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Original article

Development of a formulation of potassium iodide tablets as an antidote against nuclear incidents

Juan de Dios Azorín Abraham [a], Guillermo Torrado Durán [b], Norma Sofía Torres Pabón [b], Antonio Peña-Fernández [c], María Ángeles Peña Fernández [b,*]

[a] Military Defence Pharmacy Centre, Road M-609, Km 34, 28770 Colmenar Viejo, Madrid, Spain
[b] Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Alcala, E-28871 Alcalá de Henares, Madrid, Spain
[c] Department of Surgery and Medical and Social Sciences, Faculty of Medicine, University of Alcala, E-28871 Alcalá de Henares, Madrid, Spain

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ABSTRACT

Objectives: Potassium iodide (KI) is a treatment to neutralize radioactive agents that could be inhaled or ingested in nuclear incidents. The inorganic salt KI constitutes a source of iodine, which in the body acts by accumulating in the thyroid gland, producing its saturation, and thus preventing the fixation of radioactive iodine species. In Spain, the Military Defence Pharmacy Centre (CEMILFARDEF) was challenged to develop this antidote to be distributed among the population surrounding nuclear power plants, in only one new solid pharmaceutical form for oral administration, in order to replace the two pharmaceutical forms available, which are capsules for adults and oral solution for children, considered less versatile.
Methods: A selection of excipients was carried out to achieve pharmacotechnical behaviour suitable for the industrial manufacture of potassium iodide in tablets, complying with the pre-established process and finished product quality parameters. The development allowed the preparation of three industrial-sized batches on which the stability of the developed formulation was studied.
Results: An uncoated 65 mg double-scored potassium iodide tablet was developed using easily accessible excipients in the formulation and direct compression as the manufacturing method. The formula complied with the stability tests, with which the development carried out can respond to the eventual demand that its elaboration would entail in the event of nuclear incidents.
Conclusions: The developed formulation of a 65 mg double-scored potassium iodide tablet allows the great variability of user needs, from infants to adults with a single pharmaceutical form, which additionally implies logistical benefits in distribution, stock control and appropriate renewal according expiration dates, among the population surrounding nuclear power plants and available to deployed military personnel, in the event of potential nuclear incidents.

1. Introduction

Given global conflicts and the ever-present possibility of nuclear incidents, (World Health Organization, WHO, 2017) the Military Pharmacy Defence Centre faces the challenge of rapidly providing effective antidotes in the quality and quantity necessary to minimize the health effects resulting from contact with radioactive materials (Food and Drug Administration, 2020). In cases where radioactive material has been inhaled or ingested, it is imperative to have adequate physical or chemical treatments locally to neutralize the harmful effects caused by these contaminants. Treatments may be specific antidotes directed at the specific radioactive species involved or a combination of these with non-specific measures for the removal of any type of contaminant (Zimmermann and Anderson, 2021, Toft and Schneider, 2022a). The pharmaceutical forms of antidotes normally correspond to those of common medications, perfectly known by the potential users, and that are part of the know-how of the Military Defence

* Corresponding author.
E-mail addresses: jazoabr@et.mde.es (J. de Dios Azorín Abraham), guillermo.torrado@uah.es (G.T. Durán), sofia.torres@uah.es (N.S.T. Pabón), antonio.penafer@uah.es (A. Peña-Fernández), angeles.pena@uah.es (M.Á.P. Fernández).
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Pharmacy Centre (CEMILFARDEF) which in Spain is in charge not only of the manufacture, storage, and supply of these antidotes, but also participates in the investigation of new uses and applications of drugs for this purpose.

Due to the very specific use characteristics of these medications, their manufacture is not profitable for the civil industry. Their stocks must be sufficient and timely renewed so that potential users permanently have antidotes ready for consumption in case of need. For all these reasons, due to the strategic interest for the Armed Forces, it is essential to manufacture the most frequently used antidotes in cases of exposure to radioactive material, among which is potassium iodide, KI, which has shown in various recent studies (Tatsuzaki et al., 2023) a protective action against the action of radioactive iodine that can be released during a nuclear emergency and its use is indicated by the national protocols of different countries and global organizations such as the WHO or the International Atomic Energy Agency (WHO, 2017, Willems et al., 2022, Tatsuzaki et al., 2022). The issue of having measures against radioactive agents like antidotes with KI has recently become topical due to the events in Ukraine, whereby the damage to one of the nuclear power plants in its territory may generate a high risk of exposure to the population and considering also the possibility of an escalation in the conflict leading to the use of nuclear weapons (Ayoub et al., 2022; Toft and Schneider, 2022b).

