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Surface treatment: A potential approach for enhancement of solid-state photostability

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Abstract

The potentials of a simple surface treatment technique aiming at modifying solid-state properties with emphasis on photostability were investigated using methyldopa (MD), a photosensitive drug substance. MD was treated with a preselected solvent by stirring a drug suspension in the solvent in a predetermined solid/solvent ratio under controlled conditions. At the end of the solvent treatment period, MD powder was separated, dried and screened. Changes in the solid-state properties of surface-treated MD were monitored using flowability measurements, scanning electron microscopy, thermal analysis and dissolution rate. Further, photostability testing, according to the ICH guidelines, was conducted using compressed disks of MD treated with solvents in the absence and presence of antioxidants, namely ascorbic acid, butylated hydroxytoluene (BHT) and cysteine HCl. The color change (ΔE) was determined according to the CIELAB system. Surface treatment of MD drug substance with ethanol, methanol and isopropanol resulted in a marked improvement in flowability which was associated with morphological crystalline changes. Treatment of MD with methanol provided free flowing spherical agglomerates. Disks of solvent-treated MD showed improved photostability which was further potentiated by the inclusion of antioxidants, although only traces of the antioxidant were retained in the treated powder. Tablets containing MD surface treated with methanol containing a mixture of 2% ascorbic acid and 0.2% BHT were prepared by direct compression using a simple formula. The tablets conformed to official requirements.

Keywords: Surface treatment; Methyldopa; Antioxidants; Photostability; CIELAB system; Flowability

1. Introduction

Photochemical degradation of pharmaceutical compounds can seriously affect the pharmaceutical quality of drug products and is usually associated with reduced pharmacological activity and/or the occurrence of side effects of drugs (Nema et al., 1995; Sortino et al., 2001).

Commonly used conventional approaches to enhance photostability of pharmaceutical solids include the use of photoprotective packaging materials and inclusion of photostabilizing formulation additives. For instance, colored glass, green and white opaque blister films were shown to suppress the photolytic degradation of sulphasomidine tablets (Matsuda and Minamida, 1976) and nifedipine and molsidomine tablets (Aman and Thoma, 2002). Photostabilizing additives incorporated either as formulation ingredients or in the tablet coating or capsule shell include chemical and physical sunscreen agents (Béchard et al., 1992), food colorants (Crowley, 1999), some tablet disintegrants (Córdoba-Borrego et al., 1999) as well as antioxidants such as butylated hydroxytoluene, vitamin E, ascorbic acid, sodium metabisulphite and cysteine hydrochloride (Slaveska et al., 1995; Halbaut et al., 1997). Use of chelating agents such as EDTA with other photostabilizing additives may also be beneficial (Evans et al., 2000).

Apart from the use of photoprotective packaging materials and/or formulation additives, manipulation of the solid-state properties of pharmaceutical solids can enhance their photostability (Matsuda and Tatsumi, 1990). This approach is based on the premise that photodegradation is a topochemical reaction which depends on the amount and depth of penetration of radiation into the solid surface. The rate of photochemical reactions may be controlled to a great extent by the crystalline

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properties of the solid such as crystallographic faces, crystal defects, polymorphic forms, solvates or hydrates, as well as by particulate properties such as particle size and shape and for agglomerates, pore size and distribution. For instance, crystal packing of tyrphostin drugs was reported to affect their photochemical degradation (Kumar et al., 1995). Polymorphism was reported to influence the photostability of some drugs such as furosemide and carbamazepine (De Villiers et al., 1992; Matsuda et al., 1994). Moreover, grinding-induced crystalline modifications were associated with changes in photodegradation rates, the amorphous form being more photodegradable than the crystalline form (Teraoka et al., 2004; Qin and Frech, 2001). Increasing the grinding time may contribute to further photoinstability (Kitamura et al., 1989). Reduction in particle size was also shown to increase the rate of photodegradation of powders by increasing the surface area exposed to radiation (Teraoka et al., 1999), a finding consistent with a suppression of photolytic degradation by increasing the powder particle size via agglomeration (De Villiers et al., 1993).

A surface treatment technique, based on interactions at the solid–liquid interface, was introduced earlier as a potentially useful approach to modifying powder properties. Promising results have been obtained so far with three drug substances, namely paracetamol (Molokhia et al., 1997), sulphadiazine (Hammouda et al., 1999) and praziquantel (El-Massik et al., 2000) known to present physicotechnical problems in tablet manufacture.

