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A Research on Formulation and Evaluation of Celecoxib Fast Disintegrating Capsule (200mg)

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ABSTRACT:
Fast-disintegrating capsules have gained significant interest due to their potential to enhance patient compliance and drug efficacy. Celecoxib, a non-steroidal anti-inflammatory drug (NSAID), known for its selective inhibition of cyclooxygenase-2 (COX-2), is commonly used for the management of pain and inflammation associated with arthritis and other conditions.
Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that specifically inhibits cyclooxygenase- 2 (COX-2),enzyme involved in the synthesis of prostaglandins. Prostaglandins play a key role in inflammation, pain perception, and fever response. By selectively inhibiting COX-2, celecoxib reduces the production of prostaglandins that promote inflammation and pain, while sparing COX-1 activity to a greater extent.
This study aimed to develop and evaluate a fast-disintegrating capsule formulation of Celecoxib to provide rapid onset of action and improved patient convenience. The formulation was optimized using a combination of superdisintegrants and excipients to achieve fast disintegration in oral cavity conditions. Physicochemical characterization including disintegration time,and drug content uniformity were evaluated. In vitro dissolution studies were conducted to assess drug release profiles. The optimized formulation demonstrated rapid disintegration within seconds and showed comparable dissolution profiles to commercially available Celecoxib capsules. Further studies are warranted to evaluate the pharmacokinetic and pharmacodynamic profiles of the fast-disintegrating Celecoxib capsule in clinical settings to validate its potential therapeutic benefits.

KEYWORDS: IID- Inactive Ingredient Database, CMA- Critical Material Attributes, Quality Target Product Profile, Critical Process Parameters, Percentage Relative Standard Deviation, Particle size distribution, COX)-2 inhibitors (coxibs), NSAIDs, Celebrex, Super disintegrant, Drug interaction .

1. INTRODUCTION:

The use of nonsteroidal anti-inflammatory drugs (NSAIDs), specifically cyclo-oxygenase (COX)-2 inhibitors (coxibs), in the treatment of arthritis symptoms. NSAIDs are a class of medications commonly used to relieve pain and inflammation. They are often prescribed for conditions like arthritis to alleviate symptoms such as pain, swelling, and stiffness. COX-2 inhibitors, also known as coxibs, were developed as an alternative to non-selective NSAIDs .The goal was to minimize the risk of upper gastrointestinal (GI) toxicity associated with NSAIDs. COX-2 is an enzyme involved in inflammation, and by selectively inhibiting it, coxibs aim to reduce inflammation with fewer adverse effects on the GI tract (**1**). The distinction in consequences between NSAIDs (nonsteroidal anti-inflammatory drugs) and

celecoxib in the treatment of injuries may be related to the role that cyclooxygenase (COX) plays in the biology of the injured tissue and its restoration response. NSAIDs, such as ibuprofen and aspirin, work by inhibiting the activity of cyclooxygenase enzymes. Cyclooxygenase is responsible for the synthesis of prostaglandins, which are signaling molecules involved in inflammation, pain, and the regulation of blood flow. By blocking cyclooxygenase, NSAIDs reduce the production of prostaglandins, leading to anti-inflammatory and analgesic effects. Celecoxib, on the other hand, is a selective COX-2 inhibitor. It specifically targets cyclooxygenase-2, which is an isoform of the enzyme involved in inflammation. This selective inhibition is intended to provide anti-inflammatory benefits while minimizing the potential side effects associated with inhibiting the COX-1 isoform, which plays a role in maintaining the protective lining of the stomach. The differences in consequences between NSAIDs and celecoxib could be attributed to the distinct roles that COX-1 and COX-2 play in the injured tissue or its restoration response. For example, COX- 2 is often up regulated in response to injury, contributing to the inflammatory process and tissue repair. By selectively inhibiting COX-2, celecoxib may modulate inflammation without affecting the housekeeping functions of COX-1, potentially resulting in a different therapeutic profile compared to non-selective NSAID **(2).** Celecoxib, rofecoxib, and valdecoxib are all nonsteroidal anti-inflammatory drugs (NSAIDs) that belong to the class of COX-2 inhibitors, also known as coxibs. COX-2 (cyclooxygenase-2) is an enzyme involved in the inflammatory response.

Celecoxib was the first COX-2–specific inhibitor to be approved by the U.S. Food and Drug Administration (FDA) in December 1998. Rofecoxib followed in May 1999, and valdecoxib was approved in November 2001. These medications were developed to provide pain relief and reduce inflammation, with the aim of minimizing gastrointestinal side effects associated with traditional NSAIDs, which inhibit both COX-1 and COX-2 enzymes.

