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Formulation, Development and Evaluation of Bilayer Tablet containing Naproxen Sodiun and Domperidone for Migraine

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Abstract

Migraine is a complex neurological disorder characterized by recurrent attacks of intense headache, often accompanied by nausea, vomiting, photophobia, and phonophobia. It is ranked among the top causes of years lived with disability worldwide, severely affecting the quality of life and work productivity. Current treatment strategies usually involve the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management, along with antiemetics to counteract nausea and improve drug absorption. However, when administered separately, these medications may lead to poor patient compliance and delayed therapeutic outcomes.

Naproxen sodium, a potent NSAID, is effective in relieving migraine-associated pain and inflammation, while Domperidone, a dopamine antagonist, helps in controlling nausea and enhancing gastric motility, thereby improving drug bioavailability. A bilayer tablet combining these two drugs presents a novel and patient-friendly approach, enabling simultaneous management of pain and associated gastrointestinal symptoms in a single dosage form.

The development of such a bilayer formulation requires careful consideration of physicochemical compatibility, layer separation, and uniformity. To ensure the effectiveness and reliability of the final product, various quality control (QC) tests— such as hardness, friability, weight variation, disintegration, and dissolution studies— are essential. In addition, batch formulation evaluations help in optimizing parameters like compressibility, flow properties, and stability, ensuring consistent therapeutic performance

Thus, the present study focuses on the formulation development and evaluation of a bilayer tablet containing Naproxen sodium and Domperidone for the effective management of migraine, with an emphasis on ensuring quality, safety, and patient compliance

Introduction

- WHAT IS MIGRAINE ?

Migraine is a complex neurological disorder characterized by episodes of moderate- to-severe headache, most often unilateral

and generally associated with nausea, and light and sound sensitivity.

- SIGN AND SYMPTOMS:

Headache: Moderate to severe, often on one side. Aura (in some cases): Visual changes, or speech issues.

Sensitivity: To light, sound, and sometimes odors.

Nausea/Vomiting: Common during attacks. Other Phases: Fatigue, mood changes. [1]

• CAUSES:

Neurovascular Mechanisms Cortical Spreading Depression Genetics (family history) Stress (emotional or physical)

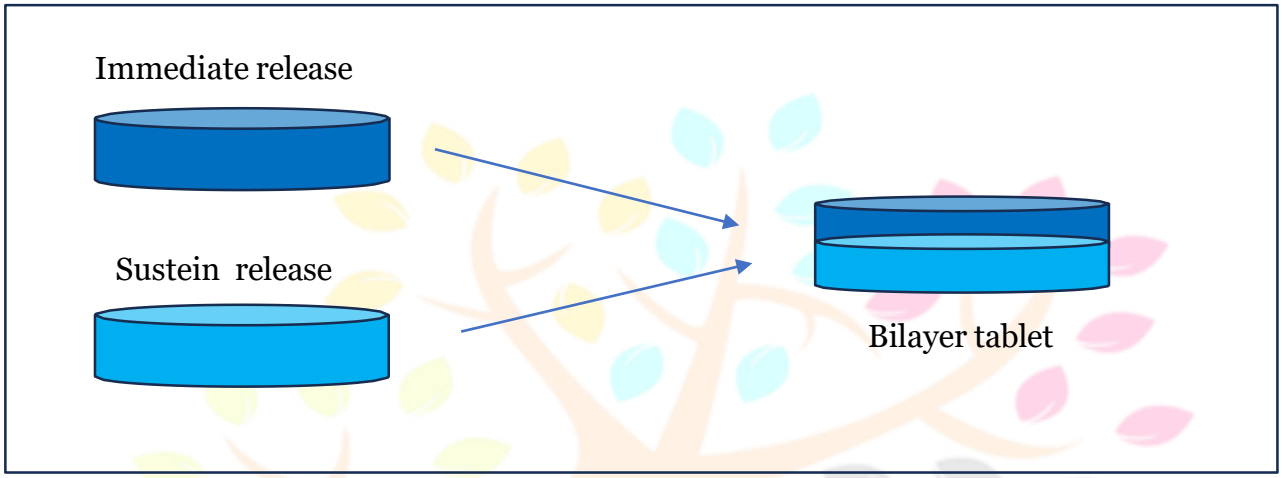
Dietary Factors (certain foods or drinks)

Bright Lights/Loud Noises (photophobia or phonophobia)

• Bilayer Tablet:

A bilayer tablet is a type of pharmaceutical tablet designed to deliver two distinct medications or provide a combination of

and immediate and controlled release of active ingredients in a single dosage form.



• PURPOSE :

Combination Therapy: To deliver two APIs that work synergistically or target different symptoms.

