RESEARCH PAPER

Accepted 1 August 2005
Revised 28 January 2005
Received 19 August 2004
Indian J. Pharm. Sci., 2005, 67(4): 438-443

# Behaviour of Marketed Packaged Formulations under Accelerated Conditions of Temperature and Humidity in the Absence and the Presence of Light

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**The authors tested 27 formulations, picked up randomly from local market under WHO and ICH prescribed accelerated stability test conditions of 40°/75% RH for 3 months in the presence and the absence of light. In several formulations, the physical changes were stronger in light than in dark, though examples existed where results were similar in the two conditions. Under light, both primary and secondary packaging was affected, and fading of container color and the print fading were the common problems. Even formulations within the packs were affected in some cases, and the changes were in the form of gain of moisture and loss of integrity in case of effervescent tablets, color fading of capsules in blisters, sticking of capsules in a glass bottle and spread of powder within strip pockets. There were other changes, that include softening of suppositories; change in viscosity of a gel, jelly, cream and ointment; melting of lozenges and phase separation of emulsions, but these were among those expected to occur normally under accelerated storage conditions.**

As of today, manufacturers of pharmaceuticals worldwide carry out stability studies on their products under long-term (25°/60% RH for Zones I and II and 30°/65% RH for Zones III and IV) and accelerated stability test conditions (40°/75% RH for all Zones as a support to long-term studies). These conditions are suggested in ICH and WHO guidelines[1,2]. Though the environment consists of temperature, humidity and light combined, ICH experts opted to keep photostability testing as a separate guideline[3], reasoning that the products in ICH countries were sold in secondary packages, thus obviating the need to test the products under light, in combination with temperature and humidity.

Recently, several reports were published, which indicated enhanced cross-linking of gelatin products[4], and increased rate of moisture gain by pure antitubercular drugs[5], their products[6] and several pure drugs and excipients[7] in the presence of light combined with accelerated conditions of temperature and humidity. The purpose of the present study was to check how marketed formulations in different dosage forms got influenced by the combination of light, temperature and humidity, in comparison to samples stored without light at the same temperature and humidity, and relative to control samples. As many as 27 products were included in the study. The observed physical changes are reported in this communication.

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## MATERIALS AND METHODS

Solid, liquid and semi-solid products in different dosage form and packaging types, like blister, strip, glass bottle, plastic bottle, pouch, metallic tube, plastic tube, etc. were sourced from local retailers. In all 27 drug formulations were procured, including 19 solid and 8 semi-solid/liquid dosage forms. Each product was purchased in sufficient quantity for the studies under different conditions.

### Storage of samples:

One set of formulations, both in primary and secondary packs, was stored under ambient conditions, while two

TABLE 1: DESCRIPTION OF VARIOUS TABLET FORMULATIONS AND THE OBSERVED CHANGES

| Active Pharmaceutical Ingredient (s) (Category) | Date of manufacture (expiry period, y) | Type of package | Changes observed | |
|---|---|---|---|---|
| | | | Initial exposure to light, followed by storage in dark chamber | Storage in dark chamber only |
| Diclofenac sodium (Tablet) | Dec 2002 (3 y) | Blister | Color fading of tablet inside blister | No change |
| Salbutamol sulphate (Tablet) | July 2003 (3 y) | Blister | No change | No change |
| Amitriptyline hydrochloride (Tablet) | Jan. 2003 (2 y) | Blister | No change | No change |
| Amlodipine besilate (Tablet) | July 2003 (3 y) | Blister | Color fading of tablet inside blister | No change |
| Ranitidine (Tablet) | July 2002 (2 y) | Strip | Fine sheet of powder seen in strip pocket | Fine sheet of powder seen in strip pocket |
| Penicillin G potassium (Tablet) | July 2002 (2 y)} | Strip | Color fading of the pack | No change |
| Desogestrel, ethinylestradiol (Tablet) | June 2002 (3 y) | Blister inside pouch | No change | No change |
| Rifampicin, isoniazid, ethambutol hydrochloride (Tablet) | May 2000 (3 y) | Blister | Severe bleeding, much faster than dark | Bleeding of tablet inside the blister |
| Rifampicin, isoniazid, ethambutol hydrochloride (Tablet) | January 2001 (2 y) | Strip | Discoloration of the strip | No change |
| Papain, fungal diastase, simethicone (Effervescent tablet) | June 2002 (2 y) | Strip | Strip pocket inflated within 3 months, however, no color fading of packaging | Strip pocket inflated after 3 months |
| Glyceryl trinitrate (CR* Tablet) | April 2002 (2 y) | Plastic Bottle | Color fading of label | No change |

