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REVIEW ARTICLE ON THE DIFFERENT ANALYTICAL TECHNIQUES FOR THE DOMPERIDONE AND NAPROXEN DOSAGE FORM

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ABSTRACT

NSAIDs, or nonsteroidal anti-inflammatory drugs, include naproxen and domperidone. Naproxen is sold separately from other comparable anti-inflammatory medications. In order to determine compositions, analytical techniques are essential because they enable the use of sophisticated analytical equipment to produce results that are both qualitative and quantitative. These include of capillary electrophoresis, UV spectrophotometry, HPLC, HPTLC, and electrochemical methods. The analysis of naproxen in biological media, bulk samples, and different dosage formulations is done using the UV spectrophotometry method. the Naproxen HPLC method used alone and in combination, which takes into account variables like matrix, stationary phase, mobile phase, wavelength detection, etc. parameters of the HPTLC technique, including the RF value, mobile combination phase, and stationary phase. Analytical technique development is required to meet regulatory requirements and maintain high standards for commercial product quality.

Keywords: Naproxen, Domperidone, Analytical Methods.

I. INTRODUCTION

Domperidone:

Domperidone is a dopamine antagonist medicine that's retailed under several trade names, including Motilium. It's used to treat nausea, puking, and gastrointestinal issues similar gastroparesis, or delayed gastric evacuating. It's used off- marker to stimulate and support the product of bone milk by adding prolactin situations in the mortal body.[1][2] It can be ingested orally or intrarectally.[2][3][4]

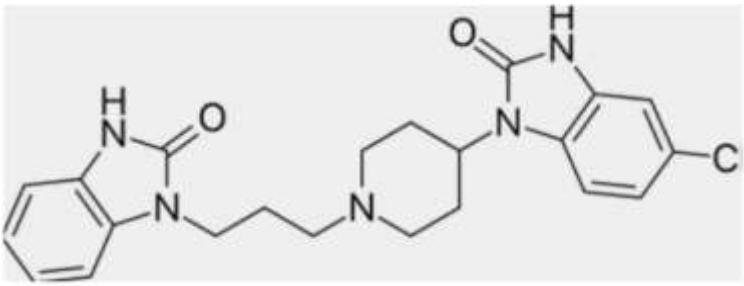

Fig 1:

Headache, anxiety, diarrhoea, cramping in the abdomen, dry mouth, and increased prolactin levels are possible side effects.[5][1][2][6] Hypogonadism, irregular menstruation, breast alterations, and milk outflow can all be secondary to elevated prolactin levels.[1][2][6] In addition to its potential to induce QT prolongation, dopamine has infrequently been linked to major cardiac side effects such sudden cardiac death.[7][8][9][10] On the other hand, the hazards are minimal and increase with high dosages.[10][11] As a peripherally selective antagonist, domperidone blocks the D2 and D3 dopamine receptors.[1][2] Domperidone has different side effects from other dopamine receptor antagonists, such as metoclopramide, because of its modest brain entrance, and it has minimal negative effects on the central nervous system.[1][2] Domperidone can nevertheless raise prolactin levels despite the pituitary gland's external location.

PHARMACOLOGY:

Depending on whether domperidone is administered intramuscularly (IM) or orally (OR), different times are needed for it to reach peak plasma levels. Peak levels are typically attained 1-2 hours after rectal suppository administration. After intramuscular therapy, bioavailability is high (90%) but significantly decreased (13–17%)

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following oral delivery. (McCallum, 1985) Antacids raise the pH of the stomach, which greatly reduces the bioavailability of oral domperidone. After oral treatment, 32% of the medicine is removed in the urine. Domperidone is not cholinergic and is not blocked by atropine, which sets it apart from other prokinetic medications. Champion et al., 1986; Reynolds, 1989; and the National Library of Medicine, 2021.[13]

MECHANISM OF ACTION:

