PACKAGING CHALLENGES AND PROBLEMS IN THE PHARMACEUTICAL COLD CHAIN DISTRIBUTION

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Abstract: *The global pharmaceutical market is expected to reach $1.1 trillion USD by 2014. This increase will pose new challenges for logistics. One of the biggest is to deliver several different temperature-controlled drugs. In this process there is a difference between the US and the European regulations. According to the Good Distribution Practice which is used in Europe every digression from the storage temperature should be reported by the distributor and the recipient. This value should be between 2°C and 8°C with drugs which require cooling. However, in the US these kinds of drugs are categorized as a 'Controlled Cold Temperature drugs'. The value of this is also between 2°C and 8°C but allows for differences in temperature between 0°C and 15°C under certain conditions. The Mean Kinetic Temperature (MKT), which is the topic of this paper, is a good opportunity to control the verification process of the packages.*

Keywords: *MKT, cold chain, cooler box.*

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1. INTRODUCTION

The aim of this article is to present the problems which are caused by the characters of the pharmaceutical logistics in aspect of the packaging technology.

We would like to demonstrate the development opportunities of the packaging which characters very important are, because every product claim different temperature. The packaging must comply to the logistics and also to the strict norms of the pharmaceutical industry, so we are giving an overview on that topic too.

Differences between the U.S. and the European Union's praxis means more opportunities to increase the efficiency of the packaging, than the physical packaging parameter changes. This called the controlled cold temperature and the Mean Kinetic Temperature.

2. DESCRIPTION OF THE PHARMACEUTICAL LOGISTICS

The sector's logistics is special, because the long-range surveillance based products strict following-up and the insurance of the just required temperature range. The topic of our presentation is related to the latter, so we would like to give an overview about that first.

The drugs can be grouped into three categories by their storage temperatures:

1) The drugs which are in the first group can be stored at Room Temperature, means we can store them between 15-25 ° C.
2) The drugs in the next group demand Cool, here between 8-15°C is the proper.
3) The drugs which are in the third group give the main theme of this article. These are the drugs which are claimed Cold. The storage temperature of these is between 2-8°C.

During warehousing, these temperature ranges are easy to solve with freeze chambers. But during the transportation and the distribution is not so easy. With cooling chamber transport vehicles and active cool boxes this could be done easily and safely, however it's not economically reasonable. This is why the drug delivery companies have started to be interested about the passive cool boxes.

The passive cool boxes can be applied basically in two way of transportation:

- Long-distance transport
- Distribution

In the first case, there is usually only one opening, like in international shipments. More boxopening have been happened in the second case. So this time obviously the device can provide the

right temperature less time and the operating time is also unpredictable.

In the supply chain, these companies are operated between the factory and the pharmacies. The drugs, required different temperature classes shipped to the warehouse where they are stored properly. By the order of pharmacies they compile the items and deliver them. The application of passive cooler appears in this type of distribution process.
Pharmacies orders small countities one time, so the active cooling method is no longer economically. The goods are varied, they exchanged rapidly, so pharmacies stores small quantities.

However, the distributor can not go to a shipping address separately with three vehicles each with three temperature ranges, because this drastically increase the freight costs. A van need to serve about 3-5 addresses, so it has to ensure three different temperature ranges at a same time. Due to the small size of the vehicle, here we can not use space separation, which has been already used in the truck. That is why we need to apply passive coolers.

The temperature of the van loading space is between 15-25°C, that is proper for the drugs, require room temperature. The 8-15°C and 2-8°C range should be provided by two differently designed passive cooler. In the next chapter a cooler going to be described, which is applied in daily practice.

3. DESCRIPTION OF A PASSIVE COOLER BOX

3.1 The construction of the cooler box

The cooler's size is 520x570x700 mm and it weights 5,65 kilograms. It is based on a five-layer corrugated fiber board box provided with a removable lid. Each side is equipped with a 50 mm thick expanded polystyrene foam insulation. The EPS foam was fastened to the side walls with gluing. In the device the 2-8°C temperature must be provided during the distribution (details in chapter 5.1) with ice accumulators according to the following composition (Figure 1.).

