SJIF Impact Factor 2021: 8.013| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 6 | Issue: 11 | November 2021 - Peer Reviewed Journal

STUDIES ON DESIGN AND DEVELOPMENT OF DISSOLVABLE ORAL DRUG DELIVERY SYSTEMS OF A POORLY WATER-SOLUBLE NON-STEROIDAL ANTI-INFLAMMATORY DRUG

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ABSTRACT

Poorly water-soluble drugs remain a challenging, yet significant, class of pharmaceutical substances used to treat a variety of disorders. NSAIDs (nonsteroidal anti-inflammatory drugs) are a class of pharmaceuticals used to treat pain, fever, and other inflammatory conditions. This exercise covers the indications, mechanism of action, administration, side effects, contraindications, monitoring, and key considerations for providers when it comes to NSAIDs. While non-steroidal anti-inflammatory drugs are typically safe, there are certain major side effects that can occur when they are used systemically or orally. The main goal of this paper is to explain the concept of Oral drug delivery, poorly water-soluble drugs and structure of NSAIDs. Because so many patients take nonsteroidal anti-inflammatory drugs, reducing or eliminating these adverse effects, such as by local drug delivery, could have a significant impact on patient quality of life. The next steps and unmet needs are offered as a roadmap for future studies in the field to examine in order to enable progress in NSAID design and development.

KEYWORDS: *Drug, Oral, Soluble, Design, System, Inflammatory.*

I. INTRODUCTION

It's difficult to find innovative drugs for illness management that are both safe and effective. Despite substantial progress in the development of new drugs, there are still unmet medical needs that require effective treatment. The drug research and development process has been accelerated due to market potential, company competitiveness, and a dry pipeline of developmental candidates from numerous businesses. As a result, many drugs that receive FDA approval have poor biopharmaceutical qualities. Poorly soluble compounds make up an estimated 40% of authorised drugs and over 90% of drugs in the development pipeline [**1]**. Several commercially available drugs have poor solubility, permeability, metabolism, and removal from the body, as well as poor safety and tolerability.

Innovative drug delivery systems may be able to solve difficulties that are usually associated with traditional formulations. Indeed, there has been ongoing study in the development of tailored particles and systems for the targeted delivery and/or controlled release of APIs over the last few years. These systems can shield drugs from degradation,

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allow for regulated release, alter pharmacokinetics and biodistribution profiles, decrease clearance and side effects, and improve drug specificity. The use of a designed delivery system to administer an existing drug may help to improve the treatment's efficacy, safety, and patient compliance while also extending its traditional therapeutic applications. Immediate or delayed drug delivery systems, for example, are critical in the treatment of both acute (i.e., postoperative pain, dental surgery) and chronic inflammatory illnesses.

According to recent studies, finding and developing novel drugs is insufficient to attain therapeutic excellence and capture market economies. As a result, changed formulations of currently available drugs are becoming increasingly important. Improved formulations of existing drugs are proving to be profitable business for the pharmaceutical industry, which is now experiencing a lack of new molecular discovery [**2**]. Pharmaceutical companies are experimenting with new dosage forms, drug formulations (ester/salt), prodrug/active metabolite of drugs, and novel methods of administration for 505(b)(2) submissions. Given the large number of insoluble drugs on the market, pharmaceutical companies can profitably file NDAs under 505(b)(2) with improved formulations that allow faster dissolving and increased bioavailability. As a result, this review compiles a list of several solubilization technologies. These technology' recent advancements, clinical benefits, and business prospects are all examined in depth. Figure 1 depicts the possible benefits of insoluble drug delivery systems

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Figure 1: Benefits of insoluble drug delivery strategies.

II. MECHANISM OF ORAL DRUG DELIVERY

Because of advantages such as comfort of drug administration via the oral route, patient preference, cost-effectiveness, and ease of large-scale manufacture of oral dosage forms, oral medication is the most prevalent way of drug administration. Oral administration accounts for over 60% of all established small-molecule drug products on the market. Oral formulations account for around 90% of the global market share of all pharmaceutical formulations intended for human use, according to current estimates. Orally administered pharmaceutical products account for about 84 percent of the best-selling pharmaceutical items, which are currently valued at $35 billion and growing at a 10% yearly pace [**3**].

