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A Review on Historical Overview of Antiemetic Drug: Metopimazine

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Abstract:
In this review article we are going to see brief historical background about some antiemetic drugs. Here we have also discussed about the analytical methods that can be carried out such as spectroscopy and chromatography. Spectroscopy is a field of research that examines how electromagnetic radiation interacts with matter. Whereas High Performance Liquid chromatography is an analytical method used to separate compounds that are soluble in a particular solvent, antiemetic medications are used to treat nausea and vomiting by inhibiting certain receptors that react to neurotransmitter molecules. The current article consists of a review and literature about the use of the drug Metopimazine as an antiemetic drug along with its analytical features. The selection of the drug Metopimazine can be made based on the literature review and improvements that can be done in available methods. Metopimazine is a phenothiazine drug used to treat nausea and vomiting. In this review article, we have also discussed. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines required for forced degradation studies. A vast literature survey and study we were conclude that not enough work done on Metopimazine in the field of analysis, and there should be improvements in the available methods were possible.

Keywords: Analytical, Antiemetic, High Performance Liquid chromatography, ICH, Spectroscopy.

INTRODUCTION:

In this review, we will look at antiemetic drugs and the research that has been done on it. In this article, we will review the analytical methods that have been reported for the drugs. In addition, we will determine which drugs had the least consideration so that more study may be conducted. First and foremost, we will look at spectroscopic approaches.

Spectroscopy methods: This field of research examines how electromagnetic radiation interacts with matter. It is one of the most effective techniques for evaluating a variety of samples and is used to analyse atomic and molecular structures. The portion of the electromagnetic spectrum between 100 and 400 µm is used in optical spectroscopy. **Table.1** shows the areas of the electromagnetic spectrum.[1,2]

Table.1. Regions of electromagnetic spectrum

Region	Wavelength
Far Ultraviolet	10-200 nm
Near Ultraviolet	200-400 nm
Visible	400-750 nm
Near Infrared	0.75-2.2 µm
Mid Infrared	2.5 -50 µm
Far Infrared	50-1000 µm

Ultraviolet-Visible spectrophotometry:

- One of the most widely used methods in pharmaceutical analysis is UV-Visible spectrophotometry. It entails determining how often UV or visible radiation a substance in solution has absorbed. Ultraviolet-Visible spectrophotometers are instruments that measure the ratio, or function of ratio, of the intensity of two beams of light in the U.V. range.[2,3]
- If any recorded data is available, a spectrophotometer can be used in qualitative analysis to identify organic substances, and quantitative spectrophotometric analysis is used to determine the number of molecular species absorbing the light.
- The spectrophotometric method is ideal for small amounts of substances as it is highly rapid, simple, moderately selective, and precise. The basic principle regulating quantitative spectrophotometric analysis is the Beer-Lambert law.[2,4]
- According to Beer's law, the number of absorbing molecules leads the intensity of a parallel monochromatic radiation beam to fall exponentially. Thus, the relationship between absorbance and concentration is based on linearity.

- Lambert's law states that a parallel monochromatic radiation beam's intensity reduces exponentially as it passes through a homogeneous medium. The Beer-Lambert law is produced whenever these two laws are combined.
- Beer-Lambert's law states that a transparent cell containing a solution of an absorbing substance may cause a light beam's intensity to be reduced.
- Beer Lambert's law is mathematically written as **A=abc.**

where A = optical density or absorbance

a-absorptivity or extinction coefficient

b-path length of radiation through sample (cm).

c is the solute concentration in the solution.

Since b and a are both constants, a and c have a direct relationship. The constant is known as A (1%, 1 cm) when c is expressed in gm/100 ml.

$$\mathbf{A = A\ ^{1\%}/_{1cm}\ bc}.^{2,3}$$

- This UV-spectrophotometric method is very sensitive, accurate, repeatable, and simple. This is an appropriate approach for their quantification in the formulation, according to the validation procedure.[2,4]

High Performance Liquid Chromatography:

One of the most effective method in analytical chemistry nowadays is HPLC.

The analytical method of high performance liquid chromatography is used to separate compounds that are soluble in a particular solvent.[5]

HPLC is a physical separation method used in the liquid phase in which a sample is divided between a mobile phase and a stationary phase to separate it into its individual components. A chromatogram is produced by an online detector, which also tracks the concentration of each separated component in the column effluent. For the assessing the number of pharmaceuticals, biomolecules, polymers, and other organic substances, HPLC is the most popular analytical method.

In liquid chromatography, such as HPLC, a mobile phase (the solvent) and a stationary phase (the column packing) separate from one another. The ability of the sample constituents to divide themselves throughout the two phases will determine whether the separation will occur.[6]

There are four main separation processes that can occur depending on the stationary phase:

- Adsorption chromatography, in which the separation is based on repeating adsorption-desorption steps;
- Partition chromatography, in which the separation is based on partition between the mobile and stationary phase;
- Ion-exchange chromatography, in which the stationary phase is composed of an ionic surface of opposite charge to that of the sample; and
- Size exclusion chromatography, in which the sample is separated based on its molecular size through a column filled with a methylene blue solution.

