Pharmacology, Pharmacokinetics and Future Prospective of Indomethacin

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Abstract
Indomethacin, categorized as a non-steroidal anti-inflammatory drug (NSAID) within the indoleacetic acid class, is widely recognized for its potent analgesic, anti-inflammatory, and antipyretic properties. As a non-selective inhibitor of cyclooxygenase (COX), it effectively hinders prostaglandin synthesis, providing relief from pain and inflammation. Indomethacin finds common application in treating various inflammatory conditions such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Despite its efficacy, the use of indomethacin is associated with potential adverse effects, particularly on the gastrointestinal tract, necessitating careful consideration of its risk-benefit profile in clinical settings. Ongoing research endeavors seek to explore its role in innovative therapeutic approaches and enhance its safety profile. A comprehensive understanding of the pharmacological characteristics of indomethacin is crucial for healthcare providers to make well-informed decisions regarding its use across diverse patient populations.

Keywords: NSAIDs; Indomethacin; Clinical trial; Drug delivery; Cancer

Abbreviations
CCV: Canine coronavirus;
FDA: Food and drug administration;
GIT: Gastrointestinal tract;
NSAIDs**:** Non-steroidal anti-inflammatory drugs;
PDA: patent ductus arteriosus

1. Introduction

Indomethacin is a non-steroidal, anti-inflammatory agent with anti-pyretic and analgesic properties discovered and developed by the Merck Sharp and Dohme Research Laboratories (1). Indomethacin is effective in patients with moderate to severe rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute painful shoulder (bursitis and/or tendinitis) and acute gouty arthritis (2-6). Recently, indomethacin has been found effective in the treatment of neonates with patent (3) ductus arteriosus and in patients with acute cystoid macular edema following cataract surgery (7-9). Worldwide, indomethacin has been formulated into many dosage forms, including formulations designed for long duration of activity. The discovery of this compound continues to provide new insights into medical treatment of disabling diseases (l0). In the past 30 years, there has been an explosion in the number of NSAID on the market (11). Among the currently marketed NSAID in Nigeria, indomethacin, a COX inhibitor, appears a popular household drug used as an antipyretic and analgesic agent (12).

2. History

An excellent antipyretic, analgesic, and anti-inflammatory property makes indomethacin a nonsteroidal anti-inflammatory medication (NSAID). The majority of NSAIDs are organic acids, however they represent a diverse class of medications that are frequently unrelated chemically. For millennia, preparations from the bark of willow trees and cinchona have served as prototype medications(13).

Quinine is the main alkaloid present in cinchona, the bark of the cinchona tree native to South America. An Augustinian friar in Peru first reported using cinchona to "cure the fever" in 1633. A few years later, Jesuit fathers were the primary importers and marketers of cinchona powder, which was later referred to as Peruvian bark or Jesuit bark. Across Europe, the powder was used as anti-pyretic. It was first formally acknowledged in 1677 when it was added as "Cortex Peruanua" to the London Pharmacopoeia. After quinine was separated from cinchona over two centuries later, the alkaloid's application grew. Quinine was later synthesized, but the process is very intricate, and quinine is now primarily derived from natural sources. It is currently primarily used to treat malaria and sporadically to alleviate nocturnal leg cramps(14).

The late 19th century saw the creation of several compounds that differed greatly from cinchona and had far better antipyretic, analgesic, and anti-inflammatory properties due to the unavailability and expensive cost of quinine. Willow bark has long been used to alleviate fevers and has been recognized as a medical benefit by many civilizations. The

glycoside known as salicin, which Leroux initially isolated in 1829 and produced sodium salicylate by hydrolysis and other chemical manipulations in 1875, was the active component of willow bark (15).
Soon after its introduction in 1899, synthetic salicylates such as acetylsalicylic acid took the lead over more costly natural sources of salicylates due to their shown anti-inflammatory effects (13). While indole compounds have been thoroughly investigated for their analgesic and anti-inflammatory qualities, indomethacin has received the majority of attention. In 1982, Carl Stevenson, MD, who was Merck Sharp & Dohme Research Laboratories' Director of Clinical Research at the time, pragmatically stated that "Indomethacin in the 1960s was the object of both praise and disappointment" (16). It was first introduced for general prescription in 1965, following the start of clinical studies in 1961 (16). After exhibiting anti-inflammatory qualities, synthetic salicylates, such as acetylsalicylic acid, were produced in 1899 and quickly replaced the natural. It was clear that while it was quite successful in reducing the symptoms associated with some arthritic illnesses, it had little influence on the underlying disease's progression (17). Its early success occurred when most people were unaware of the negative effects of NSAIDs as a class (18).
Indomethacin is a nonsteroidal anti-inflammatory derivative of indole (19). In water, indomethacin is nearly insoluble, whereas in alcohol, it is only weakly soluble. It is stable in neutral or slightly acidic environments and has a pKa of 4.5 (20).

2. Pharmakokinetic:
Indomethacin's pharmacokinetics are linear. While half-life ($T_{1/2}$), plasma and renal clearance are dose-dependent, plasma concentration and area under the curve (AUC) are proportional to the dose given.

