Evaluation of “In-Use” Stability Period of Lacidipine Tablets in Multi-dose Plastic Container-Closure

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ABSTRACT
Lacidipine (LCDP) is chemically a 1,4-dihydropyridine derivative and pharmacologically a “calcium channel blocker” used as an anti-hypertensive agent. Lacidipine is most sensitive to light and moisture, which is in line with the well-known sensitivity of the dihydropyridine class of compounds. In general, moisture protection can be obtained by packaging into moisture impermeable material, while light protection can be obtained by covering tablets with an opaque film coating. But, when film-coated tablets are packed in High Density Polyethylene (HDPE) multi-dose plastic containers and closures, repeated opening and closing may pose a risk to their contents with regard to microbiological contamination and physicochemical degradation once the closure system has been breached. The continued integrity of the product in multi-dose containers after the first opening is an important quality issue. Thus, the main objective of the present in-use stability study was to establish a period of time during which a multi-dose Lacidipine tablet product can be used whilst retaining quality within an accepted specification once the container is opened. The extent of drug product testing was established by assessing whether or not there was acceptable change, mainly in terms of impurities generated by different factors and microbial loads mainly in terms of bacteria/yeast/mould occurrence over the in-use stability or at the end of the in-use stability study period. Our results from drug assay, dissolution and impurity profile studies assessed as per the regulatory specifications suggest that the lacidipine product should be used within 4 weeks after opening of the container. The container should be closed tightly after each use to limit drug product degradation.

KEYWORDS: Lacidipine; In-Use stability; High Density Polyethylene (HDPE); Multidose container; Child Resistant Closure (CRC); Shelf-life.

Introduction
Lacidipine (LCDP) is chemically designated as (E-4-[2-[3-(1,1-dimethylethoxy)-3-oxo-1-propenyl]phenyl]-1,4-dihydro-2,6-di-methyl-3,5-pyridine-dicarboxylic acid diethyl ester), which is pharmacologically a “calcium channel blocker” used as an anti-hypertensive for the treatment of coronary diseases (Anon, 2008; BP, 2001). The drug is most sensitive to light and moisture, which is in line with the well-known sensitivity of the dihydropyridine class of compounds (Anon, 2008; BP, 2001). In general, light protection can be obtained by covering tablets with an opaque film coating, while moisture protection can be obtained by packaging into a moisture impermeable material (Anon, 2008; BP, 2001). But, when film coated tablets are packed in High Density Polyethylene (HDPE) multi-dose plastic containers and closures, repeated opening and closing may pose a risk to their content with regard to microbiological contamination, proliferation, and/or physicochemical degradation once the closure system has been breached. The continued integrity of products in multi-dose containers after the first opening is an important quality (Das Gupta, 1991; Capen et al., 2012).

Thus, the main objective of the present in-use stability study is to establish a period of time during which a multi-dose product can be used whilst retaining quality within an accepted specification once the container is opened (Anon, 2008; BP, 2001). The extent of drug product testing was established by assessing whether or not acceptable physicochemical change (mainly in terms of hardness, disintegration, assay, dissolution, and impurities generated owing to different factors (Anon, 2008; BP, 2001) as represented in Figure 1 and microbial loads (mainly in terms of bacteria/yeast/mould) have burdened over the in-use period or at the end of the in-use periods described in the proposed decision flow chart for in-use stability testing of drug products as represented in Figure 2.
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**Summary Diagram**

**START**

**PROPOSAL OF IN-USE SHELF LIFE**
According to Dosage Regimen

**STORAGE OF SAMPLES FOR CHARGING IN USE STABILITY**
At Real Time Storage Conditions on PIL/Label

**PLANNING OF SCHEDULE FOR SAMPLES WITHDRAWAL**
according to intervals comparable to those which occur in normal routine practice of that particular medicine.

