ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 2, 2022

Pharmacological Review of Domperidone

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ABSTRACT:

Domperidone is an antagonist works on dopamine receptor and act as antinauseant and antiemetic. Chemically it is 5-chloro-1-[1-(2,3-dihydro-2-oxo-1H-benzimidazole-1-yl)propyl)-4-piperidyl]-2,3-dihydro-1H-benzimidazol-2-one1.Domperidone belongs to BCS Class-II drugs having poor water solubility and higher permeability. Commonly, the average dose of domperidone is 10 mg/day. It is an anti-sickness drug used to provide relief in vomiting and nausea as well as to avoid the feeling of sickness. It can be used as a drug of choice for stomach pain treatment if palliative care is not available. The most frequent side effect of this drug is dry mouth that's why it is recommended to be used for short period therapy but this side effect is usually varies from patient to patient like 1 in 100 people. This drug is not usually prescribed for the patients having GIT hemorrhage, perforation diseases and mechanical obstruction. In this review paper, the physicochemical, pharmacological and pharmaceutical characteristics of domperidone drug have been discussed in elaborative way along with various attempts performed by the formulation scientists to improve its pharmaceutical properties like solubility and dissolution behavior.

INTRODUCTION:

Domperidona and Domperidonum are the synonyms used for the Domperidone. Domperidone (DOM) is a dopamine D2 antagonist with a low water solubility. Through its effects on the motor function of the stomach and small intestine, as well as the chemoreceptor trigger zone, it serves as an prokinetic and antiemetic agent. It has a very good safety profile for long-term oral administration in the prescribed doses. (Reddymasu et al., 2007). It has very little penetration through the blood-brain barrier, thus it doesn't create any negative neurological effects like sedation and dystonia. (Reddymasu et al., 2007; Majekodunmi&Uzoaganobi, 2017). It's a BCS Class II medication that's basic and lipophilic. It has a low oral bioavailability and a high rate of first-pass metabolism. The drug domperidone induces cardiac arrest when given intravenously. (Osborne et al., 1985 and Chavan et al., 2012)If DOM is to be administered orally, its bioavailability must be improved by increasing its water solubility and overcoming first-pass metabolism. (Reddymasu et al., 2007 and Chavan et al., 2012). The nasal route has long been used to administer medications

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to treat local infections, but it is now becoming recognized as a viable channel for drug administration, particularly with tiny molecular weight polar pharmaceuticals, peptides, and proteins. (Illum, 2003). A highly vascularized, porous epithelial cell layer covers the relatively large absorption region in the nasal cavity, allowing chemicals to enter quickly into the systemic circulation without first passing through metabolism (Fransén*el al.* 2007). Sodium alginate microsphere of domperidone ternary inclusion complex is used intranasally (Kailas K *et al., 2010).*Domperidone microspheres will deliver a consistent and long-lasting therapeutic impact, reducing dose frequency and improving patient compliance. Improved drug utilisation will increase bioavailability, minimise the occurrence or severity of side effects, and allow for more controllable variability in drug degradation and release . The utilisation of isolated chitosan from Mystilis edulis as polymers for formulation of domperidone microspheres employing wet gelation process will be suitable for sustained release distribution of the drug, either alone or in a low ratio with HPMC spectracel 15E (Majekodunmi&Uzoaganobi, 2017).The goal of developing a mucoadesive buccal tablet of domperidone was to avoid first-pass metabolism and increase bioavailability by reducing dosage frequency. Carbopol 934P, Methocel K4M, MethocelE15LV, and chitosan were utilised as mucoadhesive polymers in the formulations. (Balamurugan *et al.*, 2008). Here in this review, a detailed overview of drug domperidone has been discussed including its physicochemical properties, pharmacological effects on various body systems, its interactions and side effects along with various attempts performed by different scientists to improvise its solubility profile time to time.

