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Research Article

Preformulation Studies of Metoclopramide Hydrochloride: Fundamental Part of Formulation Design

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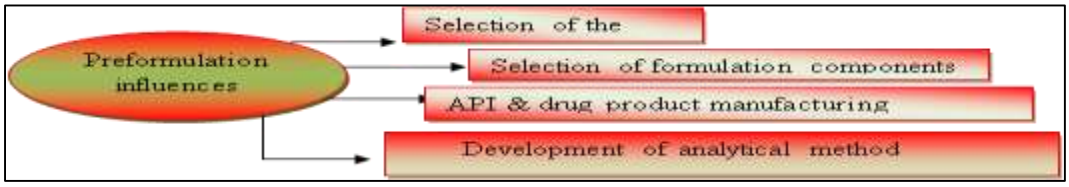
Abstract: Preformulation study is a part which is initiated once the new molecule is seeded. In a broader way, it deals with studies of physical, chemical, analytical, and pharmaceutical properties related to molecule and provides idea about suitable modification in molecule to show a better performance. Preformulation parameters study can be associated to generation of effective, safer, stable, and reliable pharmaceutical formulation. Metoclopramide is used to enhance GI motility, to treat diabetic gastro-paresis, as an anti-nauseated, and to facilitate intubation of the small bowel during radiologic examination. Metoclopramide may be used to treat chemotherapy-induced emesis and as a radiosensitizing agents in the treatment of non-small cell lung carcinoma and glioblastomas in the future. In the present works overall objective of preformulation studies of Metoclopramide HCl is to engender information useful in developing stable and Bioavailable dosage forms**.**

Keywords: Preformulation study, Metoclopramide HCL, Solubility & Analytical methods.

INTRODUCTION

Preformulation study is the chief step in the rational development of dosage forms of a drug substance. The study includes an examination of physical and chemical properties of a drug substance alone and with combined with excepient. The common endeavor of preformulation testing is to generate information helpful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico-mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials (Prasanna, K.D. *et al.*, 2015). These studies should spotlight on those physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form. A systematic considerate of these properties may eventually provide a rational for formulation design, or support the need for molecular modification. The aim of this study was to determine some of the physicochemical properties such as solubility, melting point, pKa, dissolution, assay development, stability in solution etc (Karuppusamy, C., & Venkatesan, P. 2017; Tharun, S.P. *et al.*, 2017).



Metoclopramide (Methoxy-2-chloro-5 - procainamide) a derivative of para-amino-benzoic acid, is a usually prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux and for the prevention of cancer chemotherapy- induced emesis. Metoclopramide

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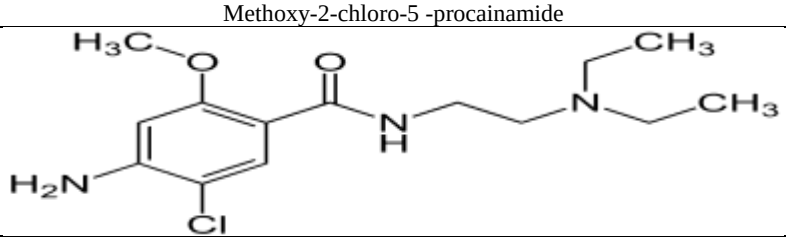
is a medication used mostly for stomach and esophageal problems. It is commonly used to treat and prevent nausea and vomiting, to help with emptying of the stomach in people with delayed stomach emptying, and to help with gastroesophageal reflux disease. It is also used to treat migraine headaches (Swati, M. *et al.*, 2017).

Drug (Metoclopramide hydrochloride) description (www.drugbank.ca/)	
IUPAC Name	Methoxy-2-chloro-5 -procainamide
Structure	
Molecular Weight	299.79638 g/mol
Proprietary name	METOCLOPRAMIDE, METOZOLV ODT, REGLAN
Molecular Formula	$C_{14}H_{22}ClN_3O_2$
Excretion	Urine (~85%); feces
Onset of Action	Oral: 30 to 60 minutes; IV: 1 to 3 minutes; IM: 10 to 15 minutes
Duration of Action	Therapeutic: 1 to 2 hours, regardless of route
Protein binding	~30%
Dose	1 to 2 mg/kg/dose (depending on the emetogenic potential of the agent) IV infused over a period of not less than 15 minutes, 30 minutes before administration of the chemotherapy.