*CR-Controlled release

other sets were charged separately to stability (KBF720, WTB Binder, Tuttlingen, Germany) and photostability (KBWF240, WTB Binder, Germany) chambers, both set at 40±1°/75±3% RH. The latter was equipped with an illumination bank on inside top consisting of a combination of two black-light UV (L73, Osram GmbH, Munich, Germany) and four white fluorescent (L20, Osram GmbH) lamps, according to option 2 of International Conference on Harmonization (ICH) guideline Q1B[3]. Both UV and visible lamps were put on simultaneously. The samples were placed at a distance of 9 inches from the light bank. The intensity of fluorescent and UV light was measured using lux (model 545, Testo, Lenzkirch, Germany) and UV-A (Dr Honle AG, Grafelfing, Germany) meters, respectively. The samples in photostability chamber were stored for a sufficient period to expose them to minimum ICH recommended dose of 1.2 million lux h fluorescent and 200 Wh/m$^2$ UV light[3]. Then they were transferred to dark chamber and the study was continued till a total period of three months. The separate studies in dark chamber were also carried out for a total period of

TABLE 2: DESCRIPTION OF VARIOUS CAPSULE, POWDER, COUGH DROP AND LOZENGE FORMULATIONS AND THE OBSERVED CHANGES

| Active Pharmaceutical Ingredient (s) (Category) | Date of manufacture (expiry period, years) | Type of package | Changes observed | |
|---|---|---|---|---|
| | | | Initial exposure to light, followed by storage in dark chamber | Storage in dark chamber only |
| Ampicillin, cloxacillin (HGC)* | May 2002 (2 y) | Strip | No change | No change |
| Dicalcium phosphate, vitamin E, vitamin C (HGC)* | June 2002 (2 y) | Blister | Color fading of capsules inside blister | No change |
| Imipramine (HGC)* | August 2003 (2 y) | Blister | Color fading of capsule inside blister within three days | No change |
| Multivitamin (SGC)* | May 2002 (2 y) | Glass bottle (Amber colored) | Color fading of label, capsule shells became sticky | Capsule shell became sticky |
| Lactic acid bacillus (Powder) | March 2002 (2 y) | Coated paper pack | Color fading of package, however no change in flowability of powder | No change |
| Neomycin, polymixin B, bacitracin (Powder) | August 2002 (2 y) | Plastic bottle | No change | No change |
| Volatile oil, flavoured sugar base (Cough Drop) | NI* | Plastic pouch | Color fading of package, whole formulation melted inside | Formulation melted inside |
| Dichloro benzyl alcohol, amyl meta cresol (Lozenge) | April 2002 (2 y) | Strip (Coated plastic pack) | Color fading of package, formulation melted inside | Formulation melted inside |

*Key: HGC-Hard gelatin capsule, SGC- Soft gelatin capsule, NI-Not indicated on the pack

three months.

**Evaluation of physical changes:**

Drug formulations stored in both the chambers were observed periodically for physical changes. After the study was over, the products were compared to control formulations stored under ambient conditions for the same period.

## RESULTS AND DISCUSSION

Out of the 27 products studied, 19 showed changes either with the secondary/primary pack or even the drug formulation within the packaging. Tables 1-3 give the details of the products investigated and the nature of physical changes observed under various conditions. Changes observed in the secondary packaging were mainly weathering of the pack and fading of label prints. Examples are shown in fig. 1. The main changes in primary packaging were only the color fading of the prints on the packs (fig. 2).