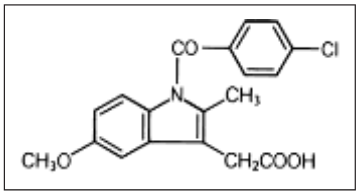

Figure 1: Struture of Indomethacin

2.1 Absorption:
When taken orally, indomethacin is quickly absorbed from the digestive system and has about 100% bioavailability. In a fasting state, the time between the peak plasma concentrations after a single dose is between 0.9-0.4 and 1.5-0.8 hours. Nonetheless, it is reasonable to anticipate that the many generic formulations will be prone to comparable variability given that capsule preparations from various formulations even branded ones show notable variations in serum concentrations (21).
Peak plasma concentrations are dose-proportional and averaged 0.76-1.54 g/mL, 1.03-2.65 g/mL, and 1.88-4.92 lg/mL after 25 mg, 50 mg, and 75 mg single doses in fasting subjects, respectively, despite significant intersubject variation as well using the same formulation (22). Following three daily dosages of 25 mg, the mean steady-state plasma concentrations range from 0.39 to 0.63 g/mL. While exact data about the therapeutic range of indomethacin for its anti-inflammatory activity are lacking, a range of 0.5–3 1g/mL has been proposed (22-23).
When indomethacin is taken with food, its absorption rate is slowed and delayed; this impact is most noticeable following a diet high in carbohydrates, followed by one high in protein, and finally one high in fat. The degree of bioavailability remains unaffected (24). Similarly, peak plasma concentrations are somewhat delayed and decreased if taken with an antacid that contains magnesium and aluminum hydroxides, although this is not considered to be clinically significant (24).

2.2 Distribution:
NSAIDs have linear kinetics, meaning they penetrate the blood-brain barrier just as quickly as solutes like water (26). Early research found very little indomethacin in spinal fluid taken from a limited sample of individuals (25). Due to the significant protein binding of NSAIDs, only the free fraction can diffuse across the blood-brain barrier, hence more sensitive analytical techniques were needed to quantify the quantities in cerebrospinal fluid (CSF). Beyond blood brain barrier permeability, additional factors may affect drug uptake and distribution into the brain. There are several transport carriers with which NSAIDs can interact. For instance, ibuprofen has shown a saturable component, indicating that brain entrance may include one or more carriers. There is no proof that flurbiprofen and indomethacin have saturable brain absorption. Indomethacin has the ability to block ibuprofen uptake, indicating that a saturable mechanism is, at least partially, responsible for mediating ibuprofen uptake in the brain (27).
As a result, the free fraction of medication that is available for brain uptake is reduced; acidic NSAIDs diffuse quantitatively poorly to the brain because they bind strongly to plasma albumin. The main factor limiting NSAID absorption in the brain is plasma protein binding (28).

2.3 Metabolism:

In addition to conjugation with glucuronic acid, the liver also undergoes significant O-desmethylation and N-deacylation in the metabolism of indomethacin.

The main inactive metabolites of indomethacin, N-deschlorobenzoyl-indomethacin, and O-desmethyl-N-deschlorobenzoyl-indomethacin, along with their glucuronides, are not anti-inflammatory. Urine, bile, and feces are the places where free and conjugated metabolites are removed, whereas plasma contains some of the metabolites. The amount of indomethacin expelled in feces is approximately 33% in the form of unconjugated demethylated metabolites and 1.5% in the form of indomethacin itself. Renal tubular secretion excretes roughly 60% of an oral dose of 5 mg as the drug and its metabolites in the urine. Domethacin's high bioavailability suggests that there is little first-pass metabolism occurring (29).

With a half-life of one hour during the first phase and 2.6–11.2 hours during the second, indomethacin's disappearance from plasma is biphasic. variances in this pattern are believed to be caused by variances in the drug's enterohepatic circulation between individuals. Variations within and between individuals are therefore not surprising (30).

2.4 Excreation:

Its glucuronide is excreted into bile during enterohepatic circulation, and indomethacin is then reabsorbed following hydrolysis. The extent, which is estimated to be between 27 and 115%, is erratic and unexpected. This could be related to variations in reported indomethacin T1=.22 and variations in plasma concentrations following the initial phase. Estimated accumulation T1/2 after multiple dosage injection varies from 4.5 to 9.0–13.1 hours [31]. Six The clinical observation that a single dose of indomethacin frequently resulted in prolonged alleviation of pain and stiffness in certain arthritic patients may also be explained by a long T1/2 (32).

The plasma half-life of healthy adults does not seem to differ from that of individuals suffering from conditions like rheumatoid arthritis (32).

3. Adverse effect:

When given conventional therapeutic doses of indomethacin, between thirty and sixty percent of patients experience adverse effects, and 10–20% cease taking the drug completely. The majority of side effects are largely caused by dosage.

When taking equivalent daily dosages of traditional or extended-release capsules, the incidence of indomethacin-induced adverse reactions is comparable; these symptoms can also occur with oral solution or rectal suppositories. Elderly populations have a heightened risk of psychotic episodes and gastrointestinal complications (33).

3.1 Cardiovascular

Adverse cardiovascular (CV) symptoms, which include palpitations, tachycardia, chest discomfort, arrhythmia, and congestive heart failure, affect less than 1% of people on indomethacin. Reports of pulmonary hypertension, edema, and hypotension have all been made. Studies and concerns about the relationship between NSAID use including selective COX-2 inhibitors and cardiovascular events are still continuing (34).

3.2 Gastrointestinal

In 3-9% of cases, patients experience nausea and dyspepsia. Constipation, diarrhea, or abdominal pain are reported in 1-3% of cases (35). Other GI issues include ulcerated stomatitis, intestinal strictures, gingival ulcers, anorexia, bloating, gas, gastroenteritis, rectal hemorrhage and proctitis that occur in less than 1% of patients (13). Less than 1% of individuals have been documented to suffer one or more ulcerations of the duodenum, stomach, small & large intestine, including reactivation of latent lesions (36). Adverse gastrointestinal symptoms were equally common in a cross-over trial of patients with rheumatoid arthritis who were given traditional capsules or suppositories (36).

