

Effect of light and heat on the stability of montelukast in solution and in its solid state

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Abstract

The chemical stability of montelukast (Monte) in solution and in its solid state was studied. A simultaneous measurement of Monte and its degradation products was determined using a selective HPLC method. The HPLC system comprised a reversed phase column (C18) as the stationary phase and a mixture of ammonium acetate buffer of pH 3.5 and methanol (15:85 v/v) as the mobile phase. The UV detection was conducted at 254 nm.

Monte in solution showed instability when exposed to light leading to the formation of its *cis*-isomer as the major photoproduct. The rate of photodegradation of Monte in solution exposed to various light sources increases in the order of; sodium < neon < tungsten < daylight < UV (254 nm). The extent of photodegradation was influenced by solvent type, where Monte was found to be most stable in 70% methanol. In solid state, Monte showed more than 20% decrease in its potency after exposure to daylight for 1 week. Also unpacked Monte chewable tablets, exposed to daylight for 2 weeks, showed a decrease of about 10% with the formation of Monte *S*-oxide as a major photoproduct. On the other hand, Monte film-coated tablets either unpacked or in its immediate pack showed excellent stability under the same condition. The thermal stress testing study of Monte in solutions at 65 °C showed that it is highly stable in NaOH solution, while it degrades rapidly in both acidic and H₂O₂ solutions. The major degradation product in the latter solvent was Monte *S*-oxide and it was also detected as a major degradation product in Monte tablet dosage form during the incubation at 40 °C/75% RH for 6 months. Findings of this study have helped to understand the stability behavior of Monte and to establish the critical parameters, which may affect its analysis and manufacturing activities.

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1. Introduction

Montelukast (Monte) is an oral selective leukotriene receptor antagonist that inhibits the cysteinyl leukotriene cysLT₁ and has been shown to be effective in the treatment of chronic asthma [1]. Chemically, it is 2-[1-[(R)-[3-[2(E)-(7-chloroquinolin-2-yl) vinyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl-sulfanylmethyl] cyclopropyl] acetic acid sodium salt (Fig. 1).

Monte is a light sensitive compound and this necessitates special handling precautions to protect it from light, in solution and in its solid state [2–9]. Several workers reported such precaution. For example, in the determination of Monte and its *S*-enantiomer

in human plasma by HPLC, it was mentioned that all samples should be protected from light during preparation and injection [2]. The use of amber glass vials was required for storage the samples prior the HPLC analysis in Monte pharmacokinetics and bioavailability study [3] and in using a pressurized liquid extraction (PLE) technology to extract Monte from chewable tablets [4]. In simultaneous analysis of Monte and loratadine by HPLC, all volumetric flasks were wrapped with black paper and stored in the dark prior to analysis [5]. During the investigation of self-association properties for Monte, samples were wrapped with aluminum foil and protected from light [6]. During the synthesis of Monte [7] and its metabolic oxidation products [8], it was also reported that the reaction mixture and the isolated product were protected from light. It was also mentioned that samples collected after the isolation of Monte from human bile should be stored in the dark and the analysis was performed under amber light conditions [9]. On the other hand, Glenn and his co-