It's worth noting that rofecoxib (marketed as Vioxx) was later withdrawn from the market in 2004 due to concerns about an increased risk of cardiovascular events. Valdecoxib (marketed as Bextra) was also withdrawn in 2005 for similar reasons. Celecoxib (marketed as Celebrex) remains available, but its use is typically reserved for specific cases due to potential cardiovascular risks associated with long-term use. It's important to consult with a healthcare professional for personalized medical advice and information on the current status of medications

- **INDICATION**

Celecoxib is used primarily to manage pain and inflammation associated with various conditions including osteoarthritis, rheumatoid arthritis, acute pain in adults, painful menstruation (dysmenorrhea), and juvenile rheumatoid arthritis. It is also indicated for reducing the risk of colorectal adenomas in individuals with familial adenomatous polyposis.

- **Mechanism of Action**

Celecoxib inhibits COX-2, thereby reducing the synthesis of prostaglandins that mediate inflammation and pain. Unlike traditional NSAIDs which inhibit both COX-1 and COX-2, celecoxib preferentially targets COX-2, theoretically reducing the risk of gastrointestinal (GI) side effects such as ulcers and bleeding, which are more commonly associated with COX-1 inhibition.

- **Analgesic and Antipyretic Properties**

Celecoxib exhibits analgesic (pain-relieving) and antipyretic (fever-reducing) properties by reducing inflammation at the site of pain.

- **GI Effects**

Despite its selective COX-2 inhibition, celecoxib can still cause GI adverse effects such as ulceration and bleeding, albeit less frequently than non-selective NSAIDs. This is due to prostaglandins, which normally protect the stomach lining, being reduced even with COX-2 inhibition.

2. The Role of Cyclooxygenase:

Cyclooxygenase (COX) is an enzyme that plays a crucial role in the synthesis of prostaglandins (PGs), which are lipid compounds involved in various physiological processes, including inflammation and pain signalling. COX catalyzes the conversion of arachidonic acid, released from the phospholipid membrane by phospholipase, into cyclic endoperoxides, specifically prostaglandin G2 (PGG2) and prostaglandin H2 (PGH2). These cyclic endoperoxides are further converted into various prostaglandins, prostacyclin, and thromboxane.

There are two isoforms of COX: COX-1 and COX-2. COX-1 is constitutively expressed in many tissues and is involved in maintaining normal physiological functions, such as protecting the stomach lining and supporting platelet function. COX-2, on the other hand, is often induced in response to inflammatory stimuli and is associated with the production of prostaglandins that contribute to inflammation and pain.

The inhibition of COX activity by NSAIDs, including COX-2 inhibitors (coxibs) like celecoxib, helps to reduce the synthesis of prostaglandins, providing relief from pain and inflammation. However, the selective inhibition of COX-2 was an attempt to minimize the gastrointestinal side effects associated with the inhibition of COX-1, which is involved in the protection of the stomach lining (**3**).

The COX molecule consists of 3 independent folding units: an epidermal growth factor-like domain. a membrane binding site, and an enzymatic domain.“’ The active COX site is a hydrophobic channel with a series of amino acids. Aspirin binds irreversibly to serine 580 by acetylation, whereas most other NSAIDs bind satirically and reversibly to tyrosine 385 or arginine 120, blocking the COX action of the enzyme. PCs exit the cell and act largely in an autocrine or paracrine fashion (**4, 5, 6).**

Research suggested that in some situations the COX enzyme was inducible (ie, could be upregulated by inflammatory stimuli such as cytokines).Because the increase in COX concentrations induced by cytokines could be prevented by administration of glucocorticoids **(7).**

Some key differences between cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which are enzymes involved in the synthesis of prostaglandins (PGs). Here are the major points:

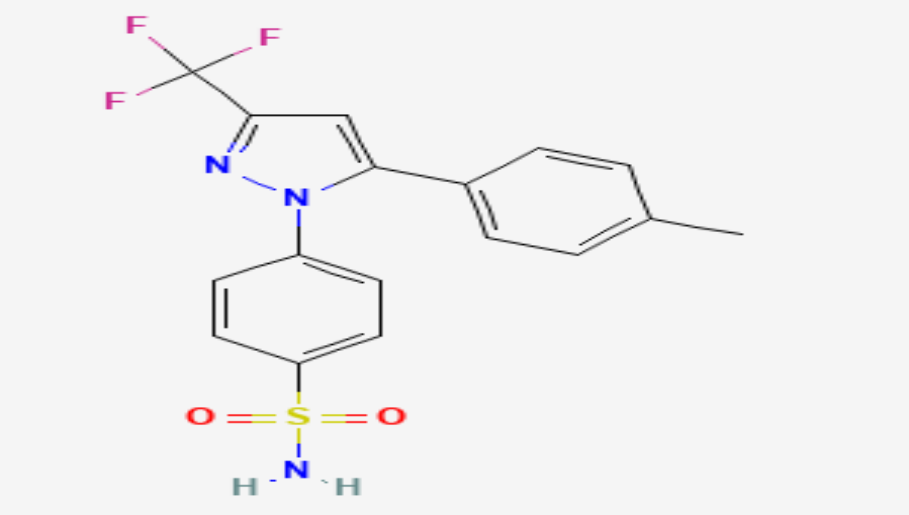
- **Tissue Distribution:**
  - **COX-1:** Present in most tissues.
  - **COX-2:** Almost undetectable in most tissues.
- **Function:**
  - **COX-1:** Performs a "housekeeping" function, synthesizing PGs that regulate normal cell activity. This includes functions such as gastrointestinal (GI) cytoprotection, vascular homeostasis, and renal function.
  - **COX-2:** Produces PGs mainly at sites of acute inflammation or arthritis. It may also be induced in response to mitogenic stimuli and cytokines.
- **Physiological Roles:**
  - **COX-1:** Involved in maintaining normal physiological functions and homeostasis in various tissues.
  - **COX-2:** Primarily associated with inflammatory responses and is induced in situations where inflammation or tissue damage occurs.