The most common form of chromatography is adsorption, and depending on the polarity of the two phases, we refer to two different modes of action:

- Normal phase chromatography, where the mobile phase (such as hexane) is non-polar and the stationary phase (such as silica or alumina) is polar in nature. In this mode, polar substances are held by the column more effectively, allowing non-polar molecules to elute first.
- Reverse-phase chromatography, in which the elution solvent (or mobile phase) is polar and the stationary phase is non-polar in nature (such as a hydrocarbon) (e.g., water or methanol). Since this is the exact opposite of normal phase chromatography, non-polar substances will be kept on the column for a longer period of time.

A mixture of solvents can be used to elute the compounds and change the polarity of the mobile phase.

- An isocratic elution occurs when the composition of such a solvent mixture remains consistent during the elution process.
- On the other hand, we use a technique known as gradient elution when the composition of the solvent combination is changed throughout the elution process.[7]

Steps involved in HPLC experimentation:

- **HPLC Pump:** The HPLC pump generates high pressure, allowing the mobile phase to flow continuously and consistently throughout the HPLC system. For example, pneumatic, syringe, and reciprocating pumps.
- **HPLC Mobile phase:** It is a solvent or contains combinations of organic solvents and water, an optimum concentration of an aqueous solution with polar solvents, or both.
- A **HPLC degasser** is a device used to purge gas from a mobile phase.
- Using an **HPLC injector**, a sample solution is injected into the HPLC system. For example, a stop flow injector, a septum injector, or a rheodyne injector.
- The **HPLC column** is the most important part of the system since it separates the analytes from the sample mixture. These days, columns are made to be used in stainless steel tubes under high pressure. The stationary phase of an HPLC column is typically filled with silica gel.
- The **HPLC Oven** is a device used to control a columns temperature.
- **HPLC Detector:** A detector is a device for identifying substances that have been separated from a column. The computer system monitors the electrical signal that the detector generates from the effluent. For example, a UV/VIS detector, a PDA detector, an LCMS mass detector, a fluorescence detector, and an infrared detector, and others.[6]

Application of HPLC:

- Quality control testing of drugs.
- Analysing data quantitatively and qualitatively.
- Separation and management of impurities are studied.
- During therapeutic monitoring of medication metabolism.

- Studies on stability.
- On analysing biological fluids.
- Study of basic biochemical pathways including metabolic pathways.
- Separation of enantiomers, positional isomers, and optical isomers.
- applications in industry.

i. The identification of artificial intermediates.
ii. In analysing impurity traces.
iii. Studies on stability[8]

High Performance Thin Layer Chromatography:

- An advanced thin-layer chromatography technique. Here, thin layer chromatography's core concepts are used. Planar chromatography and flatbed chromatography are some other names for it.[9,10]
- Conventional thin layer chromatography and its contemporary instrumented version, HPTLC, are particularly popular for a variety of reasons, including Indicative chromatogram, Convenience, Handling several samples, Low cost of operation and maintenance, Disposable layer.[10,11]
- Depending on the type of adsorbents utilized on the plates and the solvent system used for development, separation may be generated by partition, desorption, or both phenomena.
- Due to capillary action, the mobile phase passes through the plate. As they approach the adsorbent, the components move in accordance with their affinities.
- The component traveling slower is the one with a higher affinity for the stationary phase, whereas the component traveling faster is the one with a lower affinity.[10,12]

The overview for the steps involved in HPTLC can be referred according to figure 1. [13]

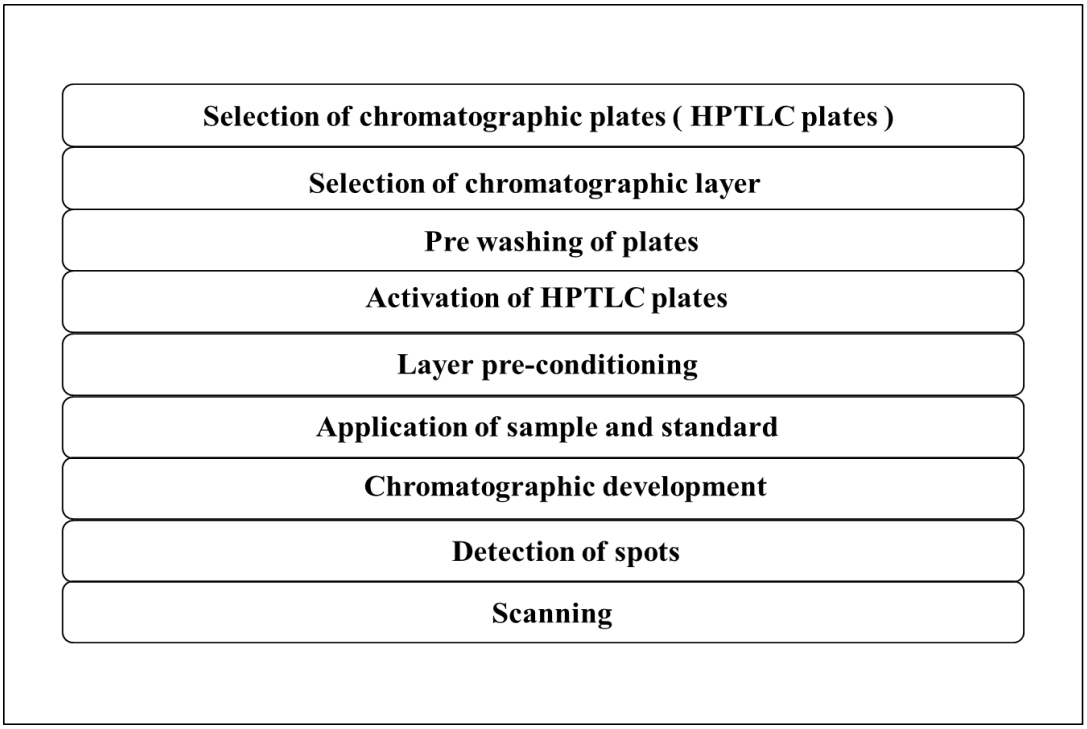

Figure 1.Steps involving in HPTLC

Applications:

- Pharmaceutical industry: uniformity test, purity test, content test, and quality control clinical applications: drug screening, stability testing, and metabolic studies.
- Food analysis includes quality assurance, testing for additives, pesticides, and stability.[10,14]
- Applications in industry include process development and optimization, in-process quality control, and validation.
- Forensic: investigations into poisoning.[10,15]

Analytical method development:

- The process of designing the methods, circumstances, and protocol for measuring the analyte is known as method development.
- When there are no concise techniques available, new methodologies are being developed for the evaluation of the specific product. New procedures are developed to reduce the cost besides time for higher precision and strength in order to determine the presence of either pharmacopeial or non-pharmacopeial product.[16,17]
- Through testing process, these methods have been improved and shown to be reliable. Alternative methods are developed and implemented in order to the current technique within the framework of comparative laboratory results with all available advantages and disadvantages.
- The identity, characterization, and resolution of the pharmaceuticals are shown in drug evaluation when they have been combined with organic fluids and dosage forms.
- The primary goal of analytical techniques is to generate data regarding efficacy (which may be directly related to the need for a specific dose), impurity (related to medication safety), bioavailability (which includes important drug characteristics like crystal characteristic, uniformity of drug, and release of drug), stability (that shows the degradation product), and effect of manufacturing parameters to confirm that the drug is safe.[17,18]

Analytical method validation:

- The concept of validation emerged in the United States around 1978.
- The concept of validation has expanded over time to encompass a wide range of activities, including analytical methods used for drug quality control and computerized systems for clinical trials.
- Validation is based on, but not endorsed by regulatory specifications, and is usually regarded as an essential component of current good manufacturing practise (cGMP). The term "validation" primarily refers to the process of evaluating a statement reliability or demonstrating its validity.[17,19]
- Validation is a team endeavour that involves individuals from various plant departments. Any new or modified technique must be validated to ensure that it can produce reliable result whether used by many operators using the same or similar instruments in the same or other facilities.

- The efficient evaluation of systems, facilities, and procedures with the objective of determining whether they carry out their intended capacity sufficiently and reliably as defined is known as validation, and it is a crucial part of quality assurance. In this manner, the accompanying circumstances should be taken into consideration during validating.[17,20]

Validation parameters:

The primary goal of method validation is to generate data that the method will operate as intended, accurately, consistently, and reliably. Below is an overview of the validation parameters according to ICH guidelines.

- Accuracy
- Precision
- Repeatability
- Intermediate precision:
- Reproducibility
- Specificity
- Limit of detection (LOD)
- Limit of Quantitation (LOQ)
- Linearity
- Range
- Ruggedness
- Robustness
- System suitability parameters[16,17]

Necessity of analytical method development and validation:

- Method Development is a series of steps that defines and optimises analytical test parameters to determine the capabilities of the test method.
- It provides a high degree of assurance that the test procedure will reach or exceed the required standard.
- Before use, the developed method must have completed the appropriate validation.
- It is important to conduct regular reviews as method development proceeds.
- Using method recommendations to standard test techniques for testing new products or materials might improve performance testing.
- The testing parameters are found during the method development phase to ensure the data's applicability and reliability.[17,21]

Antiemetic drug:

Antiemetic, which is another name for anti-vomiting, essentially means "against emesis." Antiemetic medications, which are used to treat nausea and vomiting, can be given as tablets, sublingual's, oral solutions, suppositories, transdermal patches, intravenous injections, or oral tablets. These two symptoms

can be brought on by a wide range of ailments, treatments, procedures, and drugs. Vomiting and nausea are frequent symptoms that might have a variety of causes. Several illnesses, including motion sickness, upper abdominal discomfort, food poisoning, and gastroenteritis, can cause nausea and vomiting. Several medications, including opioid analgesics, anaesthetics (postoperative nausea), and cancer treatment, can cause nausea and vomiting as side effects. Lastly but not least, hyperemesis gravidarum, or strong morning sickness with severe vomiting during pregnancy, is a condition where nausea and vomiting are frequently encountered. Antiemetic medications are frequently required to control vomiting, especially if there is severe dehydration, even though vomiting is considered to be the body's protective reflex to eliminate poisonous chemicals from the stomach and intestines.[22]

Antiemetics function by inhibiting certain receptors that react to neurotransmitter molecules like serotonin, dopamine, and histamine. This affects the neurological circuits involved in vomiting. The majority of them are central receptors located in the brainstem's vomiting centre, while the vague nerve contains the peripheral receptors. The peripheral receptors get information from the gastrointestinal system when it detects a threat, and they then pass it on to the central receptors in the vomiting centre. The vomiting centre acts by stimulating the digestive system, abdominal muscles, and diaphragm, which causes nausea and vomiting.