If indomethacin is taken orally, the GI side effects can be reduced by taking the medication after meals, with food, or with antacids. If a patient is on long-term indomethacin therapy, an occult of the blood faecestest should be done on a regular basis, even if the patient is asymptomatic. Inquiries concerning GI unusual occurrences should always be part of an in-depth examination of symptoms. Patients taking NSAIDs may experience serious gastrointestinal side effects at any moment (15). Patients taking NSAIDs may experience serious gastrointestinal adverse effects at any point. Merely 25% of patients experiencing severe upper gastrointestinal adverse effects while using NSAIDs exhibit symptoms (37).

3.3 Central nervous system:

Headache is the most frequent adverse effect associated with indomethacin, affecting a minimum of 10% of patients. It is dose-related (38). Vomiting, hearing loss, ataxia, tremor, dizziness, insomnia, or vertigo may accompany it. It was observed that in the mornings, it is more frequent and severe. 3–9% of patients experience dizziness (39). In 1-3% of patients, vertigo, somnolence, depression, and weariness are experienced (38). Less than 1% of patients experience symptoms related to the central nervous system (CNS), such as feeling lightheaded, fatigue, disorientation, psychic disturbances, illusions, recurring nightmares, detachment, feeling floaty, anxiety, insomnia, weakness of muscles, involuntary muscle movements, ataxia, a disorder known as syncope, paralysis, seizures, neuropathy of the legs, and even coma (40).

3.4 Hematologic:
Adverse hematologic effects, such as hemolytic anemia, bone marrow suppression, aplastic anemia (which can be fatal in certain cases), agranulocytosis, anemia, thrombocytopenia, and thrombocytopenic purpura, affect less than 1% of people (41). Indomethacin lengthens the bleeding period by preventing platelet aggregation. The effects on platelets vanish 24 hours after the medication is stopped(42).

3.5 Ocular and Otic:
Less than one percent of patients undergoing extended use of indomethacin have been found to have retinal abnormalities and corneal deposits, including macular changes. The following conditions were reported by less than 1% of patients receiving long-term therapy: cataracts, photophobia, which is diplopia, toxic amblyopia, blindness at night, and visual loss (43).

4. Drug Interaction:
Indomethacin shows various type of Drug interaction which is seen on table no 1.

Table 1. Interaction of Indomethacin

S. no	Drug Class	Interaction	Mechanism
1.	Anticogulant (Warfarin)	High risk of Bleeding Decreased plasma indomethacin concentration; increased risk of serious GI Events	Synergestic effects possible decreased GI absorption and increased biliary clearance of indomethacin [44].
2.	Antihypertensive (Hyralazine, ACE Inhibitor)	Reduced Hypotensive Effects, rare impaired renal function	Inhibition of Postaglandin synthesis may result in fluid retention or changes in vascular resistance [45].
3.	Digoxin	Serum Digoxin concentation may increase and $T_{1/2}$ prolonged	Unknown serum digoxin concentation maintained [46].
4.	Lithium	Increase of plasma lithium concentation; reduced lithium cioncentation	Inhibition of PG synthesis in distal renal tubule. [47]
5.	Cyclosporine	Increased nephrotoxicity of cyclosporin	Inhibition of renal PG synthesis [48]

5. Mechanism of Action:
The main mechanism of action of NSAIDs, which are mostly reversible inhibitors, is the inhibition of COX in the FDA-approved indications for which they are used. Domethacin may have distinct biomechanisms unrelated to the NSAID class, despite the fact that its first FDA-approved uses had been for moderate to severe arthritis, including ankylosing spondylitis (AS), osteoarthritis, arthritis with gout, and acute painful shoulder bursitis or tendinitis (49).
Controlling the distribution the pharmacological efficacy of NSAIDs is greatly aided by their acidic character (50). The logarithmic acid dissociation constants (pKa) of NSAIDs fall between 3 and 4.5 (20). Most physiological settings have pH values that are far higher than these pKa values, meaning that in most tissues, only very minute amounts of NSAIDs exist in the un-ionized state NSAIDs and other acidic drugs are more readily soluble in lipids in their unionized form than in their ionized form because of this. this form primarily diffuses through cellular membranes (50). After equilibration, the unionized form is usually present in equal amounts on both sides of a cell membrane. A pH gradient across a cell membrane is referred to as "ion trapping" when the overall concentration both ionized and un-ionized is greater on the region with the higher pH (51). The accumulation of living cells in acidic surroundings may be related to the GI side effects and NSAIDs' ant-inflammatory properties. Their buildup in the kidney may potentially have an impact on renal function (52).
Since NSAIDs are mostly found in parietal cells, harm to these cells might be the root reason of gastric mucosal injury(53). Because parietal cells secrete the most hydrogen ions in the GI tract, they have the largest intracellular pH gradient, which leads to the ion trapping of acidic NSAIDs (54). By lowering stomach acidity, NSAIDs generally lessen their GI adverse effects. Also, slow release or enteric coated pills can lower the functional concentration of NSAIDs in the stomach [29]. When indomethacin is given rectally, dyspepsia and dose-related stomach irritation have been documented [55]. The delivery of sulindac, an inactive pro-drug, suggests that there may be an accumulation of sufficient circulating active medication in the upper Gastric Intestinal tract to cause adverse effects [56].
In the FDA-approved indications for which they are used, the primary mechanism of action of NSAIDs is the inhibition of COX, and the majority of them are reversible inhibitors. Domethacin may have distinct as well as NSAID class-

