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# Formulation and evaluation of pulsatile drug delivery system using meloxicam

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## ABSTRACT

In the current research work, meloxicam is taken as a model drug. Meloxicam is non steroidal anti inflammatory drug which is used in the treatment of rheumatoid arthritis in children. This research work deals with the preparation of eroding or soluble barrier layer surrounding the core tablet and the drug release is time dependent. The system releases the drug after a predetermined lag time of 8 h and thus the dosage forms can be taken at bedtime so that the content will be released in the morning hours, when the symptoms are more prominent.

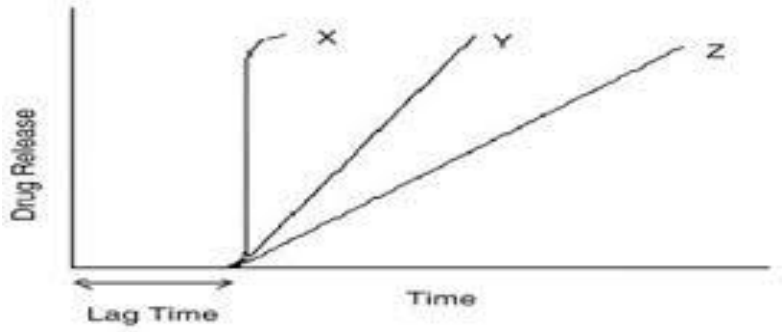
The optimized form of MELOXICAM with superdisintegrants like Xanthum gum and Guar gum in concentration (0.3-0.1g) may be attributed to rapid release of tablet. It was observed that disintegration time of tablet decrease with increased in concentration of these super disintegrants. The hardness of the pressed coated tablet was observed as 6.8 ($Kg/cm^2$) whereas friability was less than 1% which indicated that tablet had good mechanical resistance. Drug content was found to be high (>98.14%) and uniform in all tablet formulations and % drug release was found to be 99.65% after 8 hours. The order of drug release from matrix system was described by using zero order kinetics. On the basis of these evaluation parameters it was found that P3F7 shows consistent release of drug after the predetermined lag time and therefore it was optimized as a promising approach of meloxicam as Pulsatile Drug Delivery System.

**Keywords:** Pulsatile Drug Delivery System (PDDS), lag time, circadian rhythm,non steroidalanti inflammatory drugs, superdisintegrants.

## INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R &D sector. Such systems offer temporal &/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand

release of drug after a lag time. Such a release pattern is known as pulsatile release. The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases, hypercholesterolemia, ulcer and neurological diseases. Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness. A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system.




X=Complete drug release after lag time
Y=Delayed drug release after lag time
Z=Sustained drug release after lag time

In the current research work, meloxicam is taken as a model drug. Meloxicam is non steroidal anti inflammatory drug which is used in the treatment of rheumatoid arthritis in children. This research work deals with the preparation of eroding or soluble barrier layer surrounding the core tablet and the drug release is time dependent. The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, current situation and future scope, recent advances in PDDS.

## PULSATILE DRUG DELIVERY SYSTEM

Delivery systems with a pulsatile release pattern are receiving increasing interest for the development of dosage forms, because conventional systems with acontinuous release are not ideal. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release rates (lag time) followed by a rapid and complete release.

These dosage forms offer many advantages such as

- ✓ Nearly constant drug levels at the site of action.
- ✓ Avoidance of undesirable side effects.
- ✓ Reduced dose
- ✓ Improved patient compliance.
- ✓ Used for drugs with chronopharmacological behaviour, a high first pass effect.

The conditions that demand pulsatile release include:

- ➢ Many body functions that follow circadian rhythm i.e. their waxes and wanes with time. Ex: hormonal secretions.
- ➢ Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatoid diseases, ulcer and hypertension display time dependence.
- ➢ Drugs that produce biological tolerance demand for a system that will prevent continuous present at the biophase as this tend to reduce their therapeutic effect.
- ➢ The lag time is essential for the drugs that undergo degradation in gastric acidic medium (ex: peptide drugs) irritate the gastric mucosa or induce nausea and vomiting.
- ➢ Targeting to distal organs of GIT like the colon requires that the drug release is

prevented in the upper two-third portion of the GIT.