- **Expression Patterns:**
  - **COX-1:** Constitutively expressed in many tissues, suggesting a continuous and baseline synthesis of PGs for normal cellular functions.
  - **COX-2:** Inducible expression, meaning it is activated in response to specific stimuli like inflammation or mitogenic signals.

Understanding these differences is crucial for the development of drugs targeting COX enzymes. Nonsteroidal anti-inflammatory drugs (NSAIDs) often inhibit both COX-1 and COX-2, leading to potential side effects related to the housekeeping functions of COX-1, such as gastrointestinal issues.
Selective COX-2 inhibitors were developed to minimize these side effects, although their use has been associated with other concerns, including cardiovascular risks (**8, 9, 10, 11**).

3. Mechanism of Action of Celecoxib:

The identification of two isoforms of cyclooxygenase (COX), namely COX-1 and COX-2, has significantly advanced our understanding of the pharmacology and toxicity profiles of nonsteroidal anti-inflammatory drugs (NSAIDs). COX-1 is predominantly expressed constitutively and plays crucial roles in maintaining gastrointestinal mucosal integrity, regulating platelet aggregation, and supporting renal function. In contrast, COX-2 is induced primarily in response to inflammation and tissue injury.
Traditional NSAIDs typically inhibit both COX-1 and COX-2 in a non-specific manner, leading to both therapeutic efficacy and potential toxicity, particularly in the gastrointestinal tract. Despite sharing approximately 60% amino acid homology, the structural differences in the binding site of COX-2 allow for selective compounds with distinct side chains to access this site, which is not accessible in COX-1. This structural distinction has guided the targeted development of specific COX-2 inhibitors, aiming to maintain therapeutic efficacy similar to traditional NSAIDs while sparing COX-1 inhibition, thus improving the safety profile by reducing gastrointestinal adverse effects.
The evolution towards selective COX-2 inhibitors reflects a strategic approach in pharmacotherapy to optimize anti-inflammatory benefits while minimizing unwanted effects on gastrointestinal and renal function associated with non-selective NSAIDs. This targeted approach underscores the importance of understanding COX isoform biology in drug development and clinical practice.
COX- 1 and COX-2 are integral membrane proteins that sit within the inner leaflet of the lipid bilayer of intracellular phospholipid membranes. Their protein structures and enzymatic functions are remarkably similar. Apart from differences at the N-terminal signal peptide region and a Cterminal 1 g-amino-acid insertion in the COX-2 polypeptide. The remaining core sequences are 75% identical, and all residues identified as essential for catalytic activity are conserved. Both enzymes have been crystallized, and their crystal structures are virtually superimposable. The important difference between the 2 forms appears to be the substitution at position 523 of valine in COX-2 for isoleucine in COX- 1. The presence of the smaller valine side-chain in COX-2 allows the appearance of a new pocket in the channel that can accommodate the sulfurcontaining side-chain of a selective COX-2 inhibitor. The avid binding of celecoxib's phenylsulfonamide moiety to this channel is responsible for the drug's ability to prevent activation of COX-2 by the appropriate stimuli. A selective COX-2 inhibitor such as celecoxib may be able to block inflammation and pain while reducing the incidence of the GI side effects related to COX-1 inhibition that have limited the use of aspirin and other NSAIDs that inhibit both isoenzymes **(12).**



Structure of Celecoxib (13).

PHARMACOLOGICAL PROPERTIES

Celecoxib, a selective COX-2 inhibitor, exhibits a range of pharmacological activities primarily through its inhibition of prostaglandin synthesis. Here's a breakdown of its mechanisms and effects:

Anti-inflammatory, Analgesic, and Antipyretic Activities: Celecoxib inhibits prostaglandin synthesis primarily by targeting COX-2. Prostaglandins derived from COX-2 play a significant role in mediating inflammation, pain, and fever at the site of injury or inflammation. This selective inhibition allows celecoxib to reduce inflammation and alleviate pain without affecting COX-1, which is important for maintaining gastrointestinal and renal functions.