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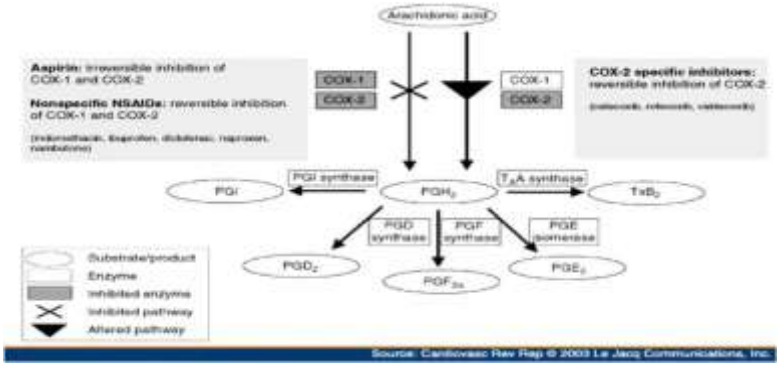

Figure 1: Mechanism of Action of Indomethacin

6. Indomethacin in Lactation and Pregnancy:

Since the 1970s, indomethacin has been used to extend pregnancy by reducing uterine contractions in women who present with premature labor (64). This use is justified by the fact that local prostaglandin synthases, which control uterine contractions, changes in the cervix, and myometrial gap junctions, have a role in the commencement of labor [33].

Despite being widely used during being pregnant, little is known about the pharmacokinetics of indomethacin, making it difficult to determine the optimal dosages and periods for a pregnant woman (65). Despite the fact that the study was limited to gestational ages of 12–31 weeks, clearance was higher (14.5–15 L/h) than in nonpregnant patients (typically 6.5–9.8 L/h) (34). Additionally, the average time to reach the highest drug concentration (Tmax) was 1.3 6 0.7 hours, similar to nonpregnant participants (66). The average steady state drug concentration of sixteen pregnant subjects (taking 25 mg four times a day) was about 37% less than that of non-pregnant subjects (taking 25 mg three times a day) (66).

Reduced albumin levels during pregnancy may have led to a rise in the amount of unbound indomethacin, which in turn may have increased drug clearance, even though the precise reasons for the higher clearance are unknown (67). Moreover, CYP2C9 increases by about 1.5 times during pregnancy and is crucial in the breakdown of indomethacin to O-desmethylindomethacin. This rise is similar to the rise in obvious indomethacin clearance seen in pregnant individuals (68).

Another factor influencing indomethacin clearance during pregnancy is the potentially significant placental transfer of the drug. This makes the relatively straightforward dose increase compensation for higher clearance during pregnancy more difficult (69).

Two studies that look at baby protection during indomethacin tocolysis the drug used to suppress premature labor show the difficulties in using pooled data from multiple studies to look at higher risk of unfavorable outcomes (70). These meta-analyses and reviews are in-depth and extensive (70). One study out of 28 that included about 6000 infants found no difference in the outcomes between those who were administered indomethacin antenatally and those who were not (71).

The second analysis, looking at about 8400 fantasies, showed that there is a connection between prenatal exposure to the tocolytic drug indomethacin and an increased risk of necrotic diarrhea, periventricular leukomalacia, and serious intraventricular hemorrhage (72).

Adverse effects for the GI system (necrotic enterocolitis), the CV system (premature closure of the ductus arteriosus, foetal pulmonary hypertension, and bleeding disorders), and the foetal renal system (development of foetal anuria and oligohydramnios) have all been linked to exposure to late the pregnancy during the 27th to 34th weeks of gestation(73).
In a separate investigation involving more than 8400 newborns, Research has shown that maternal exposure to the tocolytic drug indomethacin, is linked to a higher risk of necrotizing enterocolitis, periventricular leukomalacia, and severe intraventricular hemorrhage (73). Late pregnancy exposure between weeks 27 and 34 of gestation has been associated with adverse effects on the gastrointestinal tract (necrotizing enterocol), the CV system (premature closure of the arteriosus duct, neonatal pulmonary hypertension, and bleeding disorders), and the foetal renal system. (development of fetal anuria and oligohydramnios) (74).
The majority of current clinical research has not demonstrated that usage before 32 weeks gestation impairs newborn outcomes. However, manufacturers advise against using during the last trimester of pregnancy due to potential risks to the foetus. Food and Drug Administration risk for pregnancy group is B in the first and next trimesters and D in the third, whereas Hale's lactation risk group is L3 (75).

7. Analysis:

7.1 Assay

Using 0.2 ml of the phenolphthalein solution as an indicator, precisely weigh about 0.45 g, disperse in 75 ml of acetone, and titrate under nitrogen with carbonate-free 0.1 M sodium hydroxide. Execute an empty titration. 0.03578 g of $C_{19}H_{16}ClN0_4$ is equal to 1 ml of 0.1 M sodium hydroxide in water (76).

7.2 XRD of Indomethacin

XRD is a very quick analytical tool used for phase identification of a crystalline material.High Energy X-ray Diffraction of Dry Amorphous Indomethacin. In all cases, only the starting γ-phase formed melt quenched x-ray amorphous samples. Melt quenched α- and δ-phases formed crystals or mixed amorphous and crystalline forms (77-78).