The inorganic salt KI constitutes a source of iodine, which in the body acts by accumulation in the thyroid gland, producing its saturation, thus preventing the fixation of radioactive iodine species. This mechanism of action suggests that KI does not provide protection to other parts of the body or against other radioactive substances. To achieve thyroid blockade, KI should be administered before exposure, and if that is not possible, it should be administered as soon as possible after exposure (WHO, 1999). Several studies have demonstrated that taking potassium iodide a couple of hours after exposure only results in 50% saturation of the thyroid, leaving the remaining 50% vulnerable to radioactive iodine occupancy (WHO, 1999). According to the WHO guidelines on the optimal thyroid blockade of radioactive iodine with iodine antidote, it occurs if the administration is 24 h before exposure, and it can be an effective protective for up to 8 h after exposure. After 24 h of exposure, the administration of iodine may be counterproductive by increasing the persistence of radioactive iodine already absorbed in the thyroid (Zanzonico and Becker, 2000). The use of a high dose of potassium iodide such as that used in this preparation also presents risks. One is the Wolff-Chaikoff effect, which involves an inhibition of thyroid hormone synthesis that is reversible over time (Tng et al. 2022). There can also be cases of thyroiditis and the generation of thyroid antibodies in high doses and chronic administration of iodine, which result in a loss of glandular function (Baltisberger et al., 1995).

When looking for a starting point on which to build the development of a new pharmaceutical form for oral administration, the knowledge gathered with the two pharmaceutical forms arises, capsules for adults and oral solution for children, the manufacture of which has been covered by CEMILFARDEF before this New development. The technical data of these two pharmaceutical forms are used as a basis for the development of a single pharmaceutical form that allows greater versatility not only in terms of the age of the recipient but also in terms of the logistics of its distribution. This is the case of the excipients selected for having demonstrated compatibility with the active ingredient supported by their corresponding quality controls and stability studies, after many years of manufacturing.

Potassium iodide will appear in the form of a crystalline solid of ionic nature and highly soluble in water, with average values of 148 g/100 g of water at 25 °C. Its molecular weight is 166.003 g/mol and it has a density of 3.13 g/cm^3, giving rise to aqueous solutions with a slightly alkaline pH, at values 7–9. In addition to its high solubility in water, it will be easily soluble in glycerol and soluble in alcohol. KI can usually be obtained from the reaction that occurs when molecular iodine (I_2) is heated in the presence of a concentrated potassium hydroxide solution:

$$3\ I_2 + 6\ KOH \rightarrow 5\ KI + KIO_3 + 3\ H_2O$$

The iodide anion is sensitive to the degrading action of light and humidity (The Merck Index, 2013). One way to protect the active species is by coating the iodide particles with a hydrophobic excipient, which may include magnesium stearate or calcium stearate. Both excipients that are used in the pharmaceutical industry with lubricating functions, but they also have a high specific surface area and a high capacity for adherence to other powdered particles, so they can create a protective barrier against moisture (Chowhan and Li-Hua, 1986).

This study presents the development of an oral formulation of KI, using an industrial method that allows a rapid response to the distribution needs of KI antidote in the case of a nuclear incident. These needs led to the development of double-scored KI tablets using the direct compression method. Although this method may have drawbacks related to variations in particle size and possible segregation of the mixture, its advantages, such as the reduced number of phases, equipment, and process time, among others, make it a valuable solution for emergency situations (Al-Achi and Patel, 2015).

2. Materials and methods

2.1. Materials and reagents

KI (Williamblythe, UK), three commercial grades of microcrystalline cellulose (FMC International Health and Nutrition, Ireland), Avicel pH 101, Avicel pH 102, and Avicel pH 302, a filler like dicalcium phosphate dihydrate (DCPD) (JRS Pharma, Germany), and magnesium stearate (Italmatch, Italy), were used throughout this work.