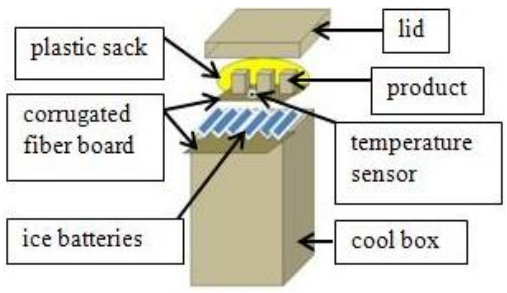

Figure 1. The construction of the cooler box

3.2 Effects of parameters

The operation time of a cooler box is influenced by the following factors:

- number of the placed ice batteries [nr]
- temperature of the placed ice batteries [°C]
- the outside temperature [°C]
- the mass of the delivered products [kg]
- temperature of the delivered products [°C]
- design of the packaging, such as the assembly quality, materials used, geometric dimensions and wall thickness

These factors are not all possible to change, and changing them will not lead to a significant improvement regarding the operational period. According to industry experiences the product which is to delivered, gets into to cooler at a temperature of about 5°C and about 3 kilograms total weight. The number of ice batteries are limited by the box size. Maximum 10 pieces can be placed side by side at the bottom of the box. Based on experience by a validation process, we can say that by increasing ice batteries number the operation time can not be increased significantly. The temperature of the ice batteries are limited by the company used chest freezer's parameters. During the validation process the outside temperature's high influence ability was observed. To know the effects of outer temperature we have to investigate the insulation of cooler box. To solve this using thermal law namely Fourier I. Code of this observation can be easily supported.

3.3 The development of the box with Fourier I. law

According to Fourier I. law (1) the heat flow which is pass through the surface (A):

$$Q = -\lambda A \frac{dt}{dx} = -\lambda \frac{t2 - t1}{d} \left[\frac{J}{s} \right] \qquad (1)$$

At the cooler box this wall is consist of several layers of 12 mm paper and 50 mm EPS foam forms. The same temperature passes through at each layers so the following equation can be written [1]:

$$\frac{A1\lambda 1(t1 - t2)}{d1} = \frac{A2\lambda 2(t2 - t3)}{d2} \qquad (2)$$

With the sorted equation and substituting the known values and selected the 18°C outside, and the 5°C inside temperature for 1m^2:

$$Q = \left(\frac{0{,}047 \frac{W}{mK}}{0{,}05m} + \frac{0{,}13 \frac{W}{mK}}{0{,}012m} \right) \cdot (18°C - 5°C) = 153{,}05W \qquad (3)$$

So that much heat enters to the insulated box through its wall. For example, if we use the same data with increasing the thickness of the EPS foam to 60 millimeters (+20%), we would get 151,02 W so less heat would enter to the box:

$$Q = \left(\frac{0{,}047\frac{W}{mK}}{0{,}06m} + \frac{0{,}13\frac{W}{mK}}{0{,}012m} \right) \cdot (18°C - 5°C) = 151{,}02W \quad (4)$$

Our previous statement that with the allowance of the outside temperature the system performance significantly amendable can be verified. Instead of 18°C, we raise this factor also with 20 % which going to be 21,6°C. Substituting this value to the original equation:

$$Q = \left(\frac{0{,}047\frac{W}{mK}}{0{,}05m} + \frac{0{,}13\frac{W}{mK}}{0{,}012m} \right) \cdot (21{,}6°C - 5°C) = 195{,}44W \quad (5)$$

It is worth to compare the solutions:

The 20% thickness increase of the insulation results a 1,3% decrease with the entered amount of heat while the same increasement of the outside temperature caused 20% increasement with the entered amount of heat. It means, that the simple modification of the construction not give quite enough advance. It can be seen that due to the many difference influencing factors there is not a specific formula which properly considers all the effects. By the high variation of parameters and the strict and narrow temperature ranges, required every possible support should be useful. For this purpose we are giving a brief overview on the regulatory system of the pharmaceutical industry.

4. REGULARIZATION

4.1 Regulatory systems

There is not just one 'supreme' regulatory system that would give specific instructions about the unabrogated rules in one particular region.

This fragmentation is evidenced by the following list of the world's largest pharmaceutical markets have regulation appertain to the cold chain [2]:

- The EU Guide to Good Manufacturing Practice, Annex 13
- The Guidelines on Good Distribution Practice (GDP) of Medicinal Products
- CDC Guidelines for Maintaining and Managing the Vaccine Cold Chain
- WHO Guidelines on the international packaging and shipping of vaccines
- PDA Technical Report 39
- The US Code of Federal Regulations
- US and European Pharmacopoeia [2]

Applying to the temperature ranges which is the topic of this presentation in Hungarian practice The Guidelines on Good Distribution Practice (GDP) of Medicinal Products is used, which include the following:

„*If a deviation such as temperature excursion or product damage has occurred during transportation, this should be reported to the distributor and recipient of the affected medicinal products. A procedure should also be in place for investigating and handling temperature excursions*." [3]

In contrast, the United States Pharmacopeia, in the General Notices and Requirements, defining a transition temperature range, it is known as Controlled Cold Temperature.