Peripheral Analgesic Action: The analgesic effect of celecoxib is mainly due to its action at peripheral sites of pain and inflammation, where COX-2 is upregulated. This is particularly effective in conditions where pain is related to inflammation.

Antipyretic Effect: Celecoxib's antipyretic (fever-reducing) effect is mediated through inhibition of COX-2-derived prostaglandins in the hypothalamus. Pro-inflammatory cytokines induce the production of prostaglandin E2 (PGE2) in the hypothalamus, which affects temperature-regulating neurons. By inhibiting COX-2, celecoxib can reduce PGE2 production and thereby lower fever.

Effects on Platelet Function and Cardiovascular System:

Unlike traditional NSAIDs, celecoxib has minimal direct effect on platelet function, specifically thromboxane A2 (TXA2) production. TXA2 is important for platelet aggregation and blood clotting. However, celecoxib can suppress the production of prostacyclin (PGI2), an antiaggregating and vasodilating prostaglandin produced by blood vessels. This imbalance between PGI2 and TXA2 may potentially increase cardiovascular (CV) risks, as TXA2 effects may become more pronounced.

Cardiovascular Effects: The alteration in the PGI2/TXA2 balance due to celecoxib's selective inhibition of COX-2 can lead to increased cardiovascular risks. This imbalance may contribute to adverse effects such as hypertension or the inhibition of prostanoid formation in arteriosclerotic plaques, potentially affecting cardiovascular health **(14).**

3.1.Drug Interaction

Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 should be done with caution. Significant interactions may occur when celecoxib is administered together with drugs that inhibit

CYP2C9. In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6.

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- **Anticoagulants (e.g., warfarin)**:
- Patients on warfarin or similar anticoagulants should be closely monitored for bleeding complications when starting or changing celecoxib therapy.
- While celecoxib did not affect prothrombin time in healthy subjects taking warfarin, postmarketing reports indicate an increased risk of serious bleeding events, particularly in the elderly.
- **Lithium**:
- Celecoxib can increase lithium plasma levels by approximately 17%. Patients on lithium therapy should be monitored closely when starting or stopping celecoxib.
- **Aspirin**:
- Celecoxib can be used concurrently with low-dose aspirin.
- However, combining aspirin with celecoxib increases the risk of gastrointestinal ulceration and other complications compared to using celecoxib alone.
- Celecoxib does not substitute for aspirin in cardiovascular prophylaxis.
- **ACE Inhibitors and Angiotensin II Antagonists**:
- NSAIDs, including celecoxib, may reduce the antihypertensive effects of ACE inhibitors and angiotensin II antagonists.
- Consider this interaction when prescribing celecoxib alongside these medications.
- **Fluconazole**:
- Fluconazole can increase celecoxib plasma concentrations twofold by inhibiting its metabolism via CYP2C9.
- Initiate celecoxib at the lowest recommended dose in patients concurrently receiving fluconazole.
- **Furosemide**:
- NSAIDs, including celecoxib, may reduce the natriuretic effect of diuretics like furosemide and thiazides by inhibiting renal prostaglandin synthesis.
- Monitor patients for reduced diuretic efficacy when using celecoxib with these medications.
- **Methotrexate**:
- Celecoxib does not affect the pharmacokinetics of methotrexate in rheumatoid arthritis patients.
- No dose adjustment is typically needed when these medications are used together.
- **Concomitant NSAID Use**:
- Avoid concomitant use of celecoxib with any dose of non-aspirin NSAIDs due to increased risk of adverse reactions **(15).**

4. Formulation Ingredients of Celecoxib Capsule

4.1.Excipients:

The excipients used in test product were selected based on the excipients used in the reference medicinal product, i.e. Celebrex capsule, drug-excipient compatibility studies, excipients used for

the manufacturing of immediate release or conventional solid oral dosage, and prior use in approved products that utilize wet granulation process. Common excipients functioning as filler, disintegrant, binder, lubricant, and film forming agents were used for the manufacturing of test product. A summary of drug-Excipients compatibility studies and the selection of each excipients grade are provided in the below section.

4. 2. Drug and Excipient Compatibility Study

The selection of excipients for compatibility study based on Reference Medicinal Product and from approved drug products, mechanistic understanding of drug substance and its impurities, excipients and their impurities, degradation pathways and manufacturing process, the compatibility of Celecoxib was evaluated with the excipients intended to be used in product development. The study was intended to evaluate the physical stability of different ratios of drug and excipient/s blends (binary mixtures) prepared by uniform mixing. Details of excipients like name of the excipient, compendia status, grade/trade name and drug to excipient ratio (D : E) and supplier/manufacturer details are summarized in:

3. Details of Drug and Excipients used in Compatibility Study

S. No.	Name of Ingredients	D:E Ratio	RT Initial	RT 40°/75%
1.	**Celecoxib**	-	White color powder	No significant Change
2.	**Celecoxib +Lactose Monohydrate**	**1:0.25**	White to off white powder	No significant Change
3.	**Celecoxib +Sodium Lauryl sulphate**	**1:0.05**	White to off white powder	No significant Change
4.	**Celecoxib +Povidone K30**	**1::0.02**	White to off white powder	No significant Change
5.	**Celecoxib +Croscarmellose sodium**	**1:0.02**	White to off white powder	No significant Change
6.	**Celecoxib +Magnesium stearate**	**1:0.02**	White to off white powder	No significant Change
7.	**Composite**	-	White to off white powder	No significant Change

4.4 Representation of the Sample:

The blend was filled in clear glass vials with inner LDPE cap, outer screw cap and stored at 40°C/75%RH as detailed below

Stability Conditions and Packaging Configuration

Sample	Stability Condition	Packaging Configuration
D:E sample (Open Condition)	40°C/ 75% RH	5 mL glass vial
D:E sample (Closed Condition)	40°C/ 75% RH	5 mL glass vial with inner LDPE cap and outer screw cap

4.5 Selection of Excipients and Grade of Excipients

Lactose Monohydrate, Sodium Lauryl sulphate, Povidone K30, Croscarmellose sodium, Magnesium stearate, were selected based on Reference Medicinal Product evaluation, intended manufacturing process, drug substance attributes, and drug- excipients compatibility studies. The selection of excipient grade and supplier was based on previous formulation experience and knowledge about excipients that have been used successfully in approved products manufactured by wet granulation process. The level of excipients used in the formulation was studied in subsequent development stage and well within the IID limit.

- **Lactose Monohydrate:** Lactose Monohydrate was selected as diluent in the drug product development. The most commonly used diluents among those which support wet granulation is Lactose Monohydrate. The filler selected has good compressibility which could support the selected process for manufacture of Capsule i.e., wet granulation. Lactose Monohydrate has well anti adherent capacity along with binding capacity whichwas necessary for good flow of powder blend through hopper.
- **Sodium Lauryl Sulphate:** Sodium Lauryl sulphate is used as surfactant in drug product development. The surfactant which could support in Dissolution. SLS lower the surfacetension between ingredients.
- **Povidone K30:** Povidone is used in a variety of pharmaceutical formulation, it is primarily used in solid-dosage forms. Povidone solutions are used as binder in Wet granulation process. Povidone is additionally used as suspending, stabilizing or viscosity increasing agent in a number of topical and oral suspensions and solutions.
- **Croscarmellose Sodium (Ac-di-sol):** Croscarmellose Sodium is commonly used as a disintegrant. Celecoxib is a BCS class II drug so rapid disintegration is necessary to ensure maximum bioavailability Croscarmellose sodium added in both the wet and dry stages of the process (intra- andextra- granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Being a super-disintegrant, croscarmellose sodium is hygroscopic in nature. It swells rapidly to about 4-8 times its original volume when it comes in contact with water.
- **Magnesium Stearate:** Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations.It is primarily used as lubricant in capsule and capsule manufacture at concentrations between 0.25%and 0.5% w/w. It is also used in barrier creams.

5. FORMULATION DEVELOPMENT OF DRUG PRODUCT

5.1 Drug Substance Particle Size Selection for Product Development

In general, for drug substance with coarser drug substance particle size improves manufacturing process because it has better flow. However, for a BCS II compound like Celecoxib, larger drug substance particle size may significantly decrease dissolution and negatively impact the in vivo performance. With an aim to identify the appropriate drug substance particle size distribution range which provides similar drug release profile across physiological pH as of Reference Medicinal Product **(16).**

5.2 Process Selection

The Celecoxib, displayed excellent flowability as evidenced by the compressibility index and Hausner ratio of drug substance during pre-formulation studies. Dry Mixing process was selected as

primary strategy for the development of Celecoxib Capsule. Flow and Weight Variation issue observed so wet granulation process by rapid mixer granulator wasselected for the development of Celecoxib Capsule.

CMA's of Excipients

S. No.	Excipients	Compendial status	CMAs
1	Lactose Monohydrate	IP/USP/NF, BP	Particle size distribution
2	Sodium Lauryl sulphate	IP/USP/NF, BP	Particle size distribution
3	Povidone K30	IP/USP/NF, BP	Viscosity
4	Croscarmellose Sodium	IP/USP/NF, BP	Particle size distribution
5	Magnesium stearate	IP/USP/NF, BP	Specific surface area

6. Drug Product

6.1.Formulation Development

Initial Risk Assessment of the Formulation Variables

Product	Formulation Variables			
	Solublizer Level (Sodium Lauryl sulphate) Level	Binder Level (Povidone K30)	Disintegrant Level (CCS)	Lubricant Level (Magnesium stearate)
Assay	Low	Low	Low	Low
Content uniformity	Low	Low	Low	Low
Dissolution	High	High	High	High
Related substance	Low	Low	Low	Low

