DEVELOPMENTS IN ACTIVE AND PASSIVE REFRIGERATED TRANSPORTATION FOR THE PHARMACEUTICAL INDUSTRY

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ABSTRACT

There have been many recent improvements to active and passive temperature controlled, transportation. This has been in response to the demands of the market and increasing legislation.

This paper discusses the various options available to the pharmaceutical industry in particular and is of interest to all those concerned with passively and actively cooled transportation modes in general.

Containers, mini containers, airfreight containers and refrigerated vehicles are covered. Cooling systems and transportation methods employing eutectics, phase-change materials and dry ice are examined and results from trial work referenced.

These developments can provide efficient and effective means of temperature regulation and offer cost effective solutions to the increasing requirements of transportation.

1. INTRODUCTION

Over recent years there has been considerable growth in the requirement for the transport of pharmaceutical products under temperature-controlled conditions. This demand has been driven by requirements for temperature sensitive commodities and is becoming increasingly complex, with a continually growing flow of guidelines and regulations. These are designed to address not only the requirements of regulatory authorities but also that of the product being transported.

Outsourcing production to contract manufacturers has also increased demand for efficient transportation and is a significant part of many major pharmaceutical organisations' strategy. This can simply be a cost consideration and may also be due to a desire to focus on core activities such as research and development and sales.

Despite the high value of such products, there is nevertheless surprising pressure to minimise transportation costs.

In order to maintain the original quality of the product, every portion of the distribution of pharmaceutical products needs to be carried out according to the principles of 'Good Manufacturing Practice', 'Good Storage Practice', 'Good Trade and Distribution Practice' and conform to appropriate legislation.

Pharmaceutical products require to be conditioned and maintained at temperatures typically between 2°C and 8°C, usually to ensure that they lose none of their potency and hence their efficacy. Less temperature-sensitive products still are required to be temperature controlled, usually at between 15°C and 25°C. Some products, for example

fractionised plasma, are stored frozen and rules set out in such publications as the European Pharmacopoeia have strict requirements for temperature deviation.

It is also no longer sufficient simply to show that the storage air temperature is acceptable but also that product temperature is adequately controlled.

Transportation can be by multiple techniques utilising active and passive temperature control systems.

Such systems include:

- Insulated mini containers
- Air freight pallet shippers
- Insulated containers with eutectics/dry ice
- Insulated air freight containers with eutectics
- Insulated refrigerated containers
- Insulated refrigerated air freight
- Refrigerated vehicles

In addition, pharmaceutical equipment must follow validation protocols that provide evidence that the equipment is fit for its intended purpose. These provide a high degree of assurance that the carriage criteria will consistently meet requirements.

2. VALIDATION REQUIREMENTS

Recently there has been increasing pressure from regulatory organisations for the validation of equipment used in the transport of pharmaceutical products. Pharmaceutical transport equipment validation provides documented evidence that equipment is fit for its intended purpose through clearly defined criteria. Validation is increasingly being seen as a requirement of cGMP (current Good Manufacturing Practice). Although there can be many stages to demonstrating that equipment is validated, the most common aspects qualified for equipment are the IQ, OQ and PQ stages:

Installation Qualification (IQ) – verifies that the equipment is installed correctly as per the original requirements and any documentation needed for use is in place.

Operational Qualification (OQ) – verifies that aspects of the equipment concerned with maintaining and ensuring product quality operates correctly over all expected ambient conditions.

Performance Qualification (PQ) - verifies that aspects of the equipment concerned with maintaining and ensuring product quality can perform as intended in an effective and repeatable manner over time.

3. AMBIENT TEMPERATURE SIMULATION PROFILES

For equipment and facilities exposed to summer and winter temperature variations it is also necessary to demonstrate that product temperature can be maintained in different ambient conditions.

