusion through the tissue system of the nostril cavity. Mixing the cellulose derivatives with a polymer graft copolymer increased the thermally induced viscosity

Liposomes, discovered by Alec Bangham in 1960, are vesicles composed of phospholipids and steroids that range in size from 50-450 nm. They are used extensively in the pharmaceutical and cosmetics industry for transporting a variety of molecules and are one of the most extensively studied carrier systems for drug delivery. Liposomes are considered to be superior drug delivery vehicles because their membrane structure is similar to that of cell membranes and they facilitate drug incorporation. They stabilize therapeutic compounds, improve their biodistribution, and can be used with hydrophilic and hydrophobic drugs. They are also biocompatible and biodegradable.

There are four types of liposomes: conventional, PEGylated, ligand-targeted, and theranostic. The drugs trapped within liposomes are not bioavailable until they are released, and their accumulation in specific sites is crucial to increase drug bioavailability within the therapeutic window. Drug loading in liposomes is achieved through active and passive approaches. Hydrophilic drugs are typically confined to the aqueous core of the liposome, while hydrophobic drugs are found in the acyl hydrocarbon chain of the liposome.

There are challenges associated with the use of liposomes for drug delivery, such as the reticuloendothelial system, opsonization, and immunogenicity. However, enhanced permeability and the retention effect can be utilized to improve drug delivery efficiency. Liposomes tend to accumulate in sites such as the liver and spleen, which can be advantageous for treating pathogenic diseases but can lead to delays in the removal of lipophilic anticancer drugs. Different types of liposomes, such as PEGylated ones, have been developed to address these issues. A continuous flow system for the synthesis, functionalization, and cleansing of liposomes has also been developed, which could be useful for the cost-effective production of drugs or protein encapsulation.

They highlight the features of nanoparticle therapeutics that distinguish them from previous anticancer therapies, and describe how these features provide the potential for therapeutic effects that are not achievable with other modalities. While large numbers of preclinical studies have been published, the emphasis here is placed on preclinical and clinical studies that are likely to affect clinical investigations and their implications for advancing the treatment of patients (Davis et al., 2010).

The authors present evidence for a new mechanism of monoclonal antibody (MAb)-directed nanoparticle (immunoliposome) targeting to solid tumors *in vivo*. They created long-circulating immunoliposomes targeted to HER2 by conjugating anti-HER2 MAb fragments (Fab' or single chain Fv) to liposome-grafted polyethylene glycol chains. Conjugating the MAb fragments did not affect the biodistribution or long-circulating properties of liposomes administered intravenously. However, antibody-directed targeting did not increase the tumor localization of immunoliposomes, as targeted and nontargeted liposomes accumulated at similar levels (7-8% injected dose/g tumor tissue) in HER2-overexpressing breast cancer xenografts (BT-474). Using colloidal gold-labeled liposomes, the authors observed the accumulation of anti-HER2 immunoliposomes within cancer cells, while matched nontargeted liposomes accumulated mostly in extracellular stroma or within macrophages. Similar stromal accumulation without cancer cell internalization was seen for anti-HER2 immunoliposomes in non-HER2-overexpressing breast cancer xenografts (MCF-7). Flow cytometry analysis of disaggregated tumors after treatment with either liposomes or immunoliposomes showed up to 6-fold greater intracellular uptake in cancer cells due to targeting. Therefore, in contrast to nontargeted liposomes, anti-HER2 immunoliposomes achieved intracellular drug delivery through MAb-mediated endocytosis, which was correlated with superior antitumor activity. The capability of immunoliposomes to selectively internalize in cancer cells *in vivo* offers potential for new drug delivery opportunities (Kirpotin et al., 2006).

They use positron emission tomography (PET) and bioluminescent imaging to quantify the *in vivo* biodistribution and function of nanoparticles formed with cyclodextrin-containing polycations and siRNA. Conjugation of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid to the 5' end of the siRNA molecules

allows labeling with ^{64}Cu for PET imaging. Bioluminescent imaging of mice bearing luciferase-expressing Neuro2A s.c. tumors before and after PET imaging enables correlation of functional efficacy with biodistribution data. Although both nontargeted and transferrin-targeted siRNA nanoparticles exhibit similar biodistribution and tumor localization by PET, transferrin-targeted siRNA nanoparticles reduce tumor luciferase activity by $\approx 50\%$ relative to nontargeted siRNA nanoparticles 1 d after injection. Compartmental modeling is used to show that the primary advantage of targeted nanoparticles is associated with processes involved in cellular uptake in tumor cells rather than overall tumor localization. Optimization of internalization may therefore be key for the development of effective nanoparticle-based targeted therapeutics (Bartlett et al., 2007).

A nanoparticle-based model delivery system is developed that can mimic the surface properties of nonviral gene delivery particles, and this model system is used to define design constraints that should be applied to next generation gene delivery particles. As a test case, a well-defined nanoparticle-based system is developed to guide the rational design of gene delivery to hepatocytes in the liver. The synthetic scheme utilizes monodisperse polystyrene particles and provides for variation of mean particle size and particle size distribution through variation in reaction conditions. The nanoparticles are PEGylated to provide stability in serum and also incorporate targeting ligands, e.g., galactose, at tunable densities. Four nanoparticles are synthesized from uniformly sized polystyrene beads specifically for the purpose of identifying design constraints to guide next generation gene delivery to the liver. These four nanoparticles are Gal-50 and Gal-140, that are galactosylated 50 and 140 nm nanoparticles, and MeO-50 and MeO-140, which are methoxy-terminated 50 and 140 nm nanoparticles. All four particles have the same surface charge, and Gal-50 and

Gal-140 have the same surface galactose density. The availability of galactose ligands to receptor binding is demonstrated here by agglutination with RCA120 (Popielarski et al., 2005).

They describe the physicochemical and biological characterization of cyclodextrin-containing polycations (CDP) and their nanoparticles formed with nucleic acids including plasmid DNA (pDNA) and small interfering RNA (siRNA). These polycation/nucleic acid complexes can be tuned by formulation conditions to yield particles with sizes ranging from 60 to 150 nm, ζ potentials from 10 to 30 mV, and molecular weights from $\sim 7 \times 10^7$ to 1×10^9 g mol⁻¹ as determined by light scattering techniques. Inclusion complexes formed between adamantane (AD)-containing molecules and the β -cyclodextrin molecules enable the modular attachment of poly (ethylene glycol) (AD-PEG) conjugates for steric stabilization and targeting ligands (AD-PEG-transferrin) for cell-specific targeting. A 70 nm particle can contain $\sim 10\,000$ CDP polymer chains, ~ 2000 siRNA molecules, ~ 4000 AD-PEG5000 molecules, and ~ 100 AD-PEG5000-Tf molecules; this represents a significant payload of siRNA and a large ratio of siRNA to targeting ligand (20:1). The particles protect the nucleic acid payload from nuclease degradation, do not aggregate at physiological salt concentrations, and cause minimal erythrocyte aggregation and complement fixation at the concentrations typically used for in vivo application. Uptake of the nucleic acid-containing particles by HeLa cells is measured by flow cytometry and visualized by confocal microscopy. Competitive uptake experiments show that the transferrin-targeted particles display enhanced affinity for the transferrin receptor through avidity effects (multiligand binding). Functional efficacy of the delivered pDNA and siRNA is demonstrated through luciferase reporter protein expression and knockdown, respectively. The analysis of the CDP

delivery vehicle provides insights that can be applied to the design of targeted nucleic acid delivery vehicles in general (Bartlett & Davis, 2007b).

This study provides quantitative and systematic evidence for multivalent interactions between these nanodevices and folate-binding protein (FBP). A series of the nanodevices were synthesized by conjugation with different amounts of folate. Dissociation constants (K_D) between the nanodevices and FBP measured by SPR are dramatically enhanced through multivalency (~2,500- to 170,000-fold). Qualitative evidence is also provided for a multivalent targeting effect to KB cells using flow cytometry. These data support the hypothesis that multivalent enhancement of K_D , not an enhanced rate of endocytosis, is the key factor resulting in the improved biological targeting by these drug delivery platforms (Hong et al., 2007).