Justification for the Initial Risk Assessment of the Critical Formulation Variables (CFVs)

API Attributes	Drug Product CQAs	Justification
Sodium Lauryl	Assay	Since the level of Sodium lauryl sulphate used is low and its impact on flow is minimal, it is unlikely to impact assay and CU. The risk is low
	Content uniformity	

Sulphate Level		Sodium lauryl sulphate level can impact the wettability mechanism and ultimately
	Dissolution	Dissolution. Since achieving rapid dissolution is important for a drug product containing a BCS class II compound, the risk is high.
	Related substance	Sodium lauryl sulphate is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
	Assay	Since the level of Povidone K30 used is low and its impact on flow is minimal,
	Content uniformity	it is unlikely to impact assay and CU. The risk is low.
Magnesium StearateLevel	**Dissolution**	Povidone K30 level can impact the disintegration time and ultimately dissolution. Since achieving rapid disintegration is important for a drug product containing a BCS class II Compound, the risk is high.
	Related substance	Povidone K30 is compatible with the drug substance and will not impact drug product degradation. Thus, the risk is low.
	Assay	Since the level of Croscarmellose Sodium used is low and its impact on flow is minimal,
	Content uniformity	it is unlikely to impact assay and CU. The risk is low.

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Process Selection

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6.1.2. Formulation Development Study

A univariate method (i.e., one-factor-at-a time (OFAT)) approach was used for the formulation development of Generic Celecoxib Capsule. Formulation development focused on evaluation of the high-risk formulation variables as identified in the initial risk assessment. The development was conducted in four stages. The first formulation study evaluated the impact of Solubilizer level (Sodium Lauryl sulphate) on the drug product dissolution. The second formulation study evaluated the impact of Binder (Povidone K30) on the drug product dissolution. The third formulation study evaluated the impact of disintegrant (Croscarmellose sodium) on the drug product dissolution and fourth formulation study evaluated the impact of lubricant (Magnesium stearate) on the drug product dissolution. All formulation development study for critical formulation variables were conducted at laboratory scale at fixed process parameters and fixed equipment.

6.1.3. Formula Composition with different Formulation Trials

S. No.	Material Name	Qty mg/cap (Dry Mix)	% w/w	Qty mg/cap (Wet Granulation)	% w/w
1.	Celecoxib	200.00	74.07	NA	NA
2.	Celecoxib (Micronized)	NA	NA	200.00	74.07
3.	Lactose Monohydrate	60.01	19.93	60.01	19.73
4.	Croscarmellose sodium	6.75	2.5	6.75	2.5
			Binder		
5.	Purified water	NA	NA	40.00	14.81
			Lubricant		
6.	Magnesium Stearate	3.24	1.20	3.24	1.20
	Avg. wt.	270.00mg	-	270.00mg	-
Remarks		Physico-chemical parameters not found satisfactory		Physicochemical parameters found ok. Assay Observed 101.13% & Dissolution-67.5%	

Results:

The drug product batches were evaluated for physical, chemical properties and data is reported below:

Batch No.	001	-002
Bulk Density (g/cc)	0.4	0.46
Tapped density(g/cc)	0.8	0.62
C.I. (%)	50	25.8
HR	2.0	1.35

PSD (% Retained)	#20	0	0
	#40	0	0
	#60	21.00	49.00
	#80	10.0	20.00
	#100	31.50	10.00
	Base	37.5	21.00

Physical properties of Celecoxib Capsule 200mg

Batch No.	**-001**	**-002**
Description	Hard Gelatin capsules of size 2 with body and cap of yellow color Content of Capsule: white to off white color powder	Hard Gelatin capsules of size 2 with body and cap of yellow color Content of Capsule: white to off white color granular powder
Average fill weight	270.0mg	270.0mg
Average weight of Intact	300-365mg	333-340mg
capsule Observed		
Disintegration Test	10min.	8min40sec
Flow	Poor flow, weight variation observed	Good flow, weight found within specification

Analysis Report:

S. No.	**Test Parameter**	**Acceptance Criteria**	**Results**
1.	**Description**	Hard Gelatin capsules of size "2" with body and cap of yellow colour. Content of capsules: powder or granular powder or powder with granular white to off white colour.	Hard gelatin capsules of size "2" with body and cap of yellow colour. Content of capsules: granular powderwith granular white colour.
2.	**Authenticity**		