7.3 FTIR of Indomethacin

FTIR spectrum of riboflavin by using an instrument Bruker 1206 0280 Germany by KBr disk technique. The spectra was recorded (Figure 6) over the range of 4000-400 cm-1 & and the spectrum were obtained. The IR spectrum of indomethacin shows characteristic bands in the following wavenumbers: 1716 cm −1 for (C=O) in the COO group, 1625-1575 and 1479 cm −1 for (C-C) stretching of the aromatic rings, 1692 cm −1 for amide group, 1261-1223 cm −1 , below 1012 and 737 cm −1 for (¼ C-O) of the ether group, (C-H) deformation (79).

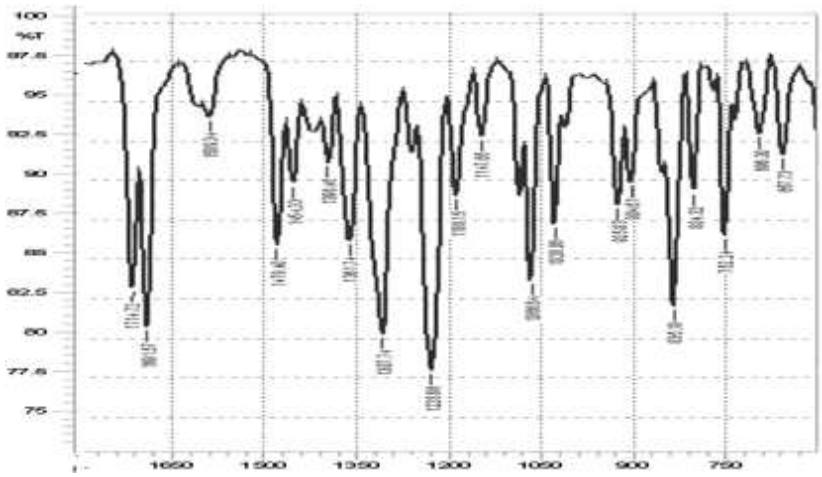

Figure 3: FTIR of indomethacin

Table 2. Functional Group Analysis

S no.	Wavelengh (cm^{-1})	Functional group
1.	1700	C=C stretch
2.	1600	Aromatic C=C stretch
3.	1450	O--CH_3 deformation
4.	1230	(C-O) stretch plus O-H deformation
5.	925	Carboxyl OH
6.	750	C-Cl
7.	900-600	Various C-H out of plane deformation for substituted aromatic

7.4 DSC of Indomethacin

Indomethacin showed a sharp endothermic peak at 161°C. Furthermore, no melting peaks were observed at depressed temperatures, indicating that IND is confined to the pores in a noncrystalline state (80).

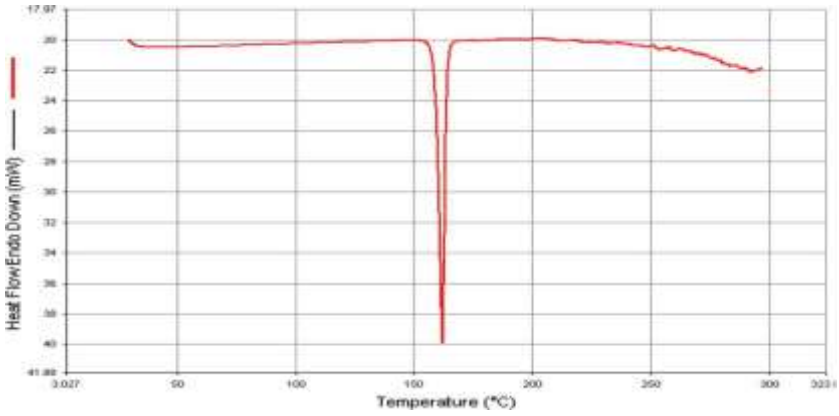

Figure 4: DSC of indomethacin

8. Recent Finding

8.1 Indomethacin-Induced Headache:

The best source of information for providers about typical medication side effects is familiarity with placebo-controlled trial results; however, for older medications, training, anecdotal evidence, and representation in recent medical literature are likely to take precedence (81). Given the growing awareness and acknowledgment of indomethacin-responsive headache, the incidence of headache as a side effect of indomethacin is under reported in the headache literature currently in publication and merits debate (82).

8.2 Indomethacin for asymptomatic patent ductus arteriosus in preterm infant

Although additional research is needed on long-term outcomes, indomethacin can prevent PDA in extremely preterm or small babies with evidence of PDA but no symptoms. PDA (patent ductus arteriosus) is a common problem for very small or very preterm newborns. PDA, an open channel that should have closed after birth, connects the heart and lungs and can result in potentially fatal consequences. All babies who are at risk for PDA are frequently given indomethacin, however this medication has side effects. Additionally, it can only be administered to infants who exhibit early PDA indications but not yet any symptoms. The review of trials found that this selective use of indomethacin can prevent PDA and has short-term benefits, but more research is needed on longer-term outcomes(83).

8.3 Antiviral effect of Indomethacin against SARS-CoV-2

African green monkey kidney (VERO) E6 cells infected with SARS CoV-2 pseudovirus and treated with varying doses of indomethacin or aspirin 48 hours after infection (p.i). The amount of luciferase activity indicated the degree of cell infection. The effectiveness of anti-coronavirus therapy in vivo was verified by measuring the recovery time in dogs infected with the canine coronavirus (CCV) after oral administration of 1 mg/kg body weight indomethacin(84).