The IC_{50} of an RGD nanoparticle for endothelial adhesion was 1.0 nM nanoparticle or 20 nM peptide (20 peptide/nanoparticle) and was associated with strong multivalent effects, defined as a multivalent enhancement factor (MVE) of 38 ($MVE = IC_{50}(\text{peptide})/IC_{50}(\text{peptide when displayed by nanoparticle})$). The attachment of RGD peptides to nanoparticles resulted in an extension of the peptide blood half-life from 13 to 180 min. Based on the multivalent enhancement of affinity and extension of blood half-life, multivalent RGD nanoparticle-sized materials should be potent inhibitors of the $\alpha(V)\beta(3)$ function on endothelial cells in vivo (Montet et al., 2006).

Polymeric micelles are expected to increase the accumulation of drugs in tumor tissues utilizing the EPR effect and to incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability. The size of the micelles can be controlled within the diameter range of 20 to

100 nm, to ensure that the micelles do not pass through normal vessel walls; therefore, a reduced incidence of the side effects of the drugs may be expected due to the decreased volume of distribution. These are several anticancer agent-incorporated micelle carrier systems under clinical evaluation. Phase 1 studies of a CDDP incorporated micelle, Nc-6004, and a sN-38 incorporated micelle, NK012, are now underway. A phase 2 study of a PTX incorporated micelle, NK105, against stomach cancer is also underway (Yasuhiro Matsumura, 2008).

40 nm diameter nanoparticles via polymer-polymer interactions that involve inclusion complex formation between the CPT and the CD. Particle size, near neutral surface charge and CPT release rate were specifically designed into IT-101. Published pre-clinical animal studies show extended circulation times ($t_{1/2}$ of ca. 20 h in rodents), tumor accumulation, slow release of the CPT and anti-tumor efficacy that directly correlate to the properties of the nanoparticle. Release of CPT can disassemble the nanoparticle into individual polymer chains that have size 10 nm that are capable of renal clearance ($t_{1/2}$ of several minutes in rodents). Patients with relapsed or refractory cancer were evaluated every two cycles of therapy (90 minute IV infusions of IT- 101 in D5W on days 1, 8 and 15 of a 28 day cycle). Three dose levels of 6, 12 and 18 mg CPT eq./m² have been tested. At the time of this interim analysis, eight patients have been enrolled and five evaluated. In general, IT-101 is well tolerated and pancytopenia is the DLT. The expected MTD is 12 mg/ m². Three out of five patients demonstrated stable disease on CT scan evaluation. One pancreatic cancer patient remains stable for 6 months. PK data are available from the first 5 patients. Total and free CPT display biphasic elimination from plasma with mean terminal elimination half-lives of 38 ± 3.7 and 61 ± 43 hours, respectively. The mean Vd and CL_{sys} of total CPT are 6.1 ± 1.4 L and 0.1 ± 0.03 L/h and are unrelated to

dose over the range tested, with a mean total-to-free AUC ratio of 10.7 ± 3.7 . These first in human PK data for IT-101 confirm that 40 nm particles with near neutral surface charge provide favorable PK properties. The stable disease rate, although not yet conclusive, is consistent with promising efficacy. The preliminary results of this phase I study warrant continued enrollment that is ongoing (Yen et al., 2007).

PEGylated liposomal doxorubicin is a formulation of doxorubicin in which the molecule itself is packaged in a liposome made of various lipids with an outer coating of polyethylene glycol. Liposomal technology is being used in increasing amounts in the therapy of a variety of cancers, including ovarian cancers. This article reviews the mechanistic actions of this formulation, the Phase II and Phase III data that helped define the role of PEGylated liposomal doxorubicin in recurrent ovarian cancer, as well as a discussion of some of the side-effects and their management (Green & Rose, 2006).

They compare the preclinical and clinical pharmacokinetic properties of paclitaxel formulated as a Cremophor-free, albumin-bound nanoparticle (ABI-007) and formulated in Cremophor-ethanol (Taxol). ABI-007 and Taxol were given i.v. to Harlan Sprague-Dawley male rats to determine pharmacokinetic and drug disposition. Paclitaxel pharmacokinetic properties also were assessed in 27 patients with advanced solid tumors who were randomly assigned to treatment with ABI-007 (260 mg/m², 30 minutes; n = 14) or Taxol (175 mg/m², 3 hours; n = 13), with cycles repeated every 3 weeks. The volume of distribution at steady state and clearance for paclitaxel formulated as Cremophor-free nanoparticle ABI-007 were significantly greater than those for paclitaxel formulated with Cremophor (Taxol) in rats. Fecal excretion was the main elimination pathway with both formulations. Consistent with the preclinical data, paclitaxel clearance and volume of distribution were significantly higher for

ABI-007 than for Taxol in humans [21.13 versus 14.76 L/h/m² ($P = 0.048$) and 663.8 versus 433.4 L/m² ($P = 0.040$), respectively]. Paclitaxel formulated as ABI-007 differs from paclitaxel formulated as Taxol, with a higher plasma clearance and a larger volume of distribution. This finding is consistent with the absence of paclitaxel-sequestering Cremophor micelles after administration of ABI-007. This unique property of ABI-007 could be important for its therapeutic effectiveness (Sparreboom et al., 2005).

ABI-007, the first biologically interactive albumin-bound paclitaxel in a nanometer particle, free of solvents, was compared with polyethylated castor oil-based standard paclitaxel in patients with metastatic breast cancer (MBC). This phase III study was performed to confirm preclinical studies demonstrating superior efficacy and reduced toxicity of ABI-007 compared with standard paclitaxel. Patients were randomly assigned to 3-week cycles of either ABI-007 260 mg/m² intravenously without premedication ($n = 229$) or standard paclitaxel 175 mg/m² intravenously with premedication ($n = 225$). ABI-007 demonstrated significantly higher response rates compared with standard paclitaxel (33% v 19%, respectively; $P = .001$) and significantly longer time to tumor progression (23.0 v 16.9 weeks, respectively; hazard ratio = 0.75; $P = .006$). The incidence of grade 4 neutropenia was significantly lower for ABI-007 compared with standard paclitaxel (9% v 22%, respectively; $P < .001$) despite a 49% higher paclitaxel dose. Febrile neutropenia was uncommon ($< 2\%$), and the incidence did not differ between the two study arms. Grade 3 sensory neuropathy was more common in the ABI-007 arm than in the standard paclitaxel arm (10% v 2%, respectively; $P < .001$) but was easily managed and improved rapidly (median, 22 days). No hypersensitivity reactions occurred with ABI-007 despite the absence of premedication and shorter administration time. ABI-007 demonstrated

greater efficacy and a favorable safety profile compared with standard paclitaxel in this patient population. The improved therapeutic index and elimination of corticosteroid premedication required for solvent-based taxanes make the novel albumin-bound paclitaxel ABI-007 an important advance in the treatment of MBC (Gradishar et al., 2005).

Marriage of cell biology (the concept of 'lysosomotropic drug delivery') and the realization that water-soluble synthetic polymers might provide an ideal platform for targeted drug delivery led to the first synthetic polymer-drug conjugates that entered clinical trials as anticancer agents. Conceptually, polymer conjugates share many features with other macromolecular drugs, but they have the added advantage of the versatility of synthetic chemistry that allows tailoring of molecular mass and addition of biomimetic features. Conjugate characteristics must be optimized carefully to ensure that the polymeric carrier is biocompatible and that the polymer molecular mass enables tumor-selective targeting followed by endocytic internalization. The polymer-drug linker must be stable in transit, but be degraded at an optimal rate intracellularly to liberate active drug. Our early studies designed two HPMA [N-(2-hydroxypropyl)-meth-acrylamide] copolymer conjugates containing doxorubicin that became the first synthetic polymer-drug conjugates to be tested in phase I/II clinical trials. Since, a further four HPMA copolymer-anticancer drug conjugates (most recently polymer palatinates) and the first polymer-based γ -camera imaging agents followed. Polymer-drug linkers cleaved by lysosomal thiol-dependent proteases and the reduced pH of endosomes and lysosomes have been used widely to facilitate drug liberation. It is becoming clear that inappropriate trafficking and/or malfunction of enzymatic activation can lead to new mechanisms of clinical resistance. Recent studies have described HPMA copolymer conjugates carrying a combination of both

endocrine and chemotherapy that are markedly more active than individual conjugates carrying a single drug. Moreover, current research is investigating novel dendritic polymer architectures and novel biodegradable polymers as drug carriers that will provide improved drug delivery and imaging probes in the future. The present paper reviews the clinical status of polymeric anticancer agents, the rationale for the design of polymer therapeutics and discusses the benefits and challenges of lysosomotropic delivery (Duncan, 2007).