All of these conditions demand for a time-programmed therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by pulsatile drug delivery system, which is characterized by a lag time that is an interval of no drug release followed by rapid drug release.

## FORMULATION DEVELOPMENT

### Formulation of core tablets by direct compression

The inner core tablets were prepared by using direct compression method. As shown in Table powder mixtures of Meloxicam, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol), SSG, crospovidone, starch ingredients were dry blended for 20 min, followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 180mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 8mm punch and die to obtain the core tablet.

**Table 1: Composition of core tablets**

| Ingredients (mg) | F 1 | F2 | F 3 | F 4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Meloxicam | **7.5** | **7.5** | **7.5** | **7.5** | **7.5** | **7.5** | **7.5** | **7.5** |
| Cross povidone | **7.5** | -- | -- | **15** | -- | -- | **18.75** | **22.5** |
| Cross caramellose sodium | -- | **7.5** | -- | -- | **15** | -- | -- | -- |
| SSG | -- | -- | **7.5** | -- | -- | **15** | -- | -- |
| Magnesium stearate | **3.75** | **3.75** | **3.75** | **3.75** | **3.75** | **3.75** | **3.75** | **3.75** |
| PVP | **3.75** | **3.75** | **3.75** | **3.75** | **3.75** | **3.75** | **3.75** | **3.75** |
| MCC | **127.5** | **127.5** | **127.5** | **120** | **120** | **120** | **116.25** | **112.5** |
| Total wt | **150mg** | **150mg** | **150mg** | **150mg** | **150mg** | **150mg** | **150mg** | **150mg** |

**MCC: Micro crystalline cellulose, SSG: Sodium starch glycolate, PVP: Poly vinyl pyrrolidone**

### Formulation of mixed blend for barrier layer

The various formulation compositions containing HPMC, Ethyl cellulose, Xanthum gum and Guar gum. Different compositions were weighed dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

### Preparation of press-coated tablets

The core tablets were press-coated with 400mg of mixed blend as given in Table. 200mg of barrier layer material was weighed and transferred into a 12mm die then the core tablet was placed manually at the centre. The remaining 200mg of the barrier layer material was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

**TABLE 2: Composition of Press coat tablets**

| Press coat | P1(mg) | P2(mg) | P3(mg) | P4(mg) | P5(mg) |
|---|---|---|---|---|---|
| HPMC | **200** | **300** | -- | **400** | -- |
| Ethyl cellulose | **200** | **100** | -- | -- | -- |
| Xanthum gum | -- | -- | **300** | -- | **200** |
| Guar gum | -- | -- | **100** | -- | **200** |
| Total wt(mg) | **400** | **400** | **400** | **400** | **400** |

## EVALUATION OF PRE COMPRESSION PARAMETERS

**TABLE 4: Pre-compression parameters for formulation batches**

| Formulation code | Bulk density (gm/mL) | Tapped density (gm/mL) | Compressibility index (%) | Hausner's ratio | Angle of repose |
|---|---|---|---|---|---|
| **F1** | 0.436 | 0.500 | 12.8 | 1.14 | $25^0$ 16' |
| **F2** | 0.428 | 0.496 | 13.7 | 1.15 | $24^0$ 14' |
| **F3** | 0.445 | 0.505 | 11.8 | 1.13 | $24^0$ 10' |
| **F4** | 0.400 | 0.470 | 14.8 | 1.17 | $23^0$ 02' |
| **F5** | 0.43 | 0.58 | 23 | 1.58 | $26^0$25' |
| **F6** | 0.48 | 0.54 | 22 | 1.63 | $25^0$ 0' |
| **F7** | 0.47 | 0.59 | 21 | 1.62 | $24^0$11' |
| **F8** | 0.45 | 0.54 | 23 | 1.55 | $20^0$ 05' |