**FIXING OF TESTING FREQUENCIES**
According to type of tests: Physical, Chemical & Microbial

**PRESENTATION & EVALUATION OF RESULTS**
With Graphical comparison by Control charts

**CHANGE IS ACCEPTABLE?**

**RE FORMULATION/RE PACKAGING/LABELING REVISION**
Depending upon study results, labeling are revised i.e. (1°) container: "Date of Opening" (2°) container: In use Shelf life period/additional storage condition

**YES**

**NO**

**TEST END**
Fig. 1. Chemical structure of pure lacidipine (dihydropyridine trans-isomer), its impurity generated by solvent action (A: Methyl derivative), impurity generated by temperature action (B: pyridine) and its impurity generated by light action (C: cis-isomer and its cyclic derivative).
Materials and Methods

Drugs and Chemicals

Lacidipine was purchased from Cadila Pharmaceuticals limited, India. Polyvinyl Pyrrolidone (Plasdone® K29/32) was purchased from ISP Technologies. Two grades of Lactose Monohydrate (Pharmatose® 200M and DCL® 11) were purchased from DMV International and used as an intragranular diluent cum powder substrate. Absolute Alcohol (Ethanol 99.6%v/v) was procured from CVKU, India. Magnesium Stearate of vegetable grade was purchased from Ferro Synpro. Pre-mixed film coating material, Opadry® white, Stearate of vegetable grade was purchased from Ferro Synpro. Pre-mixed film coating material, Opadry® white, 99.6%v/v) was procured from CVKU, India. Magnesium Stearate of vegetable grade was purchased from Ferro Synpro. Pre-mixed film coating material, Opadry® white, was directly purchased from Colorcon Asia Ltd., India. Accordingly, lacidipine 4 mg tablets (finished product) were formulated similarly as described previously (Anon, 2008; BP, 2001). In-use stability study should be conducted at the initial phase as well as at the end phase of proposed integrated product shelf life. The batch number, date of manufacture, batch size, and storage condition with details of actual containers and closures was clearly stated in the physical observations and chemical analytical tabulation. The container and closure of the product was equivalent to the proposed primary and secondary packs for commercial manufacturing and marketing.

Test Storage Condition

The product was stored under the same conditions as recommended in the product literature (SPC and PIL) throughout the in-use stability test period. Any other additional storage conditions can be justified based upon results of this in-use stability study.

Test Design (Sample withdrawal plan and testing frequency)

The test was designed to simulate the use of the product in practice taking into consideration the filling volume of the HDPE container (75 cc). At intervals comparable to those which occur in practice, appropriate quantities of tablets were removed as per routine practice as described in the product literature. This sampling was done under normal environmental conditions of use.

The appropriate physical, chemical and microbial properties of the product susceptible to change during storage were physically observed and/or chemically analyzed over the period of the proposed in use shelf life. Testing was additionally performed at intermediate time points and at the end of the proposed in-use shelf life on the final remaining amount of the product in the container(s).

Test parameters

The appropriate physical, chemical, and microbial properties of the product susceptible to change during use were monitored, analyzed, and recorded as per types of parameters which may need to be studied as given below:

| Physical: | Appearance, Hardness, Disintegration, % Loss on Drying |
| Chemical: | Assay of active substance, Related Substance(s), Dissolution |
| Microbial: | Total Viable Microbial Counts and Pathogens |

Chemical Analytical Procedures

At the end of the each exposure period, samples were examined for any changes in physical properties (e.g., appearance, hardness, disintegration, and %LOD) and analyzed for chemical properties (e.g. assay of active substance, related substances, and %dissolution) by a fully validated stability indicating the analytical method (Alyne and Tatiana, 2012; Bajaj and Singla, 2012). For Lacidipine tablets, testing was conducted on an appropriately-sized composite of 20 tablets. Analysis of the exposed sample was performed concomitantly with that of protected samples used as controls.

Sample preparations for Assay and Related substances procedures (By HPLC)

Standard preparations

20 mg of Lacidipine working standard was accurately weighed and transferred into a 100 ml volumetric flask. 20 ml of absolute ethanol was added and sonicated to dissolve. It was diluted to 100 ml with n-Hexane. For Assay procedure: 1ml of this solution was further diluted to 100ml with mobile phase (final concentration was about 2.0µg/ml). For RS Procedure: 1ml of Assay standard solution was further diluted to 100ml with mobile phase (final concentration was about 2.0µg/ml).

Sample preparations

Solution (1): 20 tablets were taken, weighed and powdered. The tablet powder equivalent to 10.0 mg of Lacidipine was accurately weighed and transferred into a quantity of to 50 ml volumetric flask. About 10 ml of absolute alcohol was added and sonicated for 10 minutes. Then, 30 ml of n-Hexane was added and sonicated for 10 minutes with intermittent shaking and diluted to volume with n-Hexane. 5 ml of solution was filtered through a 0.45µm membrane filter (Millipore Millex is suitable).