Domperidone exhibits gastroprokinetic action because it blocks the peripheral dopamine receptor. To aid in gastric emptying, dopamine augments antroduodenal coordination and gastric peristalsis. Domperidone's ability to block dopamine (D2) receptors at the chemoreceptor trigger zone (CTZ) accounts for its anti-emetic effects. It is not able to pass through the blood-brain barrier to be given in conjunction with levodopa. When used in conjunction with morphine or pethidine prophylactically, the anti-emetic properties of domperidone are short-lived, suggesting that it is ineffective as a preventive measure against opiate-induced emesis. (1979, Wilson & Dundee).[13]

PHARMACOKINETICS

- **Absorption of Domperidone:**

Domperidone is absorbed orally, reaching peak serum levels in thirty minutes; nevertheless, its bioavailability is limited to fifteen percent because of first-pass metabolism. The plasma half-life, or T1/2, is seven hours. (DRUGBANK, 2021).[14]

- **Distribution of Domperidone:**

Domperidone has a 91 – 93 list rate to tube protein. The medicine is extensively dispersed throughout the body, as indicated by the distribution volume of 5.71 L/ Kg. Following systemic remedy, domperidone accumulates in fairly large quantities outside the blood- brain hedge and in lower quantities in the striatum and other corridor of the brain.(Laduron & Leysen, 1978; Costallet al., 1979; Laduron & Leysen, 1979).[14]

- **Metabolism of Domperidone:**

Products of dopamine metabolism are eliminated in the urine and faeces. Following oral administration, 66% of the drug is found in the stools, and in healthy individuals, the elimination half-life is about 7.5 hours. In 1986, Champion et al. In patients with severe renal impairment, the elimination half-life can last up to 20 hours. (Heykant and others, 1981). [14]

Table 1:

Absorption of drug when administered orally	**93%**
Volume of distribution	5.71 L/kg
Binding with plasma protein	91-93%
Maximum serum concentration (Cmax)	18.8 ng/ml
Tmax	30 min
Pre systemic metabolism	83-87%
Pka	**7.9**

NAPROXEN:

Naproxen is a nonsteroidal anti-inflammatory medicine (NSAID) that is marketed under several brand names, including Aleve. It is used to treat fever, gout, rheumatoid arthritis, and pain as well as menstrual cramps. It is consumed orally [15] Both formulations with immediate and delayed release are offered.[15] The effects might continue up to twelve hours after they start.[15] Dizziness, headaches, bruises, allergic reactions, heartburn, and stomach discomfort are typical adverse effects.[15] An increased risk of heart disease, stroke, gastrointestinal bleeding, and stomach ulcers are among the severe adverse effects.[15] Compared to other NSAIDs, there could be a decreased risk of heart disease. It is not advised for those who have renal issues. In the third trimester of pregnancy, use is not advised.[15]

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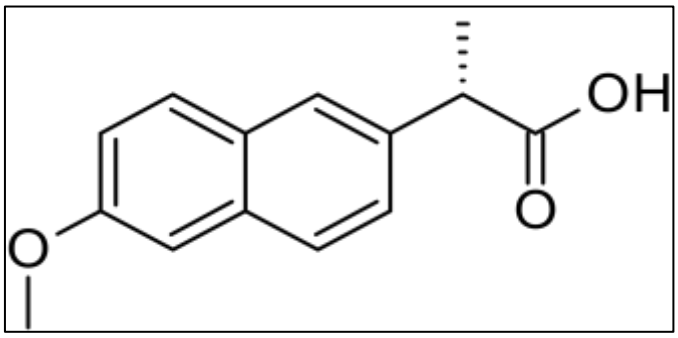

Fig 2:

MECHANISM OF ACTION:

Naproxen's primary system of action is to reversibly bind to cyclooxygenase, thus inhibiting prostaglandin conflation. This enzyme is the first in the waterfall of arachidonic acid that leads to prostaglandin product. Naproxen influences pain, inflammation, fever, uterine contractility, platelet aggregation, and vasoactivity — all of which are intermediated by prostaglandins and associated thromboxanes and prostacyclin — by reducing the quantities of these ubiquitous chemicals. It seems that allnon-steroidalanti-inflammatory medicine compositions work by gumming the waterfall's cyclooxygenase step.[16]