The objective of the present study was to assess the potentials of this surface treatment technique in enhancing the photostability of photolabile powders. Methyldopa (MD), a centrally acting antihypertensive drug showing poor photostability (Newton et al., 1975) was selected as a model material. Further, changes in other solid-state properties, induced simultaneously by surface treatment of MD were monitored. Finally, the use of surface-treated MD with improved physicotechnical properties for the preparation of tablets by direct compression was considered, as tablet making by direct compression rather than wet granulation may further contribute to photostability.

2. Materials and methods

2.1. Materials

The following materials were used as received: methyldopa (courtesy of Pharco Pharmaceuticals, Alexandria, Egypt), L-ascorbic acid, croscarmellose sodium (courtesy of Pharco Pharmaceuticals), butylated hydroxytoluene, Tenox (Eastmann, courtesy of El Amryia Pharmaceutical Company, Alexandria, Egypt) and cysteine HCl anhydrous (Cambrian Chemicals, CHR). All solvents were of analytical grade. A commercial brand of methyldopa tablets 250 mg, Aldomet® (Kahira Pharm. & Chem. Ind. Co.) BN: 410561 was also used.

2.2. Preparation of surface-treated methyldopa

Suspensions of MD in different solvents, namely ethanol, methanol, isopropanol, acetonitrile, chloroform, dioxane and toluene in a solid:solvent ratio of 1:10 were stirred in stoppered conical flasks for 2 h, protected from light. The undissolved powder was filtered under vacuum, left to dry at room temperature away from light and then screened. The same procedure was repeated for surface treatment of MD in presence of some selected additives, namely ascorbic acid (2%), BHT (0.2%) and cysteine HCl (0.1%). The additives were dissolved in the treatment solvent (ethanol or methanol) to ensure uniform distribution. MD crystals recrystallized from methanol and MD physical mixture with ascorbic acid and BHT (10:0.2:0.02) were prepared for comparison.

2.3. Characterization of MD samples under study

2.3.1. Measurement of flowability parameters

Solvent-treated MD samples (particle size range 160–400 μm), in comparison with untreated MD powder were tested for repose angle, bulk density, tapped density, Hausner ratio and Carr's index.

2.3.2. Scanning electron microscopy (SEM)

The crystal habits of untreated and solvent-treated MD samples were investigated using a scanning electron microscope, Jeol JSM-5300, Japan. Samples were coated with gold using a direct current sputter technique.

2.3.3. Thermal analysis (DSC and TGA)

The thermograms of treated and untreated MD samples were recorded using a calibrated differential scanning calorimeter (DSC 910S, TA Instruments) and thermogravimetric analyzer (TGA 951) equipped with Du Pont Analysis System Versions 4.0 and 1.3, respectively. The heating rate was 10 °C/min over a temperature range of 45–300 °C.

2.3.4. Dissolution rate testing

The dissolution rate of MD samples was determined using U.S.P. 25 dissolution apparatus type 2 with automatic sampler. The dissolution medium was 900 mL of 0.1N HCl maintained at 37 ± 1 °C. The rotation speed was 50 rpm. Filtered samples (5 mL) were removed periodically at 5, 10, 20, 30, 45 and 60 min and assayed spectrophotometrically at 280 nm. All experiments were run in triplicate.

2.3.5. HPLC method for determination of BHT content in surface-treated MD sample

The assay was carried out using HPLC system (Shimadzu) equipped with a solvent delivery module (model LC10AD), an integrator (model CR7A plus) and a variable wavelength detector (model SPD-10A) set at a wavelength of 280 nm. Novapack C_8 column (Waters) was operated at room temperature at a flow rate of 0.5 mL/min. The mobile phase was composed of acetonitrile:acetate buffer (80:20), pH 5.

2.4. Photostability testing of MD samples under study

2.4.1. Sample preparation

Samples of MD powder (p.s. < 160 μm), treated with different solvents in presence and absence of additives were

compressed into 800 mg disks, on Erweka single punch tablet machine using 20 mm flat faced punches at constant compressional force. Disks of the untreated material, physical mixture and granules were also compressed for comparison. The lower surfaces of the disks were marked to distinguish the surface exposed to incident light.

2.4.2. Sample irradiation and storage conditions

The disks of MD samples were placed in Petri dishes and stored in a thermostatically controlled light stability cabinet maintained at $40 \pm 1\,^{\circ}C$ and $75 \pm 5\%$ relative humidity. The upper surface of the disks were irradiated by two fluorescent lamps LUMILUX Daylight (60 cm long, rapid-start type, 18 W) maintained at a distance of 20 cm from the surface of each of the samples. The illuminance was set at 2600 lx. The exposure time was 10 days to provide 1.2 million lx h as indicated by ICH (1996) guidelines. The effects of temperature and humidity with exclusion of light were assessed by covering control disks with aluminum foil throughout the study period.