PHYSICOCHEMICAL PROPERTIES OF DOMPERIDONE:

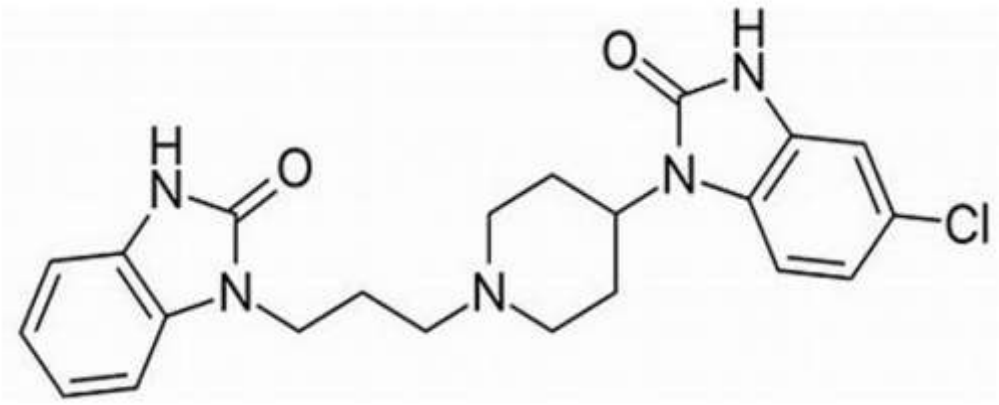

Figure 1: Chemical Structure of Domperidone (Reddymasu et al., 2007)

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Table 1: Physico-Chemical and Pharmacological Properties of Domperidone

(Ibrahim *et al.*, 2011; Tripathi, n.d.)

Chemical Name	"5-chloro-1[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-ylpropyl]piperidin-4yl]-1,3-dihydro-2H-benzimidazol-2-one"
Color	white or almost white
Form	powder
CAS	57808-66-9
Melting point	244°C - 248°C
Molecular Weight	425.9 g/mol
Empirical Formula	$C_{22}H_{24}CIN_5O_2$
Solubility	Slightly soluble in water
Category	Antiemetic
Storage	Store at room temperature
stability	Incompatible with strong oxidising agent and stable
Protein Binding	91% to 93%
pKa value	7.9
Half life	7-12 Hours
Metabolised by	Liver
Dosage form	Tablet, suspension and drops
Therapeutic Dose	10-40 mg TDS
Excreted by	Breast Milk, renal
Side Effect	Dry mouth, galactorrhoea, Rashes and headache

Solubility issue of domperidone:

Domperidone is 1-[3-(Piperidin-1-yl)propyl]-1,3-dihydro-2H-benzimidazol-2-one in which the 4-position of the piperidine ring is substituted by a 5-chloro-1,3-dihydro-2H-benzimidazol-2-on-1-yl group. Lower aliphatic amines can form hydrogen bonds with water molecules. Therefore, such amines are soluble in water. Increase in the size of hydrophobic alkyl part increases the molar mass of amines. This usually results in a decrease in its solubility in water (https://www.toppr.com/guides/chemistry/amines/physical-properties-of amines/#:~:text=Lower%20aliphatic%20amines%20can%20form,in%20its%20solubility%20in%20water). Two substances whose molecules have very similar structures and consequently similar intermolecular forces will usually be soluble in each other. Two substances whose molecules are quite different will not mix randomly on the microscopic

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level. In general, polar substances will dissolve other polar substances, while nonpolar materials will dissolve other nonpolar materials. The greater the difference in molecular structure (and hence in intermolecular attractions), the lower the mutual solubility (https://chem.libretexts.org/Bookshelves/General_Chemistry/Book%3A_ChemPRIME_(Moore_et_al.)/10%3A_Solids_Liquids_and_Solutions/10.19%3A_Solubility_and_Molecular_Structure).

While melting point of domperidone is 242^{o}C and melting point is a reflection of the lattice interactions between the solid-state molecules, while dissolution considers the lattice energy plus the hydration energies. For instance, if we consider a molecule for which the lattice energies are strong compared to hydration energy, the solubility or dissolution is poor and increasing the melting temp (say by a different molecular arrangement that increases the strength of the lattice energy) would be expected to decrease the solubility or dissolution. If another molecule has a hydration energy that is stronger relative to the lattice energy, increasing the lattice energy will likely have less of an effect on the solubility or dissolution (https://www.researchgate.net/post/Hi_all_I_am_facing_a_typical_issue_in_co-crystals).