2.2. Preparation of tablets

The mixtures are prepared in type V mixing equipment, with a capacity of 10 L for the galenic phase (Glatt Labortechnic, Spain) and 400 L for the industrial phase (Bachiller, Spain). The resulting powder is compressed in a low production capacity rotary machine suitable for working with low product load (Kilian RTS 21, Germany). A single-punch machine is also used for the first phases of development in which quantity of mixtures are minimal (J Bonals 40B Type MT, Spain). The rotary tableting machine is equipped with auxiliary elements for dedusting (Krämer C180, Germany) and the detection of possible metallic particles in the tablet (Mettler Toledo Safeline, USA). In the advanced phases of development, the packaging of pilot batches is carried out to obtain suitable containers for the stability study. This requires the use of a blistering machine (Marchesini MB 421, Italy) and a cartoner (Marchesini BA-100, Italy) commonly used in industrial production.

2.3. Potentiometry analysis

For the determination, first, a sample solution is prepared starting from a theoretical amount of KI of 1.2 g from the powdered tablets. This solid is placed in a 250 mL volumetric flask to which 100 mL of purified water is added. Stir for 20 min and dilute with water to volume. Once this solution is obtained, it is filtered

through paper, taking care to discard the first 20 mL of filtered solution.

Once the sample solution is obtained, 100 mL of the filtered solution, together with 25 mL of ethanol and 1 mL of 1 N nitric acid, are transferred to a 200 mL beaker. The resulting solution is titrated with 0.1 N silver nitrate using a silver indicator electrode and a suitable reference electrode. A determination must be made with a blank and it is established that each mL of 0.1 N silver nitrate is equivalent to 16.60 mg of KI using a potentiometer (Mettler Toledo T-50, Switzerland).

2.4. UV–visible analysis

The USP (U.S. Pharmacopeia, 2023) describes the method for the determination of the KI indicating the wavelength of maximum absorption at 227 nm. The mass of one KI tablet (535 mg) is to be taken as a sample from the mixture or from a powdered tablet. The powder is placed in a 100 mL volumetric flask with purified water, shaken for 5 min ensuring complete dissolution of the solid, and 5 mL of that solution is filtered and 1 mL of it is brought up to 50 mL with purified water in a second volumetric flask. From the solution obtained, quantifications are carried out by spectroscopy (Agilent 8453, USA).

2.5. Dissolution

The dissolution of the tablets was performed using USP apparatus (Erweka DT 800, Germany). The dissolution of the core tablets was performed in 900 mL H_2O, HCl 0.1 N y HCl 1 N, 75 and 100 rpm and 37 °C. 1 mL samples were collected at 45 min.

2.6. Stability studies according to ICH guide

Stability studies constitute the last phase of this development and are intended to demonstrate the viability of various product quality attributes at different times after manufacturing. As indicated in the ICH Q1 guide, data on product stability must be extracted from at least three primary batches like industrial batches. The frequency of checks for products with a proposed shelf life of at least 12 months should be every 3 months for the first year, every 6 months for the second year, and annually thereafter through the proposed shelf life. The storage conditions were 40°C at 75% of relative humidity for 6 months in accelerated studies and 25°C at 60% of relative humidity for long-terms studies. These studies are carried out in climatic chambers (Binder KBF-240, Germany) that keep these conditions constant during the time of the study (ICH Harmonised tripartite guideline Q1A, 2003).

3. Results

This design work for a new pharmaceutical form is divided into several sequential phases (ICH Harmonised tripartite guideline Q8 (R2), 2009). First, the most suitable excipients for the active principle, the pharmaceutical form and the therapeutic objective pursued must be selected, that is, the qualitative formula or composition must be obtained of the tablet. Next, the proportions of each of them in the tablet must be refined, seeking to optimize said proportions with the pharmacotechnical behaviour of the pharmaceutical form. With an approximate formulation, the following is to define the manufacturing process and the quality parameters that will serve as a reference to control the proposed manufacturing process. It will be necessary to manufacture a minimum of 3 batches at an industrial level to ensure that the process is not affected by the change in scale and that it is also reproducible. If the finished product resulting from these batches proves to be compliant, the corresponding stability study can be started with it, which will make it possible to assess whether the tablet obtained can maintain its quality parameters over time. From this study, it will be possible to determine the expiration date that can be granted to the finished product. Fig. 1 summarize the method structure of this study completed in the laboratory of the Department of Biomedical Sciences (University of Alcalá, Faculty of Pharmacy) and CEMILFARDEF.