2.4.3. Measurement of surface color change

Sample disks were withdrawn from the light cabinet at designated time intervals and stored in airtight containers away from light pending color measurement. The surface color of the disks was measured using an integrating sphere-type color difference meter (Superchroma, BRAIVE Instruments, Belgium). To assess the degree of surface color change, the total color difference ΔE^* was calculated as follows using the three independent variables in the CIELAB system (Wirth, 1991; Chrisment, 1998):

$$\Delta E^* = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$$

where ΔL^* is the lightness difference, Δa^* the red-green color difference and Δb^* is the yellow-blue color difference. The results obtained were the average of three measurements. A control for each sample, kept away from light, humidity and temperature, was used for calculation of ΔE^* values. Moreover, the change in surface color of the disks was assessed visually by a panel of three unbiased individuals, as previously reported (Chrisment, 1998).

2.5. Formulation and evaluation of tablets containing surface-treated MD

Methyldopa powder treated with methanol in presence of ascorbic acid (2%) and BHT (0.2%) (particle size 160–400 μm) was mixed with 5% (w/w) croscarmellose as disintegrant. The powder mix was directly compressed into 250 mg tablets using a single punch tablet machine and a flat faced 9 mm punch at a fixed compressional force. The tablets were assessed for hardness, friability and dissolution rate in 0.1N HCl using USP dissolution apparatus type 2. Dissolution data were compared to those of a commercial brand of methyldopa tablets (Aldomet®, 250 mg).

3. Results and discussion

3.1. Characterization of surface-treated MD samples

Methyldopa used in this study was MD sesquihydrate, a poorly flowable material with a relatively small particle size (p.s. range 20–100 μm). MD was treated with different solvents in a solid:solvent ratio of 1:10 for 2 h. This ratio was selected, based on solubility study to ensure only partial solubility of the drug. The solvents included methanol, ethanol, isopropanol, toluene, chloroform, acetonitrile and dioxane. The material obtained upon treatment with the last four solvents was poorly flowable, which precluded the determination of flowability parameters and led to exclusion of these solvents from the study. Poor solubility of MD in these solvents with lack of drug/solvent interaction may account for the results. On the other hand, treatment of MD with methanol, ethanol and isopropanol resulted in a marked improvement in flow properties as shown in Table 1. Methanol-treated MD showed the smallest repose angle and the best values for flowability indices (Hausner ratio and Carr's index). However, the bulk density was not consistent with the decrease in repose angle. Bulk density values themselves are of little absolute value but are used as a sensitive secondary measurement to identify slight changes in the morphology of the primary particles and their flow characteristics. The Hausner ratio and Carr's index provide a greater indicative values (Mohammadi and Harnby, 1997). The observed changes in flow properties were associated with changes in particle shape and surface characteristics of the solvent-treated material, as indicated by SEM.

Scanning electron micrographs of untreated MD (Fig. 1a) shows cubic to rectangular particles with rough surfaces and broken edges. Treatment of MD with ethanol and isopropanol (Fig. 1b and c) did not clearly affect particle shape but resulted in the formation of slightly enlarged, well-formed cubic or rectangular crystals with more angular edges and smoother surfaces. On the other hand, methanol treatment resulted in a marked change in crystal habit (Fig. 1d). The material appeared as rod-like platy crystals enclosing particles having the original cubic shape of MD drug substance. These are loosely packed into large fluffy agglomerates, which appear as microgranules

Table 1
Flow properties of MD treated with different solvents (particle size range 160–400 μm) in comparison to untreated MD (particle size range 20–100 μm)

Solvent	Repose angle (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Carr's index (%)
Untreated MD powder	45.3	0.392	0.625	1.59	37.3
Methanol	33.9	0.360	0.430	1.19	16.3
Ethanol	37.9	0.470	0.581	1.22	18.3
Isopropanol	35.0	0.460	0.557	1.21	17.4