Antiemetic drugs can be divided into a few types according to the main receptors they target. Antagonists of the serotonin, dopamine, histamine, muscarinic, and neurokinin systems, corticosteroids are among the main classes of antiemetics.

Antiemetic drugs can be divided into a few types according to the main receptors they target.

i. 5-HT3 receptor antagonists affect both the peripheral serotonin receptors in the vague nerve and the central serotonin receptors in the vomiting centre. 5-HT3 receptor antagonists are recommended for use in controlling postoperative nausea and vomiting caused on by acute gastroenteritis. Additionally, it's the primary antiemetic class used to treat nausea and vomiting that are common adverse effects of chemotherapy and radiotherapy.

ii. Dopamine antagonists are among the most used antiemetics, and they are frequently prescribed for motion sickness and postoperative nausea.

iii. H1 antihistamines, which can be administered more conveniently through a transdermal patch, are used to treat and prevent nausea and vomiting brought on by vestibular disturbances like vertigo or motion, as well as anticholinergics, which are also used to prevent motion sickness. The transdermal patch is helpful for ensuring a consistent release of the drug and reducing the possibility of side effects. Antihistamines typically cause sleepiness as a drawback.

iv. Glucocorticoids are recommended as antiemetics for nausea brought on by chemotherapy. They work effectively and are generally well accepted, but they frequently cause side effects like increased energy, mood swings, and insomnia.

v. Neurokinin 1 receptor antagonists are a relatively new class of antiemetics that are particularly effective at reducing nausea and vomiting brought on by chemotherapy and radiotherapy, as well as preventing it after surgery. Taking Neurokinin 1 receptor antagonists while pregnancy is not advised.

vi. The majority of the time, antiemetics are well tolerated, although they can have undesirable side effects, such as constipation or diarrhoea, headache, exhaustion, illness, dizziness, light-headedness, blurred vision, dry mouth, or photosensitivity.[23,24]

Historical overview:

Here, we are going to see a brief historical evidences about some antiemetic drugs which are mentioned in **table.2.**

Table.2.Historical Overview

Sr. no.	Title	Mobile phase	Column	Flow rate	Retention time	UV	References
1.	Metoclopramide	acetate buffer and acetonitrile, (75% v/v)	C18 column, 8 mm i.d. x 10 cm µ Bonda Pak C 18 column with 10 um packing	1.8 ml/min	5.7 and 14.8 min	273 nm	25
2.	Metoclopramide	Eluent consisted 30% methanol and 9% tetrahyodrofuran (v/v) in an aqueous solution of KH_2PO_4 , 0.01 M	Supelcosil LC 8 DB, 250 x 4.6 mm, 5 µ, from Supelco	1.0 ml/min	4.5 min	273 nm	26
3.	Metoclopramide hydrochloride	Acetonitrile, 20m M Potassium dihydrogen phosphate buffer solution (pH 3 adjusted with orthophosphoric acid) in the ratio of 40:60	Waters C18 3.9×300mm µ Bondapak (RP)	2 ml/minute	1.93min	275 nm	27
4.	Metoclopramide	diethylamine, methanol and methylene chloride in a ratio of 1:100:899	A 25 cm long column with an internal diameter of 2 mm was used. It was packed with 'Lichrosorb 5 Si 60'to provide conditions for normal phase chromatography.	1.5 ml/min using a Pye Unicam pump, model PU4010	4.1 and 5.0 min	309 nm	28
5.	Metoclopramide	Acetonitrile (HPLC grade), methanol (HPLC grade) and water	WATERS high performance liquid chromatography knitted with 515	1 mL/min	3.8 min	272 nm	29

		(HPLC grade) with a ratio of 25:25:50, 30:25:45 and 20:25:55 v/v/v	reciprocating single column HPLC pump and an injector MICROLITER™ #710, HAMILTON Co. RENO, NEVADA With 0.10 Ml Sample Loop, ZORBAX SB-C18 (4.6 × 250 Mm, 5.0 µm) Column As Well As Model 2487 Dual Λ And Absorbance Detector.				
6.	Domperidone	water: methanol (55:45)	C18 column BDS column (250 mm X 4.6 mm; 5µ.)	1.0 mL/min	4.5 min	291 nm	30
7.	Domperidone	disodium citrate buffer (10 mM, pH 3.4): methanol: acetonitrile: trietylamine, 54.6:34.7:9.9:0.8	Ultrasphere ODS column (250 mm × 4.6 mm × 5µM)	1.0 mL/min	Retention times were 4.2, 4.7, 5.1, 5.7, 6.5 and 12.1 min	254 nm	31
8.	Droperidol	methanol–water, 30:70 (v/v), with the pH adjusted to 3.5 with glacial acetic acid	100 mm x 3 mm i.d. Phenomenex Luna C18 column	0.8 mL min^{-1}	6.1 min	λex283 and λem 324 nm	32
9.	Haloperidol	acetonitrile (67%) and ammonium acetate buffer (final concentration 10 mM) adjusted to pH 5.4 with acetic acid.	5-µm Hypersil CPSS column (silica gel with bonded cyanopropyl groups, 250 mm x 4.6 mm I.D.) coupled with an Upright C-130B guard column (30 mm x 2 mm I.D.) packed with 5-pm Hypersil CPS column material.	1 ml/min		220 nm	33
10.	Prochlorperazine	mixture of Solvent A (0.2% TFA in water, v/v) and Solvent B (0.2% TFA in acetonitrile, v/v).	Agilent Zorbax SB-C18 (150 mm 4.6 mm i.d., 5 µm) column	0.8 mL/min		254 nm	34