Controlled Release: To achieve immediate + sustained release of the same drug. Avoid Drug Interactions: Separate incompatible drugs into different layers.

Improved Patient Compliance.

• OBJECTIVE:

To deliver multiple drugs in a single tablet.

To combine a fast-release layer and a controlled release layer.

To reduce the frequency of drug.

Easier for patients to take one tablet instead of multiple ones. Helps in chronic conditions requiring combination therapy.

• ADVANTAGES:

Optimized Drug Action: Immediate effect followed by prolonged therapeutic levels. Reduced Side Effects: Stable drug levels reduce peak-trough fluctuations.

Versatility: Can deliver two APIs with different solubility or stability profiles.

• IMMEDIATE RELEASE :

It is dosage form of medication design to disintegrate and release its active ingredient quickly after oral administration.

➢ The first layer of the bilayer tablet is designed to dissolve rapidly in the digestive system, allowing for fast absorption.

➢ Useful for conditions requiring instant effects (e.g., pain relief)

Mode of Action of Naproxen Sodium

Migraine Trigger

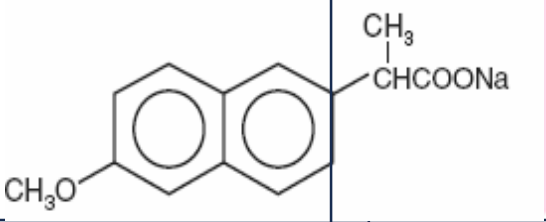
- CONVENTIONAL RELEASE :

Conventional release refers to the standard method of drug delivery from a tablet, where the drug becomes available in the body shortly after the tablet breaks apart and dissolves in the gastrointestinal fluids. There is no special mechanism to delay or control the rate, time, or site of drug release.

- Drug is absorbed based on its natural solubility and permeability.
- No special coatings or polymers to modify release behavior.

- **WHY NAPROXEN SODIUM ?**

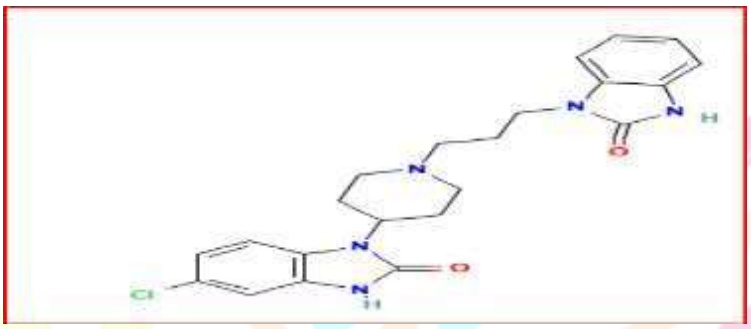
Parameter	-	Reason
Class	-	NSAID (Non-Steroidal Anti-Inflammatory Drug)
Action	-	Naproxen sodium works by reversibly inhibiting both the COX-1 and COX-2 enzymes as a non-selective cox inhibitor.
Onset	-	Rapid
Advantage	-	Controls headache, inflammation, and sensitivity in migraines



- **WHY DOMPERIDONE ?**

Mode of Action of Domperidone

Parameter	-	Reason
Class	-	Dopamine D2 receptor antagonist
Action	-	Blocks dopamine D2 receptor in the chemoreceptor trigger zone (CTZ)
Onset	-	Fast acting
Advantage	-	Stops nausea & vomiting common in migraine Enhances gastric motility, improves drug absorption



Migraine Trigger

Migraine-Associated Nausea and Vomiting

Activation of Chemoreceptor Trigger Zone (CTZ) in Brainstem

↑ Dopamine (D_2) Receptor Activity in CTZ

Stimulation of Vomiting Reflex

Domperidone Administration

Blocks Peripheral and Central D_2 Receptors

↓ Dopaminergic Activity in CTZ

Inhibition of Nausea and Vomiting Reflex

Material and Methods

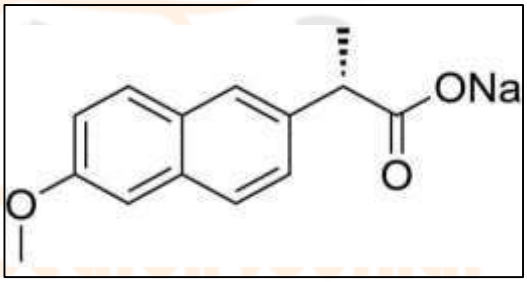
• Drug profile :-

Naproxen sodium:-

Parameter	**Details**
IUPAC NAME	6-chloro-3-[1-[3-(2-oxo-3*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1*H*-benzimidazol-2-one
Molecular Formula	$C_{22}H_{24}ClN_5O_2$
Molecular Weight	425.9 g/mol
Odour	Typically has no noticeable odor
Melting Point	242.5 °C
Dosage	Adults- 10 mg, 3 times daily (before meals)