Changes in drug formulations were evident as physi-

TABLE 3: DESCRIPTION OF VARIOUS SEMI-SOLID/LIQUID FORMULATIONS AND THE OBSERVED PHYSICAL CHANGES

| Active Pharmaceutical Ingredient(s) (Category) | Date of manufacture (expiry period, years) | Type of package | Changes observed | |
|---|---|---|---|---|
| | | | Initial exposure to light, followed by storage in dark chamber | Storage in dark chamber only |
| Bisacodyl (Suppositories) | Dec 2001(3 y) | Strip | Color fading of package, formulation melted inside | Formulation softened inside |
| Erythromycin (Gel) | July 2002 (3 y) | Plastic bottle | Color fading of package, formulation softened | Formulation softened |
| Chloramphenicol (Eye Ointment) | March 2002 (2 y) | Collapsible tube | No change | No change |
| Betamethasone valerate, neomycin (Cream) | July 2002 (1.5 y) | Metallic tube | Minor color fading of package, formulation softened slightly | Formulation softened slightly |
| Chlorphenramine maleate, dextromethorphen (Jelly) | March 2002 (1.5 y) | Plastic tube | Color fading of package, formulation softened slightly | Formulation softened slightly |
| Clotrimazole (Topical Lotion) | Dec 2001 (3 y) | Plastic bottle with dropper | No change | No change |
| Calamine (Lotion) | July 2002 (3 y) | Plastic bottle | No change | No change |
| Liquid paraffin (Emulsion) | March 2002 (2 y) | Glass bottle | Phase separation | Phase separation |

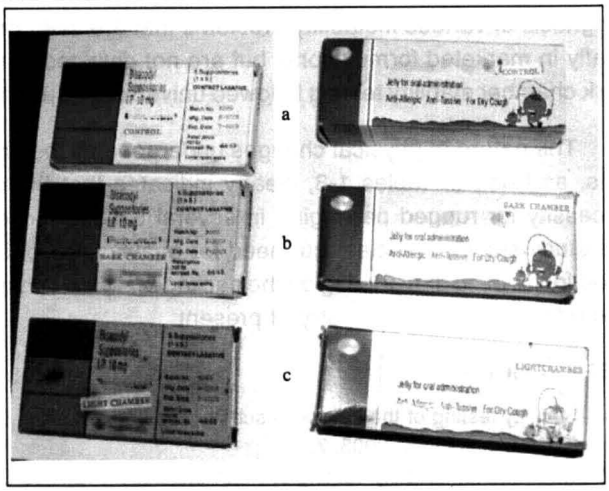


**Fig. 1: Changes in secondary packaging**

**Examples of weathering (left) and color fading (right) of prints of secondary package. a - control; b - stored for 3 months at 40°/75% RH in the absence of light; c- initially exposed to ICH recommended dose of light and subsequently stored in dark chamber (40°/75% RH) till a total period of 3 months.**

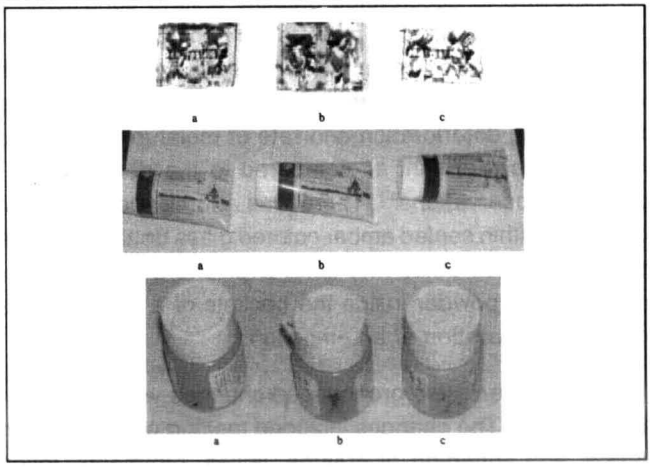


**Fig. 2: Changes in primary packaging.**

**Photographs showing color changes in primary packs on exposure to accelerated stability test conditions in the absence and the presence of light. a - control; b - stored for 3 months at 40°/75% RH in the absence of light; c- initially exposed to ICH recommended dose of light and subsequently stored in dark chamber (40°/75% RH) till a total period of 3 months.**