11.	Alizapride	methanol-pH 8.1 buffer (80:20, v/v)	A 250-mm steel column was used, packed with a monomolecular layer of octadecyl trichlorosilane chemically bonded to Porasil beads with an average particle size of 10 µm[4]	2-ml/min		323 nm and 380 nm	35
12.	Haloperidol	100 mM/L potassium dihydrogen phosphate–acetonitrile–TEA (10:90:0.1, v/v/v) and the pH was adjusted with *o*-phosphoric acid to 3.5	C-18 Cosmosil packed column (5 C18- MS-II, 250 mm x 4.6 mm x 5.0 µm)	2 mL/minute	2.536 and 3.59 min	230 nm	36
13.	Ondansetron hydrochloride	Buffer: Acetonitrile: Methanol (50:40:10% v/v/v) (pH 4.5 ± 0.05)	Princeton SPHER C18 column (250 mm x 4.6 mm id, 5µ particle size)	1.0 ml/min	2.67 ± 0.05 min	248 nm	37
14.	Domperidone	phosphate buffer (50 mM, pH 3.5) acetonitrile (80:20, v/v)	Waters symmetry C18 (15 cm × 0.46 mm, 5 µm)	2.0 mL/min	The retention, separation and resolution factors were 2.63, 3.00 and 3.20, respectively	230 nm	38
15.	Haloperidol	30% 0.1 - M ammonium carbonate: 70% methanol	LiChrosorb RP-18; 25 cm x 2.1 mm id stainless steel column	1 ml/min	5.5 minutes	254 nm	39

Metopimazine:

- According to Helle Riis Angelo et. al, research article shows that, many patients receiving therapy with cytostatic drugs suffer significantly with emesis and vomiting. In doses below the toxic level, the phenothiazine derivative metopimazine has shown to have an antiemetic effect in comparison to a placebo in the treatment of particular group of patients. They needed a relatively simple approach for analysing Metopimazine and its acid metabolite in order to determine the appropriate dose level and dose interval and

possibly improve the therapeutic impact acid metabolite of Metopimazine. Metopimazine and acid metabolite of Metopimazine were previously determined individually using a high-performance liquid chromatographic (HPLC) method. This article examined an HPLC technique that uses a simple extraction method. Metopimazine and Acid metabolite of Metopimazine could be detected simultaneously with enough sensitivity, accuracy, and selectivity using a cyano column and fluorescence detection. The guard column was a LiChroCART 4 x 4 LiChrosorb CN and the analytical column was a 5-pm Supelcosil CN 25 cm x 4.6 mm I.D. Ammonium acetate-methanol-0.1M was used as the mobile phase (50:50). The flow rate approximately 1.5 ml/min. For the separation of phenothiazines and related chemicals, ammonium acetate has been utilised as a buffer in the mobile phase. The proposed method has been used by many technicians over the past three years to determine serum levels in patients undergoing therapeutic doses of Metopimazine. It is quite easy and reliable method.[40]

- According to Ibrahim A. Naguib et.al, research article shows that, the proposed method was applied for analysis of Metopimazine in pure form, pharmaceutical formulation and human plasma over the concentration range of 0.4–1.4 μg band−1 with accuracy of mean percentage recovery 100.10 0.941. The method depends on separation of Metopimazine from its degradation products on HPTLC silica gel 60 F254 plates using chloroform–methanol–ammonia as developing system followed by densitometric measurement of bands at 254 nm. The method was validated according to ICH guidelines. The degradation products were well resolved from the pure drug with significantly different Rf values. HPTLC densitometric method has the advantage that several samples can be run simultaneously using a small quantity of developing system and that it can provide high sensitivity and selectivity. Moreover, it offers a means for analysis of Metopimazine in human plasma samples which can be applied to pharmacokinetic study and therapeutic drug monitoring for Metopimazine.[41]

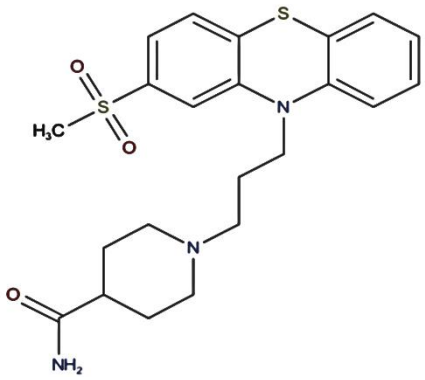

Figure 2. Structure of Metopimazine

Chemically, Metopimazine is known as l-(3-[2-(Methylsulfonyl)-10H-phenothiazin-10-yl] propyl)-4-piperidinecarboxamide. It is a part of the phenothiazine class of drugs, which includes tricyclic compounds containing nitrogen and sulfur.[42] For many years, France has used the dopamine D2 receptor antagonist metopimazine to both prevent and treat nausea and vomiting.[43]

Metopimazine is marketed in France in a variety of medical formulations. For adults, there are hard capsules, suppositories, injectable solutions, and oro-dispersible tablets; for infants, there a solution or suppositories. To customize the course of treatment for the patients' needs, several medication administration routes can be selected, which has an antiemetic effect.[44]

Dopamine receptor antagonists may be used as add-on therapy in conditions of refractoriness and in the prevention of delayed chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy, according to guidelines. Recent studies on sublingual Metopimazine suggest it may be used as an alternative to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients undergoing moderately to severely emetogenic non-cisplatin-based chemotherapy.

