CHAPTER III

PROTON PUMP INHIBITORS

Abstract

Proton pump inhibitors are widely prescribed for the treatment of gastric acid related disorders and the eradication of Helicobacter pylori. Studies pertaining to the interaction of drug with the target molecule is now a days emerging aspect in pharmacy involved in assessing the dosage of a drug. Molecular electron ionization cross section ‘Q’ a physical parameter determines the extent of interaction of electron of the drug molecule with the target molecule. Faster the reaction more is the area of cross section and less is the dosage monitored. Molecular electron ionization cross section can be evaluated from molecular polarizability and susceptibility values. The dependence of certain medicinal parameters such as protein binding, bioavailability, Log p and half life period on ‘Q’ is noted and a simplified mathematical relationship is developed to find out the dosage. To support the above analysis certain clinically important medicinal compounds such as Proton pump inhibitor drugs which involve Omeprazole, Pantoprazole, Lansoprazole and Rabeprazole are taken for study. The molecular electron ionization cross section ‘Q’ for these medicinal system is evaluated from molecular polarizability and diamagnetic susceptibilities and is used along with other medicinal parameters log P, protein binding, bioavailability and half life period etc. to calculate the dosage. The dosages of these Proton pump inhibitors are thus calculated. The dosages obtained are correlated with the reported dosage values. For example, the calculated dosage value of Lansoprazole is 0.045 grams per day agree well with the reported dosage value 0.045 grams per day. Similarity is observed in case of other medicinal compounds also.

Thus the new method of evaluation of dosage of medicine from physical properties is encouraging since it involves less cumbersome theoretical and computational difficulties.
3.1 INTRODUCTION

The most commonly and effectively used agents to combat acid peptic diseases at present are the Proton Pump inhibitor drugs and were introduced in 1980. These are the substituted benzimidazoles and act by inhibiting (H⁺/K⁺)-ATPase pump (Lanyi and Pohorille, 2001). These drugs in combination with other two antibiotics Clarithromycin and Amoxicillin are considered to eradicate nearly ≥90 per cent of *Helicobacter pylori*. Proton pump inhibitor (PPI) drug include Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole and Esomeprazole. Increased dosage or long term use of PPIs carry a possible increased risk of bone fractures in certain regions of hip, wrist and spine (Yang, et al., 2006), (Targownik et al., 2008). In connection with this FDA (Food and Drug Administration) also advises that no more than three 14 day treatment courses should be used in one year. This may be due to the reduction of stomach acid, thereby reducing the amount of calcium dissolved in the stomach. PPIs may interfere with the acid production of osteoclasts and Vitamin B12 reduction (Seppa, 2007). The profound suppression leads to alter the bacterial (*Clostridium difficile*) (Howell, et al., 2010) (Hanrahan, 2009) content of the gut i.e. raise the risk of the infection nearly up to 5per cent (Laheij et al., 2004). Recent information reveal that increased intake of PPI may cause dependence by increasing gastric symptoms. The effect of Clopidogrel on platelets and its relation to PPI treatment is under research. Development of drugs through potassium-competitive acid blockers (P-CABs) was under study (Gilard, et al., 2008).

3.2.1 OMEPRAZOLE: First PPI to reach the market in 1988 and was (Graham L. Patrick, 2006) marketed as Losec. In 1996 it became the biggest selling Pharmaceutical product.

Chemistry: Omeprazole is a substituted benzimidazolefínly), 5-methoxy-2((4methoxy -3,5-
dimethyl 1-2-Pyridinyl)methyl) Sulfinyl)1 H Benzimidazole. Its empirical formula is C₁₇H₁₉N₃O₃S, with a molecular weight of 345.42. The structure of Omeprazole is given in Fig: (3.1).

Properties: Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of Omeprazole is a
function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

**Mechanism of Action:** Omeprazole belongs to a new class of anti secretory compounds that suppress gastric acid secretion by specific inhibition of H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell. Animal studies indicate that after rapid disappearance from plasma, Omeprazole can be found within the gastric mucosa for a day or more.

