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Wajiha Gul
Faculty of Pharmacy, Jinnah University for Women, Nazimabad, Karachi, Pakistan.

Sidra Sajid
Faculty of Pharmacy, Jinnah University for Women, Nazimabad, Karachi, Pakistan.

Fouzia Hamid
Faculty of Pharmacy, Jinnah University for Women, Nazimabad, Karachi, Pakistan.

Sania Bhatti
Faculty of Pharmacy, Jinnah University for Women, Nazimabad, Karachi, Pakistan.

Correspondence:
Wajiha Gul
Asst. Prof., Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan.

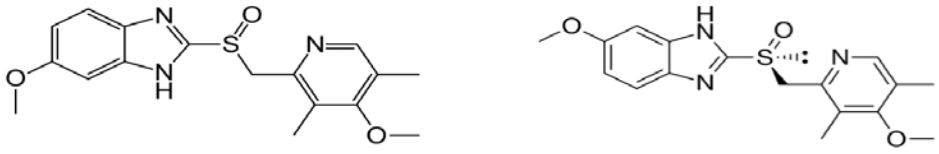
Effect of acidic Ph. and heat on the degradation of omeprazole and Esomeprazole

Wajiha Gul, Sidra Sajid, Fouzia Hamid, Sania Bhatti

Abstract
Omeprazole and esomeprazole are proton pump inhibitors. The influence of heat and acidic pH on the degradation of both the drugs has been observed and the changes in the concentration were monitored by UV spectrophotometry. These drugs are very sensitive to heat and acidic environment. Degradation was conducted on both neat solution and pharmaceutical formulation. It was found that degradation is much more pronounced by acidic medium as compared to heat. The presences of excipients has a role in affecting the degradation of the pharmaceutical product.

Keywords: omeprazole, esomeprazole, degradation, heat, acidic ph.

1. Introduction
In recent years, the importance of non-biological alteration in the breakdown of drugs has been widely noticed and there are in progress a large number of researches concerning degradation mechanisms, kinetics, isolation and toxicity of degradation products. [1, 2] The aspect of our interest is to evaluate the degradation of product. Our objective in this study was to determine the main factors that lead to degradation like heat and effect of acid.
Omeprazole (OMZ) and esomeprazole are potent inhibitors of gastric acid secretion by selectively interacting and inhibiting the gastric parietal cell proton pump. [3] (Figure 1) Proton pump inhibitors have low water solubility and degrade rapidly in acidic medium as compared to basic medium. OMZ was widely used in the treatment of active duodenal ulcer, active benign gastric ulcer, gastro esophageal reflux disease, erosive esophagitis and other pathological hyper secretary conditions like Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis. [4, 5] Esomeprazole is indicated for the treatment of acid-reflux disorders, *H. pyroli* eradication and peptic ulcer disease. [6] Physicochemical properties of the two drugs are summarized in Table 1.



(a) (b)

Fig 1: Structures of (a) OMZ and (b) esomeprazole

Table 1: Physicochemical properties of OMZ and Esomeprazole [9, 10]

	Omeprazole	Esomeprazole
IUPAC name	**6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1H-1,3-benzodiozole**	**(S)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-3H- benzimidazole**
Molecular formula	$C_{17}H_{19}N_3O_3S$	$C_{17}H_{19}N_3O_3S$
Molecular mass	345.4 g/mol	345.4
Melting point	155 C	155 C
Solubility	0.359 mg/ml (water)	0.353 mg/ml (water)
Log P	2.23	0.6
pK_a	9.29 (acid), 4.77 (base)	9.68 (acid), 4.77 (base)
Refractivity	96.33 $m^3.mol^{-1}$	93.66 $m^3.mol^{-1}$

The drawbacks are mainly related to the physicochemical instability to heat, light and acidic media, even with coated formulations. Moreover the low aqueous solubility of OMZ, ~0.4% at 25 ºC, is responsible for small dissolution rates and so low bioavailability [7]. OMZ is acid labile and a prodrug. It is converted into its active sulphenamide form by rearrangement under acidic conditions. It is a racemic mixture of S and R enantiomers. Esomeprazole is the S-enantiomer of OMZ and is optically stable in humans [8].