Trials evaluating Metopimazine with other medications used in the treatment of postponed chemotherapy-induced nausea and vomiting would be relevant. Data also support the roles that dopamine receptor antagonists are suggested for in guidelines, such as their potential use in rescue therapy for patients with breakthrough symptoms.

These roles are also supported for Metopimazine as add-on therapy in the treatment of acute emesis in patients receiving moderately emetogenic chemotherapy who are refractory to initial therapy or unable to take corticosteroids.

Metopimazine has been given in France to treat nausea and vomiting by oral, sublingual, and parenteral routes. The sublingual formulation is being used to prevent delayed emesis, while the injectable formulation is approved for the treatment and prevention of chemotherapy-induced nausea and vomiting. The recommended oral or sublingual dose is 15–30 mg/day (given in divided doses) for the treatment of nausea and vomiting. However, oral dosages of up to 120 mg/day (given in 3–4 divided doses) were used during clinical trials in chemotherapy-induced nausea and vomiting. Treatment with caution for chemotherapy-induced nausea and vomiting usually involves intramuscular injection.[43]

If Metopimazine is given intravenously, caution should be used; it should be given as a very slow intravenous infusion to prevent hypotension from occurring, and the patient should be observed.

Patients at risk of narrow angle glaucoma or urinary retention caused by urethral or prostatic abnormalities should not use Metopimazine. Due to the possibility of sedation or hypotension, it should be taken with caution in elderly patients, having a liver or kidney condition.[45]

Mechanism Of Action:

A phenothiazine derivative with anti-dopaminergic properties is Metopimazine. Although it has minimal affinity for serotonin 5-HT3 receptors, it has a significant affinity for dopamine D2 receptors. It acts on the chemoreceptor trigger zone to produce its antiemetic actions. The blood-brain barrier can be crossed by Metopimazine, but only to a very limited extent by its acid metabolite, which is the drugs main circulating form. Extrapyramidal effects and effects on prolactin are also rather rare.

Due to Metopimazine affinity for the α_1-adrenoceptor, it has been known to infrequently cause orthostatic hypotension. Peak blood concentrations are observed 60 minutes (or 20 minutes for sublingual pills) after

fasting oral dosing. Oral Metopimazine has a bioavailability of 19–34%. Food consumption decreases oral absorption. Metopimazine is quickly converted to its active acid metabolite, which contributes for 78–89% of the medication in circulation. The elimination half-life of the parent drug is around 4.5 hours, and about 30% of a dose is recovered in the urine (mainly as the acid form).[46]

Degradation studies:

In the pharmaceutical industry, forced degradation studies give a method for analysing the stability of pharmaceutical samples. The chemical stability of the molecule has an impact on the safety and effectiveness of drug products. Determining a molecule's stability facilitates the selection of an appropriate formulation and packaging as well as the selection of suitable storage conditions and shelf life, which are all necessary for regulatory validation.[47] Forced degradation is a procedure where drug products and drug compounds are degraded under conditions that are severe than accelerated conditions. This approach generates degradation products that may be analysed to find out how stable a molecule is. The necessity for the development of a stability-indicating assay method (SIAM) has become more clearly specified with the advent of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)guidelines.[48]

The International Conference on Harmonization (ICH) standards clearly define forced degradation of novel medicinal products and make it necessary to plan forced degradation studies. These investigations provide the knowledge to aid in the identification of probable degradation agents. Additionally, it shows whether pharmaceutically useful compounds decompose. Studies on forced degradation can be used to determine the intrinsic stability of medicinal molecules. Forced degradation studies can also be used to assess differences between drug-related degradation and excipient interferences as well as possibly polymorphic or enantiomeric compounds. The forced degradation studies under a variety of conditions, such as pH, light, oxidation, dry heat, acidic, basic, hydrolysis, etc., are required by ICH recommendations. Additionally, it offers the ability to separate drugs from products of degradation.[47] In **figure.3** we can see approaches for forced degradation.