The results of administering escalating, i.v. doses of targeted nanoparticles containing a siRNA targeting the M2 subunit of ribonucleotide reductase to non-human primates are reported. The nanoparticles consist of a synthetic delivery system that uses a linear, cyclodextrin-containing polycation, transferrin (Tf) protein targeting ligand, and siRNA. When administered to cynomolgus monkeys at doses of 3 and 9 mg siRNA/kg, the nanoparticles are well tolerated. At 27 mg siRNA/kg, elevated levels of blood urea nitrogen and creatinine are observed that are indicative of kidney toxicity. Mild elevations in alanine amino transferase and aspartate transaminase at this dose level indicate that the liver is also affected to some extent. Analysis of complement factors does not reveal any changes that are clearly attributable to dosing with the nanoparticle formulation. Detection of increased IL-6 levels in all animals at 27 mg siRNA/kg and increased IFN- γ in one animal indicate that this high dose level produces a mild immune response. Overall, no clinical signs of toxicity clearly attributable to treatment are observed. The multiple administrations spanning a period of 17–18 days enable assessment of antibody formation against the human Tf component of the formulation. Low titers of anti-Tf antibodies are detected, but this response is not associated with any manifestations of a hypersensitivity reaction upon re-administration of the targeted nanoparticle. Taken together, the data

presented show that multiple, systemic doses of targeted nanoparticles containing non-chemically modified siRNA can safely be administered to non-human primates (Heidel et al., 2007).

They determine the importance of single-chain Fv (scFv) affinity on binding, uptake, and cytotoxicity of tumor-targeting nanoparticles, the affinity of the epidermal growth factor receptor (EGFR) scFv antibody C10 was increased using molecular evolution and yeast display. A library containing scFv mutants was created by error-prone PCR, displayed on the surface of yeast, and higher affinity clones selected by fluorescence activated cell sorting. Ten mutant scFv were identified that had a 3–18-fold improvement in affinity ($K_D = 15\text{--}88\text{ nM}$) for EGFR-expressing A431 tumor cells compared to C10 scFv ($K_D = 264\text{ nM}$). By combining mutations, higher affinity scFv were generated with K_D ranging from 0.9 nM to 10 nM. The highest affinity scFv had a 280-fold higher affinity compared to that of the parental C10 scFv. Immunoliposome nanoparticles (ILs) were prepared using EGFR scFv with a 280-fold range of affinities, and their binding and uptake into EGFR-expressing tumor cells was quantified. At scFv densities greater than 148 scFv/IL, there was no effect of scFv affinity on IL binding and uptake into tumor cells, or on cytotoxicity. At lower scFv densities, there was less uptake and binding for ILs constructed from the very low affinity C10 scFv. The results show the importance of antibody fragment density on nanoparticle uptake, and suggest that engineering ultrahigh affinity scFv may be unnecessary for optimal nanoparticle targeting (Zhou et al., 2007).

They have used ion-pair reversed-phase high-performance liquid chromatography and a laboratory-synthesized compound, i.e., the 2-cyano-2-butylhexanoic acid, as a model for polyalkylcyanoacrylate highly polydispersed degradation products. It is shown that, compared to a counter-ion, like heptane

sulfonic acid, 2-cyano-2-butylhexanoic acid exhibits an effective ion-pairing effect at different pH values and organic mobile phase conditions. Moreover, at pH close to physiological conditions and at low mobile phase organic modifier percentage, this effect is experimentally observed, which strongly supports the initial hypothesis (Pepin et al., 1997).

Simultaneous cellular resistance to multiple lipophilic drugs represents a major problem in cancer chemotherapy. This drug resistance may appear clinically either as a lack of tumor size reduction or as the occurrence of clinical relapse after an initial positive response to antitumor treatment. The resistance mechanism can have different origins either directly linked to specific mechanisms developed by the tumor tissue or connected to the more general problem of distribution of a drug towards its targeted tissue. The purpose of this paper is to summarize the results of the use of poly(alkyl cyanoacrylate) nanoparticles to overcome multidrug resistance (MDR) phenomena at both the cellular and the non-cellular level (Vauthier et al., 2003).

The aim of the present work was to investigate the biodistribution characteristics of PEG-coated polycyanoacrylate nanoparticles prepared by the nanoprecipitation/solvent diffusion method using the previously synthesized poly(MePEGcyanoacrylate-hexadecylcyanoacrylate) copolymer. It was observed that [14C]-radiolabeled PEGylated nanoparticles remained for a longer time in the blood circulation after intravenous administration to mice, compared to the non-PEGylated poly(hexadecylcyanoacrylate) (PHDCA) nanoparticles. Furthermore, hepatic accumulation was dramatically reduced, whereas a highly increased spleen uptake was shown. The PEGylation degree of the polymer seemed not to affect the in vivo behavior of the nanoparticles, whereas previously obtained in vitro data have shown a modification of plasma protein adsorption depending on the density of PEG at the

surface of the particles. Moreover, the study of the in vitro cytotoxicity of the nanoparticles revealed that the PEGylation of the cyanoacrylate polymer reduced its toxicity. These results open up interesting perspectives for the targeting of drugs to other tissues than the liver (Peracchia et al., 1999).

They determined the efficacy of paclitaxel (Tx)-loaded biodegradable nanoparticles (NPs) on tumor inhibition. We hypothesized that NPs following conjugation to transferrin (Tf) ligand (NPs-Tf) would enhance the therapeutic efficacy of the encapsulated drug. The antiproliferative activity of NPs was determined in human prostate cancer cell line (PC3) and their effect on tumor inhibition in a murine model of prostate cancer. NPs (~ 220 nm in diameter, 5.4% w/w drug loading) under in vitro conditions exhibited sustained release of the encapsulated drug (60% release in 60 days). The IC₅₀ (concentration of drug for 50% inhibition of cell growth) of the drug with Tf-conjugated NPs (Tx-NPs-Tf) was about 5-fold lower than that with unconjugated NPs (Tx-NPs) or drug in solution. Animals that received a single-dose intratumoral injection of Tx-NPs-Tf (Tx dose = 24 mg/kg) demonstrated complete tumor regression and greater survival rate than those that received either Tx-NPs or Tx-Cremophor EL formulation. In conclusion, sustained release NPs demonstrated greater antitumor activity following their conjugation to Tf ligand (Sahoo et al., 2004).

Ibuprofen-loaded SLN (IBSLN-TG) composed of different ratios of CP and S378 were prepared and evaluated in term of size, zeta potential (ZP), entrapment efficiency (E.E.), crystallinity, lipid-drug interaction and in vitro drug release. After production, all developed IBSLN-TG prepared from different ratios of CP and S378 had the particle size in the nanometer range (180–200 nm) with the ZP values of higher than $|-40 \text{ mV}|$ and possessed approximately 100% E.E. The release of IBSLN-

TG demonstrated the biphasic pattern with a fast release followed by sustained release, which was fitted to Higuchi's kinetics. The addition of S378 into CP-matrix led to a slight decrease in particle size and surface charge, and distortion of CP crystallization. The results from $^1\text{H-NMR}$ indicated the formation of tiny liquid S378 nano-compartments within CP-matrix. The localization of ibuprofen in the S378 nano-compartments and the interaction between ibuprofen and S378 had an impact on the release profiles of IBSLN-TG depending on the ratios of CP and S378 (Chantaburanan et al., 2017).