3.1. Formulation

The excipients and their proportions were selected according to their function and due to technological aspects for a direct compression manufacturing process (Niazi, 2009, Gibson, 2009, Rowe et al., 2009). Therefore, the excipients selected during the formulation stage were binding agents, lubricants, solvents, coating agents and disintegrants (Table 1).

3.1.1. Microcrystalline cellulose

This excipient is widely used as diluents for capsules and tablets and its use is sufficiently supported by the experience obtained in the manufacture of the capsules (Juberías et al., 2009). This compatibility, its price, and its ease of obtaining make it the first-choice excipient for the development.

3.1.2. Calcium phosphate

Another widely used diluent, calcium phosphate is also a protective agent against oxidation of iodine to iodate and iodine and this oxidation is prevented with an alkaline medium and reducing agents. Calcium phosphate provides this alkalinity of the medium and helps direct compression of the mix (Rowe et al., 2009, Juberías et al., 2009, Schmidt and Herzog, 1993).

3.1.3. Magnesium stearate

Stearates are commonly used in solid formulations as lubricants, to improve powder flow and matrix filling and will prevent adherence of powder and small imperfections on the surface of the tablet (Rowe et al., 2009). In addition to these functions, stearate will serve as a coating agent for the KI particle (Zou et al., 2013). This protection has a double direction: on the one hand, the KI is protected from oxidation, and on the other hand, the equipment is protected from the corrosion induced by this salt after prolonged contact. This coating is more effective with higher stearate concentrations and longer mixing times (Tay et al., 2010). In the development of the formulation for capsules, it is shown that the coating with magnesium stearate is more effective and generates less disruption in the dissolution test than other stearates such as calcium (Table 2) (Juberías et al., 2009).

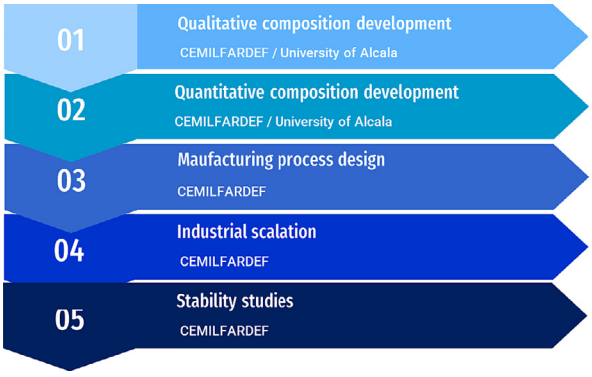

Fig. 1. Method followed during the development of KI tablets.

Table 1
Formulation.

Excipient	Function	Proportion[1]
Microcrystalline cellulose	Diluent, binding agent.	50–75%
Calcium phosphate	Diluent	10–20%
Magnesium stearate	Lubricant, coating agent	1–5%

[1] Range considered during formulation development.

3.2. Mixing process design

With the selected excipients, the aim was to obtain the final formula of the tablet. For this, the following characteristics of our product were considered (Juberías et al., 2009):

- It is advisable to carry out a KI coating with the double purpose of protecting the active principle from the degradative action of light and humidity, while protecting the equipment from the corrosive action of this salt on the metal.
- Magnesium stearate is a suitable excipient for coating the KI according to the tests carried out.
- Both the microcrystalline cellulose used as a diluent and the magnesium stearate used as a coating agent and as a lubricant are compatible with the active principle.
- The KI coating process is carried out at the beginning of manufacturing to prevent the transfer of this agent to other components. In this way, the continuous and prolonged contact of the product with the equipment is also avoided.
- The KI coating with magnesium stearate can be an independent operation to obtain a suitable raw material for the subsequent tablet manufacturing process.
- The manufacturing method of the tablet should preferably be direct compression. This is because it is a simpler and faster process, and more compatible with a possible emergency manufacturing situation.
- A tablet with a high disintegration capacity will be sought, which will facilitate the rapid incorporation of the active into the body to exercise its protective action in the event of a nuclear emergency scenario.

To avoid the transfer of the coating excipient to the diluting excipient, the mixing process is designed so that a first process is carried out during which the KI is exclusively brought into contact with the coating agent. In this first step, the KI should be covered by the selected excipient. An approximate proportion of 10% of coating excipient with respect to the weight of KI is selected, since higher proportions could be an impediment when it comes to achieving adequate dissolution times for the mixture, and this amount is the one used in mixes of stabilized KI present on the market (Mallinckrodt, 1997). To assess the influence of stearate coating on dissolution profiles, a simple test is designed in which 3 mixtures are prepared with a variable ratio for coating and the dissolution rates obtained for each mixture are measured. Only the KI coated with stearate (MgS) at different proportions and microcrystalline cellulose (MCC) as diluent is used (Table 3).