A simple ambient temperature profile might be to maintain the exterior of the equipment at a steady temperature, say +30°C. A worst-case temperature that might be an extreme for winter or summer may also be used; for example, for the transport of warm fresh human blood, the exterior might be maintained at -5°C, or for high-temperature-sensitive flu vaccine, +38°C.

Real temperature profiles can also be simulated by downloading historical data from the Met Office and programming these into the temperature controller.

Complex profiles are used to demonstrate a situation that might occur during a shipment of pharmaceuticals; for instance, where the cargo is exposed to road transport, followed by a period of air transport before final delivery.

Examples of complex summer and winter profiles are given below.

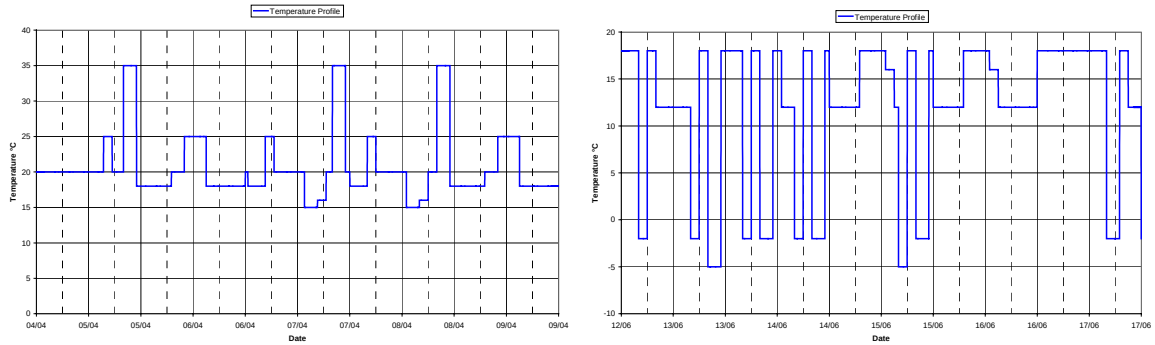


Figure 1 - Complex Ambient Summer and Winter Profiles

4. PASSIVE TEMPERATURE MAINTENANCE SYSTEMS

For the purposes of this paper the term passive temperature maintenance system will refer to systems that do not employ any mechanical or electrical components during transportation to control and maintain product temperature.

There is a range of systems available; examples of such systems include:

- Insulated mini container
- Air freight pallet shippers
- Insulated container with eutectics/dry ice
- Insulated air freight container with eutectics

4.1 Insulated Mini Container

Insulated mini containers vary widely in size and form, from small card boxes used for postal shipments to large multi-pallet shippers.

When not employing an energy source to drive heating or cooling systems, any product stored must be at the correct temperature before it is placed with in the container. These mini containers can rely simply on the specific heat capacity of their contents or can be used in conjunction with Eutectic PCM's (Phase Change Materials) or even battery driven systems driving mechanical refrigeration or Peltier devices.

Figure 2 - Insulated Mini Container

4.2 Air Freight Pallet Shippers

Airfreight pallet shippers are similar to insulated containers however they are typically supplied flat packed for assembly at point of distribution. They offer reusable packing solutions for the transport of temperature sensitive products. They consist of insulating material sandwiched between internal and external skins, normally cardboard. Often their outer surface is packed with two types of PCM's providing temperature stability within rises or falls of ambient temperature.

Figure 3 - Thermal Validation of a Pallet Shipper

Above is shown a shipper with the PCM's exposed.

5.3 Insulated Roll Containers with Eutectic PCM's/ Dry Ice

Eutectic PCM's are used within insulated roll-containers. The PCM's are frozen prior to transportation and gradually absorb heat at their phase change temperature, so maintaining the temperature. The PCM's typically contain a gel or brine-salt solution. They can be a removable or a permanent fixture. Once at the desired temperature provide reliable temperature maintenance for a specific duration without a power source.

Selection guides for eutectics are used which calculate the requirements based on the prescribed delivery rounds and take into consideration the journey length, number of door openings, weight of cargo and ambient temperature.