The stability of OMZ decreases in acidic medium, when it comes in contact of acidic medium leads a significant degradation of the drug and hence reduced bioavailability [11-13]. Due to its low bioavailability, short biological half-life [14] and hepatic first pass metabolism, various oral formulated as enteric-coated granules and tablets have been developed with a subsequent 40% increase in oral bioavailability of OMZ but have a wide individual variation of plasma concentration in human. [15-18] Omeprazole has been recently found that in surface water of Lambro river [19] stability studies have been conducted especially on OMZ and esomeprazole have revealed that it is acid labile and sensitive to light, humidity, organic solvents and heat [20, 21].

2. Materials and Methods

Omeprazole and esomeprazole capsules were taken from a local pharmacy while the source of active ingredient was China. Method use for quantitative analysis was UV visible spectroscopy and Shimadzu UV-160A UV Visible Recording spectrophotometer was used to carry out assay of Omeprazole and esomeprazole. The absorbance of all the solutions was analyzed at 305 nm.

Omeprazole (8.5% pellets)

Preparation of Standard Solution

217.6 mg of omeprazole pallets (working standard) were crushed and transferred into a 100 ml volumetric flask and 0.1 N NaOH was added upto volume. The solution was sonicated for 5 mins. 10 ml of this solution was transferred to 100 ml volumetric flask and the volume was made up with 0.1 N NaOH.

Preparation of Sample

20 capsules of omeprazole were accurately weight and 225.3 mg of pellets were crushed, transferred in a 100 ml volumetric flask and was sonicated for 5 mins. The volume was made up with 0.1 N NaOH. 10 ml of the resulting solution was transferred in a 25 ml volumetric flask and the volume was made up with 0.1 N NaOH.

Esomeprazole (22.5% pellets)

Preparation of Standard Solution

89 mg of the working pellets of esomeprazole were crushed and transferred in a 100 ml volumetric flask and sonicated for 5 mins. The volume was made up using 0.1 N NaOH. 0.5 ml of the solution was taken in a 100 ml volumetric flask and with the same solvent volume was made up.

Preparation of Sample Solution

Out of accurately weight 20 capsules, 89 mg of the esomeprazole pellets were crushed and transferred in a 100 ml volumetric flask and sonicated for 5 mins. The volume was made up with 0.1 N NaOH. 5 ml of the solution was taken in a 25 ml volumetric flask and the volume was made up with the same solvent.

Degradation by heat

The final dilutions of omeprazole and esomeprazole were subjected to heat by placing it in the water bath at 80 ºC for 45 mins.

Degradation by acidic pH

To the final dilutions of both the drugs 0.1 N HCl was added and the pH was adjusted to 3.0.

3. Result and Discussion

Degradation studies are important while manufacturing pharmaceutical formulation, especially when meant to be administered orally. The degradation properties of OMZ and esomeprazole were carried out in order to improve the pharmaceutical formulation. Results of the study of the degradation of OMZ and esomeprazole are shown in table 2 and 3 respectively. The acid has shown to degrade OMZ to a greater extend as compared to heat. Similar results were observed in case of esomeprazole where the drug had degraded more in the presence of acidic medium as compared to the heat in the water bath. Although acidic has shown to degrade the drugs more but OMZ has been found to be degraded more than esomeprazole. The effect of heat on esomeprazole is more pronounced on esomeprazole as compared to OMZs of the excipients in the formulation. It has also been observed that the neat solution has undergone more degradation as compared to the neat solution. The reason may be the presences of the excipients hindering and interfering in the process [22].

Table 2: Assay and degradation of OMZ

Parameters	Std	%	% of deg.	Sample	%	% of deg.
Assay	0.875	-	-	0.871	99.64	-
Heat	0.725	82.87	17.13	0.781	89.37	10.63
Acidic pH	0.208	23.84	76.16	0.276	31.62	68.38

Table 3: Assay and degradation of esomeprazole

Parameters	Std.	%	% of deg.	Sample	%	% of deg.
Assay	0.794	-	-	0.789	99.43	-
Heat	0.704	88.78	11.22	0.678	84.87	15.13
Acidic pH	0.190	23.98	71.02	0.292	36.87	63.13

4. Conclusion

According to the above results of degradation studies it can be concluded that both OMZ and esomeprazole shows high sensitivity to heat and acidic medium. It can also be concluded from the result that using suitable excipients will improve the stability hence maximizing the bioavailability.

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