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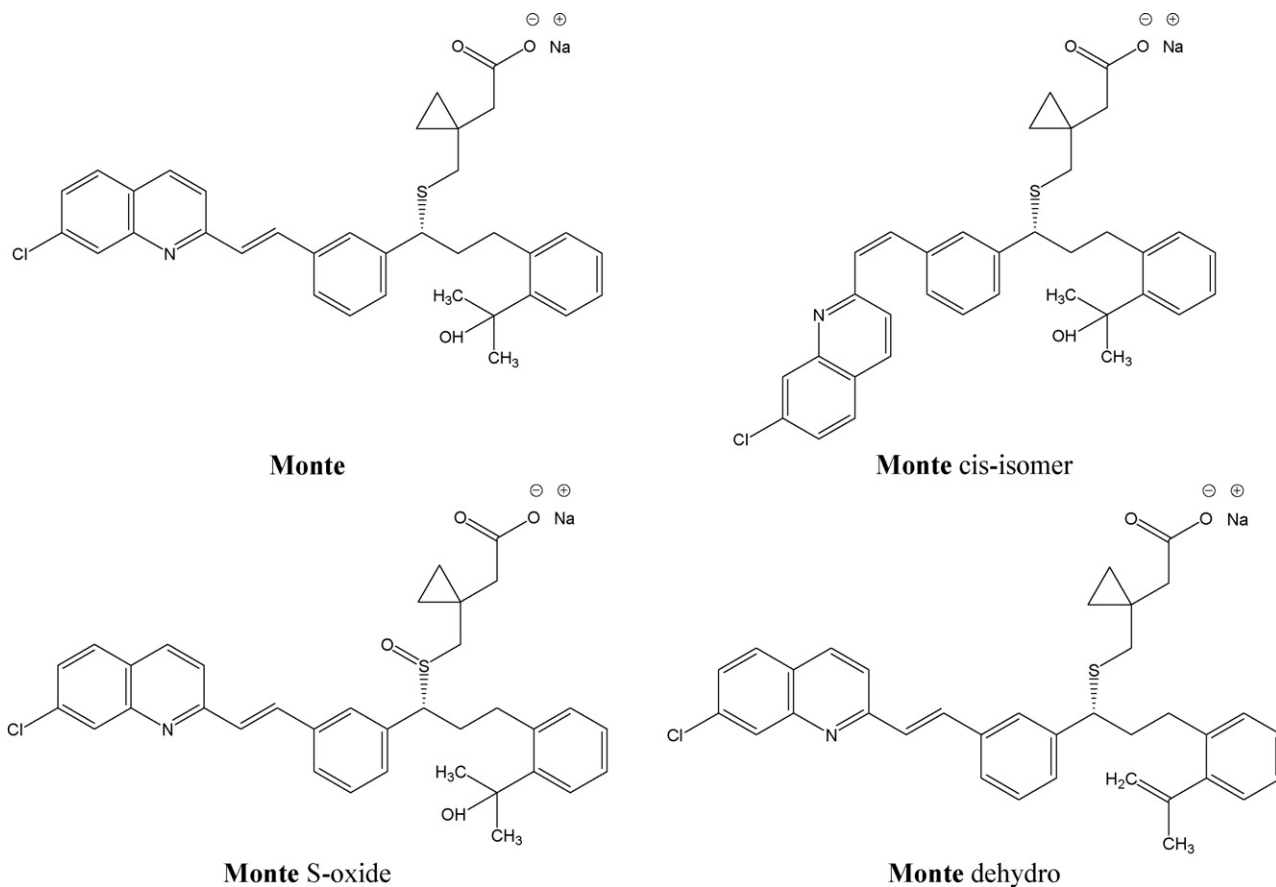


Fig. 1. Chemical structures of Monte and its related impurities.

workers, in their bioequivalence studies, suggested determining Monte under ambient conditions without any light restrictions and sample handling requirements [10]. The assay determination was based upon the summation of the Monte and its photoproduct contents. Upon exposure to light, the (E)-ethenyl moiety of Monte readily rotates to the (Z) geometric configuration leading to the formation of its *cis*-isomer (Fig. 1) [6,8,10]. From these studies, it is clear that the environmental conditions and handling requirements are critical in Monte analysis, synthesis, and formulation, since it is very sensitive to light.

As reported earlier [5], stress testing on Monte solutions by heat (60 °C) and UV light (254 nm) was performed to prove that the proposed HPLC method is stability indicating. The results indicated that Monte was thermally not stable in acidic media and also completely photodegraded in the mobile phase when exposed to the UV light for 24 h. However, oxidation of Monte was not considered in this study. The proposed HPLC method was applied to quantify Monte in Singulair[®] 5 chewable tablets at room temperature.

Using an HPLC method for the determination of Monte in human plasma and in its tablet dosage form was reported [11]. In this study, the stability of Monte in plasma samples at room temperature and photodegradation of its methanolic solution by direct room light were only used to prove the stability indicating potential of the analytical method. The developed method was adopted to determine quantitatively Monte in Singulair[®]

10 tablets at room temperature. In addition, the photodegradation rate constant was calculated for the sample exposed to direct room light (not specified) for different time intervals (up to 96 h). The photodegradation study indicated a first-order degradation behavior with a rate constant of 0.0214 h⁻¹.

To our best knowledge, there is no research published in the literature studying thoroughly the behavior of Monte towards light and heat. Meanwhile, there is no analytical method in the literature to quantify simultaneously Monte, its synthetic impurities and degradation products in pharmaceutical formulations. Thus, the present work involves a quantitative study of the stability of Monte to evaluate the effect of light source, temperature and solvent on the extent of its stability in solution and in solid state. This investigation may help in characterizing the critical parameters affecting the stability of Monte and thus proposes suitable conditions to carry out analysis, synthesis and formulation activities.

2. Experimental

2.1. Materials

Monte, Monte S-oxide and Monte dehydro were obtained from the Jordanian Pharmaceutical Manufacturing (JPM) Co. Monte *cis*-isomer was obtained by exposing the methanolic solution of Monte (10 mg/ 100 ml) to daylight to reach the max-

imum conversion to its *cis*-isomer (about 90% after 10 h) as monitored by the HPLC method described below. The chemical structures of Monte and its three related impurities are shown in Fig. 1. Monte 5 mg chewable and 10 mg film-coated tablets (Singulair®/MSD and Monkast®/JPM) were collected from the Jordanian market. All other chemicals were of analytical and HPLC grades obtained from Merck/Germany and Acros/Belgium.