Proton pump inhibitor drugs enter the parietal cells from the blood and because of their weak basic nature, accumulate in the acidic secretory canaliculi of parietal cells, where they are activated by a proton catalyzed process that results in the formation of a thiophilic sulfonamide. This activated form reacts by covalent binding with the sulfhydryl group of cysteine from the extracellular domain of the H⁺/K⁺ ATPase. Binding to cysteine 813, in particular, is essential for inhibition for that pump molecule (*Goodman and Gilman’s, 2001*).

**Indications:** Omeprazole is used in the treatment of gastric ulcer, erosive esophagitis, and gastroesophageal reflux disease with or without esophageal lesion. Omeprazole is also used in eradication of *Helicobacter pylori* in triple therapy with Clarithromycin and Amoxicillin or in double therapy with Clarithromycin only.

**Side Effects:** The most common adverse effects are head ache, diarrhea, abdominal pain, and nausea. Of the oldest agents, Omeprazole and Lansoprazole have been well established in short – term safety. PPIs are only contraindicated if the patient has a known history of hypersensitivity to them, and they should be used with caution with severe hepatic disease. (*Wayne, 2002*), (*Deerfield, 2002*), (*Titusville, 2002*).

**Drug Interactions:** Omeprazole interacts with the drugs that are substrates of CYP2C19, including diazepam, Warfarin and Phenytoin (*Saltiel and Fask, 1999*).

**3.2.2 LANSOPRAZOLE:** Lansoprazole was introduced in the year 1995.

**Chemistry:** Lansoprazole is a substituted benzimidazole, 2(((3-methyl1-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl)sulfinyl) benzimidazole, a compound that inhibits gastric acid
secretion. Its empirical formula is $\text{C}_{16}\text{H}_{14}\text{F}_{3}\text{N}_{3}\text{OS}$. The molecular structure regarding Lansoprazole is given in Fig: (3.2).

**Properties:** Lansoprazole is a white to brownish-white crystalline powder which melts with decomposition at approximately $166^0\text{C}$. Lansoprazole is freely soluble in dimethyleformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyle acetate, practically soluble in hexane and water.

**Mechanism of Action:** Lansoprazole belongs to the class of anti secretory compounds, that do not exhibit anticholinergic or histamine H2- receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the $(\text{H}^+\text{K}^+)$ATPase enzyme system at the secretary surface of the gastric parietal cell. Because, this enzyme system is regarded as the acid pump within the parietal cell, Lansoprazole has been characterized as gastric acid – pump inhibitor, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of basal and stimulated gastric acid secretion irrespective of and negative stimulus.

**Indications:** Lansoprazole is used for the treatment of duodenal ulcer (DU), both *Helicobacter pylori* positive and negative benign gastric ulcer, gastroesophageal reflux disease, erosive esophagitis and pathological hyper secretory conditions, including Zollinger- Ellision syndrome.

This is used in the eradication of *Helicobacter pyroli* in triple therapy with Clarithromycin and Amoxicillin, or in double therapy with Amoxicillin only.

**Side Effects:** The most common adverse effects are headache, diarrhea, *(Reilly, 1999), (Franko, 1998)* abdominal pain and nausea.

**Drug Interactions:** The proton pump inhibitors are metabolized by cytochrome P450 isoenzymes and therefore expected to interact with other drugs that are substrate for that enzyme system. Lansporazole interacts with theophylline through CYPI isoenzyme induction *(Welage and Berardi, 2000).*

3.2.3 PANTOPRAZOLE: Pantoprazole is introduced in year 2000.

**Chemistry:** Pantoprazole Sodium is a substituted benzimidazole, Sodium 5-(difluoromethoxy)-2((3,4-dimethoxy-2-Pyridinyl)methyl)Sulfinyl)-1H-benzimidazole sesquihydrate, a compound
that inhibits gastric acid secretion. The absolute bioavailability is approximately 77%. The molecular structure of Pantoprazole is reported in Fig: (3.3)

**Properties:** Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is recemic. Pantoprazole has weakly basic and acidic properties; It is freely soluble in water, very slightly soluble in phosphate buffer at pH7.4, and practically insoluble in n-hexane.