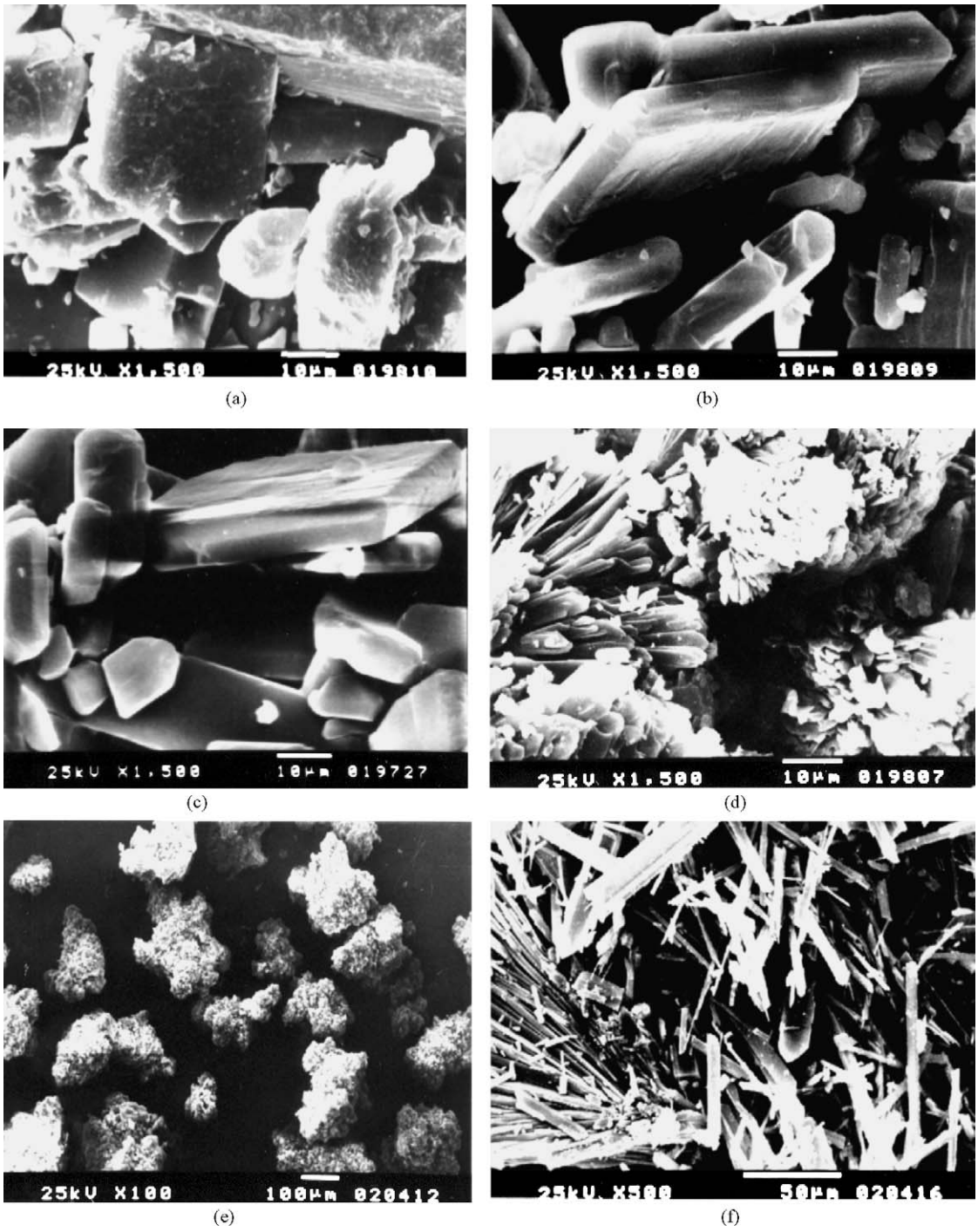

Fig. 1. Scanning electron micrographs of: (a) untreated MD, (b) ethanol-treated MD, (c) isopropanol-treated MD, (d) methanol-treated MD, (e) methanol-treated MD, at lower magnification, showing microgranules and (f) MD recrystallized from methanol.

at lower magnification (Fig. 1e). Such morphological changes may account for the marked improvement in flow properties (Table 1). SEM of MD crystals recrystallized from methanol (Fig. 1f) shows rod-like platy crystals similar to those formed upon methanol treatment. It has been reported (Budavari, 1996) that recrystallization of MD from methanol yields crystals of the anhydrous form with loss of water of crystallization. Morphological changes observed in SEM of the methanol-treated MD tend to indicate that MD partially dissolved in methanol during treatment appear to be redeposited as crystals of the anhydrous form, secondary nucleation being promoted by the surface roughness of the substrate particles (Rodriguez-Hornedo and Murphy, 1999). Similar surface-mediated nucleation events have been reported for theophylline (De Smidt et al., 1986) and carbamazepine (Luhtala, 1992).