	I. By HPLC	Retention time of the principal peak in the chromatogram of the testsolution should corresponds to the retention time of the Celecoxib peak in the chromatogram of the standard solution**.**	Complies
	II. By UV-Spectroscopy	UV-spectrum of the solution should have the maximum absorption at the wavelength of	Complies
		252±2nm.	
3.	**Average weight of Capsules**	330.0mg ± 7.5% (308.03-357.98)	339.5mg
4.	**Average fill weight of capsules**	270.0mg ± 10.0% (243.0-297.0mg)	275.2mg
5.	**Disintegration Time**	Not more than 30 minutes.	6 minutes 10 seconds
6.	**Uniformity of fill weight**	Not more than 2 of the individual weights deviate from the average fill weight by more than ±10% and none deviate by more than ±20%.	-3.78% to 0.98%
7.	**Dissolution (By HPLC)**	Not less than 75%Q of the claimed quantity of celecoxib should dissolve into the solution within 45 minutes.	94% to 99%
8.	**Uniformity of dosage units (By weight variation method)**	Acceptance value of the first 10 dosage units (capsules) should be ≤1% and no individual content of dosage unit should be less than [1+(0.01) (L2)]M.L1is equal to 25.0	AV=5.6

Capsule Filling Parameter

S. No.	Parameters	Lab Trial 001	Validation 00001
1.	Description	Hard gelatin capsules of size 2 with body and cap of yellow color Content of Capsules: powder or granular powder with granular white to off white color.	Hard gelatin capsules of size 2 with body and cap of yellow color Content of Capsules: powder or granular powder with particles from white to off white color.
2.	Average Weight of empty capsule shell	63.0mg±10.0% (56.7mg-69.3mg)	63.0mg±10.0% (56.7mg-69.3mg)
3.	Average fill weight	267.00mg	266.80mg
4.	Average Weight of Intact Capsule	327.99mg	325.9mg
5.	Body-Cap lock length(mm)	17.60-17.72mm	17.59-17.76mm
6.	Disintegration Time	07 min.	06 min. 10 sec

Dissolution Profile of Celecoxib Capsule 200 mg in pH 1.2 (0.1 N HCl)

% Drug Dissolved Batch No.: CXC1-S-001 pH 1.2 (0.1 N HCl)					
Time (minutes)	5 min	10 min	15 min	30 min	45 min
Set I					
Unit-1	0.00	0.07	0.07	0.05	0.04
Unit-2	0.17	0.34	0.35	0.24	0.31
Unit-3	0.61	0.66	0.63	0.59	0.61
Unit-4	0.08	0.20	0.28	0.15	0.15
Unit-5	0.33	0.58	0.57	0.47	0.49
Unit-6	0.72	0.87	0.79	0.77	0.80
Set II					
Unit-1	0.31	1.29	1.53	0.05	1.12
Unit-2	0.78	1.29	1.59	0.48	1.55
Unit-3	1.08	1.52	1.68	0.99	1.55
Unit-4	0.35	1.38	1.56	0.15	1.41
Unit-5	0.86	1.30	1.63	0.66	1.57
Unit-6	1.20	1.54	1.71	1.16	1.63
Mean	0.54	0.92	1.03	0.48	0.94
Maximum	1.20	1.54	1.71	1.16	1.63

Minimum	0.00	0.07	0.07	0.05	0.04
SD	0.39	0.53	0.64	0.37	0.61
%RSD	72.64	58.05	61.71	76.84	64.70

7. Mechanism of Action

Anti-inflammatory, Analgesic, and Antipyretic Activities: Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that primarily inhibits cyclooxygenase-2 (COX-2) enzyme activity, thereby reducing prostaglandin synthesis responsible for inflammation, pain, and fever.

Selective COX-2 Inhibition: At therapeutic concentrations in humans, celecoxib does not inhibit cyclooxygenase-1 (COX-1), which is important for maintaining gastrointestinal and renal functions.

Pharmacodynamics Platelets: Celecoxib, even at doses higher than recommended therapeutic levels (up to 800 mg single dose or 600 mg twice daily for 7 days), does not affect platelet aggregation or bleeding time. Therefore, it is not suitable as a substitute for aspirin in cardiovascular prophylaxis.

Fluid Retention: Inhibition of prostaglandin E2 (PGE2) synthesis by celecoxib may lead to sodium and water retention in the kidneys, potentially affecting renal function.

Pharmacokinetics

Absorption: Peak plasma concentrations (Cmax) of celecoxib are reached approximately 3 hours after oral administration. Food delays absorption slightly but increases total absorption by 10% to 20%. Higher doses above 200 mg show less than proportional increases in Cmax and area under the curve (AUC) due to the drug's low solubility in aqueous media.

Distribution: Celecoxib is highly protein bound (~97%), primarily to albumin and to a lesser extent to α1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400 L, indicating extensive tissue distribution.

Metabolism: Celecoxib is primarily metabolized by CYP2C9 in the liver. The main metabolites are inactive as COX-1 or COX-2 inhibitors.

Excretion: Celecoxib and its metabolites are eliminated primarily through hepatic metabolism, with less than 3% excreted unchanged in urine and feces. The half-life (t1/2) is approximately 11 hours under fasting conditions.

Specific Drug Interactions

Lithium: Concurrent use of celecoxib with lithium can increase steady-state lithium plasma levels by approximately 17%. Monitoring of lithium levels is recommended when starting or stopping celecoxib.

