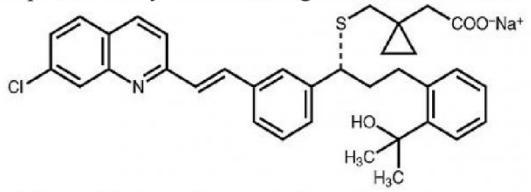
UDC 547.52.59

J. Hrakovsky, R. Tenengauzer, G. Bogomolny, Y. Dolitzky

EFFECT OF PHARMACEUTICAL FORMULATION ON THE OXIDATIVE DEGRADATION OF MONTELUKAST SODIUM

Montelukast is a selective, orally active leukotriene receptor antagonist that inhibits the leukotriene $CysLT_1$ receptor and has been shown to be effective in the treatment of chronic astma. Montelukast sodium is currently marketed by Merck in the form of film coated tablets and chewable tablets under the trade name Singulair ® [1].

The chemical name for montelukast sodium is [R -(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl]propyl] thio]methyl] cyclopropaneacetic acid, monosodium salt. Montelukast sodium salt is understood to be represented by the following structural formula:



The oxidation of montelukast due to the presence of the thioether moiety leads to form in dosage form of the sulphoxide [2], wherein its content should not be increased by more than 1% by weight from the initial amount of montelukast after storage at about 40° C and about 75% relative humidity for 3 months. Therefore, there is a need to select pharmaceutically acceptable excipients.

To perform this study the sample mixtures of montelukast sodium and each of the individual excipients [3] were prepared. The composition of each of the samples is listed in table. Each sample was stored at 55° C for 48 hours. The percentage by weight of sulfoxide relative to montelukast sodium in each preparation was measured at time zero and after storage using high performance liquid chromatography.

The analysis was carried out on a Beta-Basic C18 (150×4.6mm) 5 µm (Thermo Electron Corporation) column maintained at 40° C using an isocratic mode. Mobile phase comprising a mixture of acetonitrile and 20mM KH_2PO_4 in the ratio 60:40 was pumped at a flow rate of 1.5 mL/min. The UV detector was set at 225 nm or 281 nm. The results are shown in table.

As illustrated by table, the present of microcrystalline cellulose in the composition caused a substantial increase in the amount of the sulfoxide upon storage. The amount of sulfoxide also increased in the presence of aspartame. There was no substantial change in the amount of the sulfoxide upon storage in the presence of the other excipients.

Table 1. Analysis of Montelukast Sodium Composition with Various Exicipients

No.:	Sample composition	% Sulfoxide	
		Time zero	After storage
1	Montelukast sodium (a)	0.63	–
2	Montelukast sodium (1 g)/microcrystalline cellulose (10.1 g)	0.59	1.52
3	Montelukast sodium (1.5 g)/lactose (9.5 g)	0.60	0.63
4	Montelukast sodium (3.5 g)/hydrohypropylcellulose (7.4 g)	0.58	0.62
5	Montelukast sodium (7.5 g)/crospovidone (3.6 g)	0.69	0.68
6	Montelukast sodium (9.4 g)/magnesium stearate (1.8 g)	0.56	0.57
7	Montelukast sodium (b)	0.26	–
8	Montelukast sodium (1 g)/mannitol (36 g)	0.25	0.28
9	Montelukast sodium (2 g)/aspartame (2 g)	0.24	0.73
10	Montelukast sodium (2 g)/aerosil (2 g)	0.25	0.25
11	Montelukast sodium (2 g)/microcrystalline cellulose (20 g)/ crospovidone (8 g)	0.71	1.2

REFERENCES

1. PHYSICIANS' DESK REFERENCE® 59edition, p.2141.

2. Dufrense, C., Gallant M., Gareau Y., Ruel R., Trimbe L., Labelle M / Synthesis of montelukast (MK-0476) metabolic oxidation products //J. Organic Chem. 1996, 8518-8525.

3 Rowe, R. C; Sheskey, P. J; Owen S. C. Handbook of Pharmaceutical Excipients, 5th ed. Pharmaceutical Press, 2006,850 p.

Авторы статьи:

Храковская Юлия, руководитель отдела Teva Pharmaceutical Industries Ltd. (IL)

Тененгаузер Рут, руководитель отдела Teva Pharmaceutical Industries Ltd. (IL)

Богомольный Григорий, координатор проекта Teva Pharmaceutical Industries Ltd. (IL) E-mail: grigory.bogomolny@teva.co.il

Долитцки Юдит, руководитель аналитической лаборатории Teva Pharmaceutical Industries Ltd. (IL)