Table 2: Different Action of Domperidone

Years	Scientists	Discovery	References
1983	Amery WK &Waelkens J	The drug domperidone is used to treat migraine headaches earlier.	(Amery WK &Waelkens J 1983)
1985	Osborne *et al.*,	In women who take platinum-containing chemotherapy, domperidone can trigger cardiac arrhythmias.	(Osborne *et al.*, 1985)
1985 2001	Petraglia*et al.*,andda Silva *et al.*,	In lactation, domperidone acts as an antidopaminergic drug that encourage lactation	(Petraglia*et al.*, 1985; da Silva *et al.*, 2001)
1986	Worth *et al.*,	The gludopa-induced natriuresis is not affected by blocking renal DA2 dopamine receptors by domperidone.	(Worth *et al.*, 1986)
1999	Patterson *et al.*,	Diabetic gastroparesis is well treated with domperidone.	(Patterson *et al.*, 1999)
2007	Reddymasu*et al.*,	Domperidone is an investigational novel medicine that is used to treat gastroparesis and other conditions that cause chronic nausea and vomiting.	(Reddymasu*et al.*, 2007)
2010	Kalias K *et al.*,	The ternary inclusion complex of domperidone which includes citric acid	(Kailas K *et al.*,

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Years	Scientists	Discovery	References
		and □-CD could be delivered intranasally using sodium alginate microspheres. In vivo examination of microspheres in animals and/or people could be used to determine domperidone bioavailability via the nasal route.	*2010)*
2011	Sakamoto	A novel non-invasive technique is utilised to evaluate stomach emptying using a continuous real-time 13C breath-test (BreathID system) and found that Gastric emptying was unaffected by domperidone.	(Sakamoto*et al., 2011*)
2012	Nishikawa*et al.*	Use in Parkinson's disease management in combination with levodopa	(Nishikawa*et al.*, 2012)
2017	Majekodunmi& Uzoaganobi	Sustained release domperidone microsphere was formed.	(Majekodunmi&Uzoaganobi, 2017)

PHARMACOLOGY:

The time it takes for domperidone to reach peak plasma levels varies depending on whether it is given intramuscularly (IM) or orally (OR). Peak levels are usually reached in 1–2 hours following rectal use of suppositories. Bioavailability is high after intramuscular treatment (90%) but substantially lower after oral administration (13–17%). (McCallum, 1985) The bioavailability of oral domperidone is significantly reduced when the pH of the stomach is raised with antacids. The medication is eliminated in the urine is 32 percent after oral treatment.Domperidone differs from other prokinetic drugs in that it does not have cholinergic activity and is not inhibited by atropine. (Reynolds, 1989; Champion *et al.*, 1986, and National Library of Medicine, 2021))

Mechanism of Action

Domperidone block the peripheral dopamine receptor due to which it shows gastroprokinetic action. Domperidone increases gastric peristalsis and antroduodenal coordination to facilitate gastric emptying. The anti-emetic properties of domperidone are due to its dopamine (D2) receptor-blocking activity at the chemoreceptor trigger zone (CTZ). It does not cross the Blood brain barrier so that it can be administered with the levodopa.Domperidone anti-emetic properties is short-lived when administered prophylactically with morphine or pethidine,

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indicating that it would not be effective as a prophylaxis for opiate-induced emesis. (Willson& Dundee, 1979)

Pharmacokinetics

1. Absorption of Domperidone:

Domperidone is orallyabsorbed and reaches highest serum levels in half hour, although due to first-pass metabolism, bioavailability is only 15%. T1/2 is the plasma half-life, which is 7 hours. (DRUGBANK, 2021)

2. Distribution of Domperidone:

Domperidone shown binding with plasma protein is 91-93 percent. The distributionvolume is 5.71 L/Kg, indicating that the medication is widely distributed throughout the body. After systemic treatment, relatively high quantities of domperidone accumulate outside the blood-brain barrier, with low amounts in the striatum and other brain locations. (Costall*et at.,* 1979; Laduron&Leysen, 1978, and Laduron&Leysen 1979)

3. **Metabolism of Domperidone:**

Domperidone is tremendouslymetabolised in the liver, with N-dealkylation and hydroxylation catalysed by cytochrome P 450. The metabolism products are inactive.