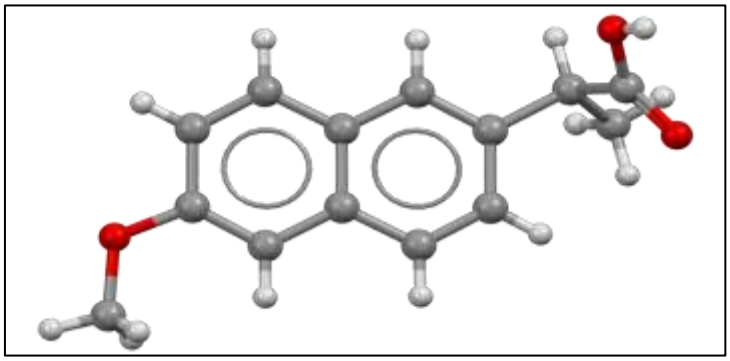

Fig 3:

Pharmacokinetic data:

- **Bioavailability:**
- Naproxen has a 95% in vivo bioavailability and is one of the drugs that is created entirely and quickly in the GI tract. While naproxen absorbs well on its own, the sodium salt form absorbs more quickly, increasing the maximum plasma concentration at the prescribed dosage. Food somewhat lowers the rate of absorption.
- **Protein binding:**

Naproxen at therapeutic dosages is >99% albumin-bound.

- **Metabolism:**

Enzyme metabolisers are not caused by naproxen, parents, or metabolites. A common metabolism of naproxen is 6-0-desmethyl.

- **Half-life:**

About fifteen hours is the practically observed elimination of half-life.

- **Excretion:**

Naproxen clearance of 0.13 mL/kg. Nearly 95% of all Naproxen doses are eliminated in the urine, primarily in the form of less than 4% Naproxen, fewer than 1% 6-0-desmethyl naproxen, or 66%-92% of its conjugates.[17]

ANALYTICAL TECHNIQUE:

A chemical or physical attribute of a chemical substance, chemical element, or combination can be ascertained using an analytical approach.[18] Analysis may be done using a broad range of methods, from straightforward weighing to sophisticated methods with extremely specialised equipment.

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Different analytical techniques involved in the Domperidone and Naproxen:

1. HPLC
2. HPTLC
3. UV spectroscopy

Introduction:

1 High-Performance Liquid Chromatography:

A type of column chromatography called high-performance liquid chromatography, frequently appertained to as high- pressure liquid chromatography, is constantly used in biochemistry and analysis to separate, identify, and quantify active composites. This extensively used logical system may be used to separate, identify, and quantify each element of a admixture. Advanced column liquid chromatography(HPLC) is a sophisticated fashion.[19] In the HPLC procedure, the detergent is forced through the column at pressures as high as 400 atmospheres, contrary to graveness's natural inflow. This allows the sample to be divided into distinct factors according to variations in relative affections. A column filled with quilting material(the stationary phase), a pump that forces the mobile phase(s) through the column, and a sensor that measures the patch retention ages are the standard factors of an HPLC system.[20] The relations between the stationary phase, the motes under study, and the detergent(s) used have an impact on the retention period. Small quantities of the sample to be analysed are introduced to the mobile phase sluice, where they're braked down by certain physical or chemical relations with the stationary phase.[21] The type of the analyte and the makeup of the stationary and mobile phases both affect the quantum of deceleration. The quantum of time it takes for an analyte to elute is known as the retention time.[22] A common detergent is any miscible admixture of organic liquids and water. During the study, the mobile phase composition was altered using grade elution. Analyte fusions are separated by the grade according to the analyte's affinity for the current mobile phase. The choice of slants, complements, and detergents is told by the characteristics of the analyte and the stationary phase.[23]