Novel chain-growth polycondensation method was used for the first time for preparation of the β -CD nanosponges. The results exhibited 6.3-fold enhancement of dexibuprofen solubilization which is higher than previously reported β -CD formulations. The particle size of nanosponges was 275.1 ± 28.5 nm and suitable negative zeta potential indicated formation of stable nanosponges. The formation of a new polymeric network in nanosponges and interaction of dexibuprofen with nanosponges were confirmed by FTIR and DSC/TGA studies. PXRD analysis also revealed the decline in crystallinity of dexibuprofen due to its complexation with nanosponges which is desirable for complete solubilization of drugs. At pH 6.8, β -CD nanosponges exhibited swelling index of 3 whereas solubility was enhanced more than 3 times as compared to pure drug and 2 times as compared to dexibuprofen loaded β -CD complexes. In-vitro release studies exhibited 89% drug release within 30 min at pH 6.8 with β -CD nanosponges. Dexibuprofen release at pH 1.2 was remarkably slower yet β -CD nanosponges showed superior dissolution as compared to β -CD or pure drug. Acute oral toxicity studies in rats exhibited no sign of illness, mortality, adverse clinical signs and toxicologically relevant changes in hematology, clinical biochemistry and histological findings. Thus, β -CD nanosponges prepared by

optimized condensation method may be superior to other nano-formulation of β -CD to improve oral administration of lipophilic drugs such as dexibuprofen (Khalid et al., 2021).

S-(+) enantiomer of ibuprofen (IBU) dexibuprofen (DXI) is known to be more potent than its R-(−) form and exhibits many advantages over the racemic mixture of IBU such as lower toxicity, greater clinical efficacy, and lesser variability in therapeutic effects. Moreover, DXI potential has been recently advocated to reduce cancer development and prevent the development of neurodegenerative diseases in addition to its anti-inflammatory properties. During the last decade, many attempts have been made to design novel formulations of DXI aimed at increasing its therapeutic benefits and minimizing the adverse effects. This article summarizes pharmacological information about DXI, its pharmacokinetics, safety, and therapeutic outcomes. Moreover, modified DXI drug delivery approaches are extensively discussed. Recent studies of DXI prodrugs and novel DXI nano-formulations are analyzed as well as reviewing their efficacy for ocular, skin, and oral applications (Gliszczyńska & Sánchez-López, 2021).

This review article very specifically outlines the drugs presently used for the treatment of AD and drugs which are currently under research either at pre-clinical or clinical level. Unlike the treatment of other disorders, the presence of blood brain barrier (BBB) possesses a hindrance in transport of drugs from systemic circulation to brain. Nanoparticles in general and particularly polymeric nanoparticles can serve as a potential carrier for delivery of drugs across BBB. A special attention was given to polymeric nanoparticles that were reported to be effective in carrying the AD drug to brain with the polymer used and the method adopted for preparing it (Kumar, Felixjoe, Masilamani, Rajini, & Ravichandiran, 2012).

There has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Polymeric nanoparticles have been extensively studied as particulate carriers in the pharmaceutical and medical fields, because they show promise as drug delivery systems as a result of their controlled and sustained release properties, subcellular size, biocompatibility with tissue and cells. Several methods to prepare polymeric nanoparticles have been developed and these techniques are classified according to whether the particle formation involves a polymerization reaction or nanoparticles form directly from a macromolecule or preformed polymer. In this review the different techniques for preparation of polymeric nanoparticles are described (Nagavarma, Yadav, Ayaz, Vasudha, & Shivakumar, 2012).

For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. They have been used *in vivo* to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. Here, we review various aspects of nanoparticle formulation, characterization, effect of their characteristics and their applications in delivery of drug molecules and therapeutic genes (Mohanraj & Chen, 2006).

A chitosan molecule form self-assembled nanoparticles that can encapsulate a quantity of drugs and deliver them to a specific site. Chemical attachment of drug to chitosan throughout the functional linker has possibility to produce useful prodrugs, exhibiting biological activity at target site. In vivo residence time of the dosage form in the gastrointestinal tract and bioavailability of various drugs increases by mucoadhesive and absorption enhancement properties of chitosan. Antitumor activity of doxorubicin (DOX)-incorporated nanoparticles in vitro on DOX- resistant C6 glioma cells. Nanoparticles showed increased cytotoxicity compared to DOX alone. These results suggest that doxorubicin (DOX) was unable to penetrate into cells and did not effectively inhibit cell proliferation. In contrast, nanoparticles can penetrate into cells and effectively inhibit cell proliferation. There are 3 batches of drug loaded nanospheres in which 2.5mg, 5mg and 10mg of DOX were loaded into nanospheres where the concentration of chitosan is 1%w/v. Anticancer drugs without targeting a specific site cause side effects. The objective of this research is to reduce side effects. HPLC device was used to quantitatively analyze amount of doxorubicin loaded in nanospheres. The result had showed concentration of anticancer drug loaded in nanospheres is directly proportional to the drug payload capacity until saturation point. The in vitro drug release studies was carried out for 48 hours to obtain a more precise result by carrying out this studies in a medium resembling our body environment such as pH7.4, 37°C with analytical grade water for this studies. In vitro release of doxorubicin is of zero order kinetic. This shows that release is independent of the concentration of drug loaded in the nanospheres. Besides that, the graphs also show a sustained release manner, indicating these nanospheres formulation are suitable for targeting drug delivery system and for efficient treatment of cancerous cells (Dhanaraj et al., 2014).

They developed ampicillin trihydrate-loaded chitosan nanoparticles by modified ionic gelation method and evaluate their antimicrobial activity. Ampicillin trihydrate-loaded chitosan nanoparticles were prepared by ionic gelation method with the aid of sonication. Parameters such as the zeta potential, polydispersity, particle size, entrapment efficiency and in vitro drug release of the nanoparticles were assessed for optimization. The antibacterial properties of the nanoparticle formulation were evaluated and compared with that of a commercial formulation (reference). Scanning electron microscopy revealed that the nanoparticles were in the nanosize range but irregular in shape. Concentrations of 0.35 %w/v of chitosan and 0.40 %w/v sodium tripolyphosphate (TPP) and a sonication time of 20 min constituted the optimum conditions for the preparation of the nanoparticles. In vitro release data showed an initial burst followed by slow sustained drug release. The nanoparticles demonstrated superior antimicrobial activity to plain nanoparticles and the reference, due probably to the synergistic effect of chitosan and ampicillin trihydrate. Modified ionic gelation method can be utilized for the development of chitosan nanoparticles of ampicillin trihydrate. Polymer and crosslinking agent concentrations and sonication time are rate-limiting factors for the development of the optimized formulation. The chitosan nanoparticles developed would be capable of sustained delivery of ampicillin trihydrate (Saha, Goyal, & Rath, 2010).

They prepared aspirin loaded albumin nanoparticles by coacervation method. Aspirin is a common anti-inflammatory and anti-platelet agent widely used for various conditions. Albumin being both bioacceptable and biodegradable has a distinct advantage as a vehicle of drug delivery. By varying aspirin albumin ratios from 0.06 to 1.0 they obtained stable nanoparticles of sizes 46.8 nm to 190.8 nm respectively with low polydispersity. Photon Correlation Spectroscopy (PCS) and

Transmission Electron Microscopy (TEM) of the samples were done to characterize the nanoparticles. Drug encapsulation measured by UV spectroscopy varied from 30% to 80% for different ratios of aspirin: albumin. In vitro release study was conducted across a Spectrapor-membrane (cut off 3500 Da) precluding albumin. In contrast to simple drug solution, whose concentration peaks within 1/2 to 1 hour, nanoparticle formulation releases aspirin at a sustained rate for prolonged duration (50% total cumulative percentage at the end of 20 hours, 90% at 72 hrs.). From the above results they can conclude that coacervation method is well suited to produce albumin nanoparticles and the preparative variables of the procedure can be fine-tuned depending on the clinical application. Nanoparticles thus produced, can be applied for intra-articular therapy in arthritis or as intraocular release agents for diabetic retinopathy (Das, Banerjee, & Bellare, 2005)

MATERIALS AND METHODOLOGY

Disinfectant, chlorine, sodium hypochlorite, sodium hydroxide, and other chemicals were used. All other chemicals were reagent grade and used without further purification.