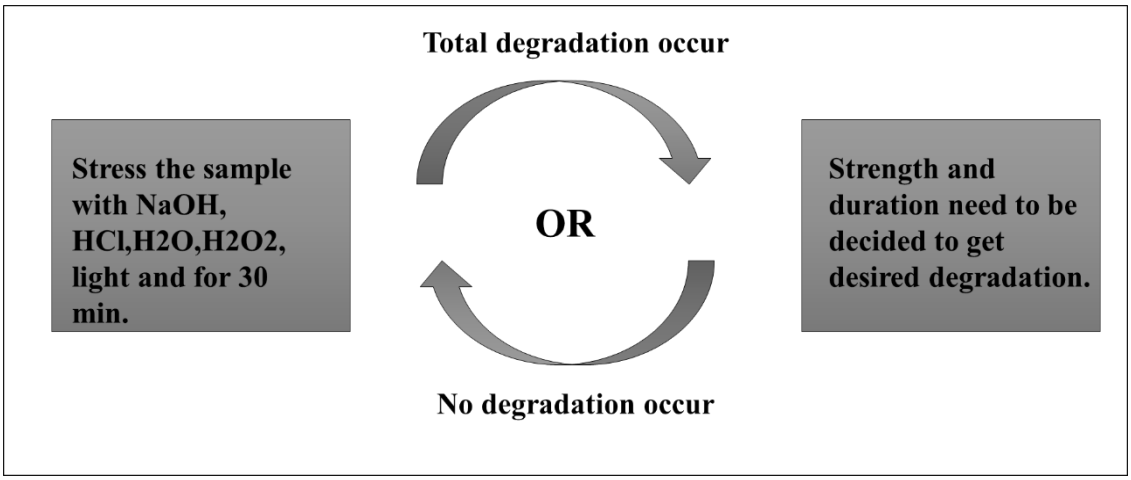

Figure 3. Approach for forced degradation

Studies on forced degradation provide the following details:

a. Identification of potential degradation products,

b. Study of degradation pathways,

c. Analysing the drug molecule's intrinsic stability,

d. Establishing an analytical approach with validated stability parameters[47]

Purpose of forced degradation:

a. To develop degradation pathways of drug substances and drug products.

b. To identify the chemical characteristics of drug compounds.

c. To characterize the composition of degradation products.

d. To address problems with stability

e. To determine a drug substance's intrinsic stability in the formulation.

f. To identify the drug substance's and the drug product's mechanisms for degradation.

g. To separate degradation products produced by drug products in a formulation from those produced by non-drug products.

h. To produce stability that identifies the characteristics of a proposed method.

i. To generate formulations that are more stable. The expiration date of a certain formulation can also be determined with its aid.

j. To produce a degrading profile approaching what would be seen in an established stability study carried out under ICH guidelines.[47]

Stress conditions:

In industry, stress study processes like thermal, hydrolysis, oxidation, and light degradation are frequently used. By determining an appropriate amount of acid, base, and oxidizer, applying a combination of stresses (such as degradation media+temperature), and exposing the material for the required amount of time, the desired level of degradation can be attained. Excessive degradation of the sample may result in secondary degradants and additional degradation of contaminants that are not apparent in real-time stability analyses. A difference in the response factor of identified contaminants may also induce excessive degradation to cause mass balance results to be inaccurate. The objective of forced degradation might not be served if the intended degradation is not achieved. According to recent complete responses from the FDA, the ideal percentage of degradation should be reached in all conditions, or at least in one.[49]

If there is no degradation under any circumstance, we should make significant scientific effort to bring about degradation. Controlling the degradation to the desired level is therefore necessary. The typically advised degradation ranges from 5-20% degradation.[49]

i.Hydrolytic degradation:

In the chemical process of hydrolysis, a compound is degraded by interaction with water. Catalysis of the molecule's ionizable functional groups occurs during hydrolytic studies conducted in acidic and basic conditions. Acid or base stress testing involves subjecting a pharmaceutical substance to acidic or basic conditions in order to force degradation that generates primary degradants in an optimal range. The type and concentration of acid or base to use depends on how stable the drug substance is. As suitable reagents for hydrolysis, sodium hydroxide or potassium hydroxide (0.1-1 M) are indicated for base hydrolysis and hydrochloric acid or sulfuric acids (0.1-1 M) for acid hydrolysis.[48]

ii.Oxidative degradation:

Many chemical compounds go through autoxidation, which is oxidation under normal storage conditions and involves ground state elemental oxygen. Consequently, it is a crucial pathway for the degradation of many medications. A free radical initiator is necessary for the free radical reaction known as autoxidation to occur. A pharmaceutical substance's trace contaminants, metal ions, or hydrogen peroxide can initiate autoxidation. The drug substance determines the type of oxidising agent to use, as well as its concentration and environmental exposures. It has been suggested that exposing the solutions to 0.1–3% hydrogen peroxide at room temperature and a pH of neutral for seven days, or up to a maximum 20% degradation, may provide pertinent degradation products.[48]

iii.Photolytic degradation:

In order to enable direct comparisons between the drug substance and drug product, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200-watt hours/square metre with a spectral distribution of 320-400nm. To verify that the desired light exposure is produced, samples may be exposed side by side with a validated chemical actinometric system, or for the

proper period of time when circumstances have been monitored with calibrated radiometers/lux metres. The oxidation of functional groups with labile hydrogen, such as benzylic, carbon, allylic, and tertiary carbon, can result in the formation of hydroperoxides, hydroxide, or ketone. Both oxidative and nonoxidative photolytic reactions can lead to photolytic degradation.[48]

iv.Thermal condition:

The specified ICH Q1A accelerated testing conditions should not be used for testing for thermal degradation (such as dry heat and wet heat). Samples of dry and wet heat should be applied to solid-state drug substances and drug products. Drug products in liquid form should be exposed to dry heat. Studies may be carried out at higher temperatures for a shorter time. The Arrhenius equation can be used to study whether temperature affects a substance's ability to withstand heat. Where k is the rate of a specific reaction, A denotes the frequency factor, Ea denotes the energy of activation, R denotes the gas constant (1.987 cal/deg mol), and T denotes the absolute temperature. At 40 to 80 C, thermal degradation studies are conducted.