2.2. Instrumentation

Du-650i UV–vis spectrophotometer (Beckman, USA). HPLC instrument equipped with a P1000 pump and a UV1000 detector (TSP, USA). The thermal stability was conducted using HC 0020 incubator (Heraeus Vötsch, Germany). The light sources include low-pressure Sodium (589 nm, 250 W, Vialox Nav-T (Son-T), Osram, Germany), Neon (600–700 nm, 36 W, MazdafLOUR, France), Tungsten (220 V, 75 W, Sumalux, PR China), and low-intensity UV (254 nm, 230 V, 80 W, 022.9610 Reprostar 3 and 022.9611 Transilluminator/Camag, Switzerland). The daylight referred to the experimental work corresponds to indoor indirect daylight (midday time) in the laboratory.

2.3. Photo and thermal degradation procedure

2.3.1. In solution

All experimental procedures were carried out in a dark chamber under subdued light. Prior to irradiation, Monte solutions were protected from light by wrapping the containers with aluminum foil and were freshly prepared for each experiment to avoid any exposure effect. All experiments were performed in triplicate. Samples were prepared by dissolving 100 mg Monte in 100 ml methanol (Monte stock solution), 10 ml portions were separately diluted with 70% methanol (in water), 0.1 M NaOH, or 0.1 M HCl (prepared in 70% methanol to prevent precipitation of Monte) to obtain a final concentration of 10 mg/100 ml. The samples were placed in Pyrex flasks prior to exposure to light at time intervals of 0, 1, 2, 4, and 6 h.

For thermal degradation, 10 ml portions of the Monte stock solution were placed in 100 ml flasks, then 40 ml of 0.1 M NaOH, 0.1 M HCl or 1% H₂O₂ was added to each flask and incubated at 25° and 65 °C for different periods of time, then the volume completed to 100 ml with methanol.

2.3.2. In solid state

To study the effect of light on Monte as a drug substance and in its tablet dosage form, the ICH guideline Q1B [12] was followed, but neon and daylight were used as light sources. Samples of Monte (20 mg each) and unpacked Monte tablets were spread in well-sealed glass vials and directly exposed to neon and daylight (at window away from the direct sunlight, summer days) for different periods of time (1, 2 and 3 weeks). Other samples of Monte tables in its immediate pack (Al/Al) were treated in the same manner described above. Control samples of each tested item were kept in a dark.

For the thermal stability, Monte tablets in their immediate pack (Al/Al) were incubated at 40 °C/75% RH for 6 months. To measure the content of Monte and its degradation products, the tablets were powdered and samples equivalent to 20 mg Monte were shaken in 70 ml of 70% (v/v) methanol for 15 min, then the volume completed to 100 ml with the same solvent. Portions of the final solution were centrifuged and analyzed using the below HPLC method.

2.4. Analytical methods

The UV–vis spectrophotometric analysis was carried out by scanning the samples over the wavelength range of 400–200 nm in 1 cm UV cell.

A stability indicating and validated HPLC method was used to determine simultaneously Monte and its degradation products as shown below. A mixture of aqueous 0.05 M ammonium acetate buffer of pH 3.5 (the pH adjusted using glacial acetic acid) and methanol in the ratio 15:85 (v/v) was used as the mobile phase and octadecyl silane column as the stationary phase (TSP, Hypersil ODS 250 mm × 4.6 mm, 10 μm). The UV detector was set at 254 nm, a flow rate of 1.5 ml/min and an injection loop of 20 μl were used.

3. Results and discussion

3.1. HPLC method evaluation

The HPLC method was initially tested for system suitability (i.e., peak symmetry, repeatability, and resolution) and for validation parameters (i.e., specificity, recovery, stability in solution, linearity and limit of quantitation (LOQ)) according to USP and ICH guidelines [13,14]. Fig. 2 represents the HPLC chromatogram for Monte (10 mg/100 ml), its two degradation products Monte *cis*-isomer (0.1 mg/100 ml) and Monte *S*-oxide (0.1 mg/ml) and its synthetic impurity Monte dehydro (0.04 mg/100 ml). The chromatogram shows a good separation between Monte and its related impurities. The summary data for system suitability (Table 1) indicates that the method is suitable to be used in stability studies, where the resolution, tailing factors and injection repeatability are within the acceptable criteria (e.g., resolution > 2, tailing factor < 3, and R.S.D. of replicate injections < 2%). In addition, analysis of samples