II. METHOD DEVELOPMENT ON HPLC

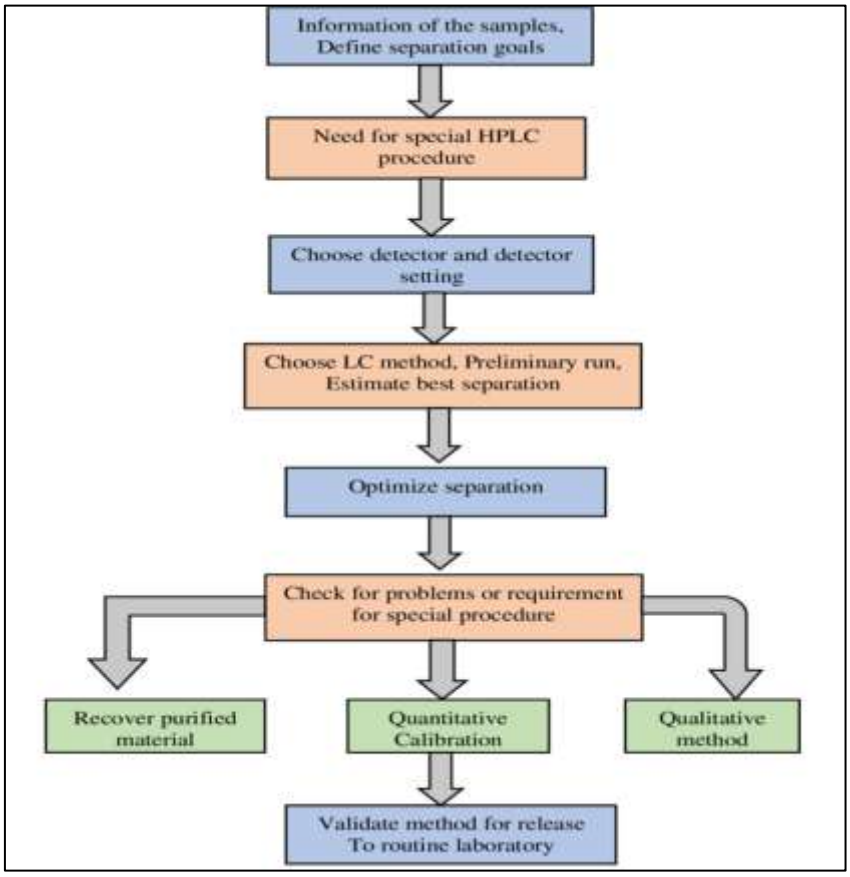

Fig 4: Steps involved in HPLC Method development

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Method development involves the following steps:

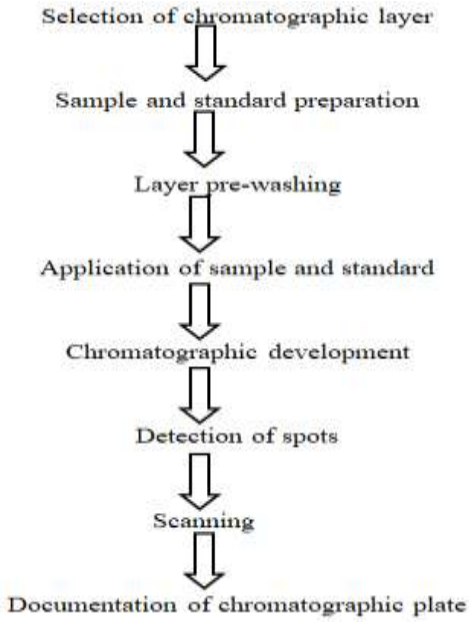
1. Understanding the Physicochemical Properties of The drug molecule.
2. Selection of chromatographic conditions.
3. Developing the approach of analysis
4. Sample preparations
5. Method optimization
6. Method validation [24]

HPTLC:-

The physical principles of HPTLC and TLC (adsorption chromatography) are the same; that is, adsorption serves as the primary unit of separation. The detergent from the mobile phase flows through due to capillary action. The factors move in agreement with their affections with the adsorbent. Moving more sluggishly is the element that's further drawn to the stationary phase. factors with a lower affinity for the stationary phase move briskly. This leads to the factors being separated using a chromatographic plate.