A randomized clinical trial study by Ravichandran et. al, evaluated safety and efficacy of indomethacin in 210 COVID-19 patients. 107 patients were allotted standard care of paracetamol, ivermectin in control arm while other 103 patients received indomethacin in case arm. The principal focus of the study was development of hypoxia/desaturation ($SpO_2 \leq 93$). In the 103 patients who received indomethacin did not develop desaturation and also experienced rapid symptomatic relief. While 20 among 107 patients who received standard care of paracetamol, ivermectin in control arm developed desaturation. Also 56 out of such 107 patients reported fever on seventh day while none in indomethacin case arm (85).

8.4 Role of indomethacin in cancer

Cancer pose a formidable threat characterized by uncontrolled cell proliferation which start in any organ and metastasize to various other parts of the body (86). As NSAIDs mainly target epithelial cells of GIT, treat inflammation. These NSAIDs might have knock on positive effects inhibiting tumorigenesis in GIT. Additionally, NSAIDs are used as co-adjuvants with anti-neoplastic agents. Study by Hernandez et. al.; demonstrated that indomethacin enhances susceptibility of cancer cells to the toxic effects of chemotherapeutic agents. This is associated with the impaired autophagy resulting from inhibitory impact on lysosomes which came up as a potential target for chemotherapy (87). Table 3 includes list of clinical trials based on role of indomethacin in cancer in different Phases (Phase 1, 2,3 and 4) and status including R: Recruiting; A, NR: Active, non-recruiting; C: Completed; T: Terminated; W: Withdraw

Table 3. Clinical Trial data of Indomethacin in Cancer

S no,	NCT number	Intervention	Condition	Phases	Study Status	Sponsor
1.	NCT00473980	Indomethacin, calecoxib, esomeprazole	Colorectal cancer	PHASE 4	C	GA||teborg University
2.	NCT01265849	Cyclophosphamide|Indomethacin| Cisplatin	Squamous Cell Carcinoma of Oral	PHASE 3	C	CEL_SCI Corporation

			Activity			
3.	NCT02609386	Indomethacin| IRX-2| Zinc containing multivitamin| Omeprazole	Prostate Cancer	PHASE 2	C	Brooklyn ImmunoTherapeutics, LLC
4.	NCT02849990	Indomethacin| Abiratone Acetate| Apalutamide| Degarelix| Prednisone	Melanoma (Skin)	PHASE 2	C	University of Washington
5.	NCT00002535	Indomethacin|aldesleukin| lymphokine-activatedkiller cells|therapeutic tumour infiltrating lymphocytes| cyclophophamide	Squamous Cell Carcinoma of Head and Neck	PHASE 2	C	
6.	NCT00210470	Indomethacin| IRX-2| Cyclophosphamide| Zinc| Omeprzaole	Breast Cancer|Arthalgia|Joint pain	PHASE 2	C	Brooklyn ImmunoTherapeutics, LLC
7.	NCT01612728	Women without Arthralgia| Women without Arthralgia	Cervical Squamous Cell Carcinoma Insitu|Vulvar	PHASE 2	W	Baylor Breast Care Center
8.	NCT03267680	Cyclophosphamide| IRX-2| Indomethacin| Omeprazole| Multivitamin	High grade Squamous Intraepithelial Lesion	PHASE 2	ANR	University of Southern California
9.	NCT02935205	Enzalutamide| Indomethacin|	Prostate Cancer	PHASE 2	R	Mamta Parik
10.	NCT00002796	Indomethacin| Fluorouracils| Sodium phenylbutyrate	Colon Cancer|Rectal Cancer	PHASE 1\2	T	National Cancer Institute
11.	NCT02950259	Cyclophosphamide| Indomethacin| Omeprazole| Multivitamin	Triple Negative Breast Cancer	PHASE 1	ANR	Provide Health and Services
12.	NCT01719926	Indomethacin	Colorectal Neoplasams|Esophageal Neoplasams|Ovarian Neoplasams	PHASE 1	C	UMC Utrecht
13.	NCT05572788	EUS-guided fine needle aspiration of pancreatic cysts	Pancreatic Cyst	NA	R	Orlando Health, Inc.

9. **Patent of Indomethacin:** Patents of indomethacin showed in table no 4.

Table 4. Patents

S no.	Patent No.	Summary and Counclusion	Technique used	Refrence
1.	US9089471B2	The current invention relates to compositions containing indomethacin, methods for producing indomethacin particles using dry milling processes, medications made using indomethacin in particulate form and/or compositions, and techniques for treating animals, including humans, with a therapeutically effective dose of indomethacin administered by way of said medications.	Dry Milling	71
2.	EP2421513	A suppository preparation that consists primarily of a dosage unit of indomethacin in a base of polyethylene glycol or a mixture of polyethylene glycols containing glycerol in an amount ranging from 4 to 12 percent by weight and from about 1.0 to not more	Suppository	72

		than 4.5% by weight of a nucleating agent chosen from the group comprising alkali halide, lactose, calcium chloride, and sucrose.		
3.	WO2019095608 A1	Provided is a indomethacin detection method, comprising: producing and providing indomethacin tablets containing different mass gradients; under the same preset conditions, acquiring characteristic absorption peaks of the indomethacin tablets under different mass gradients for terahertz wave radiation; using a terahertz wave to radiate a sample to be detected, and acquiring a characteristic absorption peak of the sample to be detected for terahertz wave radiation; and determining whether the characteristic absorption peak of the sample to be detected for the terahertz wave radiation and the characteristic absorption peaks of the indomethacin radiation under different mass gradients for the terahertz wave radiation satisfy the similarities under the set conditions, and if so, determining that the sample to be detected contains indomethacin.	Tetrahertz wave equation	73
4.	US4228160A	The invention is related to an inclusion complex including cyclodextrin at a molar ratio of roughly 2:1 and 1-(p-chloro-benzoyl)-5-methoxy-2-methyl-indol-3-yl-acetic acid (indomethacin). The inclusion complex can be made by heating approximately 1 mole of 1-(p-chloro-benzoyl)-5-methoxy-2-methyl-indol-3-yl-acetic acid and 2 moles of alpha or beta cyclodextrin together with an organic solvent that dissolves indomethacin and prevents it from forming a stable complex with cyclodextrin. The novel compound exhibits far fewer ulcerative side effects while being at least as effective an anti-inflammatory as indomethacin.	Inclusion Complexes	74