Fig. 2 shows the thermal profiles of MD samples either untreated or treated with methanol, ethanol and isopropanol. MD is reported to melt at ≈300 °C with decomposition. The DSC

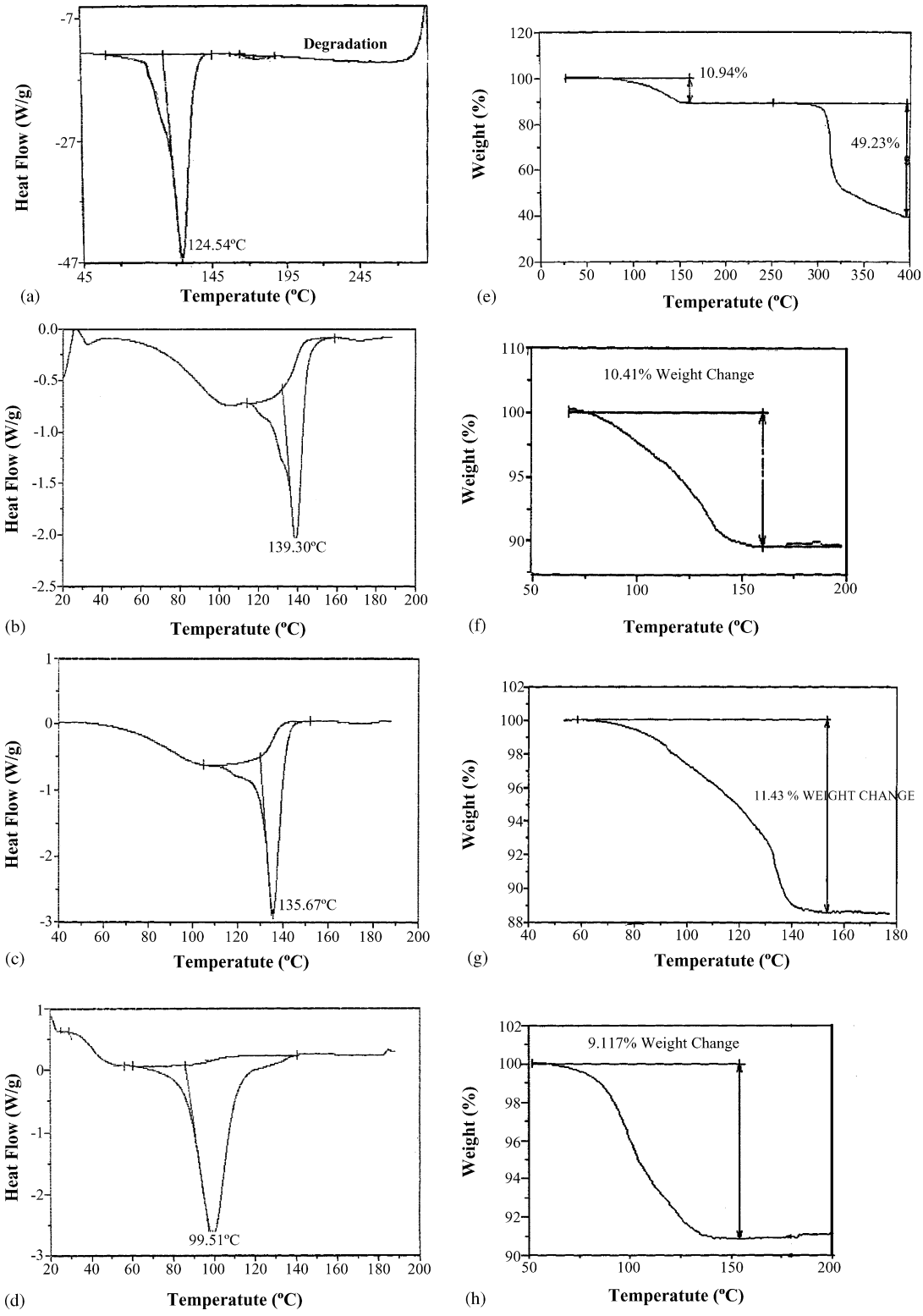

Fig. 2. DSC and TG curves of: (a and e) untreated MD, (b and f) ethanol-treated MD, (c and g) isopropanol-treated MD and (d and h) methanol-treated MD.

curve of untreated MD (Fig. 2a) shows a single endothermic peak at 124.54 °C, corresponding to the loss of water of crystallization. This is supported by the TG scan (Fig. 2e) showing about 11% weight loss which is in accordance with the calculated water content of MD sesquihydrate (≈11.3%). Fig. 2b and c reveals that treatment of MD with ethanol and isopropanol resulted in a shift of endothermic peaks to higher temperatures (139.3 and 135.7 °C, respectively). This indicates tighter binding of water in these samples probably through hydrogen bonding. The percent water loss in these samples ranged from 10.41 to 11.4