**Mechanism of Action:** Pantoprazole suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H<sup>+</sup>/K<sup>+</sup>) ATPase enzyme system at the secretary surface of the gastric parietal cell. This effect is dose related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H<sup>+</sup>/K<sup>+</sup>) ATPase, results in duration of antisecretory effect that persists longer than 24 hours.

**Indications:** Pantoprazole is used in the treatment of erosive esophagitis associated with GERD. The manufacturer of Pantoprazole IV is also pursuing the GERD indication for this formation.

**Side Effects:** The most common adverse effects are headache, diarrhea, abdominal pain, and nausea. The side effects are similar to almost all proton pump inhibitors.

**Drug Interaction:** Pantoprazole does not significantly affect the kinetics of the drugs as in the case of other proton pump inhibitor drugs. In vivo studies, ethanol, glyduride, antipyrine and caffeine had no clinically relevant interactions with pantoprazole. Pantoprazole in contrast to Omeprazole and Lansoprazole (Graham L.Patrick, 2006) is also metabolized by the conjugating enzyme sulftransferase.

### 3.2.4 RABEPRAZOLE:
Rabeprazole is introduced in the year 1999.

**Chemistry:** Rabeprazole Sodium is a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole is known as chemically as 2-(((4-(3-methoxypropoxy)-3-Methyl-2-pyridinyle)-methyl)sulfinyl)-4-benzimidazole sodium salt. It has an empirical formula of C<sub>18</sub>H<sub>20</sub>ON<sub>3</sub>NaO<sub>3</sub>S. The molecular structure regarding Rabeprazole is given in Fig: (3.4).

**Properties:** Rabeprazole Sodium is a white to slightly yellowish white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl, Chloroform and ethyl acetate and insoluble in ether and n-hexane.
**Mechanism of Action:** Rabeprazole enter the parietal cells from the blood and because of their weak basic nature accumulate in the acidic secretory canaliculi of the parietal cell, where they are activated by a proton catalyzed process that results in the formation of a thiophilic sulfonamide. This activated form reacts by covalent binding with the sulphydroxyl group of cystine from the extracellular domain of the H^+K^+ATPase. Binding to Cystein 813 (Good man and Gilman ’S, 2001) in particular, this is irreversible for the pump molecule.

**Indications:** Rabeprazole is used to treat erosive or ulceration GERD, DU and hypersecretory including ZES.

**Side Effects:** In general proton pump inhibitors are well tolerated, and the incidence of short term adverse effects is relatively uncommon. The range and occurrence of the adverse effects are similar for all the proton pump inhibitors.

Common adverse effects include: headache, nausea, diarrhea, abdominal pain, fatigue, and dizziness.
Figure: (3.1) Molecular Structure of Omeprazole

Figure: (3.2) Molecular Structure of Lansoprazole
Figure: (3.3) Molecular Structure of Pantoprazole

Figure: (3.4) Molecular Structure of Raberazole
3.3 METHODS OF INVESTIGATION: (Murthy and Raghuram, 2007) (Murthy et al., 2007), (Murthy et al., 2008).

Biomolecules such as carbohydrates, proteins, lipids, nucleic acids etc act as drug targets and the study of drug–target interactions is an emerging field in the development of new drugs. Several dread full diseases such as auto immune diseases, cancers, AIDS, certain genetic diseases (Diabetes, Alzheimer’s disease, etc.) etc are cured based on prolonged drug–dosage activity studies.

Many physico-chemical techniques as well as quantum mechanical approaches are in vogue in studying these interactions. An attempt is made by Murthy and his school since 1995 to correlate the molecular electron ionization with the dosage of the medicine and the toxic effects. The present work is the extension of the studies of these aspects of medicinally important systems that are used as proton pump inhibitors.