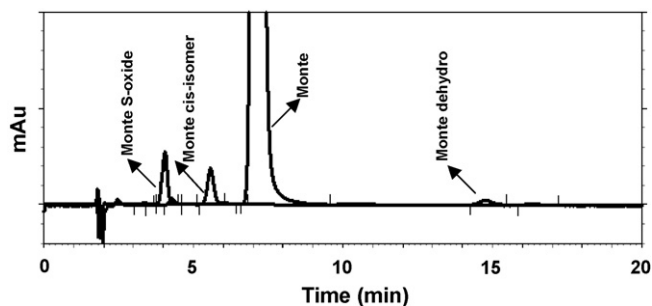


Fig. 2. HPLC chromatogram of a mixture of Monte (10 mg/100 ml), Monte dehydro (0.04 mg/100 ml), Monte *cis*-isomer and Monte *S*-oxide (0.2 mg/100 ml) in 70% methanol.

Table 1
The system suitability data for Monte and its related compounds

Compound	Retention time (min)	Repeatability (R.S.D.)	Tailing factor	Resolution	Normalization factor
Monte <i>S</i> -oxide	3.9	1.5	0.9	2.0	1.1
Monte <i>cis</i> -isomer	5.0	1.0	0.9	2.5	1.1
Monte	6.3	0.7	1.1	2.8	1.0
Monte dehydro	13.8	1.1	1.1	5.8	1.1

obtained from stress-testing study (at 25° and 65 °C for different time intervals) in solutions indicated that the HPLC method is stability indicating. Accuracy of the method was investigated by testing six different sample preparations containing Monte (10 mg/100 ml), Monte *cis*-isomer (0.1 mg/100 ml), Monte *S*-oxide (0.2 mg/100 ml) and Monte dehydro (0.04 mg/100 ml) in 70% methanol. The %recovery for each compound is calculated by using Monte reference standard taking into consideration the normalization factors for each compound (Table 1). %Recovery and R.S.D. for six replicates are within the range of 98.7–103.5 and 0.9–1.8%, respectively. The method was linear over the range of $\pm 50\%$ of the target concentrations with r^2 of more than 0.996. The LOQ values are 0.01, 0.005, 0.05, and 0.03 mg/100 ml for Monte, Monte *cis*-isomer, Monte *S*-oxide and Monte dehydro, respectively.

3.2. UV–vis spectrophotometry study of Monte photodegradation

Fig. 3(A) shows the UV–vis spectra of Monte solution (2 mg/100 ml) in 70% methanol before and after exposure to daylight for different time intervals. The spectra showed a decrease in the absorbances by the time of exposure in the region 250–400 nm. The analysis by HPLC demonstrated the appearance of a new peak at a retention time of 5 min, attributed to Monte *cis*-isomer. As obtained by a diode array detector (Fig. 3(B)), the UV–vis spectrum of Monte *cis*-isomer has a lower absorptivity than Monte at wavelength below 260 nm. It is clear from the spectra that the wavelength at about 254 nm is an isosbestic point, thus this wavelength was set as a detection wavelength in HPLC analysis to quantify both Monte and its photoproduct (Monte *cis*-isomer) as shown below. At this detection wavelength, it was observed the Monte lost due to irradiation was almost recovered in the Monte *cis*-isomer form (Table 2).

3.3. HPLC study of Monte photodegradation

3.3.1. In solution

In a preliminary work, it was found that Monte is degraded rapidly by daylight and UV light (data not shown in Table 2). This is in agreement with that was reported by Radhakrishna et al. [5]. For example, the %content of Monte and Monte *cis*-isomer were about 70 and 30%, respectively after 15 min of UV exposure in 70% methanol. Using amber flasks reduces the photodegradation, for example, 10% of Monte *cis*-isomer is produced after 4 h of daylight exposure, while 77% is produced in clear flasks. Upon exposure to daylight for 1 h in a clear

flask, 72% of Monte remained and 30% of Monte *cis*-isomer was formed. The same stability was obtained after exposure for 1 h in 0.1 M NaOH and 0.1 M HCl, where the percentages of Monte and Monte *cis*-isomer formed were in the range of 71–78 and 15–22%, respectively. Monitoring the photodegradation with time showed that there is a decrease in Monte content accompanying an increase in Monte *cis*-isomer (Fig. 4). It was noticed that the respective sums of the percentage recoveries of Monte and Monte *cis*-isomer were close to 100 (i.e., mass balance) for all cases except the irradiation by daylight in 0.1 M NaOH solution. This indicates that another degradation pathway occurred in the latter medium leading to molecular breakdown under daylight irradiation.