In the present works an attempt was made to study preformulation parameters of Metoclopramide HCl which aid to produce information helpful in developing stable and Bioavailable dosage forms.

MATERIAL AND METHODOLOGY

Procurement of Drug:

The drug Metoclopramide was obtained as gift sample from JBCPL, Ancleshwer (India) which is studied for various preformulation parameters.

Preformulation studies (Mehta, R.M. 2002; Soni, Himesh., & Singhai, A. K. 2013; Raghavan, C.V. 1995)

Identification of Drug

Melting Point Determination

To determine the M.P. of drug powder, it was filled in a capillary tube with one end open and the other end closed and then the capillary was placed in a digital melting point apparatus.

Solubility

The solubility of Metoclopramide HCl was determined in different solvent systems and buffers. An excess quantity of the drug was mixed with 10 ml of each solvent in screw capped glass tubes and shaken on constant water bath shaker for 24 hours at 25 ℃. The solutions were examined physically for the absence or presence of drug.

Partition Coefficient

About 50mg of drug was dissolved in 50ml of distilled water and n-octanol separately and both the solution was mixed together by using wrist watch shaker for 30 min. Then the solution was kept in a separating funnel until two phases separated. The aqueous phase was then filtered through the filter paper and was diluted 100 times. The absorbance of both the solutions was taken at 234nm by using UV spectrophotometer. The concentration of drug was determined with the help of standard curve and partition coefficient was determined by following formula:

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous}}$$

Identification by Infrared absorption spectrum

The I.R. absorption spectrum of Metoclopramide sample should be in accordance with the I.R. absorption spectrum of standard Metoclopramide.

Identification by UV Spectrophotometer

100 mcg/ml solution of Metoclopramide in methanol shows absorption maximum at about 273 nm.

Wavelength Maximum Determination

The λ_{max} of Metoclopramide was determined in methanol by 1700 pharmaspec shimadzu spectrophotometer.

Wavelength Maximum Determination in Methanol:

10 mg of Metoclopramide was accurately weighed and dissolved in small quantity of methanol into 10 ml of volumetric flask and the volume was made up to 10 ml with methanol to produce stock solution having a concentration of 1000 µg/ml. 1 ml of solution from stock solution was pipette out in 10 ml of volumetric flask and volume was made up to 10 ml with methanol to produce the solution having a concentration of 100 µg/ml. The prepared solution was scanned in the

range of 200-400nm by Shimadzu 1700 UV spectrophotometer using methanol as blank solution.

Calibration Curve of Metoclopramide

Preparation of primary stock solution

10mg of Metoclopramide was accurately weighed and dissolved in small quantity of methanol in10 ml of volumetric flask and volume was made upto 10 ml with methanol to produce stock solution having a concentration of 1000 µg/ml.

Preparation of secondary stock solution

From the primary stock solution, 1 ml of solution was taken in the 10 ml of volumetric flask and diluted upto 10 ml with methanol to produce secondary stock solution having concentration of 100 µg/ml.

Preparation of aliquots

Aliquots having concentration range of 2-20 µg/ml was prepared by approximately diluting the secondary stock solution with methanol separately. The absorbance of each aliquot was measured at λ max 273 nm using methanol as a blank & standard curve was plotted between concentration in µg/ml on X-axis & absorbance on Y-axis.

HPLC STUDY

Preparation of Mobile phase

Mix 720 ml of methanol and 280 ml of acetonitrile. Filter and degas.

Preparation of Diluents

Mix each 500 ml of methanol and acetonitrile. Filter and degas the mixture.

Preparation of Standard Solution

Weigh accurately about 50 mg of Metoclopramide HCl working standard and transfer it into a 50 ml volumetric flask. Dissolve and make up the volume with diluent. Take 1 ml of the above solution into a 10 ml volumetric flask and dilute to the volume with diluent.

Preparation of Test Solution

Weigh accurately about 50 mg of sample and transfer it into a 50 ml volumetric flask. Dissolve and make up the volume with diluents. Take 1 ml of the above solution into a 10 ml volumetric flask and dilute to the volume with diluents.