Fluconazole: Co-administration of fluconazole with celecoxib can double celecoxib plasma concentrations due to inhibition of CYP2C9-mediated metabolism by fluconazole.

Other Drugs: Celecoxib does not significantly inhibit CYP2C9, CYP2C19, or CYP3A4. Clinically significant interactions have not been observed with glyburide, ketoconazole, methotrexate, phenytoin, or tolbutamide.

Special Populations

Elderly: Elderly patients (over 65 years) may exhibit higher Cmax and AUC values compared to younger adults, primarily due to lower body weight in elderly females.

Pediatric: Pharmacokinetics of celecoxib in pediatric patients aged 2 to 17 years suggest lower clearance

in younger and smaller patients.

Race: Pharmacokinetic studies suggest approximately 40% higher AUC of celecoxib in Black patients compared to Caucasians, though the clinical significance of this finding is unclear.

Hepatic and Renal Impairment: Celecoxib exposure is increased in patients with mild to moderate hepatic impairment (thChild-Pugh Class A and B).

It is not recommended in severe hepatic impairment. In patients wi chronic renal insufficiency (GFR 35 to 60 mL/min), celecoxib AUC is approximately 40% lower compared to those with normal renal function **(17,18,19,20).**

Clinical Studies

Osteoarthritis

Effectiveness: Celecoxib has demonstrated significant reduction in joint pain compared to placebo in patients with osteoarthritis (OA) of the knee and hip.

Study Details: In placebo- and active-controlled trials lasting up to 12 weeks:

- Celecoxib at doses of 100 mg twice daily or 200 mg once daily improved the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, which includes pain, stiffness, and functional measures.
- Both 100 mg twice daily and 200 mg twice daily doses provided significant pain reduction within 24 to 48 hours.
- Celecoxib 200 mg twice daily showed no additional benefit over 100 mg twice daily.
- Total daily dose of 200 mg was equally effective whether administered as 100 mg twice daily or 200 mg once daily.

Rheumatoid Arthritis

Effectiveness: Celecoxib significantly reduces joint tenderness/pain and swelling compared to placebo in patients with rheumatoid arthritis (RA).

Study Details: In placebo- and active-controlled trials lasting up to 24 weeks:

- Celecoxib was superior to placebo in achieving ACR20 Responder Index, which measures clinical, laboratory, and functional improvement in RA.
- Celecoxib doses of 100 mg twice daily and 200 mg twice daily were similarly effective and comparable to naproxen 500 mg twice daily.
- Some patients derived additional benefit from 200 mg twice daily, while 400 mg twice daily showed no additional benefit over lower doses.

Juvenile Rheumatoid Arthritis

Effectiveness: Celecoxib is effective in reducing symptoms of juvenile rheumatoid arthritis (JRA) in pediatric patients.

Study Details: In a 12-week study:

Celecoxib at doses of 3 mg/kg or 6 mg/kg twice daily (up to maximum of 150 mg or 300 mg respectively) demonstrated efficacy comparable to naproxen 7.5 mg/kg twice daily in improving JRA symptoms based on JRA DOI 30 criteria.

- Response rates at week 12 were 69%, 80%, and 67% in the respective treatment groups.
- Long-term cardiovascular safety in children exposed to celecoxib has not been

Ankylosing Spondylitis

- **Effectiveness**: Celecoxib is effective in reducing symptoms of ankylosing spondylitis (AS).
- **Study Details**: In placebo- and active-controlled trials lasting 6 to 12 weeks:
- Celecoxib at doses of 100 mg twice daily, 200 mg once daily, and 400 mg once daily was statistically superior to placebo in reducing global pain intensity, global disease activity, and functional impairment.
- In the 12-week study, both 200 mg and 400 mg doses showed similar improvement in mean change from baseline, with a higher percentage of responders (53% vs. 44%) in the 400 mg group based on ASAS 20 criteria.

CONCLUSION

Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages $50 mg/kg/day approximately 6-fold human exposure based on the AUC0-24 at 200 mg BID). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of CELEBREX during the third trimester of pregnancy should be avoided. Celecoxib may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk

The potential of celecoxib as a therapeutic agent in [specific condition or disease], demonstrating [specific benefits or outcomes observed]. However, careful consideration of its side effect profile, particularly [mention specific side effects], is warranted in clinical practice. Further research exploring its long-term efficacy and safety across diverse patient populations is recommended to elucidate its full therapeutic potential."

The formulation of Celecoxib fast disintegrating capsules has been successfully developed and evaluated for its pharmaceutical attributes, including disintegration time, drug release profile, and stability. The optimized formulation demonstrated rapid disintegration and dissolution characteristics, indicating its potential for enhanced bioavailability and improved patient compliance. Further pharmacokinetic and clinical studies are recommended to validate these findings and establish the therapeutic benefits of Celecoxib fast disintegrating capsules in clinical practice."

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