However, when Monte was exposed to a light source of lower irradiation energy such as sodium or neon (wavelength less than 500 nm), it was found that it is more stable compared with the

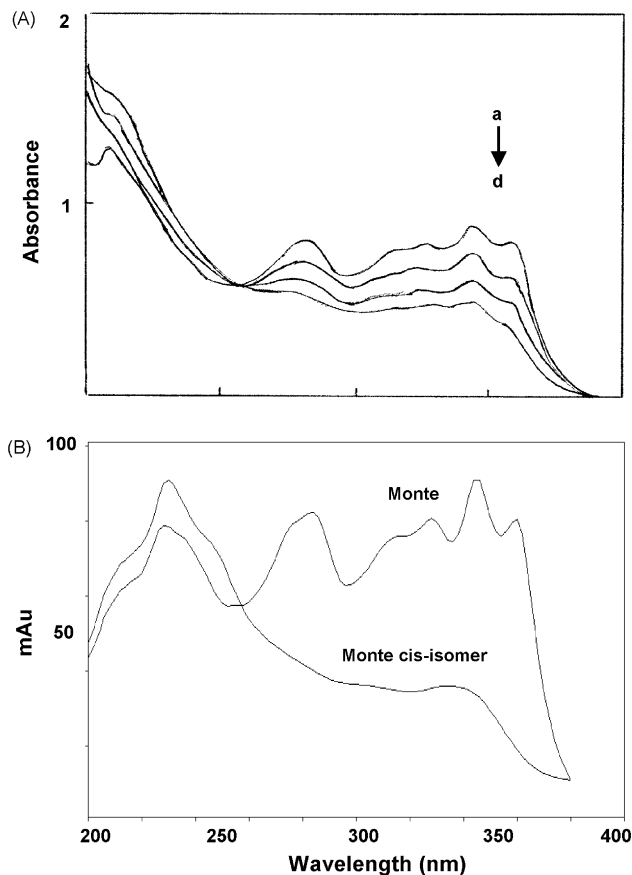


Fig. 3. (A) UV–vis spectra of Monte (2 mg/100 ml) in 70% methanol after exposure to daylight for (a) 0.0 h, (b) 1.0 h, (c) 2.0 h and (d) 4.0 h. (B) UV–vis spectra of Monte and Monte *cis*-isomer obtained by diode array HPLC detector.

Table 2
The photodegradation of 10 mg/100 ml solution of Monte in different solvents and by using different light sources

Time (h)	Sodium		Neon		Tungsten	
	%Monte	%Monte <i>cis</i> -isomer	%Monte	%Monte <i>cis</i> -isomer	%Monte	%Monte <i>cis</i> -isomer
In 70% methanol						
0	100.0 (1.4)	0.1 (0.0)	100.0 (1.1)	0.1 (0.0)	100.0 (0.4)	0.1 (0.0)
1	101.1 (0.9)	0.3 (0.0)	100.0 (0.3)	0.5 (0.0)	98.5 (0.4)	1.0 (5.1)
2	101.2 (0.4)	0.5 (0.0)	100.4 (1.0)	0.6 (0.0)	97.7 (0.1)	2.3 (10.2)
4	99.8 (1.1)	1.0 (4.9)	99.2 (0.5)	1.3 (4.0)	97.0 (0.6)	3.9 (5.4)
6	99.8 (0.9)	1.5 (9.2)	98.2 (0.1)	1.9 (2.8)	94.0 (0.8)	6.7 (5.5)
$K (\times 10^3 \text{ h}^{-1})$	1.5		3.3		9.2	
S.E.	1.4		1.0		1.3	
r^2	0.2546		0.7859		0.9437	
In 0.1 M NaOH solution						
0	100.0 (1.4)	0.1 (0.0)	100.0 (1.4)	0.1 (0.0)	100.0 (1.2)	0.1 (0.0)
1	99.9 (1.7)	0.4 (0.0)	100.0 (1.4)	0.5 (9.1)	96.3 (0.8)	1.3 (11.2)
2	100.0 (1.2)	0.6 (7.9)	99.9 (0.6)	0.9 (6.0)	93.3 (1.4)	2.8 (7.5)
4	99.2 (0.6)	1.3 (4.2)	99.6 (0.4)	1.7 (3.1)	91.0 (0.9)	4.1 (2.5)
6	99.1 (0.7)	1.6 (6.3)	98.1 (0.5)	2.5 (4.1)	86.6 (0.5)	6.3 (4.3)
$K (\times 10^3 \text{ h}^{-1})$	1.7		3.0		22.4	
S.E.	0.4		0.9		2.3	
r^2	0.8580		0.7933		0.9696	
In 0.1 M HCl solution						
0	100.0 (1.6)	0.1 (0.0)	100.0 (0.6)	0.1 (0.0)	100.0 (0.4)	0.1 (0.0)
1	97.7 (1.1)	2.8 (3.7)	95.8 (0.5)	3.7 (5.1)	96.0 (0.1)	1.9 (10.1)
2	93.4 (0.2)	5.8 (5.0)	91.7 (0.7)	6.0 (5.2)	92.0 (1.5)	5.0 (3.2)
4	87.2 (0.6)	10.8 (6.3)	85.2 (0.7)	12.6 (5.4)	87.7 (0.3)	6.7 (4.8)
6	82.9 (1.5)	14.6 (3.0)	79.7 (1.3)	15.4 (5.3)	82.4 (1.0)	9.8 (5.1)
$K (\times 10^3 \text{ h}^{-1})$	32.4		37.7		31.3	
S.E.	1.7		1.2		1.8	
r^2	0.9922		0.9969		0.9897	