4.2 Controlled Cold Temperature and The Mean Kinetic Temperature

"Controlled cold temperature" is defined as temperature maintained thermostatically between 2°C and 8°C (36° and 46°F), that allows for excursions in temperature between 0°C and 15°C (32° and 59°F) that may be experienced during storage, shipping, and distribution such that the allowable calculated mean kinetic temperature is not more than 8°C (46° F). Transient spikes up to 25°C (77° F) may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise." [4]

The Mean Kinetic Temperature (MKT) which is used in the definition is defined in the International Conference on Harmonization (ICH) Q1A(R2) document as:

"A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation." [5]

„The use of MKT to represent the expected impact of temperature variations on the quality of a drug product." [6]

The transformed formula is the following:

$$MKT = \frac{\Delta H / R}{-\ln\left(\frac{e^{-\frac{\Delta H}{RT_1}} + e^{-\frac{\Delta H}{RT_2}} + \ldots + e^{-\frac{\Delta H}{RT_n}}}{n}\right)} \quad (6)$$

where:

ΔH = the heat of activation for the degradation reaction; assumed to be 83,144 kJ per mol unless more accurate information is available from experimental studies.

R = the universal gas constant, 8,3144 × 10^{-3} $\left[\frac{kJ}{molK}\right]$

T_1 = the average temperature, during the 1st time period $[K]$

T_2 = the average temperature, during the 2nd time period $[K]$

T_n = the average temperature, during the nth time period $[K]$

n = the total number of temperatures recorded. Note that the interval between temperature measurements is assumed to be identical.

The activation energy E_a is assumed to be 83.144 kJ/mol. This value has been derived from evaluating published data for more than 100 chemical substances, namely small molecules that are commonly used as active ingredients in pharmaceutical products, and calculating the mean. *„If feasible, and definitely in case of biological/biotech products, it is advisable to use the actual activation energy found for the particular substance instead of the mean value. The actual activation energy can be derived by calculating the intercept of the Arrhenius plot with the y-axis."* [7]

5. APPLYING THE MKT IN THE DAILY PRACTICE

5.1 The validation process of a passive cooler

One passive cool box which is applied to insure 2-8°C range and used in every day practice has been introduced in the chapter third. The operation period have to be determined by a validation process.

8 pieces underneath ice batteries reached 8°C after 616 minutes. During the validation in the first six hours the box and the bag was open for 1-1minute once in every hour simulating a take out of a product, and after the sixth opening we let it closed till 18 hours.

According to the original idea the cooler box would have to provide the appropriate temperature range for 24 hours, that is why there was an investigation on the impacts of the influencing factors in the second chapter. During the test, the average outside temperature was 17,7°C, which is closed to the allowed 15-25°C, so we can not increase the performance of the box by this solution. To solve a small structural change is needed on the box, in according to the required thermodynamic laws.

5.2 Modification of the cooler

It is a well known context that the warm air raises, cold air moves into position.

So it means that in the original assembly the bottom placed ice was cooled just partly of the products, and mainly the bottom of the box. After the modification of the cooler, the ice batteries placed below the lid, over the products in a 4 points fixed netbag. The netbag also can be closed, so after the transportation the ice batteries can be managed by boxgroups, not by piece by piece so they can be re-freezable. Because of the frequent product pull out, the fixation has to be easily soluble and it also has to be easy to fix. The task has been by the following manner (Figure 2.):

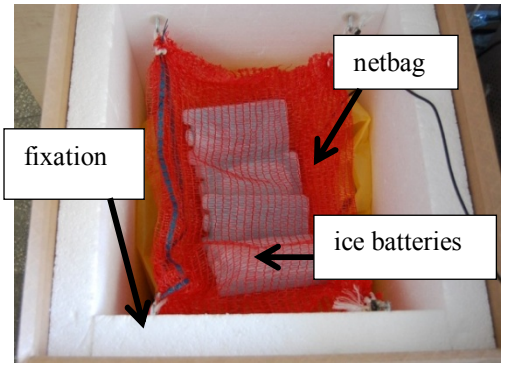

Figure 2. Placement of the ice batteries

It can be seen that the courier can easily unhang it from one side to the opposite and put it back after removing the goods.

