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Analysis of injection systems ampulla-syringe vs. ampulla with respect to application of parenteral medicinal products on the example of ibadronic sodium

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Summary:

Nowadays, equally to the development of modern pharmaceutical technology and introduction of new biologically active substances to pharmacology we observe a development of techniques with the use of which medicinal products are applied into a living organism. The above regard many types of drug forms, among others, medicinal aerosols, fillers, injections, anal and vaginal forms, etc. Many times the medicinal effect depends on a high technical level of these devices, which are also medical materials. In this work at attempt has been made to analyze the mutual relations between a way of administering an injection in a standard form with the use of a standard syringe and technically higher forms, namely integrated ampulla-syringe systems.

Key words: ampulla-syringes, injections, fillers, parenteral administration.

Introduction

Durability of medicines for injections to a large extent depends on the direct packaging in which the target form of the medicine is stored (a solution, a colloid, an emulsion, etc.) and a way of storing them. Containers to store medicines for injections: ampulla-syringe or ampullas should have the following functions:

- Protect a medicine against the impact of the environment (air, moisture, light);
- Protect against mechanical contaminations;
- Protect against microbiological contaminations [1,2,4];

A direct container having contact with a medicine should be chemically neutral, cannot react with particular substances forming a pharmaceutical form of a medicinal agent, and a biologically active substance itself. Ampulla-syringes and ampullas should be characterized by a proper mechanical durability. They should also have specific thermal durability because of the method of sterilization. Also additional elements such as stoppers, pistons, sealing rings must be chemically and physically neutral, cannot react with the content of the container (a biologically active substance, auxiliary substances), cannot have an impact on any properties of the medicinal product [3,4].

Ampulla

This is a glass container that saves the airtight closing of the particular volume and dosage of the medicinal product after the sealing. An ampulla protects against the air and levels down a problem related to the secondary infection of a sterilized medicine. If a biologically active substance or any of the auxiliary substances is UV sensitive (light, the direct sun light), ampullas made of orange glass are used. However, the intensity of ampulla coloring cannot collide with the visual control of the content assessment. A volume of the containers which serve the purpose of an ampulla is from 1ml up to 20ml, they are mainly designed for solutions [4]. So far in order to open an ampulla one has had to use a file sawing through the structural narrowing of the neck so that the opening of an ampulla was easier.

Currently ampullas are produced in the way which enables the opening by breaking off the top part, without using a file. Such a way of opening the container is risky because tiny mechanical contaminations in the form of glass scraps can get to the solution of a medicine. The opening of an ampulla should take place immediately before injection, however a medicinal product contained in an ampulla after the opening is exposed to the contact with external conditions (moisture, microbiological contaminations!). The content of an ampulla is then taken with the use of a working needle to a syringe. During this process part of the volume of the liquid medicine is lost because it remains either on the bottom of an ampulla or/and in a needle, depending on a suction pressure. The next activity before administering the medicine to a patient is an exchange of a working needle (suction from an ampulla) into a injection needle (introduced to the patient's tissues). After putting an injection needle the air sucked with a medicinal product into a syringe must be removed externally. Some part of the volume of a medicinal product is also lost resulting from the type of a needle used, its diameter, pressure force into the piston and the amount of the ejected medicine directly after the removed air [5].

The above information indicates that administration of a sterile medicinal product ion the form of an ampulla has certain procedural inconvenience, and also gives a possibility of a loss of some part of a medicinal product and/or its potential microbiological contamination. This is more dangerous in a situation when an administered medicinal product contains 'difficult' biologically active substances, e.g. of a low index o biological access or of a narrow therapeutic index. The loss of some medicinal product in the aforementioned stages of an injection procedure can lead to dissatisfying treatment results. Because of small sizes and fragility of glass during handling of a medicinal product a total or partial loss of the content of an ampulla as a result of breaking or spilling. Generally, application of a medicinal product in the form of an ampulla must be administered by a qualified personnel who performs these injections [6,7,8].

Ampulla-syringe

A technological reply to the above presented inconveniences related to the use of ampulla-type containers is the application of modern injection forms combining the functions of ampullas, needles and syringes, namely, ampulla-syringes. An ampulla-syringe is a medicinal product container designed for single use (disposable). It guarantees a fast provision of a medicine in a proper, precisely measured dose. The easiness of the use makes patients use it on their own. An ampulla-syringe is sterile, with the use of it the injection is performed without the need to take the preparation from an ampulla or a flask. The whole set prepared in a factory is sterile and ready for direct use. The use of an ampulla-syringe prevents a loss of a biologically active substance and any form of microbiological secondary infection and/or mechanical contamination [9-12].