Chromatographic Condition

Column : C18, 250 × 4.6mm, 5µm or equivalent
Flow Rate : 1.9 ml/min
Injection Volume : 20µl
Wavelength : 273 nm
Run time : 40 minutes
Retention time : Metoclopramide peak about 4.3 min.

Table 1: Solubility of Metoclopramide in different solvent

S.NO.	SOLVENT	OBSERVED SOLUBILITY
1.	Methanol	Soluble
2.	Ethanol	Sparingly soluble
3.	Water	Sparingly soluble
4.	0.1 N HCL	Sparingly soluble
5.	0.1 N NaOH	Sparingly soluble
6,	Phosphate buffer saline (pH 7.4)	Sparingly soluble

Table 2: Melting point determination

Sample no.	Melting point (^{0}C)
1.	183-185
2.	183-184
3.	182-185

Table 3: Partition coefficient of Metoclopramide

S. No.	Solvent system	Partition coefficient
1.	n-octanol:distilled water	1.99

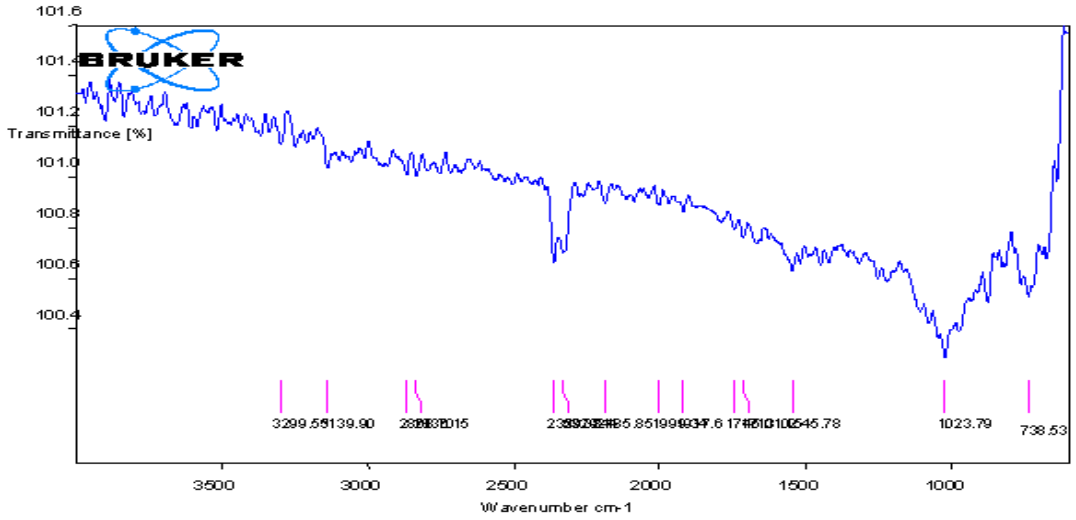


Fig. 1: IR spectra of pure drug Metoclopramide

Table 4: Interpretation of IR spectrums

Sample	Theoretical frequency(cm^{-1})	Functional group
Metoclopramide HCl	2856-2939	C-H Stretching of alkane
	1650-1690	C=O stretching of amide
	1550	C=C stretching aromatic
	3249-3323	N-H stretching of amine
	1000-1410	Amine C-N(S)
	1275	C-N stretching