Solution (2): 1 volume of solution (2) of assay to 100 volumes were diluted with the mobile phase.

Solution (3): 1 volume of a 0.1% w/v solution of Lacidipine impurity standard BPCRS was diluted in absolute ethanol to 5 volumes with the mobile phase.

Mobile phase: 3 volumes of absolute alcohol and 97 volumes of n-hexane.

Chromatographic parameters: A liquid chromatograph is equipped with a variable wavelength Photo Diode Array detector, an injector and a data processor.

Column: A stainless steel column (25 cm x 4.6 mm) packed with cyanosilyl silica gel for chromatography (5 µm) (Spherisorb CN is suitable)

Flow rate: 2.0 ml/min
Detection wavelength: 240 nm
Injection volume: 20 µl

Procedure for Assay

Solution 1 was injected (in duplicate) into the chromatograph. The chromatograms were recorded and the principal peak area was measured. The percentage of Lacidipine was calculated by using the following formula.

\[
\text{Lacidipine (as %w/w of L.C.)} = \frac{Au \times W_1 \times 50 \times \text{Avg.wt} \times P}{As \times 100 \times W_s \times LC \times 100} \times 100
\]

Where,

- \(Au\) = Average area of Lacidipine obtained with sample preparation.
- \(As\) = Average area of Lacidipine obtained with replicate injections of standard preparation.
- \(W_1\) = Weight of Lacidipine working standard, in mg.
- \(W_2\) = Weight of sample, in mg.
- \(Avg.wt\) = Average weight of Lacidipine tablets.
- \(LC\) = Label claim of Lacidipine, in mg.
- \(P\) = Potency of Lacidipine working standard in percentage on as is basis.

Procedure for related substance (RS)

A single injection of blank and solution (1) was injected into the chromatograph. Any peak due to blank was disregarded. The chromatograms were recorded and the area response of peaks was measured. The percentage of individual impurity was calculated using the following formula. Any peak with a relative retention time of 1.5 was disregarded with respect to the peak due to Lacidipine impurity B.

\[
\text{Impurity B (%w/w)} = \frac{Au \times W_1 \times 1 \times 100}{As \times 50 \times W_s \times LC \times 100} \times 100 \times CF
\]

Where,

- \(Au\) = Area of Impurity B obtained with sample preparation (Solution 1).
- \(As\) = Average area of Lacidipine peak obtained with replicate injections of standard preparation (Solution 2).
- \(W_1\) = Weight of Lacidipine working standard, in mg.
- \(W_2\) = Weight of sample taken, in mg.
- \(W_s\) = Average weight of the tablet in mg.
- \(LC\) = Label claim of Lacidipine, in mg.
- \(CF\) = Correction factor of Impurity B (2.0)

Any other secondary impurity (%w/w) =

\[
\frac{Au \times W_1 \times 1 \times 50 \times W_s \times P}{As \times 100 \times W_2 \times LC \times 100} \times 100
\]

Procedure for dissolution

Dissolution was carried out using BP Dissolution Apparatus II. Paddle-stirring assembly was used and the following parameters were maintained.

- Medium: 1% Polysorbate 20 in purified water (Mix 100 ml of water with 10 ml of Polysorbate 20, shaking gently and diluting to 1000 ml with water)
- Volume: 500 ml
- RPM: 50
- Temperature: 37°C ± 0.5°C

Standard Preparation

20.0 mg of Lacidipine working standard was accurately weighed and transferred to a 100 ml volumetric flask. It was dissolved and diluted to volume with absolute ethanol, mixed well, and used as stock solution. 4 ml of stock solution was diluted to 100 ml with dissolution medium and used as standard preparation (final concentration: 8.0 µg/ml).