Patients are more likely to comply with oral formulations than with alternative parenteral routes such as intravenous, subcutaneous, and intramuscular injections, as well as inhalation for asthma treatments [**4**]. Furthermore, orally delivered drugs can be targeted to specific parts of the GI tract for localised therapy of pathological illnesses such stomach and colorectal malignancies, infections, inflammations, bowel diseases, gastro-duodenal ulcers, and gastroesophageal reflux problems (Figure 2)

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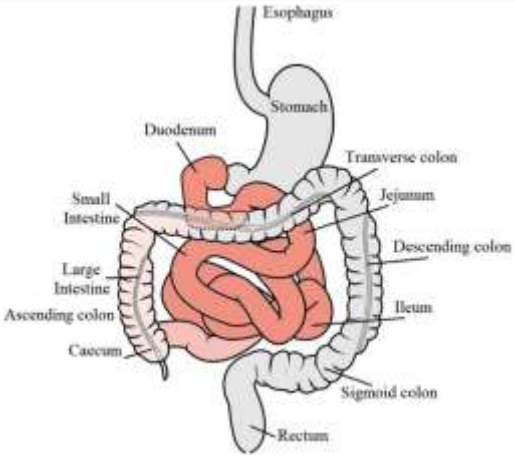

Figure 2: Schematic diagram of the gastrointestinal tract showing the major regions for drug absorption denoted in red color.

Despite these benefits, developing oral formulations poses a number of obstacles, most of which can be attributable to drug physicochemical qualities such as poor water solubility and membrane permeability. Furthermore, medicines' poor chemical and biological stability, as well as physiological obstacles such as pH, efflux transporters, and metabolic enzymes, can limit their absorption. Additionally, some drugs can induce physical discomfort and nausea [**5**]. Several research have focused on understanding the mechanism of drug absorption and transport, intestinal transit, GI tract microenvironment, and drug stability in GI fluids throughout the previous four decades [**6**]. As a result, developing oral drug delivery systems involves a full understanding of drug physicochemical qualities, gastrointestinal permeability, biological barriers, pharmacokinetics, and pharmacodynamics.

III. POORLY WATER-SOLUBLE DRUGS

Solubility is a crucial characteristic for achieving the appropriate drug concentration in the systemic circulation and demonstrating pharmacological response. Only 8% of novel drug candidates have both good solubility and permeability at the moment **[7]**. A solute's solubility is defined as the maximum amount of solute that may dissolve in a given amount of solvent or solution at a given temperature. In other terms, solubility is defined as a material's ability to form a solution with another substance. The substance to be dissolved is referred to as a solute, and the dissolving fluid in which the solute dissolves is referred to as a solvent. If the solvent is water, the process of dissolving the solute into the solvent is known as solution or hydration.

The breaking of inter-ionic or intermolecular bonds in the solute, the separation of solvent molecules to provide space in the solvent for the solute, and the interaction between the solvent and the solute molecule or ion are all part of the solubilisation process. When the solute bond breaks down during the solubilisation process, holes appear, as seen in Figure 3. Solid molecules break down as a result of intermolecular bonds breaking during the solubilisation process, as depicted in Figure 4. In the solvent depicted in Figure 5, about a liberated solid molecule is incorporated.

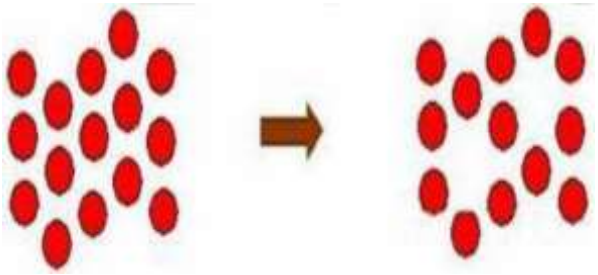

Figure 3: Holes opens in the solvent

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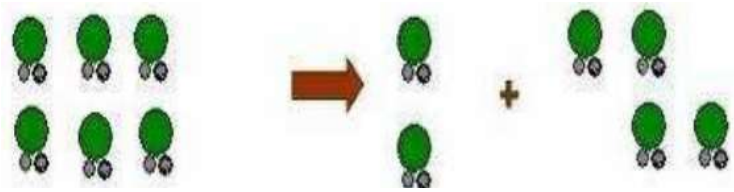