4. Elimination of Domperidone:

Domperidone metabolism products are excreted in the urine and faeces. fter oral administration, 66% of the medication is detected in the faeces, with an elimination half-life of around 7.5 hours in healthy people. (Champion *et al.,* 1986). The elimination half-life in patients with significant renal impairment can reach 20 hours. (Heykants*et al.,* 1981)

Absorption, Distribution, Metabolism, Excretion od Domperidone (ADME)

Table 3: ADME of Domperidone

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

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PATHO PHYSIOLOGY:

2.2.3.1 Dosage

Given dosage forms are available of the domperidone: syrup, capsule, suspension, tablet. A maximum everydayamountis 120 mg domperidone is commonly necessary in chronic nausea, gastroparesis and vomiting. Domperidone is available as 10-mg pills all around the world.The normal starting dose of suppositories 20mg taken at bed time or 15-30minutes before meal. After 2-4 weeks ofperiod the dose can be enhanced to 30 milligram if expected results are not observed.For children, an oral suspension (1 mg/mL) at a dose of 0.3 mg/kg of body weight three times a day and at bedtime is recommended.The recommended adult dosage for nausea and vomiting associated with medications used to treat Parkinson's disease is up to 20 mg four times a day.Instead of four times a day, patients with renal impairment should be dosed once or twice a day. In the case of liver impairment, there is no need to change the dose. (Reddymasu*et al.*, 2007). 10 mg three times a day for 4-109 days used as galactagogue

Toxicity

De & Taylor, 2007 stated that domperidone was responsible for patient's galactorrhoea, irritability, fevers, hyperprolactinemia, extrapyramidal symptoms, and gynecomastia. It's possible that this patient was particularly vulnerable to CNS poisoning. He had a slight rise in cerebrospinal fluid (CSF) protein, suggesting that his blood brain barrier was more permeable. Children on renal replacement therapy, domperidone must be taken with caution. (De & Taylor, 2007) Side effects include galactorrhea, gynecomastia, or menstrual irregularities.

Drug-Interactions

1. Anti-cholinergic medicines may interfere with Domperidone's anti-dyspeptic effects if taken together.
2. Dopaminergic agonists side effects (digestive problems, nausea, and vomiting) are suppressed by domperidone.
3. Domperidone may be counteracted by anti-muscarinic drugs and opioid analgesics.
4. Antacids and anti-secretory drugs reduce Domperidone oral bioavailability. They should be taken after meals rather than before, and they should not be used at the same time as Domperidone.
5. Domperidone may conflict with other hypoprolactinaemic medicines since it affects blood prolactin levels.

As per swann*et al.*, 1979 Domperidoneinteracts with many drugs some of the reported interaction of domperidone with other drugs is mentioned in theTable 2.2.3.1: Example of Domperidone Drug interaction and effect of interaction

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Adverse Reaction

Central nervous system (CNS): headache/migraine (1%); does not pass the blood-brain barrier; has less CNS side effects than metaclopramide.

Gastrointestinal: Constipation, abdominal cramps, dizziness, diarrhea, dysuria, extrapyramidal symptoms (EPS) rarely, edema, galactorrhea, heartburn, hot flashes, gynecomastia, increased prolactin, nervousness, thirst, insomnia, irritability, lethargy, mastalgia, leg cramps, nausea, rash, palpitation, pruritus, menstrual irregularities, regurgitation, weakness, stomatitis, urticaria, urinary frequency. (Rossi, 2006)

Cardiovascular System: On the basis of risk- benefit assessment USFDA banned the drug domperidone for wide use in US on 7th June 2004 due to its cardiac side effects. Although in many countries domperidone is a approved drug and used for therapeutic purpose. It has been reveal that use of domperidone related to sudden cardiac death and an increase risk of QT interval prolongation. (Fais et al., 2015)

Therapeutic Use

In most countries, domperidone is the first-line antiemetic, and it has also been found to be useful in the treatment of gastroparesis, a stomach motility disorder, and pediatric acid reflux (infant vomiting).Dyspepsia, heartburn, and epigastric discomfort can all be treated with this medication.