Sample Preparation

The parameters of the instrument were set as mentioned in test method and the medium was degassed prior to use. One tablet each was transferred into six different vessels using 500 ml of medium and the apparatus was operated for exactly 45 minutes. At the time intervals of 10, 15, 20, 30, and 45 minutes, 10 ml of the solution was withdrawn from the midway zone between the surface of medium and top of the rotating paddle not less than 1 cm from the vessel wall and the same 10 ml was replaced with dissolution media for correction. The sampled solution was filtered through a 0.20 µm membrane filter, which was first activated with 3 ml of methanol followed by 5ml of a 1% w/v solution of Polysorbate 20, discarding first 5 ml of the filtrate. This solution was used as a test preparation (final concentration of lacidipine in sample: 8.0 µg/ml for lacidipine 4 mg tablets). Absorbance of the standard preparation (six times) and sample preparation (once) were measured on a suitable spectrophotometer at wavelength of maximum absorbance at 284 nm with the medium as the blank. Percentage of lacidipine dissolved
was calculated in individual tablets using the following formula:

\[
\% \text{ Lacidipine dissolved} = \frac{\text{Au} \times \frac{\text{W}_1}{100} \times 4 \times 500}{\text{As} \times 100} \times \frac{\text{P} \times 100}{4}
\]

Where,

\[\text{Au} = \text{Absorbance of Sample Preparation.}\]

\[\text{As} = \text{Average absorbance of Standard Preparation.}\]

\[\text{W}_1 = \text{Weight of Lacidipine working standard, in mg.}\]

\[\text{P} = \text{Potency of Lacidipine working standard in percentage, on as is basis.}\]

**Presentation and Evaluation of the Results**

Results for samples withdrawn daywise/stagewise were tabulated and graphically compared by use of Control charts: (A) X chart (For Mean location deviation) (B) R chart (for data range dispersion deviation). Anomalous results were explained, and where applicable and justified, an in-use shelf life specification was given.

**Revision of Label of the Primary Container**

Based upon results obtained by this in-use study, the label of the primary container was revised by adding in-use shelf life. In addition, a clear space was given in this label for the end-user (patient of hypertension) to write the “date of opening” and/or the “best before use date.”

**SPC, Leaflet and Labeling of the Secondary Container**

In-use shelf life and additional in-use storage recommendations (if applicable) were included in the revised SPC, leaflet and outer carton text of the secondary container.

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**Fig. 2.** Proposed decision flow chart for in-use stability testing of drug products.
Results and Discussion

Test Storage Condition

According to PIL, lacidipine Tablets should not be stored above 30 °C with protection from moisture in HDPE containers closed with CRC. As lacidipine is a light and moisture sensitive drug, tablets should be stored in the original HDPE container (with filling volume of 75 cc) and should not be removed until required for administration. After removal of tablets, HDPE containers should be immediately closed with CR Closure.

Test Design (Sample Withdrawal Plan and Testing Frequency)

The recommended initial dose of Lacidipine is 4 mg once daily for the full pharmacological effect to occur. In practice, this should not be less than 3 to 4 weeks (21 to 28 days). Considering moisture sensitivity, light sensitivity, and dosage regimen of lacidipine, a minimum in-use shelf life of 28 days is proposed for multi-dose packs (Anon, 2009). Thus, everyday one tablet was withdrawn by manually opening the closure under normal environmental conditions.

Samples withdrawn were physically examined for any changes in physical properties (e.g., appearance, hardness, disintegration and %LOD) over the period of proposed in-use shelf life, i.e. everyday up to 28 days from the individual of 20 containers (as at least 20 tablets are required for all tests specified in in-use shelf life stability profiling at individual time point). Chemical tests (Tang et al., 2008; Alyne and Tatiana, 2012; Bajaj and Singla, 2012) like assay of active substance, related substance(s) and %dissolution) were done on a periodic basis by fully validated analytical methods at the predetermined interval of 7 days with understanding that the samples withdrawn everyday not tested still must meet all specifications. Microbial limit tests (Bacteria/yeast/mould/pathogens) were skipped for the pre-determined interval of 14 days with understanding that the samples withdrawn everyday not tested still must meet all specifications. Additional testing was performed by fully validated analytical methods at intermediate time points (i.e. 2 weeks/14 days) and at the end of the proposed in-use shelf life (i.e. 4 weeks/28 days) on the final remaining amount of the product in the container. In-use stability study was conducted also towards the end of product shelf life (i.e. 24 months).

Presentation and Evaluation of the Results

The results of exposed samples as well as remaining samples in the container were clearly summarized and tabulated in Table 1, Table 2, and Table 3 with graphical comparisons in Figure 3 and Figure 4. Acceptable change is a change within limits justified in product specifications, i.e. NMT (±) 5% for assay and dissolution value and NMT (±) 0.1% for related substances (impurities).