• **Pharmacokinetic**

1. Absorption: Well absorbed orally
2. Onset of action: 1–2 hours
3. Half-life: 12–17 hours
4. Metabolism: Hepatic Phase I and Phase II
5. Excretion: Urine



• **Advers effect**

1. Dizziness
2. Drowsiness
3. Gastrointestinal upset.

• **Contraindications:**

1. Peptic ulcer
2. Severe renal or hepatic impairment
3. Hypersensitivity to NSAIDs
4. Pregnancy (especially 3rd trimester)

• **Domperidom** :-

Parameter	**Details**
IUPAC NAME	6-chloro-3-[1-[3-(2-oxo-3*H*- benzimidazol-1-yl)propyl]piperidin-4-yl]-1*H*- benzimidazol-2-one
Molecular Formula	$C_{22}H_{24}ClN_5O_2$
Molecular Weight	425.9 g/mol
Odour	Typically has no noticeable odor
Melting Point	242.5 °C
Category	Antiemetics; Dopamine Antagonists
Dosage	Adults- 10 mg, 3 times daily (before meals)

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• **Adverse Effects:**

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2. Drowsiness
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1. Peptic ulcer
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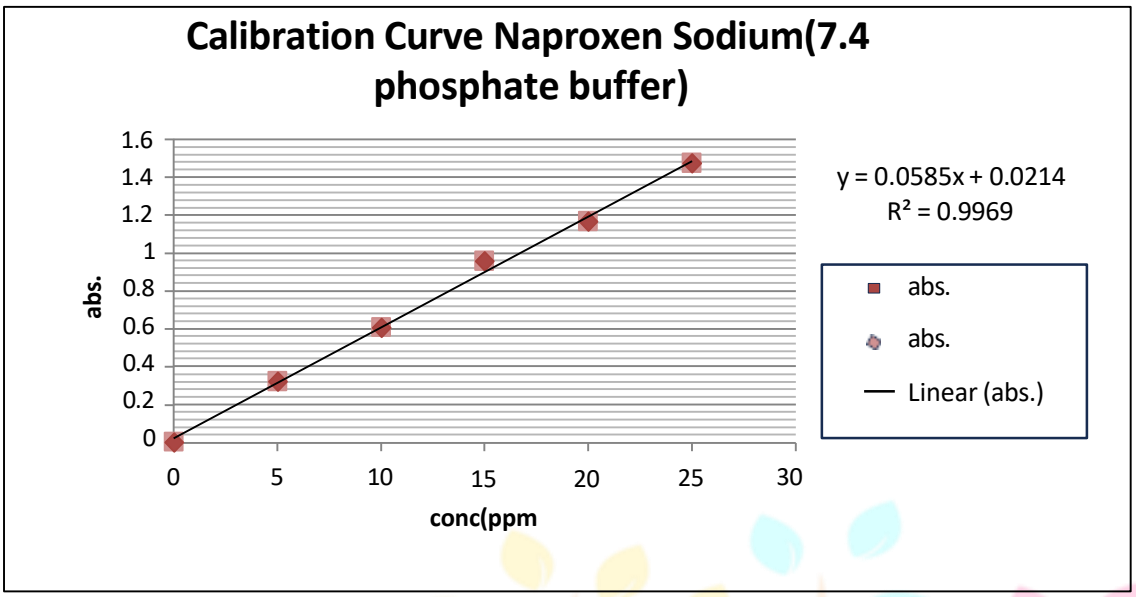
PRE-FORMULATION EVALUATION

Properties	**A.Naproxen sodium**	**B.Domperidom**
1.Appearance	White crystalline powder	White Crystalline powder
2.Solubility	Soluble in ethanol and phosphate buffer	Soluble in Dimethyl Formamide, Phosphate buffer
3. Melting point	254.5 °C	242.5 °C