Figure 4 - Validation of an Insulated Eutectic Container

Figure 5 - Freezing Down Eutectic Plates

Another method of heat absorption, which is in common use, is solid carbon dioxide. This is employed by distributors as a means of cooling without the weight of PCM's or the need for mechanical or electronic refrigeration. It's usually referred to as a dry ice system or cryogenic cooling. Specially designed containers and packaging is required for the use of dry ice as it is extremely cold (-78.5°C) and therefore has to be separated from the products being transported. It is frequently used to preserve perishable foodstuffs and it also has applications in the pharmaceutical and healthcare sectors.

4.4 Insulated Air Freight Containers with Dry Ice/Eutectics

Aircrafts have custom designed containers that precisely fit into aircraft holds. In some instances these are insulated or custom built to facilitate the storage of temperature-sensitive products.

A relatively recent development is the use of large multiple pallet shippers that slot together around up to five euro pallets. The slot together sections are insulating and the temperature is maintained by the specific heat capacity of the product and appropriate eutectic PCM's.

Figure 6 - LD3 Air Freight Container and Multiple Shipper

5. ACTIVE TEMPERATURE MAINTENANCE SYSTEMS

Active temperature maintenance systems measure and control temperature within the product storage compartment either mechanically or electronically. These systems are commonplace in cold chain distribution networks and some of the main types are:

- Refrigerated roll container
- Insulated refrigerated air freight container
- Refrigerated vehicle
- Refrigerated marine container

5.1 Roll Container Refrigerated

This type of container is usually fitted with mechanical refrigeration powered by battery or municipal supply electricity. When operating on municipal supply electricity the battery is charged.

Figure 7 - Mechanically Refrigerated Insulated Container

They are typically used for the distribution of pharmaceuticals and vaccines.

5.2 Refrigerated Airfreight Containers

In principle this is the same as the passive insulated air freight container discussed earlier, however, it is fitted with a temperature controlling system such as a battery driven mechanical refrigeration unit, or a system of battery driven circulation fans which circulate air around dry ice.

These types of systems have been available for many years and have been shown to function satisfactorily though there is a substantial weight penalty.

5.3 Refrigerated Vehicles

Refrigerated vehicles are commonplace, well developed, and designed to carry goods, usually foodstuffs, within a particular temperature range. They come in a variety of forms together with an equally diverse variety of temperature systems. They range from small insulated vehicles with a direct drive mechanical refrigeration system to large multi-compartment articulated trailers with sophisticated diesel electric refrigeration systems. They typically employ active temperature measuring and control systems in addition to insulation and fresh air ventilation. Some vehicles employ additional passive cooling systems utilising eutectics usually for local delivery where there are frequent door openings.

Most refrigerated vehicles maintain tight temperature levels for food transport and are capable of meeting the requirements of the pharmaceutical industry.

Figure 8 - Refrigerated Vehicles Undergoing Summer PQ Testing in the CRT Test Chamber

Smaller vans tend to have a refrigeration compressor driven from their engine and the cooling efficacy is largely dependant on the driving cycle.

5.4 Refrigerated Marine Containers

Refrigerated marine containers are effectively an insulated box with an electrically powered refrigeration unit that allows accurate temperature control within its storage space. Electrical power for the unit is generally taken from an external source: the municipal supply, a generator set or the ship's supply.

Figure 9 - Marine Refrigerated Container

Marine containers are easily capable of maintaining the required temperatures for the transportation of pharmaceuticals. The difficulty arises during the interruptions to cooling such as occurs at the terminals during loading and the final leg of transportation by truck where a generator is required.

6. TEST RESULTS

Below are sample test results from trials conducted by CRT on various temperature-controlling solutions that serve to highlight the effectiveness and limitations in certain situations. It should be noted that the data does not necessarily correspond to the equipment shown in section 5.