Numbers between the brackets correspond to the R.S.D. K and S.E. are the photodegradation rate constant and its standard error ($n=3$).

daylight exposure (Table 2, Fig. 5). From the previous spectral data, Monte absorbs light at wavelengths over 400 nm and thus would be capable of absorbing the visible and UV energy of the daylight leading to photodegradation.

In 0.1 M HCl ($\text{pH} \approx 1$), where Monte exists as a protonated species ($\text{p}K_a$ values are 2.8 and 5.7) [6], it degraded faster than in

70% methanol and 0.1 M NaOH (Table 2, Fig. 5). This may indicate that the molecular rearrangements in acidic media occurred rapidly to form the Monte *cis*-isomer [15]. All control samples in dark at 25 °C showed that Monte solutions are stable in 70% methanol and 0.1 M NaOH, however, in acidic solution, other degradation products (about 2%) were observed after 6 h.

Nevertheless, quantitative comparison between the present work and that reported earlier [11] is difficult because the experimental conditions were significantly different (e.g., light source, solvent, exposure time), but both studies proved the sensitivity of Monte to light.

3.3.2. In solid state

Fully exposure of Monte powder to daylight showed that it is not stable. Its content dropped by 20% after 1 week with the formation of Monte *S*-oxide and Monte *cis*-isomer as major photoproducts. Meanwhile, control samples in dark and samples exposed to neon light for 3 weeks proved that Monte is stable ($\% \text{Monte} > 99\%$, $\% \text{Monte } cis\text{-isomer}$ and $\% \text{Monte } S\text{-oxide} < 0.3\%$). In addition, packed Monte tablets (Both chewable and film-coated) in Al/Al blisters proved to be highly stable when exposed to neon and daylight for 3 weeks (data not shown). However, unpacked Monte chewable tablets, when exposed to daylight for the same period of time (Table 3), showed a gradual

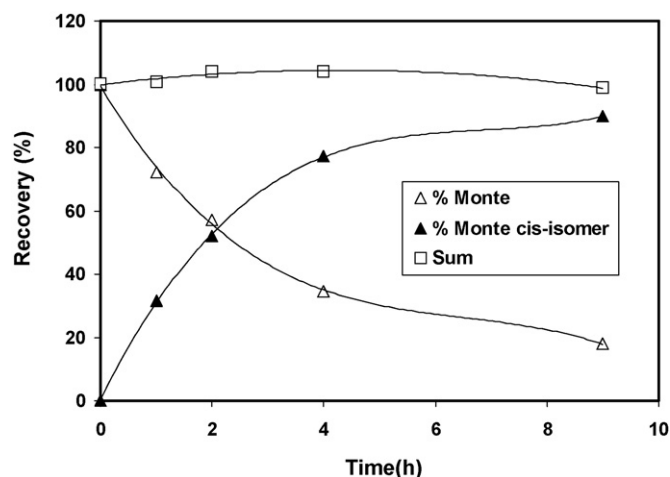


Fig. 4. Photodegradation curve of Monte (10 mg/100 ml) in 70% methanol exposed to daylight at different time intervals.