Figure 4: Molecules of the solid breaks away from the bulk

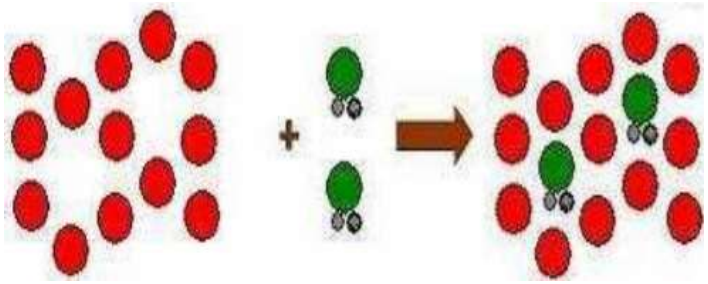

Figure5: The freed solid molecule is integrated into the hole in the solvent

The translation of poorly water-soluble drugs into viable medical products continues to be a concern. A complex network of physical-chemical, biological, physiological, and anatomical variables acts independently and in concert to limit drug absorption, making oral delivery difficult. The effects of mechanical and environmental factors on the initial dose form are fairly well established - disintegration or rupture of dosage forms is mostly understood through imaging and other research [**8**]. However, the processing of the drug after it is removed from the dosage form is still a mystery. In complicated dynamic environments, it is difficult to analyse the drug's solid-state properties and transitions between distinct states in the gastrointestinal environment. The recent trend toward amorphous high-energy drug forms raises the issue of unanticipated crystallisation, which has implications for solubility and bioavailability. Although the potential for crystallisation can be predicted, the complex media of the gastrointestinal tract adds a layer of uncertainty. Individual differences in excipient response to the complex digestive environment of the stomach through changes in solubility, breakdown by lipases, proteases, and other enzymes, and the resulting interaction of dissolving drug with those components are still unknown. The gut also reacts to the composition of the excipients in a unique and particular way, complicating the gastric phase of delivery even more. Drug precipitation during dilution and digestion is a constant concern with lipid formulations. Self-assembled colloid formation is caused by lipases digesting the lipids in the formulation, and we don't yet understand the cascade of structures and specific interactions with poorly soluble drugs that can aid or impede bioavailability as a result. Even after the drug is entirely dissolved in the formulation remains and ready for absorption, biochemical and post-absorption processes normally conspire to reduce bioavailability further, though they may in rare situations help by boosting lymphatic transport, for example [**9**].

In light of this multifaceted situation, it is necessary to tackle it from an interdisciplinary perspective. For decades, research organisations have attacked elements of this conundrum in isolation - while significant progress has been made in certain areas, there has been no internationally unifying approach to bring these discoveries together to provide ways to manage such hazardous drugs holistically. We may never get there, but by bringing interdisciplinary clusters together to work at the intersections of groups, we give ourselves the best chance of learning how to overcome these numerous barriers using novel delivery technologies, diagnostic procedures, and analytical improvements.

IV. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs (nonsteroidal anti-inflammatory drugs) are one of the most commonly utilised drug classes in the treatment of Diseases. COX is inhibited by these chemicals, which prevents the synthesis of prostaglandins and other inflammatory mediators. NSAIDs are useful as adjuvant medication for the symptomatic management of illnesses, lowering inflammation and discomfort, according to their mechanism of action. Patients are frequently given NSAIDs to relieve symptoms via the oral route at several times of the day (after waking up, after lunch, and at night) in the form of immediate release formulations. Drugs are rapidly absorbed in this manner, and their actions are explained independently of the circadian rhythms of hormones and cytokines that cause EMP symptomatology. Because drug liberation from the dosage form is not synced with the symptom peak, this traditional technique frequently results in inadequate therapy,

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leading in an increase in side effects and, as a result, poor patient compliance. This is why, in recent years, a growing number of studies have focused on the possibility of treating EMPs via an oral chronotherapeutic strategy.