Use of Domperidone during pregnancy for Nausea and vomiting

Various Dopamine Antagonist drugs such as metoclopramide, dorperidol, phenothiazine, chlorpromazine, promethazine are used in the treatment of NVPs because the adverse effect risk is overcome by the benefits of the treatment. Dopamine antagonist teratogenicity is still not been conclusively determined. Hyperemesis gravidarum is caused by the drug when NVP symptoms became severe these include electrolytic imbalance, fluid depletion, weight loss, dehydration, excessive vomiting and mandate the hospital admission. During 1st 10 weeks of pregnancy steroids are not recommended. (Thomas et al., 2015)

Use during lactation

Domperidone is used as galactagogue that can be increased milk production 90-94 mL/Daily. It should be used as dose prescribed by doctor. With increasing the do\se of domperidone there will be no increase in the milk production. While dosage more than 30mg/Daily increase the risk of sudden cardiac death and cardiac arrythmias. Mother with sign of heart disease should not take domperidone or seek medical attention. According to ----- no serious side effects were reported in the infants on a dose 10 mg three times in a day. Studies were performed in India, Pakistan, Indonesia and Toronto to use as galactagogue.

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Overdose

Symptoms of overdose include CNS effects (drowsiness, disorientation, and extrapyramidal reactions) and cardiovascular effects (arrhythmias and hypotension). Treatment is supportive. Cardiovascular consequences (hypotension and arrhythmias) CNS effects (drowsiness, extrapyramidal reactions and confusion) are common overdose symptoms. (Roila*et al.*, 1987).

Table 4: Example of Domperidone Drug interaction and effect of interaction

SR. NO.	OBJECT DRUG	INTERACTING DRUG	EFFEC OF INTERACTION
1.	Domperidone	Abametapir, Abiraterone	Serum concentration increase
2.	Domperidone	Anagrelide, Acrivastine, Amodiaquine	Increase risk of severity of prolongation of QTc time
3.	Domperidone	Abatacept	Increased metabolism
4.	Domperidone	Acalabrutinib, Acebutolol, Acetaminophen, Acyclovir, Amphetamine	Decreased metabolism
5.	Domperidone	Aclidinium, Amoxapine	Reduce therapeutic efficacy

EFFECT OF DOMPERIDONE ON MAJOR BODY SYSTEM:

Cardiovascular System: Domperidone and risk of QT prolongation

The Medicines Adverse Reactions Committee Meeting in December 2004 advised that the product sponsor include the following statement in the domperidone data sheet:

"Domperidone should not be prescribed in combination with CYP3A4 inhibitors such as erythromycin"

The following information was requested to be included in the Warnings and Precautions section of the domperidone data sheet by Janssen-Cilag:

"Cases of QTc prolongation, arrhythmia and sudden death have occurred with domperidone use. Although most reported cases have occurred in patients receiving the intravenous form of domperidone, an association with oral domperidone cannot be ruled out. Therefore, domperidone should be used with caution in patients with other risk factors for QTc prolongation including hypokalaemia, severe hypomagnesaemia, structural heart disease, the concomitant administration of other QTc prolonging medicines or an underlying genetic predisposition." (MEDSAFE, 2013) Some case report of cardiac adverse events Associated with use of domperidone given in the table 2.2.4.1.1 (Rossi & Giorgi 2010).

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Table 5: Cardiac Events related with the Domperidone: Case Reports

References	Dose/ Administration Route	Patient Sex/Age	Eventsof Cardiac Adverse	Associated drug	Associated disease
Rocha *et al.*, 2005	1.8 mg/kg /day oral	M/4 month	Prolongation of QT	Not at all	Not at all
Joss *et al.*, 1982	i.v. bolus200 mg	M/69	Ventricular fibrillation	Bleomycin, methotrexate, cisplatin	EAC
Roussak*et al.*, 1984 Case 3	20 mg i.v. bolus	F/38	Cardiac arrest	Metronidazole, Daunorubicin,gentamicin, cimetidine, vancomycin, amphotericin,	Leukaemia, Promyelocytic
Brueraet *al.*, 1986	60 mg i.v. bolus	F/57	TdP, prolongation of QT	Dexamethasone	Ovarian carcinoma
Pham *et al.*, 2006	180 mg/day oral	F/33	TdP	furosemide, Fluconazole, amoxicillin alprazolam, oxazepam. piritramide, gentamicin, prednisone, potassium chloride,short-acting insulin, magnesium sulfate, calcium chloride, pantoprazole, nadroparin,metoprolol, albuterol, ipratropium,	pulmonary eosinophilia, systemic lupus erythematous, glomerulonephritis, hemolytic pericarditis, anemia, hypertension