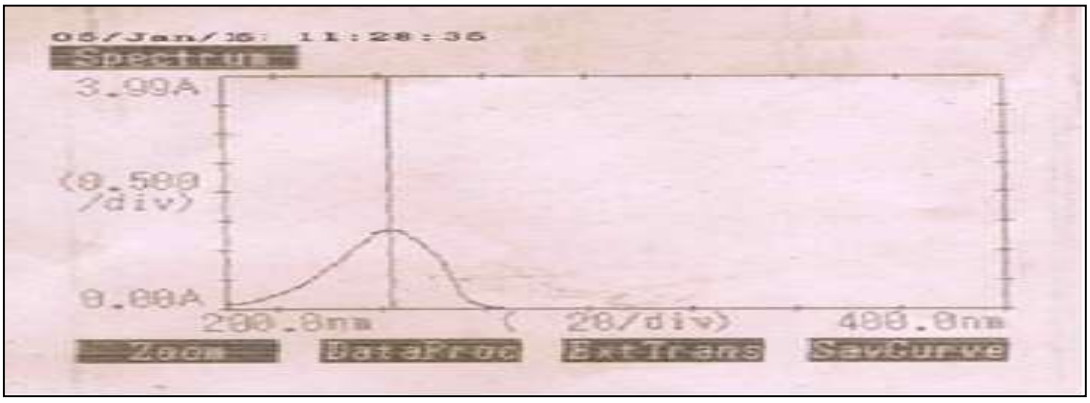


Fig.2: UV spectrum analysis of Metoclopramide in methanol

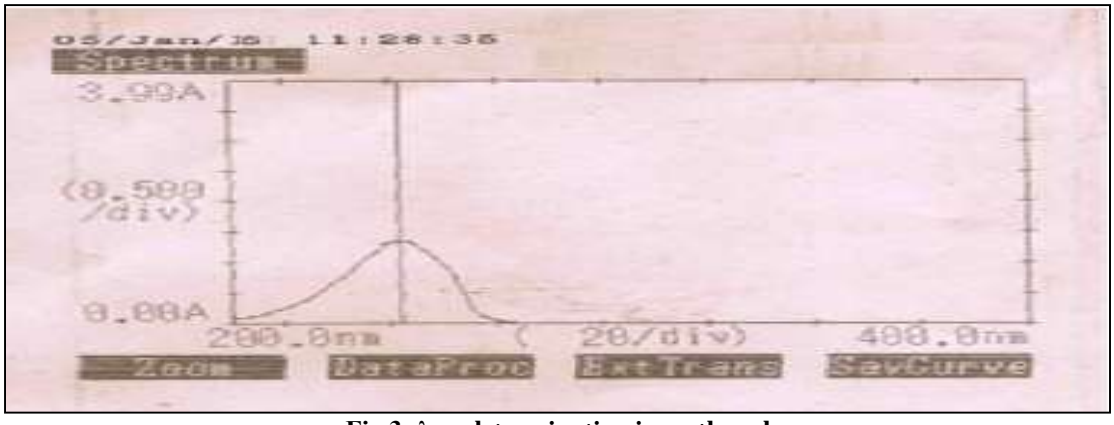


Fig.3: λ_{max} determination in methanol

Table 5: Standard curve of Metoclopramide in methanol at λ max 273 nm

S.No.	Concentration (µg/ml)	Absorbance
1.	2	0.022
2.	4	0.041
3.	6	0.067
4.	8	0.089
5.	10	0.102
6.	12	0.128
7.	14	0.145
8.	16	0.172
9.	18	0.196
10.	20	0.227