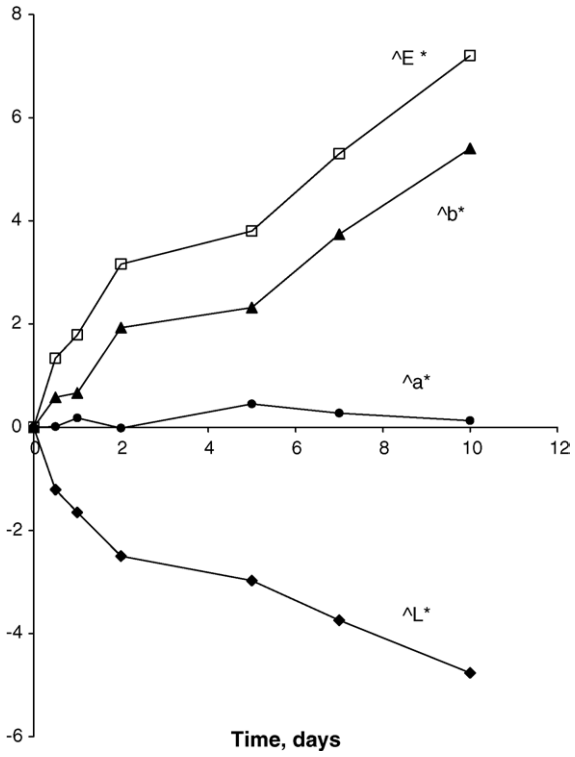

Fig. 3. Colorimetric differences profiles: (♦) ΔL^*, (●) Δa^*, (▲) Δb^* and (□) ΔE^* for untreated MD compressed disks subjected for a 10-day photostability study period.

as detected by the thermogravimetric curves shown in Fig. 2f and g. On the other hand, the DSC curve for methanol-treated MD (Fig. 2d) showed lower peak temperature for dehydration endotherm (99.51 °C), pointing to a smaller enthalpy of water dissociation. This indicates that part of the water in methanol-treated MD was loosely bound. Moreover, TG scan (Fig. 2h) shows that the water content of the material was smaller (about 9.1%). This can be attributed to the loss of part of water of crystallization liberated upon conversion to the anhydrous form, in the filtrate during sample preparation.

Dissolution rate study showed fast dissolution of untreated as well as solvent-treated MD powders ($t_{90\%}$ was less than 5 min). Treatment with ethanol, methanol or isopropanol did not affect the dissolution rate of MD (p.s. range 20–100 μm) in spite of the larger particle size range of the treated samples (160–400 μm). This implies an increase in hydrophilicity of the solid. Solvent treatment of paracetamol, sulphadiazine and praziquantel was reported earlier (El-Massik et al., 2000; Hammouda et al., 1999; Molokhia et al., 1997) to bring about surface hydrophilization of these drug substances.

3.2. Photostability study

Fig. 3 shows plots of ΔL^*, Δa^* and Δb^* versus time for compressed disks of untreated MD for a 10-day study period. At zero time, a^* and b^* values were close to zero and L^* value was about 91, indicating nearly white surface color of disks (Chrisment, 1998). The disks then started to darken with excessive exposure to irradiation. This was evidenced by the decrease of ΔL^* and increase of Δb^* values, indicating color change towards black and yellow shades, respectively. Δa^* values of the disks slightly increased with time, indicating slight development of red shade. This could be attributed to quinone formation, an intermediate of MD oxidation (Young et al., 1980). ΔE^* showed positive values which increased by time.

In order to investigate the effect of light as an integral component of the propagation step in photodegradation of MD, untreated MD disks covered with aluminum foil were subjected to similar irradiation and exposure conditions. ΔE^* value after 5-day exposure for shielded disks was 1.2, compared to 3.80 for exposed disks. These results prove that light exposure in combination with temperature and humidity are responsible for the color changes of MD disks. Accordingly, discoloration of MD may be the result of autoxidation, light being a triggering force promoting oxidation (Carstensen, 1990).

Data for surface color change (ΔE^* values) of compressed disks of MD treated with methanol, ethanol and isopropanol for a 10-day study period, relative to that of untreated control MD disks are shown in Fig. 4. A reduction in ΔE^* values for solvent-treated samples was observed at the beginning of the study indicating partial photostabilization of MD. Upon further exposure to irradiation, ΔE^* values of solvent-treated samples approached those of untreated MD. Visual observation of the disks of treated samples showed that white disks surfaces turned yellow after 10 days of irradiation. The partial photostabilization of MD provided by solvent treatment could be attributed to the relative increase in crystal size and surface smoothness of the treated material as indicated by SEM (Fig. 1).