Pre-Formulation

The formulation studies were carried out to determine the effect of different concentrations of the drug with other excipients. The pre-formulation studies were carried out for the purpose of determining the stability of the formulation.

CHAPTER 3

MATERIALS AND METHODS

The formulation studies were carried out to determine the effect of different concentrations of the drug with other excipients. The pre-formulation studies were carried out for the purpose of determining the stability of the formulation.

Preparation of Calibration Curve: A series of standard solutions of the drug were prepared in the range of 10 to 100 µg/ml. The absorbance of these solutions was measured at 254 nm using a UV-Visible Spectrophotometer.

The absorbance values were plotted against the concentration of the drug to obtain a linear calibration curve. The correlation coefficient (r^2) was found to be 0.998, indicating a very high degree of linearity.

The calibration curve was used to determine the concentration of the drug in the samples. The absorbance of the samples was measured at 254 nm and compared with the calibration curve to obtain the concentration of the drug in the samples.

The results of the calibration curve studies are shown in Table 3.1. The correlation coefficient (r^2) was found to be 0.998, indicating a very high degree of linearity.

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MATERIALS AND METHODOLOGY

Dexibuprofen, chitosan, ethanol, Potassium dihydrogen phosphate, orthophosphoric acid were used. All other chemicals and reagents used were of analytical grade.

Pre-formulation

Pre-formulation studies were performed to confirm the absence of interaction of the drug with other additives. The pre-formulation studies carried out for the present work were;

- Preparation of calibration graph for dexibuprofen
- Preparation of calibration curve in pH 1.2, pH 7.4, and pH 6.8 buffer solutions.

Preparation of Calibration Curve in pH 1.2, pH 7.4, and pH 6.8 Buffer Solutions

The experiment involved dissolving a precise amount of 100mg dexibuprofen in a small volume of buffer solution. The solution was then made up to a total volume of 100 mL using three different pH buffers - 1.2 pH buffer, 7.4 pH buffer, and 6.8 pH buffer - in three separate 100 mL volumetric flasks. To create a series of standard solutions with concentrations ranging from 10 to 50 $\mu\text{g/mL}$ of dexibuprofen, the same procedure was followed for each of the three buffer solutions. Absorbance measurements were taken at 222 nm, and a calibration curve was generated by plotting concentration against absorbance.

Drug-excipient Compatibility Studies

To analyze the drug-excipient samples, both the individual components and each drug-excipient combination were weighed directly into pierced aluminum crucible pans. The weight of each sample was between 5 to 10 mg. Shimadzu DSC-60 equipment was used to scan the samples in the temperature range of 50-300°C under

static air, with a heating rate of 10°C/min. Plagiarism can be avoided by rephrasing the original statement using different words and sentence structures while still conveying the same information. Additionally, any specific information or data must be cited appropriately (Gurny, Peppas, Harrington, & Banker, 1981).

Preparation of Chitosan-Based NP

The emulsion-droplet coalescence method was utilized to produce chitosan nanoparticles loaded with dexibuprofen. Various concentrations of polymer were used according to the formula outlined in Table 1. Chitosan was dissolved in 1% acetic acid and mixed with 300 mg of dexibuprofen in phosphate buffered saline. This mixture was added to 10 mL of liquid paraffin containing 5% v/v tween 20, and the resulting w/o emulsion was stirred for 3 minutes using a homogenizer. The resultant dexibuprofen nanoparticles were then centrifuged at 3000 rpm for 60 minutes and washed with ethanol and water to remove the remaining surfactant and liquid paraffin. They were dried in air for 3 hours and then in a hot air oven at 50°C for 4 hours, after which they were stored in a desiccator. By varying the drug and polymeric ratio, several batches (F1, F2, F3, F4, and F5) were formulated to study the impact of polymer concentration on encapsulation efficiency and drug loading capacity. To avoid plagiarism, it is important to use your own words when rephrasing and to provide proper citations for any specific information used (Dhanaraj et al., 2014; El-Houssieny, El-Dein, & El-Messiry, 2016; Mohajeri, Ansari, & Pardakhty, 2015; Saha et al., 2010).

Table 1: formulation used for Preparation of Nanoparticles

Formulation	F1	F2	F3	F4	F5
Dexibuprofen	300mg	300mg	300mg	300mg	300mg

Chitosan (%v/v)	1	1.5	2	2.5	3
Tween 20 (%v/v)	5	5	5	5	5
Acetic Acid (%v/v)	1	1	1	1	1
Liquid Paraffin	10ml	10ml	10ml	10ml	10ml

Characterization of NP

Particle size and surface charge

The surface charge of particles plays a crucial role in their adhesion and interaction with cells, and it can be quantified by measuring their zeta-potential. One commonly used instrument to measure zeta-potential is the Malvern MasterSizer. To determine the particle size and surface charge of the prepared nanoparticles, photon correlation spectroscopy with zetasizer was utilized. To achieve a suitable kcps (kilo counts per second), the formulations were diluted to 1:1000 with the aqueous phase of the formulation, and the analysis was performed at 25°C with a 90° detection angle. Six replicates were taken for each measurement in this experimentt (Elshafeey, Kamel, & Awad, 2010).

Drug content

1g of dexibuprofen NP were accurately weighed and transferred into a 25 mL volumetric standard flask. The sample was dissolved with 5mL of pH 6.8 phosphate buffer weighed accurately 1g of budesonide NP and transferred into a 25mL standard flask. The sample was dissolved with 5 mL of pH 6.8 phosphate buffer and diluted to 25 mL with pH 6.8 phosphate buffer. 1mL of this solution was diluted to 25mL with buffer solution. Then, the standard and sample absorbance was measured at 253nm using an ultraviolet (UV)-visible spectrophotometer. The percentage of drug content was calculated.

Drug content % = Weight of drug in nanoparticles/Weight of nanoparticles $\times 100$

Entrapment efficiency

The drug-loaded NPs were exposed to centrifugation at 15,000 rpm for 30 min. The supernatant liquid was separated, and 1 mL of this solution was diluted with water, and the absorbance was measured at 253 nm. The amount of dexibuprofen untrapped in the supernatant was calculated. The amount of dexibuprofen entrapped was determined by subtracting the amount of free untrapped dexibuprofen from the total amount of dexibuprofen taken for the preparation (Das et al., 2005). The formula used to calculate entrapment efficiency was given below

Drug entrapment % = Mass of drug in nanoparticles / Mass of drug used in formulation $\times 100$

In vitro release

In vitro release studies were performed for 24 h using dialysis membrane using the Franz diffusion cell. The prepared dexibuprofen NPs formulations were placed inside a dialysis membrane and immersed in pH 6.8 phosphate buffer. At predetermined time intervals, the sample was withdrawn, and the amount of dexibuprofen released was determined by measuring the absorbance at 253 nm using a UV-visible spectrophotometer (Kalantzi, Karavas, Koutris, & Bikiaris, 2009). From the absorbance values, the cumulative percentage drug release was calculated.

RESULTS

RESULTS:

The preformulation results obtained for the drug dexibuprofen were found to be within the limits and desirable standards for the preparation of dexibuprofen NPs. Dexibuprofen loaded chitosan NPs were prepared as per the formula is given in Table 1. Standard calibration curve of dexibuprofen was carried out in 1.2 pH, 7.4 pH, and 6.8 pH buffer at 220 nm. The r^2 value in the entire medium shows nearly 1, which signifies linearity [Table 2 and Figure 1].