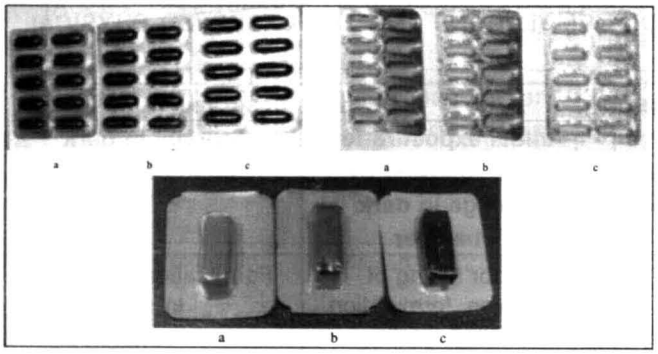

**Fig. 3: Changes in primary packaging and the products packed in blisters**

**Photographs showing color changes in capsules/caplets within the blister packs on exposure to 40°/75% RH in the absence and the presence of light. a - control; b - stored for 3 months at 40°/75% RH in the absence of light; c- initially exposed to ICH recommended dose of light and subsequently stored in dark chamber (40°/75% RH) till a total period of 3 months.**

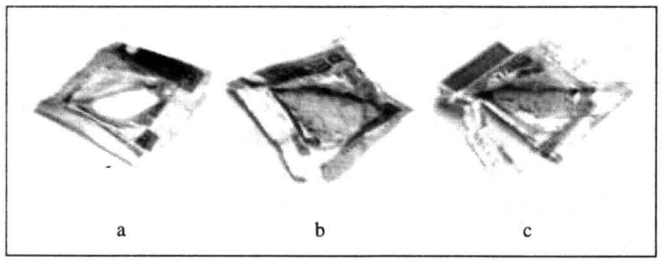


**Fig. 4: Changes in a product packed in a single-tablet strip.**

**Photographs showing conversion of an effervescent tablet into powder on storage in dark and light conditions. a - control; b - stored for 3 months at 40°/75% RH in the absence of light; c- initially exposed to ICH recommended dose of light and subsequently stored in dark chamber (40°/75% RH) till a total period of 3 months.**

cal changes in the formulations even within the packs. It was found that the problem of color fading was not only restricted to prints on packages, labels, containers, but also applicable to the capsules inside the blister packs, as shown in fig. 3. Another significant change was conversion of an effervescent tablet into powder due to pick up of moisture on exposure to accelerated stability testing conditions, as shown in fig. 4. The strip pockets containing the tablet were found to swell with time and when the strip was opened, the white well-formed tablet had turned into a brownish powder. In this case, deterioration and rate of moisture pick up was higher under the light as compared to the dark, similar to previous observations[5-7]. There was another case, in which capsules within sealed amber colored glass bottle were found to stick to each other with time. Even there was a case of spreading of powder inside the pockets of a strip, and also of phase separation of an emulsion.

There were also pronounced changes with some other formulations. The changes included melting of lozenges and drops; and softening of creams, jellies, ointments, lotions and suppositories. For such products, changes were expected at 40° due to the presence of low melting ingredients.

The study shows that exposure of marketed products to accelerated stability test conditions prescribed in ICH and WHO guidelines resulted in physical changes both of the secondary and primary packs and even of formulations contained inside. It suggests that there is a need for the manufacturers of pharmaceuticals to appropriately focus on stability testing according to latest guidelines before sending the products into the market. The finding that several products showed stronger changes on simultaneous exposure to light suggests that it might be more useful to carry out accelerated stability testing at 40°/75% RH by first exposing the products to ICH prescribed dose of light[3] and then shifting them to the dark chamber. The test is expected to help in prognosis of various instability problems that are seen practically in marketed formulations, but are not divulged during dark chamber stability testing followed universally at present.

The nature of physical changes undergone by the products, as listed in Tables 1-3, clearly indicates that there is necessity for rugged packaging in several cases. Above it, the study suggests a clear-cut need for qualification of inks used for labeling and printing on the packages, which is hardly being followed by the industry at present.

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