		The single-type indomethacin coated pellets found in the controlled release formulation are in line with the current invention. Indomethacin is released from the pellet in two different forms: immediately and gradually. Indomethacin with instant release is quickly absorbed from the stomach to deliver an active agent bolus dosage. To keep blood levels at useful quantities for extended periods of time, sustained release indomethacin is delivered steadily over time.		
5.	US4752470A	The single-type indomethacin coated pellets found in the controlled release formulation are in line with the current invention. Indomethacin is released from the pellet in two different forms: immediately and gradually. Indomethacin with instant release is quickly absorbed from the stomach to deliver an active agent bolus dosage. To keep blood levels at useful quantities for extended periods of time, sustained release indomethacin is delivered steadily over time. A continuous release rate indomethacin formulation in tablet unit dosage form, with the tablet containing an intimate mixture of 50–200 mg of indomethacin, 1.7–3.7 weight percent of a water-insoluble, slow-dissolving cellulose derivative, 1.5–5.0 weight percent of a tabletting disintegrant, and 40–80% weight percent of a bulking agent or diluent that is approved by pharmaceuticals.	Coated Tablet	75
6.	US4525345A	A continuous release rate indomethacin formulation in tablet unit dosage form, with the tablet containing an intimate mixture of 50–200 mg of indomethacin, 1.7–3.7 weight percent of a water-insoluble, slow-dissolving cellulose derivative, 1.5–5.0 weight percent of a tabletting disintegrant, and 40–80%	Tablet Dosage form	76

		weight percent of a bulking agent or diluent that is approved by pharmaceuticals.		
8.	US20200140388 A1	Provided herein are methods, systems, kits, and compositions useful for determining small molecule-protein interactions and protein-protein interactions. The photo-click tags provided herein can be conjugated to a small molecule or amino acid analog to provide compounds that can be integrated into a protein through photo-conjugation, allowing for identification of a small molecule-protein interaction or protein-protein interaction to elucidate the small molecules mechanism of action or the protein targeted by the small molecule. In some embodiments, the photo-click tags comprise a photo-conjugation moiety and a click chemistry handle, allowing for the attachment of various functional groups (e.g., affinity tags) to the small molecule or amino acid analog	Photoconjugation	77
9.	US10561673B2	A nanodevice composition including N-acetyl cysteine linked to a dendrimer, such as a PAMAM dendrimer or a multiarm PEG polymer, is provided. Also provided is a nanodevice for targeted delivery of a compound to a location in need of treatment. The nanodevice includes a PAMAM dendrimer or multiarm PEG polymer, linked to the compound via a disulfide bond. There is provided a nanodevice composition for localizing and delivering therapeutically active agents, the nanodevice includes a PAMAM dendrimer or multiarm PEG polymer and at least one therapeutically active agent attached to the PAMAM dendrimer or multiarm PEG polymer. A method of site-specific delivery of a therapeutically active agent, by attaching a therapeutically active agent to a PAMAM dendrimer or multiarm	Imaging Process	78

		PEG polymer using a disulfide bond, administering the PAMAM dendrimer or multiarm PEG polymer to a patient in need of treatment, localizing the dendrimer or multiarm PEG polymer to a site in need of treatment, and releasing the therapeutically active agent at the site in need of treatment.		

10. **Future Prospects of Indomethacin**

Indomethacin, a well-established nonsteroidal anti-inflammatory drug (NSAID), has played a pivotal role in alleviating pain and reducing inflammation for decades. As we look to the future, this article delves into the potential avenues that could shape the continued relevance and evolution of indomethacin in the field of medicine.

10.1. Traditional Applications:

Arthritis and Gout: Indomethacin has been a cornerstone in the treatment of arthritis and gout. Future research may focus on refining its usage in these conditions and exploring novel formulations for enhanced efficacy (96).

10.2 Innovative Drug Delivery Systems:

Targeted Drug Delivery: Advancements in drug delivery technology could lead to more targeted and efficient administration of indomethacin. This may minimize side effects and increase the drug's therapeutic impact (97).

10.3 Combination Therapies:

Synergistic Approaches: Future studies might investigate the potential benefits of combining indomethacin with other drugs to create synergistic effects, offering improved pain relief and anti-inflammatory outcomes (98).

10.4 Emerging Therapeutic Areas:

Neurological Disorders: Exploring indomethacin's impact on neurological conditions could be an area of future interest. Research might uncover its potential in mitigating neuroinflammation associated with disorders like Alzheimer's or multiple sclerosis.

Cancer Treatment Support: Investigating the role of indomethacin as an adjuvant in cancer treatment could reveal its anti-inflammatory properties aiding in managing cancer-related symptoms and enhancing the effectiveness of existing therapies (99).

10.5 Personalized Medicine:

Genetic Variability: Understanding how an individual's genetic makeup influences their response to indomethacin may pave the way for personalized treatment plans, optimizing outcomes based on genetic factors (100).