An attempt was made to potentiate the photostabilizing effect of solvent treatment of MD by inclusion of photostabilizing additives in the treatment solvent. It is worth mentioning that only trace amounts of additives are speculated to remain in the crystalline structure of MD upon solvent treatment, as the largest part of these additives is removed by filtration of the solvent. Fig. 5 shows the effect of inclusion of each of the following antioxidants: ascorbic acid (2%, w/v), butylated hydroxytoluene (BHT, 0.2%, w/v) and cysteine HCl (0.1%, w/v) in ethanol on the photostability of MD over a 5-day exposure period. While BHT did not enhance the photostabilizing effect of ethanol treatment, ascorbic acid showed a marked improvement in MD photostability. Cysteine showed an intermediate stabilizing effect. Yellow discoloration of ascorbic acid-treated samples was observed, an effect mostly attributed to the oxidation of ascorbic acid which resulted in increased b^* values (10.16 and 12.51) determined at 5 and 10 days of exposure, respectively. Ascorbic acid undergoes oxidation in the solid state and ascorbic acid tablets discolor during storage under normal conditions of temperature and humidity (Vemuri et al., 1985).

To enhance the effectiveness of an antioxidant approach, it is sometimes useful to use more than one antioxidant. Fig. 5 shows the effect of including a mixture of 2% ascorbic acid and 0.2% BHT in ethanol on the photostability of MD over a 5-day exposure period. A marked reduction in color change was observed, probably as a result of suppressed ascorbic acid oxidation in the presence of BHT. Ascorbic acid was reported (De Ritter, 1982) to be more stable in presence of other

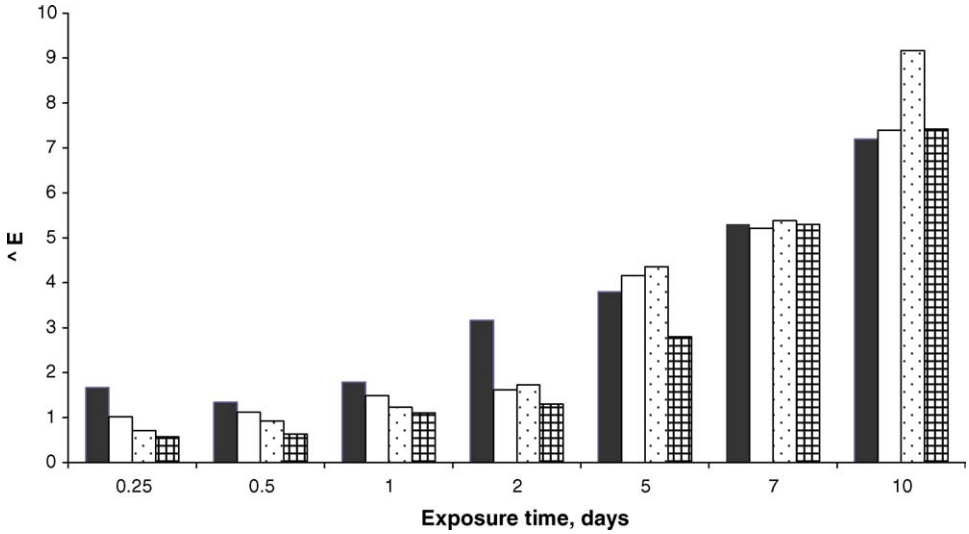

Fig. 4. Surface color change (ΔE^*) of compressed disks of: (■) untreated MD, (□) methanol-treated MD, (▫) ethanol-treated MD and (▦) isopropanol-treated MD.

antioxidants. Treatment of MD with methanol containing both additives resulted in a similar enhancement of photostability (Fig. 6). It is worth noting that only 5% of the amount of BHT was retained by MD upon surface treatment as determined by HPLC. Further, the color change of MD treated with ethanol or methanol containing a mixture of 2% ascorbic acid and 0.2% BHT was compared to that of a physical mixture of the drug with ascorbic acid and BHT in a ratio of 10:0.2:0.02 (Fig. 6). Surface-treated samples were less photosensitive than the physical mixture, indicating high efficiency of the surface treatment technique.