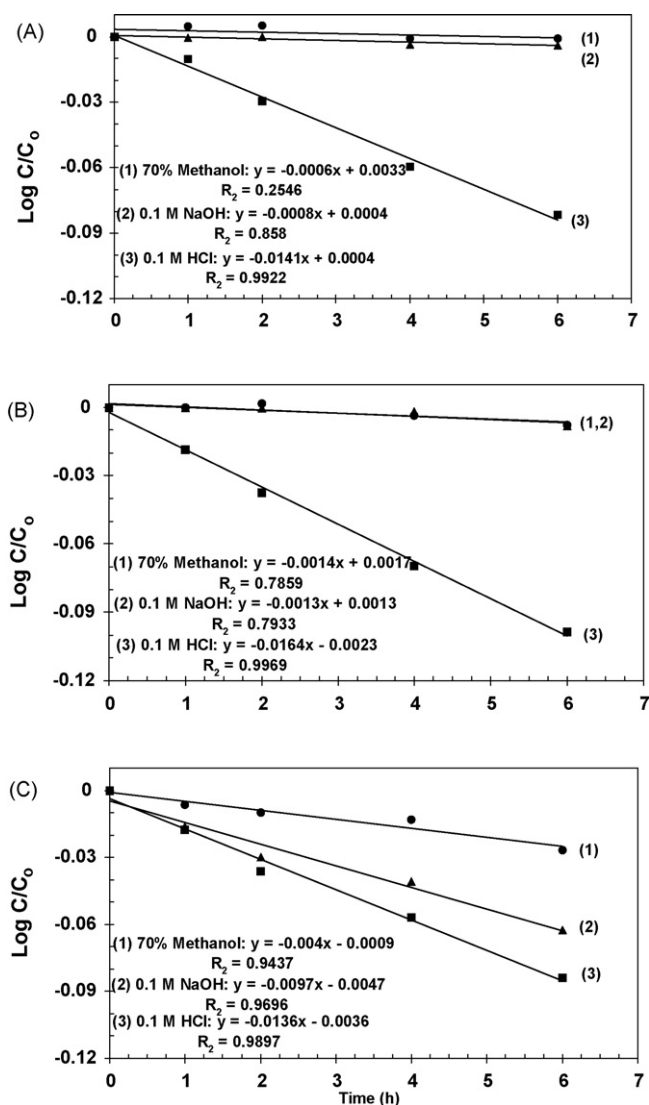


Fig. 5. First-order plots of degradation rate of Monte obtained in different solvents after exposure to different light sources: (A) sodium, (B) neon and (C) tungsten.

decrease in Monte content (about 96 and 90% after 1 and 2 weeks, respectively). The decrease in Monte content was accompanied by a significant increase in the Monte *S*-oxide (2%) compared with the content of Monte *cis*-isomer (0.3–0.5%). This phenomena was not observed with unpacked Monte film-coated tablets, which proves that the film coating in this case served to protect Monte against daylight degradation.

It is worth mentioning that the major photoproduct in solution is Monte *cis*-isomer (as shown in Section 3.3.1), while in solid state it is Monte *S*-oxide indicating that solvents used in this work facilitate photoisomerization rather than photooxidation.

3.4. Montelukast thermal degradation

Monte in its solid state and in water showed excellent stability when incubated at 65 °C for 70 days, where the %Monte was more than 99% and only Monte *S*-oxide was found as a degradation product. The 0.2% of Monte *S*-oxide was detected

Table 3

The %content of Monte and it impurities in its tablet dosage form (unpacked) after exposure to daylight for 1, 2 and 3 weeks

Compound	Initial	1 week	2 weeks	3 weeks
Singular 5 chewable				
Monte	104.4	96.8	91.7	91.0
Monte <i>S</i> -oxide	0.5	1.8	2.3	2.4
Monte <i>cis</i> -isomer	<0.2	0.3	0.3	0.2
Monte dehydro	<0.1	<0.1	<0.1	<0.1
Other	<0.1	0.8	0.7	0.7
Monkast 5 chewable				
Monte	101.3	95.1	91.2	89.1
Monte <i>S</i> -oxide	0.6	1.4	1.7	1.8
Monte <i>cis</i> -isomer	<0.2	0.5	0.5	0.4
Monte dehydro	<0.1	<0.1	<0.1	<0.1
Other	<0.1	0.8	0.8	0.8
Singular 10 film-coated				
Monte	100.3	101.8	102.8	99.0
Monte <i>S</i> -oxide	0.3	0.5	0.5	0.5
Monte <i>cis</i> -isomer	<0.2	<0.2	<0.2	0.4
Monte dehydro	<0.1	<0.1	<0.1	<0.1
Other	<0.1	<0.1	<0.1	0.3
Monkast 10 film-coated				
Monte	100.5	101.8	102.8	98.9
Monte <i>S</i> -oxide	0.3	0.5	0.5	0.5
Monte <i>cis</i> -isomer	<0.2	<0.2	<0.2	<0.2
Monte dehydro	<0.1	<0.1	<0.1	<0.1
Other	<0.1	<0.1	<0.1	<0.1

Table 4

The %content of Monte and it impurities in its tablet dosage form after incubation at 40 °C/75% RH for 1 and 6 months

Compound	Initial	1 month	6 months
Singular 5 chewable			
Monte	104.4	104.5	104.5
Monte <i>S</i> -oxide	0.5	0.7	1.5
Monte <i>cis</i> -isomer	<0.2	<0.2	<0.2
Monte dehydro	<0.1	<0.1	<0.1
Other	<0.1	<0.1	<0.1
Monkast 5 chewable			
Monte	101.3	101.6	100.2
Monte <i>S</i> -oxide	0.6	0.9	1.7
Monte <i>cis</i> -isomer	<0.2	<0.2	<0.2
Monte dehydro	<0.1	<0.1	<0.1
Other	<0.1	<0.1	<0.1
Singular 10 film-coated			
Monte	100.3	99.6	98.0
Monte <i>S</i> -oxide	0.3	0.4	0.6
Monte <i>cis</i> -isomer	<0.2	<0.2	<0.2
Monte dehydro	<0.1	<0.1	<0.1
Other	<0.1	<0.1	<0.1
Monkast 10 film-coated			
Monte	100.5	101.7	99.0
Monte <i>S</i> -oxide	0.3	0.5	1.5
Monte <i>cis</i> -isomer	<0.2	<0.2	<0.2
Monte dehydro	<0.1	<0.1	<0.1
Other	<0.1	<0.1	<0.1