6.1 Insulated Mini Container

The following successful test result shows a trial where a mini container was to maintain products at between 2°C and 8°C for a period of not less than 96 hours, whilst subject to controlled fluctuating ambient temperatures. The ambient temperatures were a specified complex winter related to the ambient conditions experienced within the distribution network.

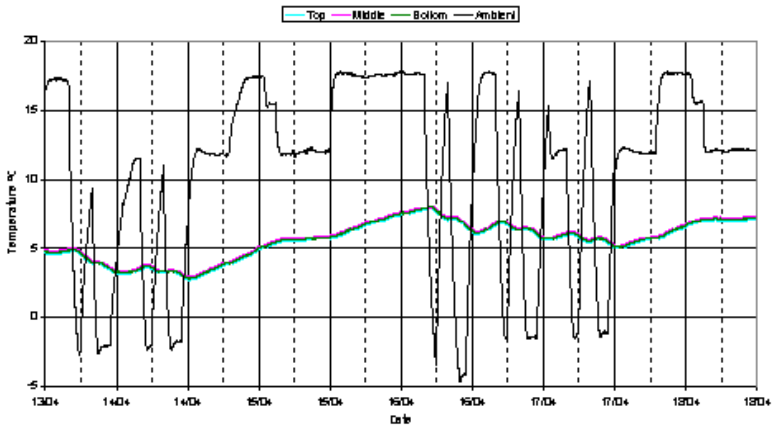


Figure 10 Mini Container Exposed to Simulate Complex Winter Profile

6.2 Air Freight Pallet Shipper

Reusable pallet shippers using eutectic PCM's as a passive cooling system are now regularly used for the transport of temperature sensitive commodities. Two CRT trials on similar pallet shippers are referenced below: the first was to validate whether pharmaceutical products could be held at between 2°C and 8°C in a complex summer profile, the second required 15°C to 25°C in a complex winter profile. Both sets of results indicated unsatisfactory performance.

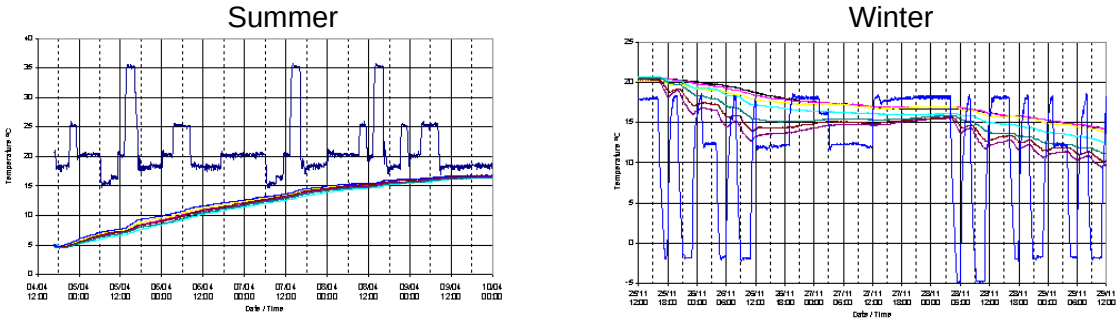


Figure 11 - Pallet Shippers Exposed to Complex Summer and Winter Temperature Profiles

6.3 Insulated Refrigerated Roll Container

Tests were conducted to test an insulated roll container in which pre-cooled eutectic plates were used to maintain product temperatures at between 2°C and 8°C. The products were to be medicines being transported from the primary to the secondary warehouses. The tests were carried out at 25°C followed by 35°C, typical worst-case summer conditions in the UK. The trials were successful and the results are given below. The graph shows the temperatures of the ambient, the products on different shelves and the eutectic plates.