The advantage of the present work is based on the molecular structure and fundamental properties like refraction, susceptibilities etc., from which the activity of the electrons partaking in the interaction can be understood. This is a non destructive novel method.

The physical parameters like molecular polarizability, diamagnetic susceptibility and molecular electron ionization cross section are utilized in evaluating the dosage of a drug. The above parameters are obtained through Quantum mechanical approach of Lippincott, Bond polarizability and bond refraction from Le F’evre.

3.3.1 THEORETICAL METHODS:

The mean molecular polarizability of these proton pump inhibitors has been derived by the theoretical approaches of Lippincott and Stutmann, additivity of bind refractions and bond polarizabilities. The details of these techniques are given in the earlier papers of Murthy and et al., (Rao et al.,1976)(Murthy et al.,1979), (Rao and Murthy, 1979) (Rao et al., 1979),(Murthy et al., 1980), (Subbaiah et al., 1983), (Murthy et al., 1991), (Subbaiah et al., 1994), (Murthy et al., 1996), (Murthy and Sreenivasulu, 1997) and (Murthy et al., 2003) and explained in Chapter II.
3.3.1.1 **Lippincott-δ function potential model:** (Lippincott and Stutmann, 1964) (Lippincott et al., 1966) Evaluation of polarizability by Lippincott method involves four steps.

1) The parallel component of polarizability of each bond.
2) The non-bond region electron contribution to the parallel component of polarizability.
3) The estimation of perpendicular component of polarizability from atomic polarizabilities knowing number of degrees of freedom and
4) Determination of mean molecular polarizability from above components.

\[ \alpha_M = \frac{1}{3} [\sum \alpha_{\parallel P} + \sum \alpha_{\parallel n} + \sum 2 \alpha_{\perp}] \]  

Equation (3.1)

The method of evaluation of above these components of polarizability are given in Chapter II.

Using bond lengths of the bonded atoms and other relevant parameters, the parallel components of polarizability from bond region and non-bond region of electrons are calculated. The perpendicular component of polarizability is estimated from the atomic polarizability by appropriate relation given in Chapter II. From these values the mean molecular polarizabilities are calculated using the expression (3.1).

The data required for the calculation of the molecular polarizability such as the bond lengths of all bonds, electro negativities and other relevant information on parameters like C and H etc. are taken from the latest edition of CRC hand book (85th edition.) (David R. Lide, 2004). The δ function strength, reduced electron negativities are taken from the work of Lippincott and Stutmann. (Lippincott and Stutmann, 1964) (Lippincott et al., 1966) The values of \( \sum \alpha_{\parallel P} \), \( \sum \alpha_{\parallel n} \) and \( \sum 2 \alpha_{\perp} \) calculated for these Proton pump inhibitors are given in Table (3.1).

3.3.1.2 **BOND REFRACTION:** The information regarding bond refractivities of various bonds present in these systems are taken from Le Fevre (Le Fevre, 1965) and the mean molecular polarizability is obtained through the equation (3.2).

\[ \alpha_M = [3/4\pi N] \gamma (R_\infty) \]  

Equation (3.2)
N is the Avogadro number, $R_\infty$ is the molar refraction at infinitive wave length; $\gamma$ is the specific density or molar density. And the mean molecular of these molecules ($\alpha_M$) is thus calculated.

**3.3.1.3 BOND POLARIZABILITY:** Molecular polarizability can also be obtained by the above method. The data on bond polarizability $\alpha_i$ required to calculate the mean molecular polarizability is taken from the values of Le F'evre. *(Le F'evre, 1965).*

The formula for calculating $\alpha_M$ is given by

$$\alpha_M = n_1 \alpha_{(c=c)} + n_2 \alpha_{(c-c)} + \ldots = \sum n_j \alpha_j$$

Where, $\alpha_j$ is the bond polarizability of the $j^{th}$ kind and $n_j$ is the number of such bonds. The values of mean molecular polarizabilities by various methods are reported in Table (3.2).