Table 2: Absorbance of Dexibuprofen in Buffer Solutions

Concentration ($\mu\text{g/mL}$)	Absorbance		
	pH 1.2	pH 7.4	pH 6.8
10	0.125	0.120	0.151
20	0.252	0.242	0.305
30	0.374	0.364	0.454
40	0.503	0.486	0.608
50	0.627	0.607	0.756

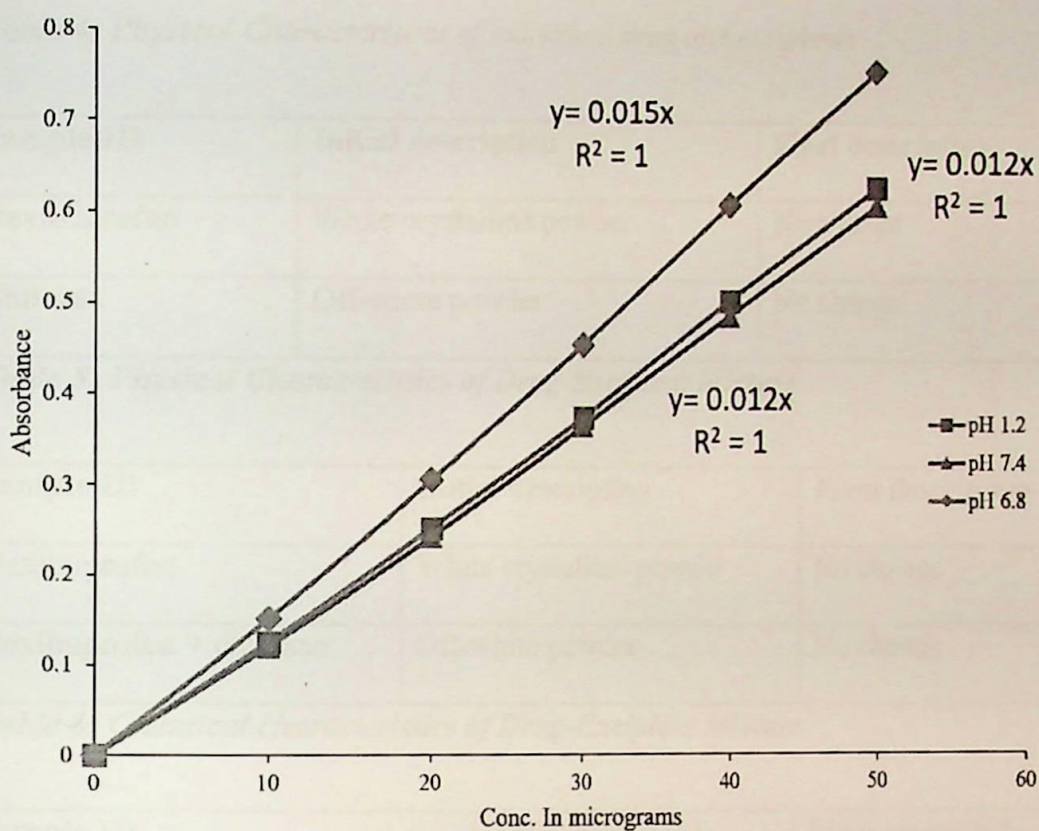


Figure 1: Calibration curve of Dexibuprofen

Drug-excipients Accelerated Compatibility Study On analysis of the drug-excipient mixture for their physical characteristics, no color change was observed. Based on the chemical evaluation, it was found that there was no significant change observed indicating that the drug is compatible with the added ingredients. The results were given in Tables 3-6.

Table 3: Physical characteristics of Dexibuprofen:

Physical parameters	Results
Description	White crystalline powder
Melting point	98.2°C
Loss on drying	0.08%
Assay	99.80%

Table 4: Physical Characteristics of individual drug and excipients

Sample ID	Initial description	Final description
Dexibuprofen	White crystalline powder	No change
Chitosan	Off-white powder	No change

Table 5: Physical Characteristics of Drug-Excipient Mixture

Sample ID	Initial description	Final description
Dexibuprofen	White crystalline powder	No change
Dexibuprofen + chitosan	Off-white powder	No change

Table 6: Chemical characteristics of Drug-Excipient Mixture

Sample ID	Initial assay (%)	Final assay (%)
Dexibuprofen	99.80±0.64	99.79±0.65
Dexibuprofen+chitosan	99.78±0.18	99.71±0.34

Drug Content and Entrapment Efficiency

Particle size and entrapment efficiency of the dexibuprofen NPs (F1-F5) were increased with increasing chitosan concentration as can be seen in Fig: 2. This may be due to the high amount of availability of chitosan to encapsulate the drug, on increasing the chitosan content, number of layers coated the drug was increased, this resulted in increased particle size and entrapment efficiency. Further increase in the chitosan concentration (F5), there is no much increase in the entrapment efficiency due to the availability of the drug to be incorporated is low, which is not enough for further encapsulation of drug by chitosan. The results were given in Table 7 and Fig: 3.

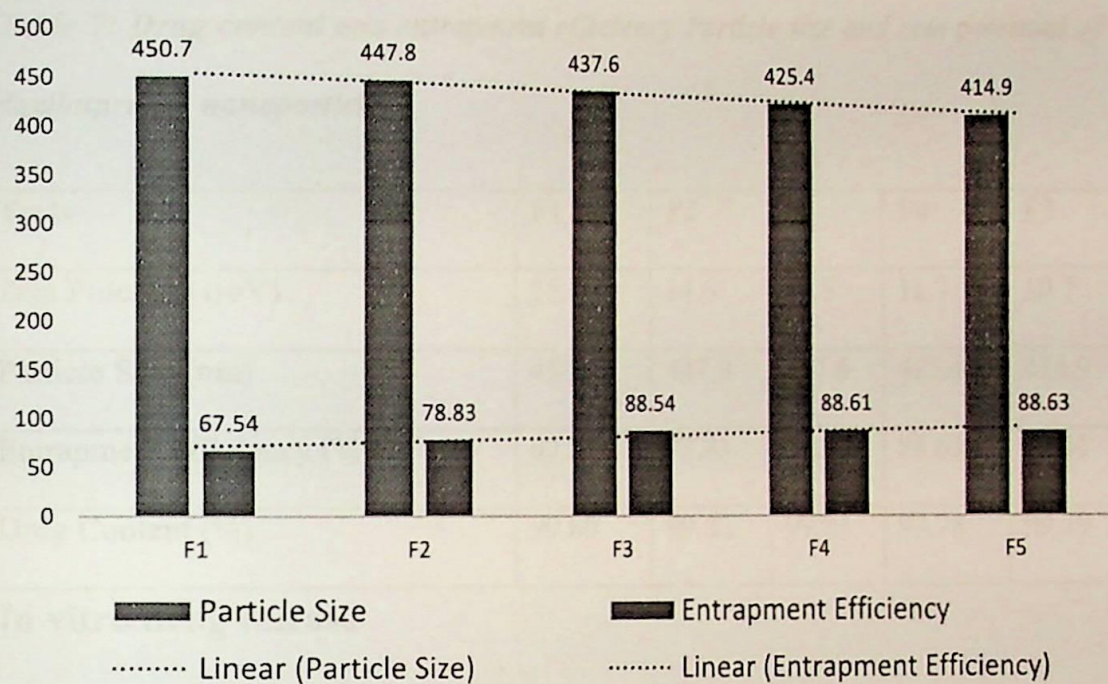


Figure 2: Particle Size and Entrapment efficiency of Dexibuprofen

Figure 3: Zeta Potential of optimized Dexibuprofen (F3) loaded chitosan nanoparticles

Table 7: Drug content and entrapment efficiency Particle size and zeta potential of dexibuprofen nanoparticles

Tests	F1	F2	F3	F4	F5
Zeta Potential (mV)	15.8	14.6	12.8	11.7	10.7
Particle Size (nm)	450.7	447.8	437.6	425.4	414.9
Entrapment efficiency (%)	67.54	78.83	88.54	88.61	88.63
Drug Content (%)	99.80	99.82	99.81	99.78	99.79

In vitro drug release

From the in vitro drug release study results, the maximum percentage drug release (99.81 ± 0.92) at the end of 24 h was observed with trial F3 which contains 2% w/v of Chitosan. Below 2% w/v of Chitosan concentration as in the case of trials F1 and F2 the maximum percentage drug release 99.79 ± 0.12 and 99.81 ± 0.29 were obtained at the end of 12 and 20, respectively, which was not desirable. Above 2% w/v of Chitosan concentration, reduction in drug release was observed as in the case of trial F4 and F5. The maximum percentage drug release for F4 and F5 was found to be 90.67 ± 0.19 and 83.75 ± 0.76 , respectively, at the end of 24 h was obtained. From the in vitro drug release data for F1-F5, it was observed that increase in Chitosan concentration delays the drug release due to increased particle size and reduced surface area of the prepared NPs. From all the formulations, F3 was selected as best formulation due to its ideal particle size (437.6 nm), high entrapment efficiency (88.54%), and desirable drug release ($99.81 \pm 0.92\%$ at the end of 24 h). The results were shown in Table 8 and Fig: 4.