With this setup, a new measurement was performed. We have applied just 6 pieces ice batteries because we have to decrease the cost, and to investigate the new construction. 6 pieces ice batteries were placed above the products, apart from that the test was the same as the previous one. After 992 minutes, the inside temperature of the cooler box exceed 8°C. Therefore with less ice batteries this system assured the proper temperature 6 hours longer than the previous one. Another advantage may can be that all of this was reached at 20,3°C outside average temperature, which means nearly 3°C higher temperature, comparing to the previous measurement. It could even be cost-saving factor, as it is not unimportant because of the fuel costs,

considering that in a summer day how much the interior of the transport vehicle has to be cooled, comparing to the surrounding temperature. The exact definition of this is beyond the topic of this article, therefore it is not discussed in detail here, but it can be treated as an advantage.

5.3 Analysis of measurements

The interesting was that the excursions was just after 24 minutes after the starts, when the temperature went lower under limit (2°C).

According to The Guidelines on Good Distribution Practice (GDP) of Medicinal Products, which was presented among the regulation systems it should not be used in the European practice. If we take a count about the advantage of this modification, we can see that applying the American options can be a possible solution. The American options namely are the Controlled Cold Temperature and the MKT.

According to the original idea, analyzing the measurement results in 24 hours, the lowest temperature was 0,9°C and the maximum was 8,7°C, so it is in the controlled cold temperature range (0-15°C). So the MKT can be applied. During the measurement the temperature changed in every minute, so we choose one minute to be one period. Substituting to the formula:

$$MKT_1 = \frac{83{,}14472/0{,}008314}{-\ln\left(\frac{e^{-\frac{83{,}14472}{0{,}008314\cdot 290{,}45}}+\ldots+e^{-\frac{83{,}14472}{0{,}008314\cdot 281{,}85}}}{1440}\right)} \quad (7)$$

$$MKT_1 = 7{,}4°C$$

Therefore, the effect of temperature fluctuations occurring during the 24 hours is the same, as, if the product had been stored at 7,4°C for 24 hours. The number of intervals can be reduced, if we select one hour as a period and the value of these will be the average of the temperatures which are changing in every minute. Thus, MKT_{60} 's value is 7,3°C. [8]

The temperature stayed within the allowable range, with both of the counting methods, so according to the American regulatory system that could be used in everyday practice with the modified cooler box design. We summarized the measurements results in the following table (Table 1.).

6. CONCLUSION

In this presentation, we demonstrated that the use of passive cooling box is unavoidable for the economical delivery of the products.

We demonstrated that the development possibilities of the device is significantly limited, so in a dynamic, large-scale, highly regulated market such as the pharmaceutical industry, every reliever, cost-cutting option is required.

Table 1. Comparative table of measurements

Ice batteries	Pieces	8	6
	Location	bottom	above
Operation time [min]		617	992
Temperature in the van [°C]		17,7	20,3
Calculated temperature with MKT after 24 hours [°C]		8,9	7,4
Cost of cooler box [€]		38	36
Applicable without MKT		yes	no

Such a helpful option can be to extend the strict, narrow temperature ranges, bearing in mind, of course, to preserve the quality of the products.
Suitable for that for example the MKT defined by the ICH and the Controlled Cold Temperature which is used in the USA.

The permit of the MKT and Controlled Cold Temperature the drug delivery companies could be applied new packaging devices in Europe, too.

Very important expectations of these new packaging is to satisfy the logistics requirements. Our demonstrated cool box is a good possibility for this.

REFERENCES

[1] Hodúr, C. and Sárosi, H. 2007. *Hőtani műveletek*, 4-9, Szeged

[2] FDA & ICH, , 2012. *Regulations and Standards for Temperature-Controlled Supply Chains*, Vaisala-Application Note.

[3] *Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use*, Official Journal of the European Union, C 68/10, 2013.

[4] *United States Pharmacopeia General Notices and Requirements*, USP 35–NF 30, 2011.

[5] *Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products*, ICH, 2003.

[6] Seevers H., R., et al. 2008. *The Use of Mean Kinetic Temperature (MKT) in the Handling, Storage, and Distribution of Temperature Sensitive Pharmaceuticals*, Pharmaceutical Outsourcing, Volume 9, Issue 5.

[7] Huynh-Ba, K., 2009. *Handbook of Stability Testing in Pharmaceutical Development*, ISBN 978-0-387-85627-8, 35-36, New York.

[8] Farrugia, A.C., 2005. *Controlled temperature storage of medicinals - Good practice measures in the community pharmacy*, Journal of the Malta College of Pharmacy Practice, Issue 10, 30-33.