**3.3.1.4 DIAMAGNETIC SUSCEPTIBILITY:**

**THEORETICAL METHOD:** Murthy et al. *(Rao et al., 1979), (Murthy et al., 1996)* suggested a relation to evaluate the diamagnetic susceptibility which is given by the equation (3.4)

$$\chi_M = \gamma m \sigma_1 \alpha_M$$

Where, $\gamma$ represents the saturation factor $(0.9)^n$, $n$ is the number of unsaturated bonds or rings present in the molecule. The details of this method are given in Chapter II. The diamagnetic susceptibility evaluated by this method using the equation (3.4) are reported in Table (3.3).

The theoretical diamagnetic susceptibility values are supported by experimental method by Vibrating Sample Magnetometer (VSM), Indian Institute of Technology (IIT), Madras, Chennai, India. The experimental $\chi_M$ values are presented in Table (3.3).

**3.3.1.5 MOLECULAR ELECTRON IONIZATION CROSS SECTION, ‘Q’:** An introductory note on molecular electron ionization cross section ‘Q’ and its relation to molecular polarizability ($\alpha_M$) and diamagnetic susceptibility ($\chi_M$) has already been given in Chapter II. Beran and Kevan *(Beran and Kevan, 1969)* observed the proportionality between ($\alpha_M$) and $\chi_M$ on one hand, $\chi_M$ and Q on the other hand. When these two methods are put together the dependence of Q on $\lambda$ becomes explicit. The unsaturated characters of these bonds are expected
to affect the Q values. So, Rao et al. (Rao et al., 1979) modified the equation (3.5). The values of Q obtained from diamagnetic susceptibility are presented in Table (3.4).

\[ Q \left( \text{in } 10^{-16} \text{cm}^2 \right) = 0.278 \gamma \chi_M \]  \hspace{1cm} \text{------------------------ (3.5)}

A comparative study on Q along with other medicinal parameters such as protein binding, log P (Hydrophobic nature), bioavailability and half life period was attempted. The importance of these medicinal parameters on drug activity is described in Chapter I. The necessary information on medicinal parameters and other data of these systems are collected from Drug bank of Wikipedia and reference (Good man and Gilman, 2001) and reported in Table (3.5).

### 3.3.2 EXPERIMENTAL METHODS:

The experimental results regarding diamagnetic susceptibility can be obtained from Vibrating Sample Magnetometer method (VSM) as a support to the theoretical approach.

**Vibrating Sample Magnetometer Method (VSM):** VSM measures the magnetic properties of materials like diamagnetic, paramagnetic, ferromagnetic and antiferromagnetic susceptibilities. The present experimental results are obtained using VSM from IIT, Madras, Chennai, India.

Two drugs belonging to proton pump inhibitors namely Omeprazole and Pantoprazole responded to experimental determination of diamagnetic susceptibility by Vibrating Sample Magnetometer method. The experimental data related to \( \chi_M \) values of Omeprazole and Pantoprazole are reported in Table (3.3.1) and Table (3.3.2). Thus evaluated diamagnetic susceptibility values from the data obtained experimentally are specified in Table (3.3).

### 3.4 THE PRESENT METHOD:

The evaluation of dosage based on the electro ionization cross section ‘Q’ and interdependence of certain medicinal parameters such as PB, BA, log P and Half life has been done with the help of a mathematical expression (3.6) (Murthy et al., 2010a) (Murthy et al., 2010b) (Murthy et al., 2011).

\[ \beta = \left[ (Q/D)^{2/3} L(\log P) \right]^{\gamma/5} \]  \hspace{1cm} \text{------------------------ (3.6)}

Where,

Q - Electron ionization cross section in \( 10^{-16} \text{cm}^2 \)
D - Dosage of the drug in grams per day

L - is the half life period of drug in hours

Log P – Hydrophobicity of the medicinal compound

\[ \alpha = \frac{(PB)(BA)}{6n}\sigma^{3} \]

Where,

\( \alpha \) - is the characteristic parameter depending on the activity of the drug.