Labeling of the primary container and secondary container

The in-use shelf life was stated on the revised label as represented in Figure 5. In addition, there was a space for the user to write the “date of opening” or the “best before use date” on the primary HDPE container. The in-use shelf life and in-use storage recommendations, if applicable, were included in the SPC, leaflet and outer carton text, shown in Figure 6.

TABLE 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Lacidipine Tablets 4mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch Number</td>
<td>CO2PHER</td>
</tr>
<tr>
<td>Date of Manufacturing</td>
<td>Jan 1</td>
</tr>
</tbody>
</table>

Proposed Product Shelf Life

In-use shelf life in days: 28

In-use shelf life stability

Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial Phase of Proposed Shelf-life under Normal Storage Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disintegration</strong></td>
<td>NMT 20 min</td>
</tr>
<tr>
<td><strong>Related Substance</strong></td>
<td>NMT 0.5%</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>NMT 99.5%</td>
</tr>
<tr>
<td><strong>Microbial Limit Tests</strong></td>
<td>NMT (±) 5%</td>
</tr>
</tbody>
</table>

Microbial Limit Tests

(A) Total Microbial Count

(B) Yeasts

(C) Pathogens

*Chemical tests (highlighted yellow) done on periodic basis at predetermined interval of 7 days with understanding that the samples withdrawn everyday not tested still must meet all specifications

*Microbial limit tests (highlighted red) were skipped at predetermined interval of 14 days with understanding that the samples withdrawn everyday not tested still must meet all specifications

*Impurity A generated due to solvent effect during synthesis of Drug Substance and/or manufacturing of drug product

*Impurity B generated due to temperature effect during synthesis and/or storage of drug substance and/or manufacturing and/or storage of drug product

*Impurity C generated due to light exposure during synthesis and/or storage of drug substance and/or manufacturing and/or storage of drug product

Note: Any other impurity mainly includes cyclic derivative of cis-isomer of Lacidipine.
TABLE 2
Results for individual In-use stability study at the end phase of proposed shelf-life under normal storage condition.

<table>
<thead>
<tr>
<th>Product Name:</th>
<th>Lacidipine Tablets 4mg</th>
<th>Batch Size</th>
<th>100,000 Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch Number</td>
<td>C001-001-001</td>
<td>Date of Manufacture</td>
<td>Jan 9</td>
</tr>
<tr>
<td>Pack Material &amp; Pack count</td>
<td>536 PTP HCPE Container</td>
<td>100 (Counts)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proposed Product Shelf Life</th>
<th>End Phase of Shelf Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Use shelf Life (in days)</td>
<td>0</td>
</tr>
<tr>
<td>Description</td>
<td>White to off white oval shaped, film coated tablet.</td>
</tr>
<tr>
<td>Assay</td>
<td>35% to 92% of label claim</td>
</tr>
<tr>
<td>Related Substance</td>
<td></td>
</tr>
<tr>
<td>Impurity A</td>
<td>Not detected</td>
</tr>
<tr>
<td>Impurity B</td>
<td>Not detected</td>
</tr>
<tr>
<td>Impurity C</td>
<td>Not detected</td>
</tr>
<tr>
<td>Total Impurities</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* Chemical tests (highlighted yellow) done on periodic basis at predetermined interval of 7 days with understanding that the samples withdrawn everyday not tested still must meet all specifications

* Microbial limit tests (highlighted red) were skipped at predetermined interval of 14 days with understanding that the samples withdrawn everyday not tested still must meet all specifications

1Impurity A generated due to solvent effect during synthesis of Drug Substance and/or manufacturing of drug product
2Impurity B generated due to temperature effect during synthesis and/or storage of drug substance and/or manufacturing and/or storage of drug product
3Impurity C generated due to light exposure during synthesis and/or storage of drug substance and/or manufacturing and/or storage of drug product

Note: Any other impurity mainly includes cyclic derivative of cis-isomer of Lacidipine

TABLE 3
Results for stage wise In-use stability study at the initial and end phase of proposed shelf-life under normal storage condition.