10.6 Safety and Side Effect Profiles:

Reducing Adverse Effects: Future research may focus on developing formulations with minimized side effects, addressing concerns related to gastrointestinal issues and cardiovascular risks associated with long-term NSAID use (101).

11. Conclusion:

In summary, delving into the pharmacology and pharmacokinetics of indomethacin provides valuable insights into its diverse mechanisms of action and effective modulation of inflammatory processes. As a non-selective inhibitor of cyclooxygenase, indomethacin demonstrates robust analgesic, anti-inflammatory, and antipyretic effects, positioning it as a key player in managing various inflammatory conditions. Its pharmacokinetic characteristics, marked by swift absorption and metabolism with a relatively short elimination half-life, contribute to its efficacy. The ongoing research endeavors hold promise for further uncovering the potential of indomethacin. Exploring novel formulations, combination therapies, and targeted delivery systems may amplify its therapeutic benefits while minimizing adverse effects. Moreover, delving into the molecular pathways underlying its actions could lay the groundwork for personalized medicine approaches, tailoring indomethacin therapy to individual patient characteristics. As we navigate the dynamic landscape of pharmaceutical advancements, the continual exploration of indomethacin's pharmacology and pharmacokinetics presents opportunities to refine its clinical applications and optimize patient outcomes. Remaining attuned to emerging research ensures healthcare practitioners can leverage the full potential of indomethacin while managing associated risks, securing its ongoing relevance in the treatment of inflammatory disorders.

13. Conflict of Interest

The author has no conflict of Interest

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List of Tables

Table 1. Interaction of Indomethacin

T. no	Drug Class	Interaction	Mechanism
1.	Anticogulant (Warfarin)	High risk of Bleeding Decreased plasma indomethacin concentration; increased risk of serious GI Events	Synergestic effects possible decreased GI absorption and increased biliary clearance of indomethacin [44].
2.	Antihypertensive (Hyralazine, ACE Inhibitor)	Reduced Hypotensive Effects, rare impaired renal function	Inhibition of Postaglandin synthesis may result in fluid retention or changes in vascular resistance [45].
3.	Digoxin	Serum Digoxin concentation may increase and $T_{1/2}$ prolonged	Unknown serum digoxin concentation maintained [46].
4.	Lithium	Increase of plasma lithium concentation; reduced lithium cioncentation	Inhibition of PG synthesis in distal renal tubule. [47]
5.	Cyclosporine	Increased nephrotoxicity of cyclosporin	Inhibition of renal PG synthesis [48]

Table 2. Functional Group Analysis

S no.	Wavelengh (cm^{-1})	Functional group

1.	1700	C=C stretch
2.	1600	Aromatic C=C stretch
3.	1450	O--CH_3 deformation
4.	1230	(C-O) stretch plus O-H deformation
5.	925	Carboxyl OH
6.	750	C-Cl
7.	900-600	Various C-H out of plane deformation for substituted aromatic

Table 4. Clinical Trial data of Indomethacin in Cancer

Sno,	NCT number	Intervention	Condition	Phases	Study Status	Sponsor
1.	NCT00473980	Indomethacin, calecoxib, esomeprazole	Colorectal cancer	PHASE 4	C	GA||teborg University
2.	NCT01265849	Cyclophosphamide|Indomethacin| Cisplatin	Squamous Cell Carcinoma of Oral Activity	PHASE 3	C	CEL_SCI Corporation
3.	NCT02609386	Indomethacin| IRX-2| Zinc containing multivitamin| Omeprazole	Prostate Cancer	PHASE 2	C	Brooklyn ImmunoTherapeutics, LLC
4.	NCT02849990	Indomethacin| Abiratone Acetate| Apalutamide| Degarelix| Prednisone	Melanoma (Skin)	PHASE 2	C	University of Washington
5.	NCT00002535	Indomethacin|aldesleukin| lymphokine-activatedkiller cells|therapeutic tumour infiltrating lymphocytes| cyclophophamide	Squamous Cell Carcinoma of Head and Neck	PHASE 2	C	
6.	NCT00210470	Indomethacin| IRX-2| Cyclophosphamide| Zinc| Omeprzaole	Breast Cancer|Arthalgia|Joint pain	PHASE 2	C	Brooklyn ImmunoTherapeutics, LLC
7.	NCT01612728	Women without Arthralgia| Women without Arthralgia	Cervical Squamous Cell Carcinoma Insitu|Vulvar	PHASE 2	W	Baylor Breast Care Center
8.	NCT03267680	Cyclophosphamide| IRX-2| Indomethacin| Omeprazole| Multivitamin	High grade Squamous Intraepithelial Lesion	PHASE 2	ANR	University of Southern California
9.	NCT02935205	Enzalutamide| Indomethacin|	Prostate Cancer	PHASE 2	R	Mamta Parik
10.	NCT00002796	Indomethacin| Fluorouracils| Sodium phenylbutyrate	Colon Cancer|Rectal Cancer	PHASE 1\2	T	National Cancer Institute
11.	NCT02950259	Cyclophosphamide| Indomethacin| Omeprazole| Multivitamin	Triple Negative Breast Cancer	PHASE 1	ANR	Provide Health and Services
12.	NCT01719926	Indomethacin	Colorectal Neoplasams|Esophageal Neoplasams|Ovarian Neoplasams	PHASE 1	C	UMC Utrecht
13.	NCT05572788	EUS-guided fine needle aspiration of pancreatic cysts	Pancreatic Cyst	NA	R	Orlando Health, Inc.

NA: Not applicable; R: Recuiting; A, NR: Active, non-recuiting; C: Completed; T: Terminated; W: Withdraw