The analysis of a loss of an injection preparation administered with the use of an ampulla-syringe and a traditional method with the use of a standard ampulla.

Both in a traditional method and a modern one injection needles are used. In the case of an ampulla-syringe a needle is joined with the set and constitutes it integral part, and during a traditional administration from an ampulla, it is a separate element, exchangeable and exposed to the contact with non-sterile environment. Additionally when exchanging a working needle into an injection one, a medicinal product

contained in an ampulla and in a needle is lost. An injection needle is a pipe set on a cap.

Table 1: Parametric list of most frequently used needles in a pharmacy trade (No. 1-8) and needles with ampulla-syringes in an original medicinal product with ibandronate sodium by Roche (No. 9).

o.	Commercial marking of a needle	Outer width of a needle 2R,[mm]	Measured outer width of a needle 2R,[mm]	Length of a needle L,[mm]
1	0.45 x 16	0.45	0.45	16
2	0.5 x 25	0.50	0.50	25
3	0.6 x 30	0.60	0.63	30
4	0.7 x 40	0.70	0.71	40
5	0.8 x 40	0.80	0.80	40
6	0.9 x 40	0.90	0.90	40
7	1.1 x 40	1.10	1.11	40
8	1.2 x 40	1.20	1.22	40
9	0.6 x 25	0.60	0.62	25

A needle pipe is made of high-class stainless steel. The technological priority is to make needles of the possibly thinnest wall, which leads to the increase of the inner diameter, without the increase of the outer diameter. All needles must have the rigidity and flexibility of a pipe according to the plant-specific and pharmacopeial standards. Razors of needles are modeled in such a way as to ensure a relatively fast and moderately painless penetration of tissues in order to reduce traumatization, as well as minimization of pain.

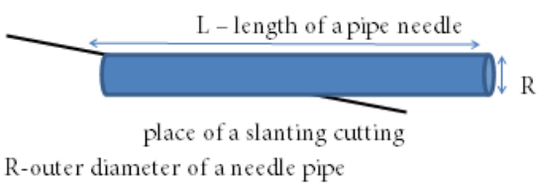

Figure 1: Scheme of a needle pipe with the marked place of cutting.

Depending on a purpose, needles can be cut short (surface of cutting to a needle creates an angle of 16˚-18˚) or needles of long razors (an angle of 11˚-13˚). Injections needles most often used have outer diameters of 0.35-1.4 mm, and preferred lengths of pipes 8-40 mm. a good solution preventing the remains of a preparation is a system of an integrated needle with a cylinder of a syringe as it is used in ampulla-syringe systems [4,8,13-18].

If we assume that a needle pipe from the point of spatial geometry is a cylinder of the height of h and the radius r, (picture 1 and 2), the a cylinder base and a cylinder upper part is a circle, ad its width is in every place the same. This solid figure in a Cartesian coordinate system is described as a collection of points (x, y, z) meeting the criteria of the inequality

$$\begin{cases} x^2 + y^2 \leqslant r^2 \\ 0 \leqslant z \leqslant h \end{cases}$$

where: r>0 and is a cylinder radius and h>0 and is its height.

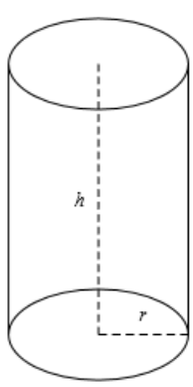

Figure 2: A right circular cylinder of the base radius – r and height – h.

In relations to the aforementioned on the basis of the following dependence:

$$V = \pi r^2 h$$

we can calculate a figure value of a right circular cylinder volume, that is, in our case, an approximate volume of an injection remaining in a needle after operations connected with performing an injection (table 2) [20].

Calculations of volume of a pipe needle – V show that when a length and a measured outer diameter of pipe needle increase, it volume also increases, and at the same time, the content of a solution of a medicine with a biologically active substance. To compare, needle parameters of an original medicinal product with ibandronate sodium by Roche has been listed table 3.