Table 8: In-Vitro release studies of Dexibuprofen

Time (hr)	% Cumulative drug release				
	DNP1	DNP 2	DNP 3	DNP 4	DNP 5
0.5	51.45±0.34	45.86±0.45	25.65±0.28	15.43±0.33	10.63±0.33
1	75.87±0.67	62.18±0.73	42.76±0.14	25.42±0.11	20.45±0.85
6	88.65±0.45	79.76±0.25	55.83±0.25	40.76±0.42	35.83±0.43
12	99.79±0.12	87.73±0.87	64.64±0.46	55.47±0.24	44.63±0.41
16	99.78±0.34	96.82±0.25	75.83±0.56	66.83±0.37	60.35±0.12
20	99.79±0.25	99.81±0.29	83.79±0.27	79.85±0.54	75.72±0.35
24	99.75±0.34	99.79±0.34	99.81±0.92	90.67±0.19	83.75±0.76

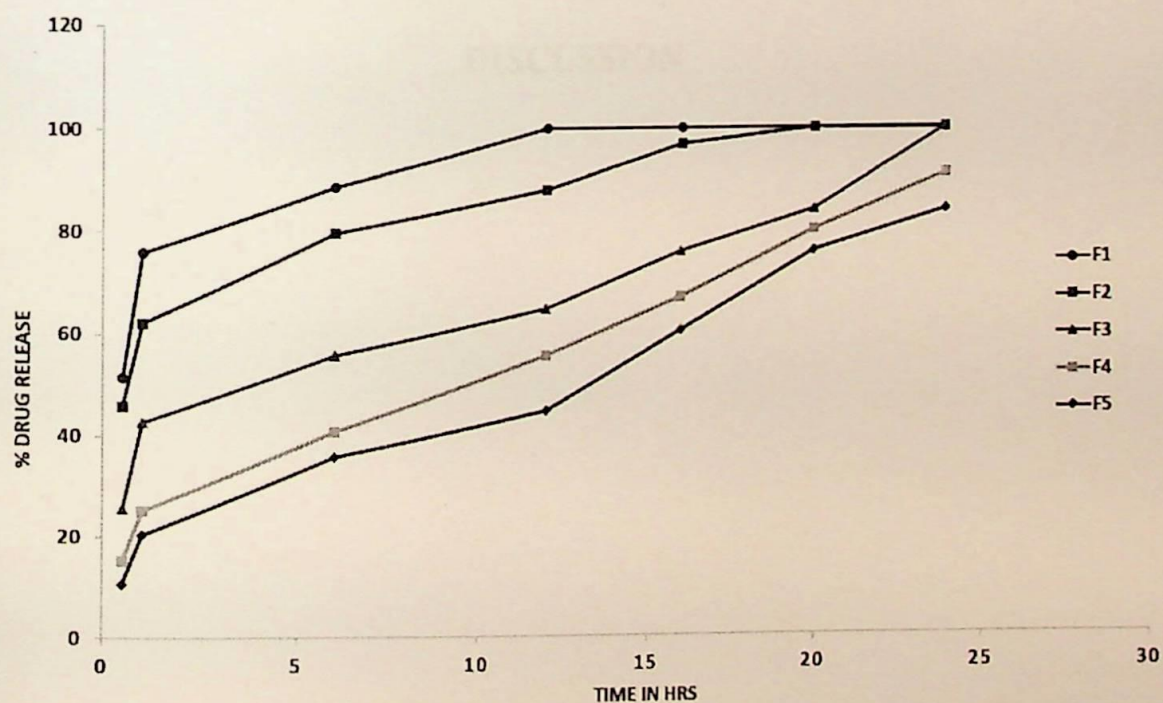


Figure 4: In-Vitro Drug Release of Dexibuprofen Loaded Chitosan Nanoparticles (F1-F2)

CHAPTER 5

DISCUSSION

Discussion

NSAIDs have been utilized in clinical practice for systemic drug delivery via oral administration to achieve pain relief, analgesia, and antipyretic effects. They have also been used for localized drug delivery through oral mucosal tissue. Several strategies have been employed to achieve systemic delivery of dexibuprofen (DXI), including the development of chewable tablets by Naeem et al. to enhance DXI dissolution rate. More sophisticated approaches, such as the use of acidic montmorillonite composites developed by Li et al., have also been utilized to encapsulate DXI. Montmorillonite, a clay mineral with swelling and adsorption properties, was able to encapsulate DXI at a concentration of 298 mg/g. DXI composites had an average micrometric size of $0.96 \pm 0.12 \mu\text{m}$ and a negative surface charge of $-26.5 \pm 0.94 \text{ mV}$. DXI composites from acidic montmorillonite composites were released within 12 hours in simulated intestinal fluid, compared to DXI which was released in 4 hours. Additionally, DXI composites were found to retard drug release in vivo in a rat preclinical model while increasing DXI bioavailability compared to commercial DXI suspension (T. Li et al., 2018).

To improve the solubility of DXI in water, Khalid et al. developed hydrogel nanoparticles composed of hydroxypropyl- β -cyclodextrin (HP β CD). These nanoparticles formed a stable polymeric network and increased the solubility of DXI in water. The nanoparticles had an average size of 287 nm and released DXI preferentially at pH 1.2 and 6.8. In addition, no signs of acute toxicity were observed in preclinical in vivo administration. Hydrogels are formed by cross-linked polymers that absorb water and create a three-dimensional matrix (Khalid et al., 2017).

In a related study by the same research group, Khalid et al. developed hybrid nanogels to improve the solubility of DXI. Nanogels are hydrogels that form nanoscopic

networks, combining the benefits of hydrogels and nanocarriers. In their study, the researchers used HP β CD hybrid nanogels to encapsulate DXI, resulting in a significant release of the drug in aqueous media. Preclinical in vivo studies demonstrated the biocompatibility of the nanogels, as no toxic effects of DXI were observed. However, the therapeutic effects of the nanogels in vivo have not yet been reported(Khalid, Ahmad, & Usman Minhas, 2018).

Other researchers have also enhanced the solubility of DXI by utilizing innovative techniques, including spray-drying, to develop a solid dispersion loaded with DXI. In one study, the authors created a formulation for immediate DXI release by combining Poloxamer 407, HPMC, and sodium lauryl sulphate with DXI. This formulation resulted in higher plasma concentrations compared to DXI powder. In another study, the authors developed a DXI formulation for sustained release by combining DXI, ethylcellulose, HPMC, and magnesium stearate. The resulting powder was encapsulated in gelatin capsules via spray-drying. After oral administration in an animal model, this formulation increased the residence time of DXI and also its maximum plasma concentration compared to DXI powder (Ali et al., 2018). Other authors have also recently developed DXI sustained release supermicro-pellets-based dry suspensions using a bottom spray fluid bed with suitable properties for prolonged drug release (Xia et al., 2020).

Table 9: Oral DXI drug delivery systems.