\( n \) - the number of unsaturated bonds

PB - Plasma protein binding of drug in percentage

BA – Bioavailability of drug expressed in percentage

\( \sigma \) - the Covalence factor

3.5 RESULTS AND DISCUSSION:

The mean molecular polarizabilities evaluated by different methods Lippincott, Bond polarizability, Bond refraction method show similar values. The \( \alpha_{M} \) value of Rabeprazole by bond polarizability is 471.284 in \( 10^{-25} \) cm\(^3\), by bond refraction is 451.545 in \( 10^{-25} \) cm\(^3\) and by Lippincott method is 360.581 in \( 10^{-25} \) cm\(^3\) (Table 3.2). The susceptibility and ‘Q’ obtained by polarizability also agree well with each other. This gives strong support to the theoretical approach (Table 3.3 and 3.4). For example \( \chi_{M} \) value of Omeprazole derived from Lippincott method is 16.230x10\(^6\) C.G.S. Units, bond polarizability is 22.213x10\(^6\) C.G.S. Units, and that of bond refraction is 22.984x10\(^6\) C.G.S. Units and for ‘Q’ is 3.289, 4.502, 4.658 in \( 10^{-16} \) cm\(^2\). Similarity is observed in case of other medicinal compounds also.

The experimental diamagnetic susceptibility values of both Omeprazole and Pantoprazole exhibit proximate values compared to the theoretical values (Table 3.3). The experimental value of Omeprazole is 22.00 in \( 10^{-6} \) C.G.S. units against the theoretical value 22.212 in \( 10^{-6} \) C.G.S. units. Similarly Pantoprazole has theoretical value 25.967 in \( 10^{-6} \) C.G.S. units against the
experimental value 28.02 in $10^{-6}$ C.G.S. units. The difference in the value may be due to the other constituents interfering within the medicinal compound.

Table (3.4) comprises the evaluated theoretical electron ionization cross section values obtained by Lippincott method, bond polarizability and bond refraction methods and experimental value of ‘Q’ derived from $\chi_M$ of VSM. The experimental values of ‘Q’ agree well with the theoretical values. For example the reported value of ‘Q’ is $4.545 \times 10^{-16}\text{cm}^2$ for Omeprazole against the theoretical value $4.658 \times 10^{-16}\text{cm}^2$.

A close look at the dosage of the medicinal compounds, calculated and reported, reveals the following features. The calculated dosage of Pantoprazole i.e. 0.060 grams per day agree well with the reported dosage value 0.060 grams per day. In the same way Lansoprazole has the suggested dosage value 0.045 grams per day agree well with the calculated dosage value 0.045 gram per day. Similar observation is done in case of other proton pump inhibitor drugs, Omeprazole and Rabeprazole.

An analytical approach on Q and certain medicinal parameters reveal some observations. Generally medicinal compounds having similarity in their structure are analyzed. In case of proton pump inhibitor drugs, Pantoprazole has the ‘Q’ value $7.25 \times 10^{-16}\text{cm}^2$ against reported dosage value 0.60 grams per day which is less, compared to the Lansoprazole ‘Q’ value 8.1 in $10^{-16}\text{cm}^2$.and decreased dosage value 0.45 grams per day. Similarly Rabeprazole has higher ‘Q’ value i.e. $14.15 \times 10^{-16}\text{cm}^2$ higher than ‘Q’ value of Lansoprazole and Pantoprazole and lower dosage value i.e. 0.30 grams per day when compared to Lansoprazole (0.045 grams per day) and Pantoprazole (0.06 grams per day) reported dosage values. From the above data, it is inferred that the drugs having higher ‘Q’ value are preferred than the drugs having lower ‘Q’ value because they are suggested in lower dosages. These type of drugs may also reduce the side effects and toxicity caused by the drug. Much variation has not been observed with ‘Q’, Electron ionization cross section and other medicinal parameters such as half life and log P.