COMMON METHODOLOGY FOR HPTLC:

An essential phase in both qualitative and quantitative analysis in thin-layer (planar) chromatography is technique development. A comprehensive examination of the literature is always the first stage in creating a novel analytical procedure is to give pertinent information on the nature and physicochemical characteristics of the sample (structure, polarity, volatility, stability, and solubility). There are several steps of trial and error involved. The general stages needed to construct an HPTLC approach are as follows:



SELECTION OF THE STATIONARY PHASE:

The kind of chemicals to be separated should guide stationary phase selections during technique development [22, 23]. Smaller plates (10*10 or 10*20 cm) are used in HPTLC, and the analysis duration (7–20 min) and development distance (usually 6 cm) are greatly reduced. HPTLC plates are employed in industrial pharmaceutical densitometric quantitative analysis because they offer better resolution, greater detection sensitivity, and superior in situ quantification.

MOBILE PHASE SELECTION AND OPTIMIZATION:

The analyte's physical and chemical characteristics, as well as the adsorbent material utilised as the stationary phase, are taken into consideration while choosing the mobile phase.

SAMPLE PREPARATION AND APPLICATION:

All of the Mixture's components are moved off the baseline by a competent solvent system, but nothing is added on the solvent front. Resolution of the interest peaks should occur between Rf 0.15 and 0.85. The eluent

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strength, which is correlated with the polarity of the mobile phase components, determines the mobile phase's elution power. Compounds exhibiting more nonpolarity will elute more quickly, spending less time in the stationary phase; conversely, compounds exhibiting greater polarity will elute more slowly, spending more time in the stationary phase. The sequence of elution can be predicted using the following chart. In order to create a test solution that can be placed straight onto an HPTLC plate, pharmaceutical preparation with a suitably high analyte concentration is simply dissolved in a suitable solvent that will completely solubilise the analyte and leave the excipients undissolved. It is a known fact that applying the sample is the most important step in getting a decent resolution for HPTLC quantitation. The kind of sample matrix, workload, and time limitations are some of the variables that affect sample application strategy.

CHROMATOGRAM DEVELOPMENT (SEPARATION):

Significant factors are constantly disregarded, despite the fact that chromatogram conformation is the most significant phase in the HTLC process[32]. Binary- trough chambers or vertical development chambers are used to induce HPTLC plates. The stylish reproducibility is frequently handed by impregnated binary- trough chambers with sludge paper installed. Binary- through chambers help moisture and solvent vapour preloading.

DETECTION:

Quenching of luminescence caused by UV radiation (frequently range at 200- 400 nm) improves the discovery of promised chemicals on the spongy layers. The common term for this procedure is luminescence quenching.

VISUALIZATION AT UV 254 NM:-

It's stylish to characterise F254 as phosphorescence quenching. In this case, the luminescence persists for a brief duration following the junking of the excitation source. It lasts longer than ten seconds, although it is n't extremely lengthy. Green luminescence is released by F254 fluorescent pointers when they're agitated by UV light at a wavelength of 254 nm. The emigration on the subcaste is reduced by composites that absorb light at 254 nm, and the emulsion zones are seen as a dark violet spot on a green background.[35] It's substances with conjugated double bonds that beget this quenching. Among the polyphenols set up in essential canvases are anthraglycosides, coumarins, flavonoids, and some alkaloid classes as isoquinoline, indole, and quinoline alkaloids. Ought to be seen at lower than 254 nm.

VISUALIZATION AT UV 366 NM:

It's stylish to characterise F 366 as luminescence quenching. In this case, the junking of the excitation source results in the loss of luminescence. All anthraglycosides, coumarins, flavonoids, phenolcarboxylic acids, and some alkaloid types (Rauwolfia, Ipecacuanha alkaloids) parade this quenching.

VISUALIZATION OF WHITE LIGHT:

By observing the separated chemicals' natural colour in daylight (white light), the zone holding them may be linked.

DERIVATIZATION:

Derivatisation is a procedural approach that substantially modifies the functionality of an analyte in order to grease chromatographic separations. Derivatisation can be done on the plates by scattering them with an applicable reagent or by submerging them. The stylish derivatisation system is absorption because of its bettered repetition.[25]

UV SPECTROSCOPY:

Ultraviolet visible, or UV- Vis, spectroscopy is extensively used to assay and characterise a wide range of accoutrements . UV-Visible spectroscopy may be used to observe inorganic or organic, solid or liquid groups, similar as organic motes and functional groups. It can also be used to assess band gaps, biochemical analysis, and reflectance for coatings, maquillages, fabrics, and dissolution kinetics. The UV- Vis provides these data grounded on the degree of transmittance or immersion of a distinct wavelength of ray light and the varying responses of samples.