NSAIDs (i.e., indomethacin, aceclofenac, ketoprofen, flurbiporfen, and lornoxicam) are an appealing API to modify in order to achieve chronotherapeutic drug delivery systems (ChDDSs) for the treatment of early morning diseases [**10**]. For example, in rheumatoid arthritis, a pHresponsive dual pulse multiparticulate dosage form containing ketoprofen was created and evaluated. This formulation was found to be effective in alleviating circadian symptoms at midnight and early in the morning [**11].** Levi et al. found that taking indomethacin in a controlled release formulation in the evening helped to reduce morning symptoms better than taking the same formulation at other times of the day [**12**].

Microtechnologies have been employed as a creative and efficient technique in the development of pharmacological dosage forms adapted to follow the human chronobiological cycle. Spray drying, fluid bed coating, solvent evaporation, coacervation phase separation, prilling, and other processes and procedures could be effective in the creation of polymeric microparticles. The nature of the polymer, the chemical properties of the drug, the required particle size, as well as the method's reproducibility and scalability, all influence the choice of microencapsulation technology [**13**].

Classification of NSAIDs

NSAIDs are classified into the following groups based on their chemical structure and selectivity: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen), acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam), anthranilic (celecoxib, etoricoxib).

Acute tenosynovitis, ankle sprains, and soft tissue injuries can all benefit from topical NSAIDs (diclofenac gel) [**14**].

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The FDA-approved NSAIDs are listed below (organized alphabetically):

Non-selective NSAIDs

- Diclofenac
- Diflunisal
- Etodolac
- Fenoprofen
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Ketoprofen
- Ketorolac
- Mefenamic acid
- Meloxicam
- Nabumetone
- Naproxen
- Oxaprozin
- Piroxicam
- Sulindac
- Tolmetin

COX-2 Selective NSAIDs

- Celecoxib
- Rofecoxib
- Valdecoxib

V. GENERAL DESIGN AND PROPERTIES OF THE NSAIDS

The following are the sub-categories of NSAIDs based on their chemical structure:

- Salicylates
- Propionic Acids (Profens)
- Aryl and Heteroarylacetic Acids
- Anthranilates (Fenamates)
- Oxicams (“Enol Acids”)
- Phenylpyrazolones
- Anilides

In general, an acidic moiety (carboxylic acid, enols) is coupled to a planar, aromatic activity in NSAIDs. A polar connecting group, found in several analgesics, connects the planar moiety to another lipophilic group. This can be expressed in the following way

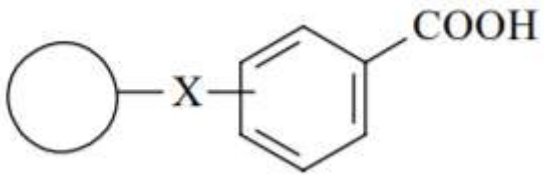

Figure 6: NSAID General Structure

As a result, the molecular and pharmacologic features of NSAIDs are as follows:

- All of the organic acids are relatively strong, having pKas in the 3-5 range. Carboxylic acids make up the majority, but not all (see drug classes). As a result of the base treatment, salts forms can be formed, and all of these compounds are substantially ionised at physiological pH. COX inhibitory action requires the acidic group!
- The lipophilic character of their aryl groups, as well as additional lipophilic moieties and

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substituents, determines how lipophilic the NSAIDs are.

- The acidic group in these chemicals acts as a primary binding group for plasma proteins (ionic binding). As a result, plasma proteins bind all NSAIDs strongly (drug interactions!).
- Conjugation is a significant site of metabolism for the acidic group. Glucuronidation (and inactivation), followed by renal elimination, is a key mechanism of clearance for several NSAIDs [**15**].

Many non-steroidal anti-inflammatory drugs (NSAIDs) target COX isoforms as part of their therapeutic activity. Around 3,500 years ago, the Greek physician Hippocrates employed a willow bark and leaf extract to treat fever and inflammation for the first time. In the 17th century, the active ingredient of the extract was identified as salicylic acid. Bayer [**16**] first introduced acetylsalicylic acid, an acetyl derivative of salicylic acid (aspirin), in 1869, although the route of action was unknown at the time. Vane and colleagues investigated the molecular mechanistic role of aspirin after over a century, and the discovery that all of these NSAIDs inhibit the COX enzyme has now become a basis for generating new NSAIDs. GI symptoms such as stomach discomfort, constipation, diarrhoea, stomach ulcers, and others are the most prevalent adverse effects linked with these NSAIDs, the severity of which varies depending on the kind of NSAID. There have also been reports of kidney and liver issues [**17**]. NSAIDs such as aspirin, indomethacin, ibuprofen, and others have been in use for over a century, however it is unclear how these therapeutic and side-effects are mediated by NSAIDs at the same time.