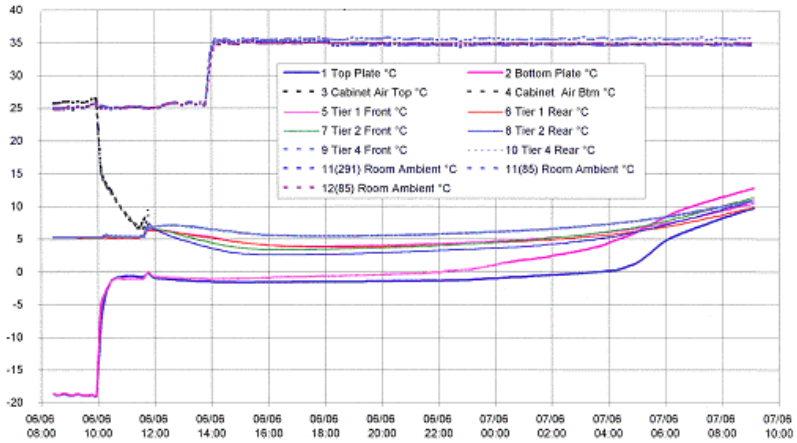


Figure 12 – Roll Container Internal Temperatures in a Summer Simulation

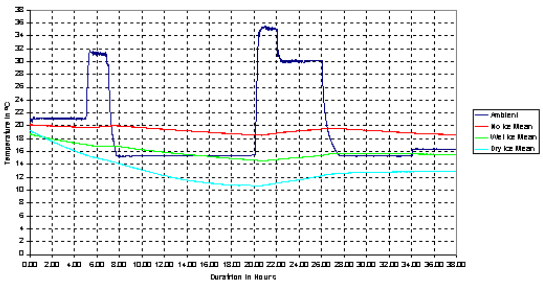
6.4 Multi Pallet Airfreight Shippers

A relatively recent development is the use of a series of insulated panels that connect and lock together around 5-euro pallets.

Three trials were carried out to compare the efficacy of the insulation and the additional effects of using standard ice (water) packs or dry ice (CO_2) packs, whilst being exposed to winter and summer temperature profiles. The target temperature for the cargo was between 15 – 20°C in both summer and winter.

Temperature profiles followed were for an airfreight cargo on a journey such as London to Sydney, via Kuala Lumpur and a cold climate, such as Milan to Chicago via Frankfurt. These simulated temperature profiles and the average temperatures of the contents for each cooling system tested are shown below.

Summer



Winter

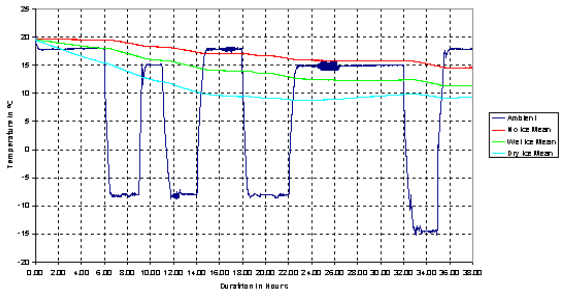


Figure 13 - Internal Enclosure Exposed to Summer and Winter Temperature Profiles (Time in hours in 2 hour intervals)

We can see from above that the best results in this case were obtained with no additional cooling system, stability being provided by the mass of the material being transported alone.

In the trials that used the additional ice packs or dry ice packs, both overcooled the product. In the summer temperature simulation, the dry ice system cooled to 10.9°C and the water ice system fell to 14.2°C. In the winter simulation, the water / ice system and the dry ice system cooled the cargo to 10.8°C and 9.4°C respectively.

6.5 Refrigerated Vehicles

There is now an ongoing demand for validation of refrigerated road vehicles for the transport of pharmaceutical products to be maintained.

In this trial a conventional mechanical refrigeration system directly driven from the van's engine was tested. In this case the required range was between 6°C and 10°C in high ambient temperature condition.