PRINCIPLE OF UV:-

VIS SPECTROSCOPY An point will show immersion in the visible or ultraviolet diapason when radiation causes an electronic change in the structure of a patch or an ion. Accordingly, the electronic state of the motes inside a

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sample changes as it absorbs light in the ultraviolet or visible diapason. The energy from the light will elevate electrons from their ground state orbital to an agitated state orbital with a lesser energy. or orbitalanti-bonding. Three different kinds of ground state orbitals might be involved.

1) The molecular bonding Σ

2) The molecular orbital Π (bonding)

3) The atomic orbital of N (bonding).

An n* anti-bonding orbital does not exist as n electrons do not form bonds. Therefore, the absorption of visible and ultraviolet light might result in the following electronic transitions.

1) N to σ*

2) N to σ*

3) N to π*

4) Π to π*

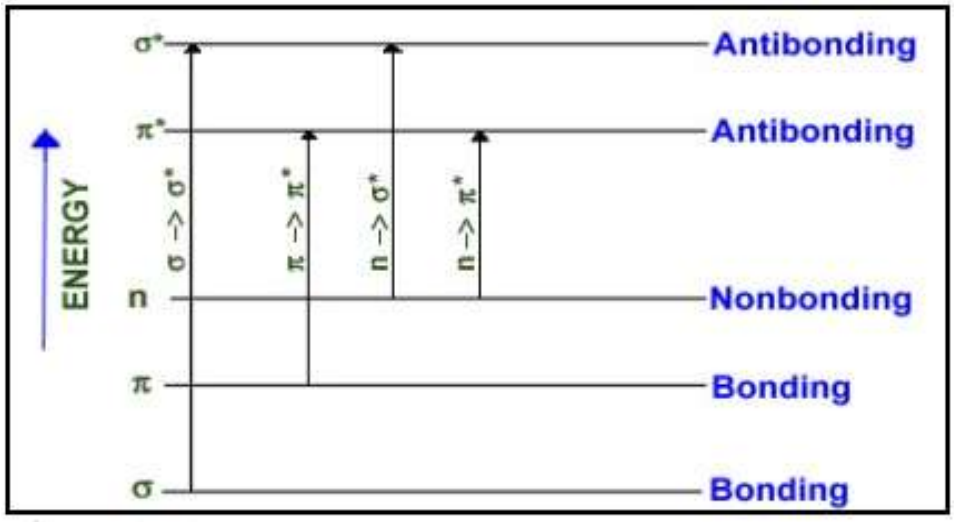

Fig 5: Electron Transition graphically represented.[26]

III. RESULTS

UV SPECTROPHOTOMETR RESULT PARAMETERS OF DOMPERIDONE AND NAPROXEN

Table 2: Validation parameters for NAP and DOM [27]

Validation Parameter	MEAN±SD	
	Naproxen	Domperidone
Linearity Range	10-35 µg/ml	5-30 µg/ml
Correlation coefficient	0.9999	0.9998
Slope	0.0222	0.0292
Intercept	0.0226	0.0149
Interday		
1st day	101%±0·0018626	106±0.000566
2nd day	97%±0·0014136	94±0.000404
3rd day	97%±0·000375	100.7±0.000499
Intraday		
(1st h)	98%±0·001002	94±0.000927
(2nd h)	96%±0·002631	94±0.000432

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(3rd h)	98%±0·000608	94±0.00034
Recovery		
80%	107%±0·00391	98±0.0059
100%	105%±0·00254	96±0.00033
120%	106%±0·00928	99±0.00091
LOD(mg/ml)	0·454 µg/ml	0.657 mg/ml
LOQ(mg/ml)	0·151 µg/ml	2.18 mg/ml
Robustness	106%±0·00389	91±0.000125