Table 2: List of necessary empirical figure values r and h, needed to calculate volume V of examined types of injection needles

No.	Measured diameter of a needle 2r[mm]	Radius of a base of a needle pipe r [mm]	Square radius of a base of a needle pipe r^2 [mm^2]	Height of a needle pipe h[mm]	Volume of a needle pipe	
					V[mm^3]	V[ml]
1	0.45	0.225	0.050625	16	2.5434	0.0025
2	0.50	0.25	0.0625	25	4.9063	0.0049
3	0.63	0,315	0.099225	30	9.3469	0.0093
4	0.71	0.355	0.126025	40	15.8570	0.0159
5	0.80	0.4	0.16	40	20.0960	0.0201
6	0.90	0.45	0.2025	40	25.4340	0.0254
7	1.11	0.56	0.3136	40	40.9847	0.0410
8	1.22	0,61	0.3721	40	46.7358	0.0467

Table 3: List of necessary empirical figure values r and h, needed to calculate volume V of examined types of injection needles

No.	Measured diameter of a needle 2r[mm]	Radius of a base of a needle pipe r 2 [mm]	Square radius of a base of a needle pipe r^2 [mm^2]	Height of a needle pipe h[mm]	Volume of a needle pipe V[mm^3]	
					V[mm^3]	V[ml]
1	0.62	0.31	0.0961	25	7.5439	0.0075

Table 4: Losses of an active substance in relations with the way of administering an injection.

No.	Declared dose of a medicine [mg/ml]	Volume of a needle pipe V[mm3]	Dose of a medicine in mg/mm3 of injection	Dose of a medicine remaining in a needle pipe [% of a declared dose]
Needle of application system of an original medicinal product				
1	3.0/3,0	7.5439	0.001	0.75
Random needles available in a pharmacy sale				
1	3.0/3.0	2.5434	0.001	0.25
2	3.0/3.0	4.9063	0.001	0.49
3	3.0/3.0	9.3469	0.001	0.93
4	3.0/3.0	15.8570	0.001	1.59
5	3.0/3.0	20.0960	0.001	2.01
6	3.0/3.0	25.4340	0.001	2.54
7	3.0/3.0	40.9847	0.001	4.10
8	3.0/3.0	46.7358	0.001	4.67

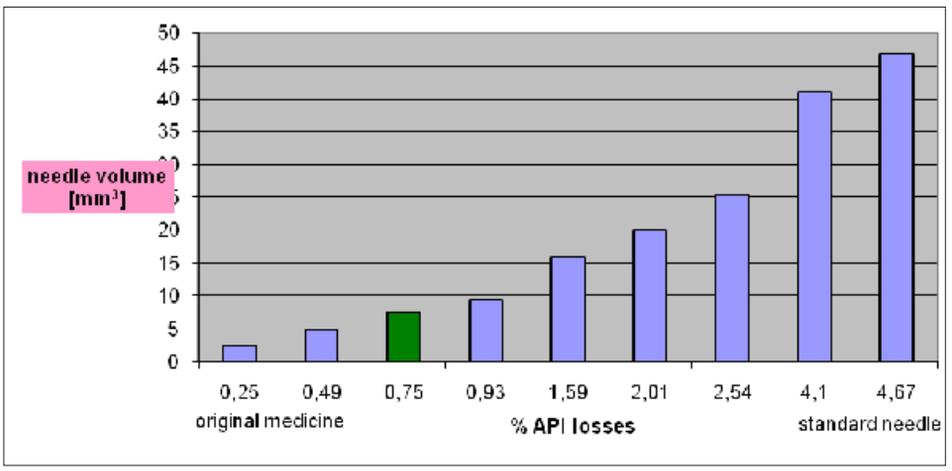

Figure 3: Illustration of a potential loss of an active substance [%] occurring during an injection with the use of an ampulla-syringe with an originally selected needle and a needle chosen randomly.

The data presented show that dozing in an original medicinal product is arranged in such a way that prevents a loss of a biologically active substance. A unit packaging of a medicine contains a needle of specified parameters. Therefore, an error of medical personnel connected with choosing an improper needle is eliminated. In case of using a generic medicinal product being a form of a standard ampulla, a number of potential errors related to administration and influencing on a reduction of an already small active substance increases [21,22].

Conclusions

- the conducted loss analysis shows that a loss value increases proportionally to a size of an needle measured by a volume of a pipe needle.
- application of a needle of the sizes bigger than 0.6 x 25mm makes a risk of administering a dose smaller than a recommended one bigger.
- negative phenomena related to API loss in a product increase, if application is from a standard ampulla, with the use of working needles and an injection needle.
- at this stage of research one needs to state that a way of application of an original medicinal product with sodium ibandronate arranged with a set of ampulla-syringe and needle is an optimal guarantee of providing a patient with a full dose of a biologically active substance expected for an effective therapy.

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