## EVALUATION OF POST COMPRESSION PARAMETERS

**TABLE 5: Physical Evaluation Parameters For Core Tablets**

| S. No | Physical parameter | F 1 | F 2 | F 3 | F 4 | F 5 | F 6 | F 7 | F 8 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Weight (mg)** | 152 | 150 | 148 | 149 | 148 | 150 | 151 | 151 |
| 2 | **Hardness ($Kg/cm^2$)** | 7.3 | 7.9 | 7.5 | 7.2 | 7.4 | 7.8 | 7.5 | 7.4 |
| 3 | **Thickness (mm)** | 3.28 | 3.16 | 3.82 | 3.74 | 3.44 | 3.25 | 3.11 | 3.15 |
| 4 | **Friability %** | 0.2 | 0.4 | 0.2 | 0.4 | 0.3 | 0.5 | 0.4 | 0.5 |
| 5 | **Disintegrationtime (min)** | 2 min 10sec | 3mins | 3mins 40sec | 2mins | 2 min 3 sec | 3mins | 1min 30 sec | 1 min 40secs |

## DISSOLUTION OF CORE TABLET

**TABLE 6: Dissolution for core tablet**

| Time in mins | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| **5** | 22.5 | 19.8 | 17.9 | 25 | 21.62 | 20.8 | 32.0 | 35.1 |
| **10** | 30.82 | 31.8 | 28.6 | 34 | 37.4 | 32.83 | 47.43 | 46.14 |
| **15** | 38.7 | 45.5 | 40.1 | 48 | 45.6 | 49.25 | 58.98 | 52.22 |
| **20** | 55.5 | 53.4 | 52.5 | 60 | 50.3 | 55.33 | 78.6 | 71.74 |
| **30** | 69.2 | 56.6 | 59.7 | 82 | 74.45 | 62.8 | 96.1 | 80.5 |
| **45** | 86.4 | 76.8 | 68.6 | 96.4 | 89.36 | 79.5 | -- | 95.5 |
| **60** | 95.5 | 88.8 | 79.6 | -- | -- | -- | -- | -- |

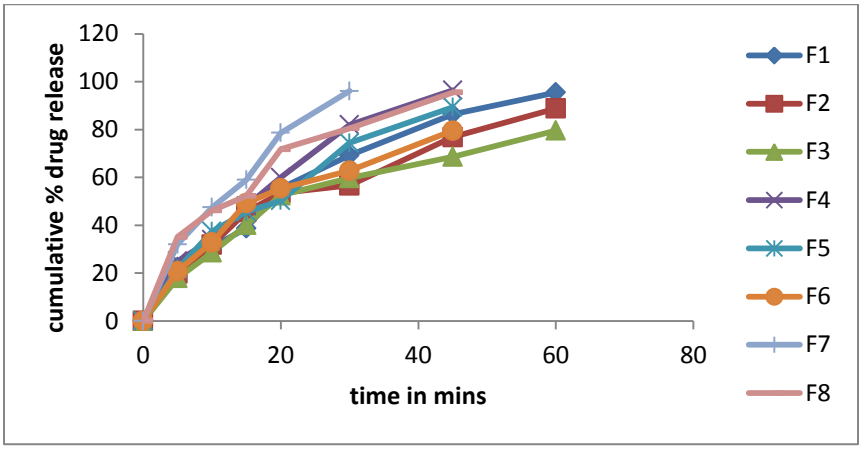



**Fig 3- Comparative Dissolution of all the formulations of core tablet.**

## EVALUATION PARAMETERS OF PRESS COATED TABLETS

**TABLE 7: Evaluation Parameters Of Press Coated Tablet ( F7 formulation of core tablet)**

| S. No | Physical parameter | P1F7 | P2F7 | P3F7 | P4F7 |
|---|---|---|---|---|---|
| **1** | Weight (mg) | 502 | 501 | 500 | 501 |
| **2** | Hardness ($Kg/cm^2$) | 6.5 | 6.7 | 6.8 | 6.2 |
| **3** | Thickness (mm) | 4.5 | 4.4 | 4.3 | 4.7 |
| **4** | Friability % | 0.56 | 0.55 | 0.62 | 0.54 |