Humidity: For the establishment of forced degradation samples, typically 90% humidity for a week will be recommended. Degradation products generated from forced degradation studies are potential degradation products that may or may not be formed under relevant storage conditions but they assist in developing stability indicating method. The aim of any strategy used for forced degradation is to produce desired amount of degradation i.e. 5% to 20%.[47]

Table.3. Conditions for force degradation studies

Degradation type	Experimental conditions	Storage conditions	Sampling time (Days)
Hydrolysis	Control (no acid or base)	40^0C, 60^0C	1,3,5
	0.1 M Sodium Hydroxide	40^0C, 60^0C	1,3,5
	0.1 M Hydrochloric acid	40^0C, 60^0C	1,3,5
	Acid control (no API)	40^0C, 60^0C	1,3,5
	Base control (no API)	40^0C, 60^0C	1,3,5
	pH :2,4,6,8	40^0C, 60^0C	1,3,5
Oxidation	3% H2O2	25^0C, 60^0C	1,3,5
	Peroxide control	25^0C, 60^0C	1,3,5
	Azobisisobutyronitrile (AIBN)	40^0C, 60^0C	1,3,5
	AIBN control	40^0C, 60^0C	1,3,5
Photolytic	Light 1 ICH	Not Applicable	1,3,5
	Light 3 ICH	Not Applicable	1,3,5
	Light control	Not Applicable	1,3,5
Thermal	Heat chamber	60^0C	1,3,5
	Heat chamber	60^0C/ 75%RH	1,3,5
	Heat chamber	80^0C	1,3,5
	Heat chamber	80^0C/ 75%RH	1,3,5
	Heat control	Room temperature	1,3,5

In above mentioned **Table 3** we can refer the conditions that shall be undertaken while carrying out the forced degradation studies.[49]

Stability Indicating Studies:

The stability-indicating assay is a technique used in the pharmaceutical industry for the analysis of stability samples. The International Conference on Harmonization (ICH) recommendations have made it more evident that the development of a stability-indicating assay technique (SIAM) is a prerequisite.

An analytical technique that accurately quantitates the active components without being influenced by excipients, degradation products, process impurities, or other possible impurities is known as a stability-indicating method. Another type of stability indicating technique is one that precisely quantifies major degradants. Stability studies are used to predict the shelf life, expiration date, choose the best storage conditions, and provide labelling guidelines for products that have been developed.[48]

Development of a stability-indicating technique:

Although the requirements for stability indicating methods have been specified in regulatory regulations, neither the regulatory guidelines nor the pharmacopoeias contain information on the essential processes that must be followed for the creation and validation of stability-indicating methods. The general procedures for the stability indication technique are,

Step 1: Analyse the drug structure critically to determine the most likely degradation route

Step 2: Information gathering about physicochemical properties

Step 3: Studies on stress (forced decomposition)

Step 4: Analyses of the preliminary separation on stressed samples

Step 5: Complete method development and development

Step 6: Characterizing and identifying degradation products and creating criteria

Step 7: Validation[48]

Specific and Selective stability-indicating assay methods:

There is a lack of clarity in the terms used to distinguish between techniques that quantitatively evaluate the component of interest in the sample matrix without separating it and those that separate the drug as well as all other degradation products. As a result, a "Specific stability-indicating assay method (Specific SIAM)" is described as "a method that is able to quantify the drug(s) definitively in the presence of all degradation products, excipients, and additives, expected to be present in the formulation."[48]

CONCLUSION:

In this article, the study was carried out on several antiemetic drugs as well as dopamine antagonists. Here, in this study, we have summarised the basic principles along with the working of the analytical instruments such as UV, HPLC and HPTLC etc. In addition, we have also reviewed the parameters that are involved in analytical method development and validation. Here is a brief overview of antiemetics, including the general mechanism of action, side effects, and drug classes included in the category of antiemetic drugs. The drug profile of the antiemetic drug Metopimazine was discussed in detail. We have also discussed the potential of Metopimazine as an antiemetic drug by comparing it with the existing drugs. A detailed review of the therapeutic uses of Metopimazine was outlined. A thorough comparative study and literature review were

conducted on all available Metopimazine studies and research. The literature showed the available chromatographic techniques or methods that have been reported by various researchers for the qualitative and quantitative determination of Metopimazine in various pharmaceutical preparations. A vast historical background was done, and from this we can conclude that we cannot see much work done on Metopimazine in the field of analysis. The research or study that has been done on Metopimazine is not enough, and there should be improvements in the available methods. A gist about force degradation and stability indicating studies was also discussed. There are no studies on UV and HPLC degradation and stability indicating studies for Metopimazine available. In this way, we can conclude that the selection of the drug Metopimazine can be done on the basis of the literature review that was done in this article. The future prospective shows a wide scope of work for the drug in the field of analytical method development and validation, along with the force degradation studies that need to be developed that could provide a cost effective, rapid, and precise determination of Metopimazine in pharmaceutical dosage form.

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