3.3. Application of the solvent-treatment technique in the formulation of methyldopa tablets

Photodegradation of MD imposed complex formulation and processing of commercial oral products, including the use of antioxidants, complexing agents and organic acids in addition to the film coating of tablets (PDR, 2000). As tablet making by direct compression rather than wet granulation may further contribute to the photostability of MD tablets, simultaneous changes

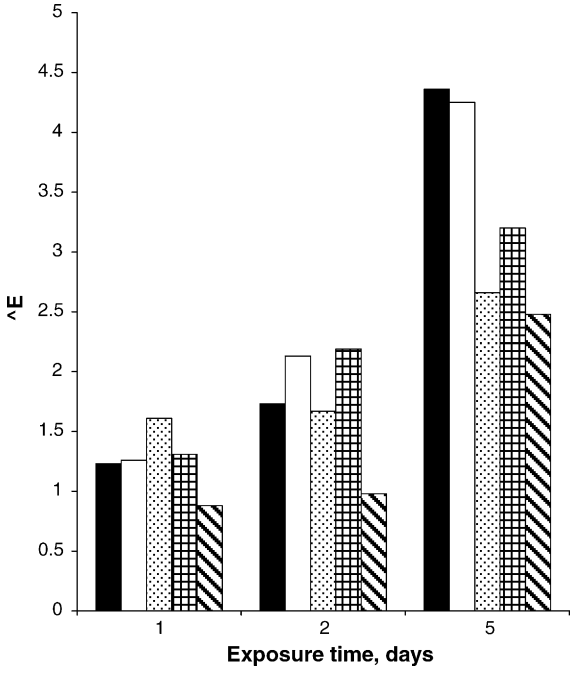

Fig. 5. Surface color change (ΔE^*) of compressed disks of MD treated with ethanol in presence of additives: (■) ethanol, (□) ethanol/0.2% BHT, (▫) ethanol/2% ascorbic acid, (▦) ethanol/0.1% cysteine and (▨) ethanol/2% ascorbic acid + 0.2% BHT.

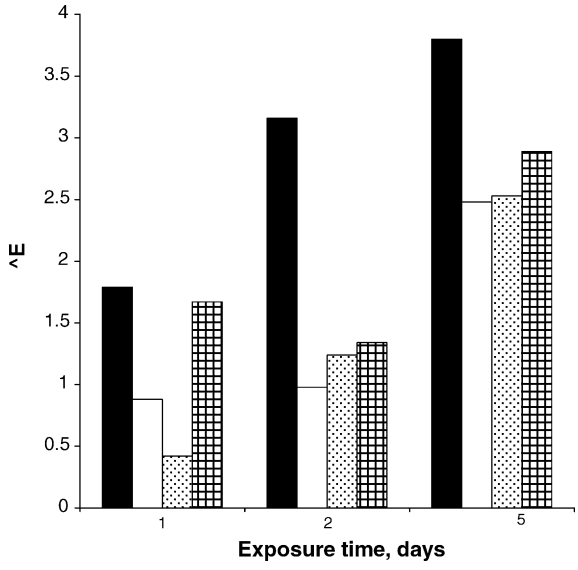

Fig. 6. Surface color change (ΔE^*) of compressed disks prepared from: (■) untreated MD, (□) ethanol/2% ascorbic acid + 0.2% BHT-treated MD, (▫) methanol/2% ascorbic acid + 0.2% BHT-treated MD and (▦) MD/ascorbic acid/BHT (10:0.2:0.02) physical mixture.

in physicotechnical properties (good flowability, compressibility and lubricating properties) conferred by surface treatment were made use of in the formulation of MD tablets by direct compression. MD treated with methanol containing 2% ascorbic acid and 0.2% BHT was used to prepare 250 mg MD tablets containing 5% croscarmellose as disintegrant. Tablets obtained were evaluated in comparison to commercial MD coated tablets (Aldomet® 250 mg). The formulated MD tablets of average weight 265 mg (versus 350 mg average weight of Aldomet® tablets) complied with the BP weight variation test. They also showed good mechanical strength (hardness = 5–6 kg and friability < 1%) and complied with the USP dissolution test for MD tablets ($t_{99\%} \approx 5$ min).

4. Conclusions

Surface treatment of MD drug substance with solvents, specially methanol, resulted in a material with improved flowability and photostability, particularly when exposure to irradiation was not excessive. The photostabilizing effect was further enhanced by the inclusion of antioxidants. The material could be compressed into tablets by direct compression using a simple formula. From a practical standpoint, the surface treatment technique offers potentials of improving solid-state photostability and other powder properties. Building such properties into drug substances and other pharmaceutical solids could have great implications in the manufacture of solid dosage forms as simpler formulation, processing and fewer precautions would be required.

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