With the discovery of COX-2, an inducible isoform of COX, it became obvious that there are two types of COX: the constitutive isoform, COX-1, which is cytoprotective and mediates a variety of physiological tasks, and the inducible isoform, COX-2, which is an inflammatory mediator. COX-1 and COX-2 isoforms are both inhibited by traditional NSAIDs. COX-2's discovery led to the creation of selective COX-2 inhibitors (COXIBs), such as celecoxib, which was co-developed by G. D. Searle and Pfizer in 1999, followed by rofecoxib by Merck, and a slew of others, all of which became blockbuster drugs.

VI. CURRENT TARGETS AND LIMITATIONS

As previously stated, NSAIDs have gastrointestinal and renal side effects in general. In a rat model, aspirin was found to produce harm to the gastrointestinal system by lowering the expression of occludin, a plasma membrane protein of tight junctions, which was reversed by pre-treatment with another drug, mosapride [**18**]. Even in short-courses, high-dose ibuprofen produced jejunal perforations. Another anti-inflammatory drug, naproxen, produces stomach antral ulcers and raises lipid peroxide levels, while curcumin reverses this effect. With the use of NSAIDs, perforated jejunal ulcers and small bowel ulcerations have also been described. When proton pump inhibitors and non-selective short-course NSAIDs are taken together, the risk of intestinal damage increases [**19**]. Similarly, even at therapeutic doses, a combination of ibuprofen and acetaminophen produces renal and liver issues. Another drug, rofecoxib, has been linked to an increased risk of renal failure and arrhythmia. Within days of intake, diclofenac, an NSAID, has been proven to raise the risk of heart attacks and strokes by 50%. The drug causes a lot of acidity and stomach intolerance in Indian patients, according to one study, which looked at 6.3 million cases over a 20-year period from 1996 to 2016. Adverse reactions to NSAIDs are common in individuals on long-term therapy, and these side effects have been linked to the cytoprotective COX-1 enzyme being targeted.

COX-2 selective drugs, or COXIBs, have become the most popular anti-inflammatory drugs due to their good anti-inflammatory effectiveness and reduced gastrointestinal toxicity in some cases [**20**].However, it was quickly shown that long-term use of COXIBs in arthritic patients is linked to cardiac adverse effects.As a result, some COXIBs, such as rofecoxib, have been pulled from the market, while others, such as celecoxib, have a warning label for usage in patients with cardiovascular issues. 31 COX-2 was first discovered in inflammatory tissues, but it is now known that it is also expressed in tissues such as the kidney, brain, and testis [**21**].

The simultaneous lowering of prostacyclin, also a product of COX-2, which is a natural inhibitor of platelet aggregation and also implicated in renal hemodynamics, and the regulation of blood pressure were related to the side-effects associated with COXIBs.30 Inhibition of COX has also been demonstrated to transfer arachidonic acid metabolism to the 5-LOX pathway, resulting in higher levels of leukotrienes, which have been linked to COX inhibitor adverse effects. As a result of these advances, the quest for anti-inflammatory drugs with no stomach or cardiac adverse effects has begun. NO-NSAIDs, biologicals, cytokine inhibitors, and other anti-inflammatory medicines have appeared in the modern period, which are beyond the scope of this review [**22**].

VII. CONCLUSION

The tale of how to treat fever, pain, and inflammation is still unfolding. For nearly a century, small

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molecule NSAIDs have dominated the market. A drug delivery system, such rapid dissolving tablets, aims to increase patient compliance and convenience in addition to delivering drugs to the body. Fast dissolving dosage forms have eliminated some of the challenges associated with drug administration to drugs and the elderly, who account for a significant section of the world's population. As a result of patient demand and the availability of various technologies, the market share of Fast dissolving tablets has increased, hence extending the patent life of a drug. The creation of fast-acting drug products also allows for a line extension in the market, allowing for a wider selection of drugs.

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