A plausible explanation for this behavior may be given as follows. An increase in electron transportation activity reflected by higher electron ionization cross section will tender the chemical reaction to be faster. Hence the transfer of electron from the donor to the place of
malignity will make the process curing faster. Thus very little dosage of the medicine will be sufficient. A long continued impingement of the electrons on the malign cells might develop saturation effects. Hence the life time of the drug for limited time suggested. Thus an increase in $Q$ explains lower half life and lower dosage. A continued dosage of such medicine might result in undesirable toxic effects.

Rigorous work is under study to understand the relation between ’$Q$’, dosage and other medicinal parameters of certain clinically important medicinal compounds.
Table 3.1 Molecular polarizabilities of drugs by Lippincott method (in $10^{-25}$ cm$^3$)

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name of the drug</th>
<th>$\sum \alpha_{\parallel P}$</th>
<th>$\sum \alpha_{\parallel n}$</th>
<th>$\sum 2\alpha_{\perp}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole</td>
<td>711.313</td>
<td>32.889</td>
<td>238.492</td>
</tr>
<tr>
<td>2</td>
<td>Pantoprazole</td>
<td>681.306</td>
<td>45.503</td>
<td>281.175</td>
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<tr>
<td>3</td>
<td>Rabeprazole</td>
<td>748.494</td>
<td>32.869</td>
<td>300.379</td>
</tr>
<tr>
<td>4</td>
<td>Lansoprazole</td>
<td>676.334</td>
<td>41.543</td>
<td>266.677</td>
</tr>
</tbody>
</table>

Table 3.2 Molecular Polarizablities ($\alpha_M$) (in $10^{-25}$ cm$^3$)

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name of the drug</th>
<th>$\alpha_M$ by Bond Polarizability</th>
<th>$\alpha_M$ by Bond Refraction</th>
<th>$\alpha_M$ by Lippincott method</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Omeprazole</td>
<td>448.351</td>
<td>463.925</td>
<td>327.565</td>
</tr>
<tr>
<td>2</td>
<td>Pantoprazole</td>
<td>431.059</td>
<td>463.136</td>
<td>335.994</td>
</tr>
<tr>
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<td>Rabeprazole</td>
<td>471.284</td>
<td>451.544</td>
<td>360.581</td>
</tr>
<tr>
<td>4</td>
<td>Lansoprazole</td>
<td>406.283</td>
<td>437.384</td>
<td>328.184</td>
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### Table 3.3 The diamagnetic susceptibility values $\chi_M$ in $10^6$ CGS Units

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of the drug</th>
<th>From $\alpha_M$ by Bond Polarizability</th>
<th>From $\alpha_M$ by Bond Refraction</th>
<th>From $\alpha_M$ by Lippincott method</th>
<th>Experimental values by VSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole</td>
<td>22.213</td>
<td>22.984</td>
<td>16.230</td>
<td>22.00</td>
</tr>
<tr>
<td>2</td>
<td>Pantoprazole</td>
<td>33.314</td>
<td>35.793</td>
<td>25.967</td>
<td>28.02</td>
</tr>
<tr>
<td>3</td>
<td>Rabeprazole</td>
<td>72.872</td>
<td>69.820</td>
<td>55.755</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Lansoprazole</td>
<td>37.566</td>
<td>40.461</td>
<td>30.328</td>
<td>-</td>
</tr>
</tbody>
</table>

### Table 3.3.1 Diamagnetic susceptibility values of Omeprazole obtained from VSM

<table>
<thead>
<tr>
<th>Field(G)</th>
<th>Moment(emu)$\times 10^4$</th>
</tr>
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<tbody>
<tr>
<td>10000.2</td>
<td>1.66</td>
</tr>
<tr>
<td>10500.2</td>
<td>3.80</td>
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<tr>
<td>12000.3</td>
<td>4.16</td>
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<tr>
<td>18000.4</td>
<td>5.28</td>
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<tr>
<td>18500.3</td>
<td>5.74</td>
</tr>
<tr>
<td>20000.4</td>
<td>5.87</td>
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</table>
Table 3.3.2 Diamagnetic susceptibility values of Pantoprazole obtained from VSM