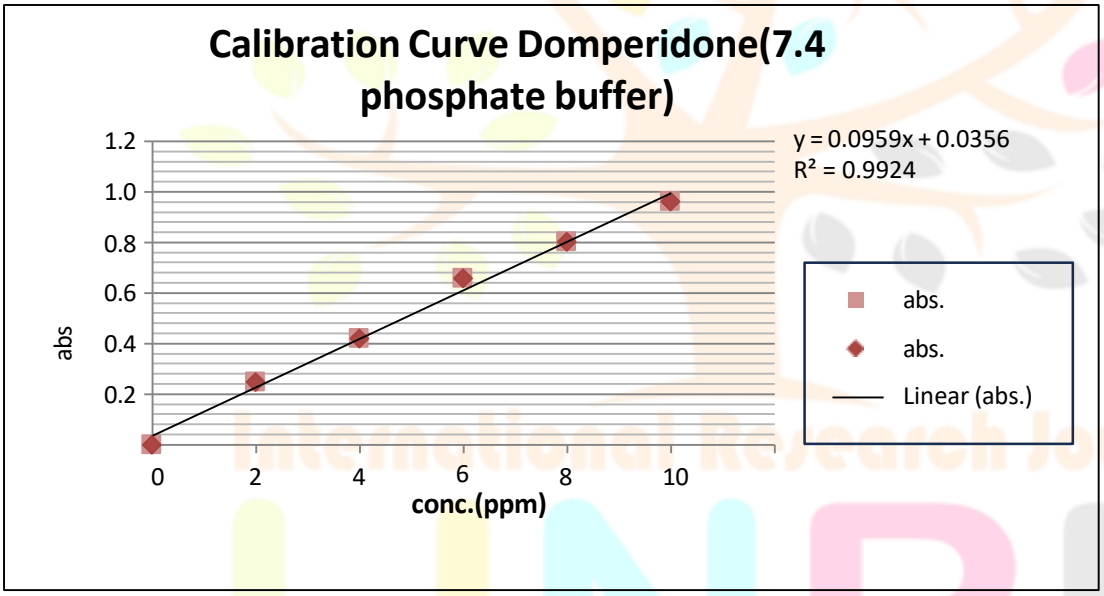
c. Powder blend :-

Properties	**Details**
1. Bulk Density	0.385 g/ml
2. Tapped Density	0.417 g/ml
3. Angle of Repose	44.4^0
4. Hausner Ratio	1.08
5. Carrs Index	7.66

D. Calibration Curve of Naproxen Sodium :-



E. Calibration Curve of Domperidone :-



API :-

1. **Naproxen Sodium** - Controls headache and sensitivity in migraine.
2. **Domperidone** - Stops nausea & vomiting.

Excipients	**Examples**	**Use**
Diluents	Lactose, MCC	Increases volume
Binders	PVP, Starch	Promote granule formation
Super Disintegrants	SSG, Croscarmellose	Immediate disintegratin
Lubricants	Magnesium stearate	Reduce friction

Glidants	Talc	Improve flow
Colorants	Sunset yellow 6	Appearance identification

FORMULATION APPARATUS :-

Process	**Apparatus**
Weighing	Digital weighing balance
Blending	Double Cone Blender
Screening	Sieve
Compression	Tablet punching machine

Fig .-Digital Weghing Balance

TABLET PUNCHING MACHINE –

Key Components:

- **Hopper** – Holds granulated material
- **Die & Punches** – Shapes and compresses the tablet

Fig .- Tablet punching machine

Evoluation appartus

Fig.- Vernier capillary **Fig.- Pfizer Hardness Tester**

Fig.- Friability Test Appartus **Fig.- Disintegration Appartus**

Result and Evoluation

BATCH	WEIGHT VARIATION (Avg. Wt.)	AVERAGE THICKNESS	AVG. HARDNESS	FRIABILIT Y Loss of drug in %
F1	530 ±1.73	3.401	3.75	0.23%
F2	523 ±0.38	3.328	3.6	0.34%
F3	516 ±0.96	3.323	3.52	0.65%

F4	509 ±2.30	3.33	3.73	0.27%
F5	518 ±0.58	3.271	3.62	0.35%
F6	527 ±1.15	3.296	3.55	0.68%

CONCLUSION

The present study focused on the formulation and evaluation of a Bilayer tablet containing both Naproxen Sodium and Domperidone in each of its layers as an immediate-release layer and a conventional- release layer.

Among the formulated batches, **Batch F2** demonstrated the most favourable dissolution profile, successfully releasing 50 mg of drug within 10 minutes. **Batch F1**, containing 5% superdisintegrant, showed slower drug release due to insufficient disintegration, while **Batch F3,** with 10% superdisintegrant, released the drug more rapidly but may compromise tablet integrity or stability.

Therefore, **Batch F2**, with an optimal concentration of superdisintegrant, achieved balanced and efficient drug release, making it the most suitable formulation for further development.

Initially in migraine attack dose requirement is high and thus our formulation fulfil the requirement by delivering 50mg of drug within 10 minutes.

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last but not least we thanks our colleges staff , the project team who worked hard with dedication, efforts and teamwork that lead to the fulfil knowledgeable scientific research work .

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