HPTLC RESULT PARAMETERS OF DOMPERIDONE AND NAPROXEN

Table 3: Validation Parameter of HPTLC NAP and DOM

	Naproxen			**Domperidone**		
Parameters	Average	SD	%RSD	Average	SD	%RSD
Retention time	5.424	0.004	0.076	3.168	0.001	0.041
Area	1622441.500	376.285	0.023	125978.00	1249.903	0.992
Theoretical plates	8739.667	5.750	0.066	4561.153	18.792	0.412
Tailing factor	1.355	0.015	1.090	1.357	0.004	0.287
Resolution	10.719	0.018	0.168	-	-	-

HPLC METHOD PARAMETERS OF DOMPERIDONE AND NAPROXEN

Table 4: Validation Parameter Of HPLC NAP and DOM [28]

Year	**2011.**		**2023**	
Parameter	NAP	DOM	NAP	DOM
Recovery %	99.39	99.50	99.93	100.23
Precision				
%RSD(Intra Day)	0.054	0.929	0.30	0.58
%RSD(Inter Day)	0.374	0.824	1.76	0.50
Robustness Test				
Flow rate	98.71	98.89		
Column	99.64	99.27		
Potency%	99.98	98.90		

Combination of Domperidone and Naproxen Marketed Formulation

1. NAPROXEN AND DOMPERIDONE TABLETS (GEDUNAP-D)

Tablets containing Naproxen and Domperidone are marketed under the Gedunap-D name. This combination of two pharmaceuticals is classified as a "analgesic." It aids in the treatment of migraines. In addition, gout, dysmenorrhea (pain during menstruation), and rheumatoid arthritis are treated with tablets of naproxen and domperidone. A severe ailment known as migraine is typified by abrupt headaches. Pian is the symptom that arises from a number of underlying issues.

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Fig 6: Gedunap-D [29]

2. NAPRA D 250 TABLET

Napra D 250 Tablets can be administered either by themselves or in addition to other medications. You can take it with or without meals. The severity of your illness and how well it relieves your symptoms will determine the dosage and length of time. Use it consistently, and wait to stop using it until your doctor gives the all-clear.

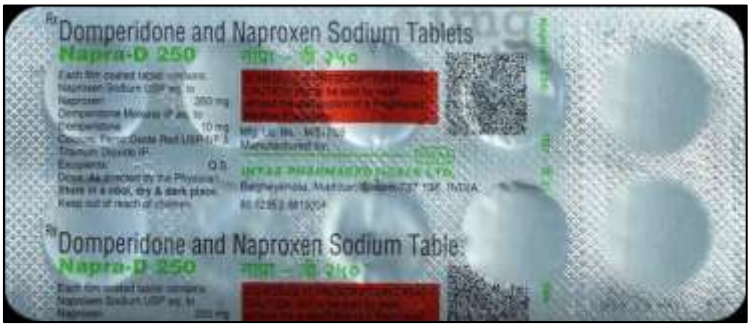

Fig 7: Napra-D 250 [30]

3. MACPROX DP 500 TABLET

Mitigation of migraines. It prevents several chemical messengers that are responsible for fever, inflammation, and pain from being released. Additionally, it inhibits the brain processes responsible for migraine-related nausea and vomiting.

Fig 8: MACPROX DP 500[31]

4. NAPRODOM 500MG TABLET

A combination of two medications called Naprodom 500mg Tablet is used to prevent migraines. It prevents several chemical messengers that are responsible for fever, inflammation, and pain from being released. Additionally, it inhibits the brain processes responsible for migraine-related nausea and vomiting.

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Fig 9: NAPRODOM 500 MG TABLETS [32]

5. PACINAC NP 250MG/10MG TABLET

A combination of two medications called Pacinac NP 250mg/10mg Tablet is used to prevent migraines. It prevents several chemical messengers that are responsible for fever, inflammation, and pain from being released. Additionally, it inhibits the brain processes responsible for migraine-related nausea and vomiting.

IV. CONCLUSION

According to review articles published on naproxen and domperidone, various analytical methods such as HCLC, HPTLC, and UV Spectroscopy are available; however, LC-MS (liquid chromatography mass spectroscopy) and GC-MS (gas chromatography mass chromatography) are not. Therefore, future research on the analytic study of naproxen and doperidone using LC-MS & GC-MS can be conducted.

V. REFFERANCE

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