<table>
<thead>
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<th>Field(G)</th>
<th>Moment(emu)x10⁴</th>
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<tbody>
<tr>
<td>3000.1</td>
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</tr>
<tr>
<td>4500.0</td>
<td>1.90</td>
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<tr>
<td>6000.1</td>
<td>3.10</td>
</tr>
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<td>8500.1</td>
<td>3.80</td>
</tr>
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<td>9500.1</td>
<td>4.00</td>
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<td>10500.2</td>
<td>4.30</td>
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<tr>
<td>12000.2</td>
<td>5.80</td>
</tr>
<tr>
<td>12500.3</td>
<td>6.50</td>
</tr>
<tr>
<td>13500.3</td>
<td>7.50</td>
</tr>
</tbody>
</table>

Table 3.4 Electron ionization cross section in 10⁻¹⁶cm²

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of the drug</th>
<th>From αₚ by Bond Polarizability</th>
<th>From αₚ by Bond Refraction</th>
<th>From αₚ by Lippincott Method</th>
<th>From Experimental value of χₚ by VSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole</td>
<td>4.502</td>
<td>4.658</td>
<td>3.289</td>
<td>4.545</td>
</tr>
<tr>
<td>2</td>
<td>Pantoprazole</td>
<td>6.751</td>
<td>7.254</td>
<td>5.263</td>
<td>5.678</td>
</tr>
<tr>
<td>3</td>
<td>Rabeprazole</td>
<td>14.768</td>
<td>14.149</td>
<td>11.299</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Lansoprazole</td>
<td>7.614</td>
<td>8.199</td>
<td>6.070</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 3.5 Electron ionization cross section (in $10^{-16}$ cm$^2$) and other medicinal parameters

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of the drug</th>
<th>$Q$</th>
<th>Protein Binding(%)</th>
<th>Bioavailability (%)</th>
<th>LogP</th>
<th>Half Life(hrs)</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole</td>
<td>4.658</td>
<td>95</td>
<td>35</td>
<td>1.166</td>
<td>0.5-1</td>
<td>1.387</td>
</tr>
<tr>
<td>2</td>
<td>Pantoprazole</td>
<td>7.254</td>
<td>98</td>
<td>77</td>
<td>1.268</td>
<td>1</td>
<td>2.025</td>
</tr>
<tr>
<td>3</td>
<td>Rabeprazole</td>
<td>14.149</td>
<td>96.3</td>
<td>52</td>
<td>1.177</td>
<td>1-2</td>
<td>1.340</td>
</tr>
<tr>
<td>4</td>
<td>Lansoprazole</td>
<td>8.199</td>
<td>97</td>
<td>80</td>
<td>1.733</td>
<td>1.5</td>
<td>1.598</td>
</tr>
</tbody>
</table>

Table 3.6 Drug dosage (in grams per day)

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name of the drug</th>
<th>$\alpha$</th>
<th>$\beta'$</th>
<th>Calculated dosages</th>
<th>Reported dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole</td>
<td>0.065</td>
<td>1.389</td>
<td>0.028</td>
<td>0.030</td>
</tr>
<tr>
<td>2</td>
<td>Pantoprazole</td>
<td>0.285</td>
<td>2.018</td>
<td>0.060</td>
<td>0.060</td>
</tr>
<tr>
<td>3</td>
<td>Rabeprazole</td>
<td>0.035</td>
<td>1.344</td>
<td>0.027</td>
<td>0.030</td>
</tr>
<tr>
<td>4</td>
<td>Lansoprazole</td>
<td>0.095</td>
<td>1.598</td>
<td>0.045</td>
<td>0.045</td>
</tr>
</tbody>
</table>
REFERENCES


• Possible Increased Risk of Bone Fractures With Certain Antacid Drugs”. U S Food and Drug Administration. 25 May 2010.