<table>
<thead>
<tr>
<th>Product Name:</th>
<th>Lacidipine Tablets 4mg</th>
<th>Batch Size</th>
<th>100,000 Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch Number</td>
<td>C001-001-001</td>
<td>Date of Manufacture</td>
<td>Jan 9</td>
</tr>
<tr>
<td>Pack Material &amp; Pack count</td>
<td>536 PTP HCPE Container</td>
<td>100 (Counts)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proposed Product Shelf Life</th>
<th>0 Months (Initial)</th>
<th>24 Months (End)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Use shelf Life (in days)</td>
<td>0 Day (Initial)</td>
<td>14 Days (Intermediate)</td>
</tr>
<tr>
<td>Description</td>
<td>White to off white oval shaped, film coated tablet.</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>35% to 92% of label claim</td>
<td>90</td>
</tr>
<tr>
<td>Related Substance</td>
<td></td>
<td>Not Performed*</td>
</tr>
<tr>
<td>Impurity A</td>
<td>Not detected</td>
<td>0.02</td>
</tr>
<tr>
<td>Impurity B</td>
<td>Not detected</td>
<td>0.03</td>
</tr>
<tr>
<td>Impurity C</td>
<td>Not detected</td>
<td>0.06</td>
</tr>
<tr>
<td>Total Impurities</td>
<td>0.15</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Note: Any other impurity mainly includes cyclic derivative of cis-isomer of Lacidipine

"Impurity A generated due to solvent effect during synthesis of Drug Substance and/or manufacturing of drug product
"Impurity B generated due to temperature effect during synthesis and/or storage of drug substance and/or manufacturing and/or storage of drug product
"Impurity C generated due to light exposure during synthesis and/or storage of drug substance and/or manufacturing and/or storage of drug product
Fig. 3. Quality control charts for (A) Physical tests: LOD, hardness and disintegration (B) Chemical tests: assay, impurities and dissolution for individual in-use stability study at initial phase of proposed shelf-life under normal storage condition.

Fig. 4. Quality control charts for (A) Physical tests: LOD, hardness and disintegration (B) Chemical tests: assay, impurities and dissolution for individual in-use stability study at the end phase of proposed shelf-life under normal storage condition.
Conclusions

After discovering the results of in-use stability study conducted at normal storage conditions recommended on label/PIL at “initial phase (1 month)” of integrated product shelf life (24 months), the following conclusions can be extracted successively: (i) After 1 week (7 days), 2 weeks (14 days), and 3 weeks (21 days) of regular in-use, changes were observed in physical parameters: LOD, hardness, and disintegration were almost same and within proposed acceptance criteria of in-process release specifications, while chemical changes analyzed in assay, dissolution, and impurity profiles were also almost the same and within proposed acceptance criteria of finished product specifications. But, the observed in-line trend was moving towards higher limits for LOD, hardness, disintegration, and levels of impurities, while the trend was moving towards lower limits for assay and dissolution. (ii) After 4 weeks (28 days) of regular in-use, results for physical parameters LOD, hardness, and disintegration, as well as results for chemical parameters assay, dissolution, and impurity profile passed at borderline set release and regulatory specifications.

As a result of absorption of moisture from the atmosphere during repeated opening and closing of container in routine use, values of loss on drying and corresponding hardness and disintegration rate of tablet was also increased due to hardening of a high proportion of drug: binder content (i.e. drug (1): binder (10)) in tablet formulation). However, by reason of repeated exposure of product to temperature, moisture, and light, assay and dissolution values dropped and impurity levels increased. Thus, depending on the comparative extent of change the in physicochemical characteristics of finished product as mentioned in Table 1 and as represented graphically by means of control charts in Figure 3, a total of 4 weeks (28 days) of in-use shelf life was proposed for Lacidipine Tablets BP, 4 mg in the proposed marketing pack consisting of 75 cc HDPE container with 33 mm CRC, which was appropriate to mitigate exposure to moisture and light. A total of 28 days (4 weeks) of in-use shelf life is also sufficient for the full pharmacological effect of anti-hypertension to occur without compromise of quality and performance of product in-use. The same observations and trends were recorded for in-use stability study conducted at normal storage conditions recommended on label/PIL at “intermediate” and “end phase (23 months)” of integrated product shelf life (24 months) as mentioned in Table 2 and as represented graphically by means of control charts in Figure 4. Results of microbial limit tests conducted in in-use stability study at the initial phase as well as at end phase of integrated product shelf life were passed comfortably within specification; a minute increase in microbial limits may be due to physical contact of product with microbial load in surrounding environments including atmosphere, personnel and container-closure itself.

Fig. 5. Revised label of primary pack with a space for the user to write the “date of opening” or the “best before use”.

Fig. 6. Revised label of secondary pack with in-use shelf life and additional in-use storage recommendations.
References


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