**TABLE 9: DISSOLUTION PROFILE OF OPTIMIZED FORMULATION – P3F7**

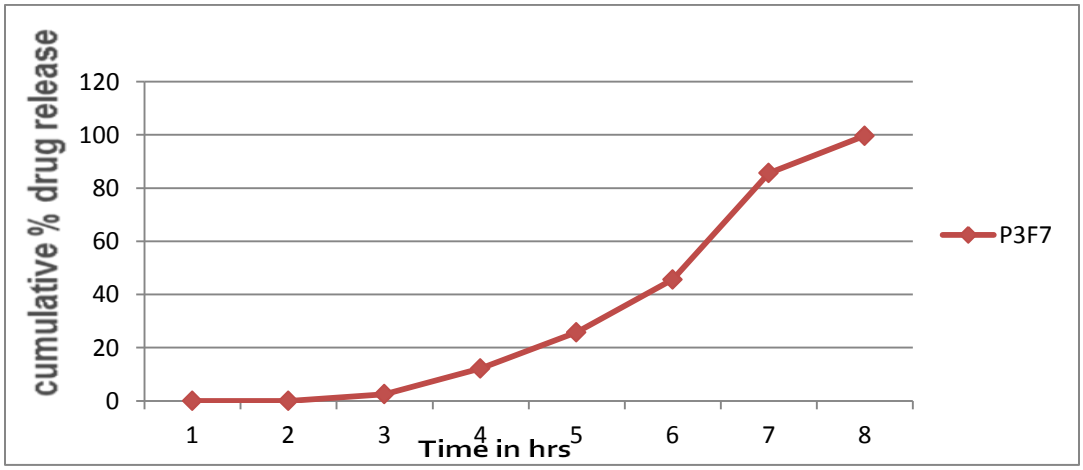



**Fig 6- Release of drug in optimized formulation P3F7**

**TABLE 10: DRUG RELEASE KINETICS OF OPTIMIZED FORMULATION P3F7**

| P3F7 FACTORS | ZERO % CDR Vs T | FIRST Log % Remain Vs T | HIGUCHI %CDR Vs √T | PEPPAS Log C Vs Log T |
|---|---|---|---|---|
| **Slope** | 11.43866667 | -0.208246028 | 28.69857353 | 2.0608 |
| **Intercept** | -21.8224444 | 2.45121207 | -28.06321723 | -0.2571 |
| **Correlation** | 0.796128873 | -0.691848171 | 0.655259131 | 0.901964906 |
| **R 2** | 0.633821183 | 0.478653891 | 0.429364529 | 0.8206 |