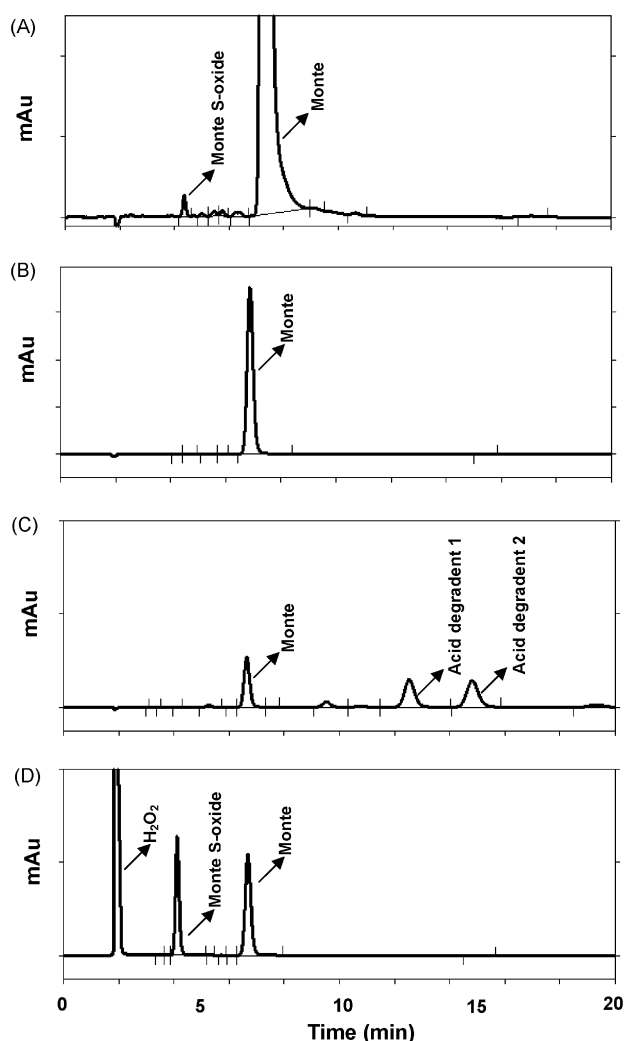


Fig. 6. HPLC chromatograms of Monte after stress testing in (A) its solid state/3 months, (B) 0.1 M NaOH/3 days and (C) 0.1 M HCl/6 h, all at 65 °C; (D) 1% H₂O₂/0.5 h at room temperature.

in solid state as obtained by HPLC method (Fig. 6(A)). Also it is highly stable in 0.1 M NaOH solution (Fig. 6(B)). On the other hand, it degrades rapidly in 0.1 M HCl and 1% H₂O₂ solutions. For example, %Monte in 0.1 M HCl after 6 h at 65 °C only 30% of Monte remained (Fig. 6(C)) and in 1% H₂O₂ after 30 min at room temperature only 60% of Monte remained (Fig. 6(D)). In 0.1 M HCl, two major unknown degradation products were detected at retention times of 12.5 and 14.5 min (Fig. 6(C)), while the major degradation product in the presence of H₂O₂ detected at retention time of about 4 min is Monte S-oxide (Fig. 6(D)).

Meanwhile, the stability of Monte in tablets dosage form was investigated at 40 °C/75% RH for 6 months in its immediate

pack (Al/Al). The stability data for Singulair® and Monkast® tablets are shown in Table 4 indicated that the major degradation product is Monte S-oxide and its percentage increases by 3 times after 6 months of incubation at 40 °C/75% RH. However, Monte *cis*-isomer exists with a low percentage (<0.2) as both products are protected from light by using Al/Al package.

4. Conclusion

It was demonstrated that the stability of Monte against light and heat varied with light source and media. As a result, working under neon or sodium light was found to be a suitable environment, where Monte showed maximum stability even in solution.

Since the major thermal degradation product in solid state is Monte S-oxide, this indicates that using anti-oxidant agents may suppress the oxidation pathway.

These findings have helped to characterize the critical parameters affecting the stability of Monte and may provide useful insight into the way of handling, storage, formulation and analysis.

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