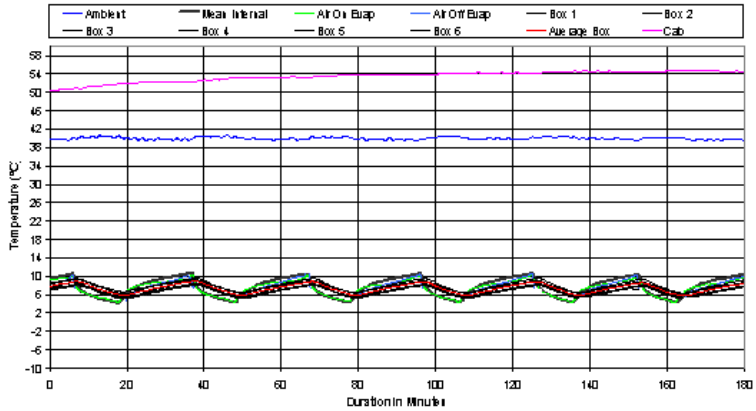


Figure 14 - Active Cooling Systems - Direct Drive Mode

As this graph shows, the average box temperature was efficiently maintained throughout the test though there were slight violations of the required temperature regime in some of the cartons due to the hysteresis of the controller.

6.6 Refrigerated Marine Containers

Blood plasma is now regularly transported by refrigerated container and is a high value product. Although the transport requirements can be quite complex for blood plasma the general rule is to maintain it at or below –20°C. The European Pharmacopoeia 4.5 states that blood "plasma may still be used if the temperature is between –20°C to –15°C for not more than 72 hours without exceeding -15°C on more than one occasion: and as long as the temperature is at all times lower than -5°C". Below we see an instance of two extended periods of off power outside the transport protocol making this cargo a total loss.

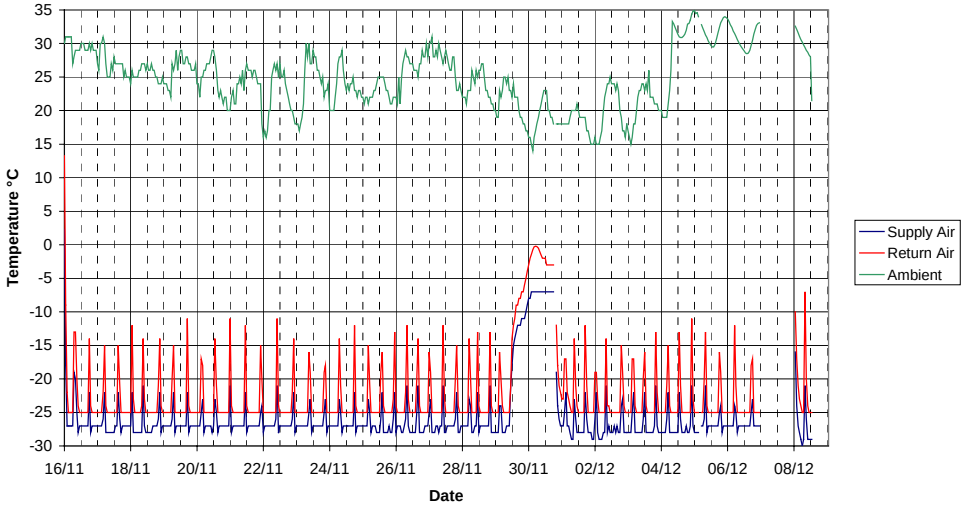


Figure 15 - Power Interruption during Marine Refrigerated Container Transportation

Refrigerated marine containers have to be unplugged during several areas of their inter modal journey leaving opportunities for errors. There would therefore appear to be an opportunity to introduce PCM's to reduce sensitivity to such mishaps especially as such container transportation is less weight sensitive.

7. CONCLUSIONS

Passive and active cooling systems used during the transport of temperature sensitive products are shown to have different levels of effectiveness and some limitations. The efficacy of a system will be dependent on the temperature sensitivity of the product and the ambient profile. Therefore, in some cases it might be advisable to employ more than one solution to ensure the shipment's temperature requirements are maintained.

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