Central Nervous System:

Because it doesn't penetrate the blood-brain barrier, domperidone (gastrokinetic and antiemetic) has no central nervous system side effects. (Bron&Massih, 1980)

Gastrointestinal System

In healthy volunteers, a single intravenous dose of 10 mg domperidone consistently elevated lower oesophageal sphincter pressure by 15 to 20 mmHg. (Brogden*et al.*, 1982) Domperidone treatment relieves upper gastrointestinal symptoms and speeds up gastric emptying after a solid meal. (Soykan*et al.*, 1997)

Safety

Domperidone has been well tolerated in clinical trials and has generated relatively few side effects. After reports of cardiac arrhythmias following IV administration of high doses of domperidone, this method of administration was discontinued. It has a very good safety profile for long-term oral administration in the authorised doses. Domperidone is widely used

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in many countries and, according to an experimental new drug application, can now be formally prescribed to patients in the United States for the treatment of gastroparesis and any condition producing chronic nausea and vomiting**.** (Reddymasu*et al.,* 2007)

METHOD OF ANALYSIS:

Identification of Domperidone

As per Indian Pharmacopoeia domperidone is almost white powder. Related substances are determined by liquid chromatography.

1. Absorbance of domperidone is examined in the range between 200 to 400 nm by UV visible spectrometer. The absorption maxima of domperidone was found to be **284nm. (**Alim *et al.,* 2015)
2. According to the IP identification test of domperidone is performed by Infrared absorption spectroscopy. Obtained spectrum of drug compare with the spectrum given in the monograph. 1% w/v solution of drug in the dimethylformamide (DMF) is clear. (IP 2007)
3. As per Abd Alazi*et al.,* 2014 Differential scanning calorimetry is used to identify the drug. 1.5-2.5mg sample of domperidonewilltakeinacrimpedpanandheatedfrom30°to300°Crangeand constant rate of10°C/min. The flow of Nitrogen gas was maintained at 30ml/min. For this analysis, as reference, an empty aluminum pan was used. The melting endotherm peak of domperidone should be near to the melting point of the drug. (Abd Alazi*et al.*, 2014)
4. FT-IR spectra of pure domperidone can be recorded using FT-IR spectrophotometer. The range for running the spectra for domperidone is 400 to 4000cm^{-1} as specified by Abd Alazi*et al.,* 2014 and using pressure 6-8tons, 13mm of die size and resolution of cm^{-1}.

ASSAY:

IP (2007), EP ()gives a derivatization method of the domperidone assay which includes following steps: 0.3g sample is dissolved in a 50 mL mixture (7 volumes of methyl ethy ketone and 1 volume of anhydrous acetic acid). Using 0.2 m1 of naphtholbenzein solution as an indicator, titrate with 0.1 M perchloric acid until the colour changes from orange-yellow to green. (IP 2007). On dried basis: not less than 99% and not more than 101.0% of $C_{22}H_{24}CIN_5O_2$

K.K.Rajasekhar*et al.,* performed spectrophotometric based assay analysis of domperidone. Accurately weighed 25 mg of Domperidone was dissolved in 25 ml of 0.1N HCL to get a concentration of 1 mg/ml. The stock solution is further diluted suitably with 0.1N HCL to obtain working standard solutions of 10,100 and 150µg/ml. Aliquots of solution 0.5 to 3.0 ml were transferred into a series of 10 ml volumetric flasks and the volume was made up to 10

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ml with 0.1 N HCL. The absorbance of the prepared solutions was measured at 284 nm for Domperidone against 0.1N HCL as blank. The amount of Domperidone present in the sample solution was computed from its calibration curve (K.K.Rajasekhar*et al.*, 2009)

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