Pharmaceutical Form	Physicochemical Characteristics	In Vitro Outcomes	In Vivo Outcomes	Ref
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Montmorillonite acid DXI composites	DXI loading of 298 mg/g	In vitro DXI released (92%) within 12 h in simulated intestinal fluid	Rat animal model. Better pharmacokinetic profile (AUC ₀₋₂₄ 644.49 µg/h/mL and MRT ₀₋₂₄ 7.65 ± 0.48 h) than DXI suspension (AUC ₀₋₂₄ 439.88 µg/h/mL and MRT ₀₋₂₄ 3.10 h). Increased bioavailability (154.11%) against commercial DXI	(T. Li et al., 2018)
DXI chewable tablets	Preparation using wet-co grinding of DXI adding mannitol and/or meglumine	DXI dissolution enhanced. Mannitol based tablets showed prompt drug release. Meglumine based tablets required crushing for fast drug release	Data not shown	(Naeem et al., 2020)
DXI loaded β cyclodextrin hydrogel nanoparticles	Nanoparticles size: 287 nm	DXI release higher than DXI tablets at pH 1.2 and 6.8	Animal model: Wistar albino rats Acute toxicity studies: no modification of behavioural, physiological, biochemical or histopathologic parameters were observed	(Khalid et al., 2017)

DXI loaded hydroxypropyl- β -cyclodextrin (HP β CD) hybrid nanogels	Solubility enhancement of DXI confirmed Particle size 310.65 $\pm$ 18.75 nm Polydispersity index: 0.21 Zeta potential: -36.49 ± 2.34 mV	Highly porous and amorphous nanogels DXI release higher than DXI tablets at pH 1.2 and 6.8	Animal model: Wistar albino rats Toxicity studies: no modification of behavioural, physiological, biochemical or histopathologic parameters were observed	(Khalid, Ahmad, & Usman Minhas, 2018)
pH controlled DXI release hydrogel containing Dexibuprofen	Maximal gel swelling and drug release at pH 1.2.	Swelling and drug release pH dependent Fast release at pH 1.2	Data not shown	(Ali et al., 2018)
DXI super micro-pellet based dry suspensions	Pellets preparation using spray dry fluid bed coating technique Suitable stability (sedimentation rate 0.8 Hu/H) Aqueate flowability (θ 27°).	DXI release around 8 h being pH dependent	Data not shown	(Xia et al., 2020)
DXI loaded PLGA PEG nanoparticles	Nanoparticles size: 195.4 nm Polydispersity index: <0.1 Negative surface charge Stable for 2 months at 25 and 4 °C	100% nanoparticles uptaken by cells within 5 min Nanoparticles were able to cross trough and in vitro BBB model	Model: C57bl6 mice and APPswe/PS1dE9 transgenic Nanoparticles were effective for Alzheimer's disease: inflammation and β-amyloid plaque reduction; behavioural improvement	(Sánchez-López et al., 2017)

DXI loaded chitosan nanoparticles	Particle size: 437.6 nm High entrapment efficiency (88.54%)	In vitro DXI release of 99.81% within 24 h	Data not shown	(Senthilnathan et al., 2018)
DXI Eudragit based micro-particles	High entrapment efficiency (>70%)	In vitro DXI release at pH 1.2 < 21% while at pH 6.8 was high (around 60% within 8h): gastro resistant formulation development	Data not shown	(Khalid, Ahmad, Minhas, et al., 2018)
DXI Eudragit solid dispersed nanoparticles	Size: <300 nm	Improved dissolution rate	Animal model: sprague-dawley rats Improved pharmacokinetic parameters: AUC ₀₋₂₄ and C _{max} increased 4.6 and 5.7 times respectively	(Bertalero et al., 2013)

DXI loaded chitosan nanoparticles	Particle size: 437.6 nm High entrapment efficiency (88.54%)	In vitro DXI release of 99.81% within 24 h	Data not shown	(Senthilnathan et al., 2018)
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DXI loaded polymeric micelle based tablets	Size: 28.11 nm Polydispersity index: 0.15 Zeta potential: -2.88 mV	Faster DXI release from the polymeric micelle based tablets	Human studies developed Pharmacokinetic studies: DXI polymeric micelles based tablets show better pharmacokinetic profile	(Abdelbary & Makhoulouf, 2014)
		(80.1% of DXI was released within 30 min) than the commercial tablet (35.35% within 30 min)	(AUC ₀₋₂₄ 407.45 µg mL h ⁻¹ ; C _{max} 20.99 µg/mL; T _{max} 1 h; MRT 12.79 h) than commercial tablets (AUC ₀₋₂₄ 71.91 µg mL h ⁻¹ ; C _{max} 12.94 µg/mL; T _{max} 2.75 h; MRT 10.53 h) Relative bioavailability was 160.15%	

A potential approach involves utilizing hydrogels, cyclodextrins, and gelatin capsules to create a mucoadhesive oral administration for systemic delivery of DXI. The formulation exhibits pH-dependent swelling properties, with maximum swelling observed at pH 1.2, as well as controlled drug release in response to pH changes. These findings demonstrate the potential of this multi-strategy approach as a carrier for DXI and warrant further investigation through in vivo studies (Ali et al., 2018).

Various polymeric nanoparticles have been developed to encapsulate DXI for drug delivery purposes. For instance, PLGA PEGylated nanoparticles with a particle size below 200 nm and a low polydispersity index (below 0.1) were created for oral administration. In vitro studies showed that the release rate of DXI from PLGA PEGylated nanoparticles was slower than that of DXI alone. Furthermore, in a mice model, the DXI-loaded nanoparticles exhibited decreased gastric damage. When tested on transgenic mice with Alzheimer's disease, the developed drug delivery system showed the potential to effectively reduce brain inflammation and the number of β -amyloid plaques compared to DXI alone. Additionally, the use of DXI

nanoparticles led to a reduction in memory impairment in transgenic mice (Sánchez-López et al., 2017).

Chitosan-based nanoparticles have also been developed as a potential carrier for DXI drug delivery. Chitosan is a biodegradable natural polymer with a positively charged surface that is commonly used in drug delivery. DXI-chitosan formulations have been shown to have an average particle size of 437.6 nm and high drug loading, with drug release sustained for up to 24 hours. However, there is currently no available in vivo data to support the efficacy of these nanosystems for DXI drug delivery. Eudragit, another widely used polymer for systemic oral drug delivery, has also been utilized to create microparticles containing DXI. These microparticles exhibited enhanced rheological properties and an entrapment efficacy of 70%. In vitro studies also confirmed the gastro-resistant ability of the microparticles (Khalid, Ahmad, Minhas, et al., 2018).

ABertalero and colleagues utilized Eudragit to create solid dispersion nanoparticles of DXI-Eudragit-TPGS with a particle size of <300 nm using the supercritical antisolvent technique. This approach resulted in an improved in vitro dissolution rate and oral absorption of DXI, leading to increased plasma concentration and bioavailability of DXI (Bertalero et al., 2013).

Polymeric micelles of DXI prepared using Pluronic have also been investigated as a means of enhancing the oral availability of DXI. Clinical pharmacokinetic studies were conducted to demonstrate the enhanced oral bioavailability of the marketed formulation and its ability to deliver DXI effectively to human patients (Abdelbary & Makhlouf, 2014).

Our study found that the in vitro drug release of dexibuprofen NPs formulations (F1-F5) were as follows: F1, 99.75 ± 0.34 ; F2, 99.79 ± 0.34 ; F3, 99.81 ± 0.92 ; F4, 90.67 ± 0.19 ; and F5, 83.75 ± 0.76 at the 24-hour mark. Among the formulations tested, F3 exhibited the most favorable in vitro drug release profile with a particle size of 437.6 nm and a drug release percentage of 99.81 ± 0.92 . This formulation has the potential to be an effective and suitable option for managing rheumatoid arthritis. These newly formulated controlled release nanoparticulate drug delivery systems for dexibuprofen offer a promising solution for managing pain associated with arthritis by continuously releasing the drug over a period of 24 hours.

CHAPTER 6

CONCLUSION AND FUTURE RESEARCH DIRECTION

Conclusion and future research direction

The study utilized the emulsion-droplet coalescence method to prepare nanoparticles of dexibuprofen, with varying concentrations of chitosan polymer. The effect of increasing chitosan concentration on particle size and in-vitro drug release was investigated. The formulations (F1-F5) were evaluated for their in vitro drug release profile, with results showing that formulation F3, with a particle size of 437.6 nm, had the highest drug release percentage of 99.81 ± 0.92 at 24 hours. This formulation was deemed suitable for managing rheumatoid arthritis pain, as it provided continuous drug release for 24 hours. Therefore, these newly developed controlled release nanoparticulate drug delivery systems of dexibuprofen may be effective in managing arthritis pain

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