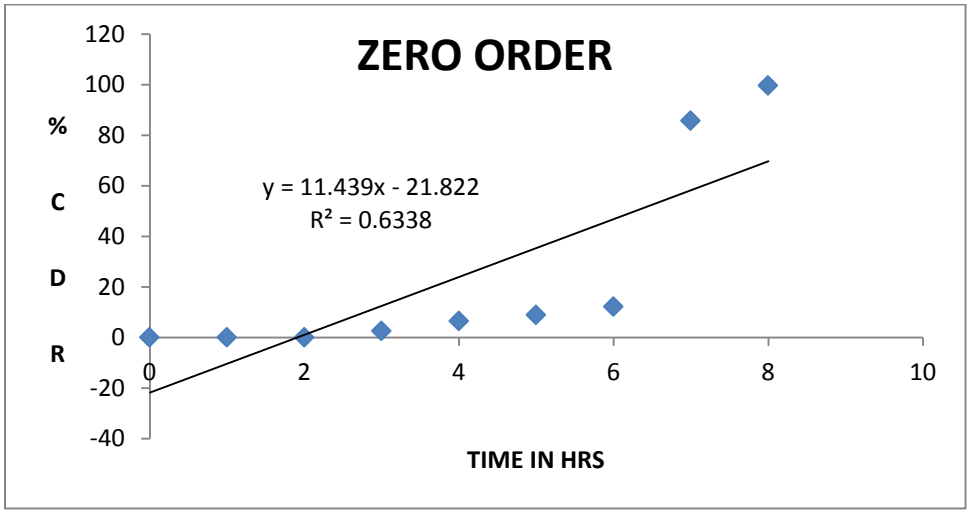



**Fig 7- Zero Order release of optimized formulation**

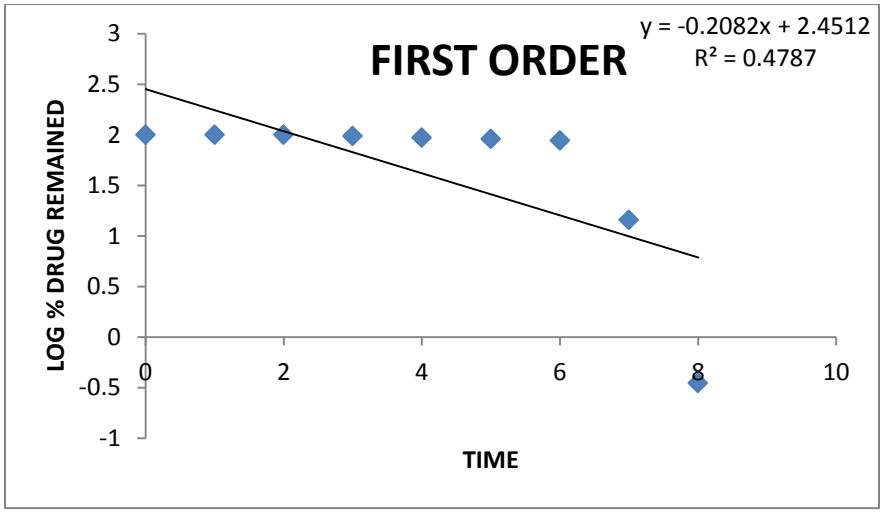



**Fig 8- First Order release of optimized formulation**

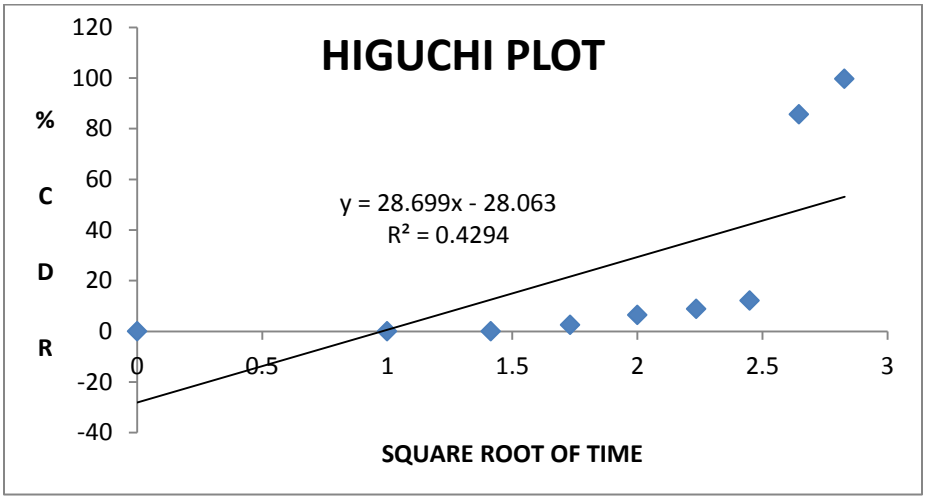



**Fig 9- Higuchi plot of optimized formulation**

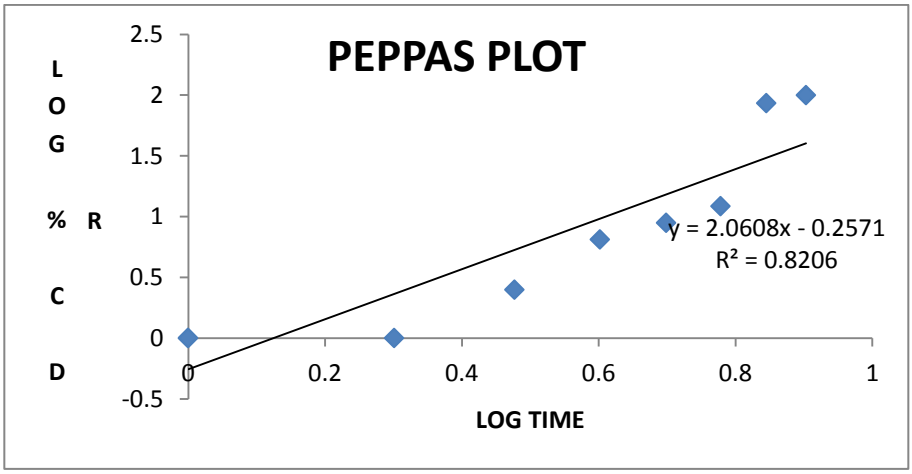



**Fig 10- Peppas plot of optimized formulation**

## STABILITY STUDIES

**TABLE 11: Stability studies results**

| Time | Colour | Assay | | Cumulative % drug release at 12 hrs | |
|---|---|---|---|---|---|
| | | 25±2$^0$c and 65±5 %RH | 40±2$^0$c and 75±5%RH | 25±2$^0$c and 65±5%RH | 40±2$^0$c and 75±5%RH |
| First day | White | 99 | 99.25 | 99.6 | 98.4 |
| 30 days | White | 98.88 | 99 | 97.9 | 100 |
| 60 days | White | 98.85 | 98.73 | 98.3 | 98 |
| 90 days | White | 99.30 | 98.43 | 98.1 | 99.3 |

## CONCLUSIONS

Various conclusions can be withdrawn from the present work are as follows:

- FTIR Spectroscopic studies indicated that the drug is compatible with the polymer and co-excipients.
- The flow properties of all the powders are tested for all the formulations and it was observed that all the formulations shows good flow properties. Among this. F7 is considered as optimized formulation as it is showing bulk density of 0.47gm/mL, tapped density of 0.59gm/mL, Carr's index as 21%, Hausner's ratio as 1.62 and Angle of repose as $24^0 11'$ which is considered as excellent.
- The evaluation parameters including dissolution shows F7 as best formulation as its disintegration time is very less and for the core tablet, it is essential that the drug is released as early as possible. After all these evaluation test, F7 is selected as best formulation and therefore it is optimized as pulsatile tablet.
- The optimised form of meloxicam with Polymers like Xanthum gum and Guar gum in concentration (0.3-0.1g) may be attributed to rapid release of tablet. It was observed that disintegration time of tablet decrease with increased in concentration of these polymer. The hardness of the pressed coated tablet was observed as 6.8 ($Kg/cm^2$) whereas friability was less than 1% which indicated that tablet had good mechanical resistance. Drug content was found to be high (>98.14%) and uniform in all tablet formulations and % drug release was found to be 99.65% after 8 hours.
- Kinetics of drug release was performed and the result shows that release of drug follows zero order kinetics and drug is released by erosion that is it follows korsemeyer-peppas plot.
- Based on the obtained results best formulation was subjected for further stability study. The stability study was conducted as per ICH guidelines for the period of six months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH.

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