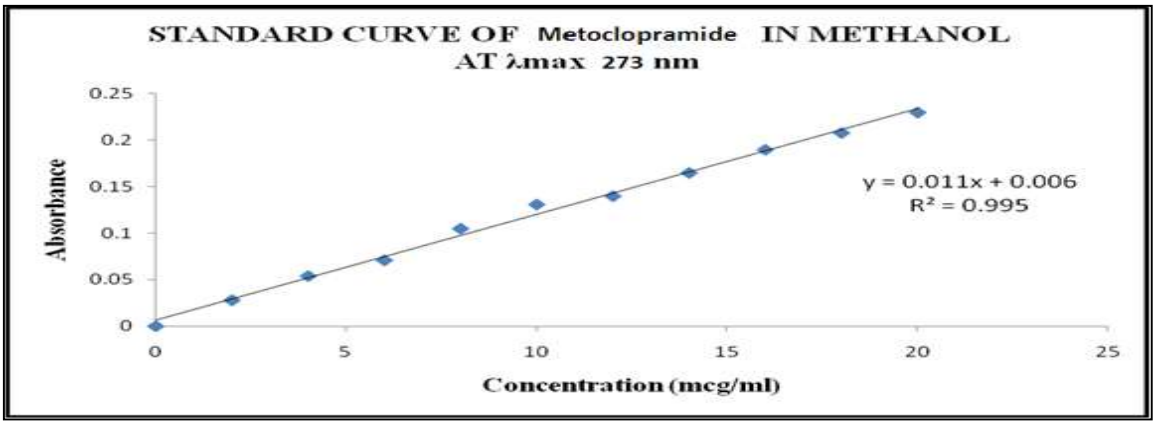


Fig.4: Standard curve of Metoclopramide in methanol at λ_{max} 273 nm

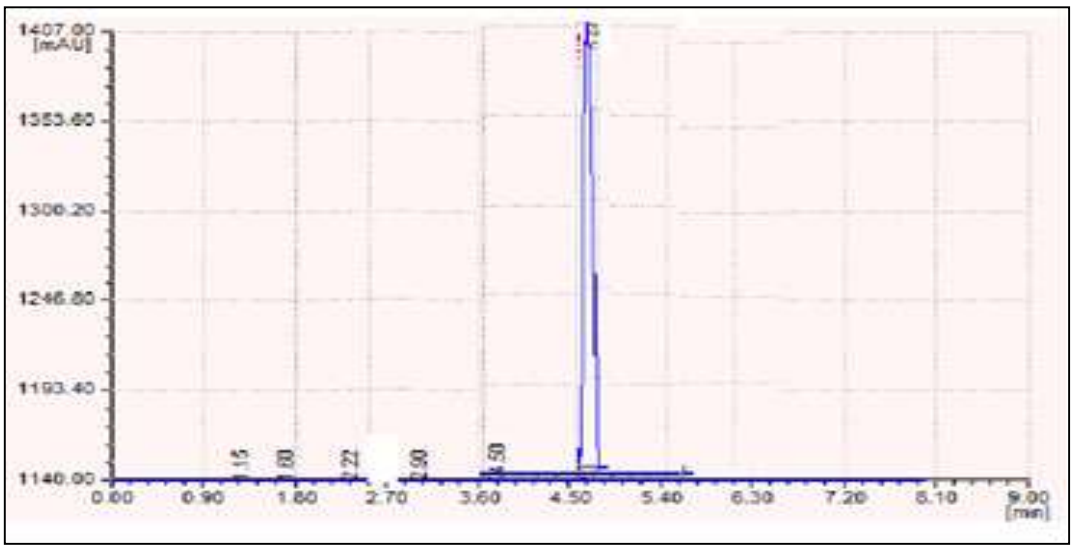


Fig.5: HPLC graph of standard Metoclopramide HCl

RESULTS AND DISCUSSION

The overall aim of the present work was to examine preformulation studies of Metoclopramide HCl is to engender information useful in developing stable and Bioavailable dosage forms. Various Preformulation Characteristics were tabulated in table 1-3. Qualitative solubility of drug was checked in various solvent and found that the drug was soluble in methanol, sparingly soluble in 0.1N HCl, phosphate buffer saline (pH 7.4) and 0.1N NaOH, insoluble in water which shows that the drug is lipophilic. Partition coefficient of the drug was determined in n-octanol:distilled water. The value of partition coefficient was found to be 1.99(table3). It confirms its lipophilic character. Melting point of drug was determined by digital melting point apparatus. The melting point was found to be in the range of 183-185^{0}C which was matched with standard melting point. The drug sample was firstly identified spectrophotometrically by UV, FTIR(fig 1 & table 4) and HPLC(Fig 5) and the result showed the authencity and purity of drug sample. The maximum absorbance of drug was determined by 1700 UV Shimadzu

spectrophotometer and was found to be at 273 nm (fig 3) which was in accordance with the standard. Standard curve of Metoclopramide was prepared using methanol by 1700 UV Shimadzu spectrophotometer. The result was tabulated in table 5 & fig 4). The result showed that Metoclopramide follows the Lambert beer's law between the concentration ranges of 2-20 µg/ml.

CONCLUSION

The preformulation phase is a crucial part in establishing the properties of drug that will allow suitable risk assessment for development. Usually it begins right through the lead optimization phase, continues through predomination, and on into the early phases of development. Hence, it is vital that preformulation should be performed as cautiously as possible to facilitate rational decisions to be made. The preformulation study of Metoclopramide HCl is to generate information constructive in developing stable and Bioavailable dosage forms.

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