In addition, Fig. 2 shows the graphics of dissolution speed of these mixtures. It can be visually verified that, as expected, the dissolution rate is clearly affected by the increase in the proportion of a hydrophobic component such as stearate. A relatively small variation in the amounts of stearate, such as increasing the amount of this excipient by only 3%, has a great influence on the speed, reducing it to less than half, which means that there is a small margin to adjust the quantitative formula with the stearate (Ariyasu et al., 2016).

The manufacture of the new pharmaceutical form is oriented towards a round tablet with a double groove, 13 mm in diameter, containing a dose of KI of 65 mg with an optimal weight per tablet of 535 mg. It is established that one of the most critical aspects of the manufacturing process is the mixing phase, since the active ingredient is found in a low proportion with respect to the total number of excipients, there are differences between the size and shape of the particles because in direct compression there is no prior granulation process (Niazi, 2009, Gabbott et al., 2016). In addition, before beginning the tests to find the ideal method of preparing the mixture, a series of homogeneity tests of binary mixtures is carried out, combining the KI with each of the different excipients separately to verify how the active principle is distributed in each of the excipients that have been selected, to form part of the final formula of the tablet (Massol-Chaudeur et al., 2002). For the preparation of these mixtures, equal quantities of previously sieved products are used, which are mixed at 50%. In this case, 100 g of mixture is prepared by mixing 50 g of KI and 50 g of the excipient. It is important to consider that this type of blend is not done based on a reproducible process, so the results obtained must be considered merely indicative. The KI quantification results are made by UV spectroscopy based on the theoretical

Table 2
Comparative study of stearates as coating agents.

MAGNESIUM STEARATE					
Speed (r.p.m.)	**Dissolution medium**			**Stirring system**	
	H_2O	HCl 0,1N	HCl 1 N	Paddle	Basket
50	Fail	Fail	Pass	X	
	Fail	Pass	Pass		X
75	Fail	Pass	Pass	X	
	Fail	Pass	Pass		X
100	Fail	Pass	Pass	X	
	Fail	Pass	Pass		X
CALCIUM STEARATE					
Speed (r.p.m.)	**Dissolution medium**			**Stirring system**	
	H_2O	HCl 0,1N	HCl 1 N	Paddle	Basket
50	Fail	Fail	Fail	X	
	Fail	Fail	Fail		X
75	Fail	Fail	Fail	X	
	Fail	Fail	Pass		X
100	Fail	Fail	Pass	X	
	Fail	Fail	Pass		X

Table 3
Mixtures for stearate estimation[2].

Mixture A	Mixture B	Mixture C
MCC 858.75 g	MCC 898.75 g	MCC 918.75 g
KI 1061.2 g	KI 1061.2 g	KI 1061.2 g
MgS 80 g	MgS 40 g	MgS 20 g

[2] MgS proportion is 4% for mixture A, 2% for B and 1% for C.

Table 4
Binary mixtures results.

Mixture	Result[3]
KI / Phosphate	61.9 mg
KI / Cellulose	61.4 mg
KI / Stearate	57.7 mg

[3] mean values for each of 3 repetitions performed.

amount of 65 mg that a tablet should contain from a sample with double mass (Table 4).

In this case, the three results are below the theoretical, obtaining a value of approximately 95% of active principle in mixture with the diluents and 88.5% in the case of stearate, which would be data out of specification if we stick to the criterion of ± 10%. The value of stearate is to be expected as it is a solid with a very small particle size, with an important difference with respect to KI, and since it is in a very low proportion in the formulation, largely as a coating and protection agent, its influence in the mix shouldn't be important (Staniforth et al., 1982). In addition to these tests with the binary mixtures, a test is proposed prior to the establishment of an adequate mixture method that allows guaranteeing that the analytical method used for the evaluation of these methods is appropriate. Uncertainty about the analytical method arises from the repetition of out-of-specification results in which values above the set value are mostly obtained. This test for the evaluation of the method will consist of using tablets of a mixture whose dissolution tests gave an adequate result, crushing said tablets until they are reduced to powder and analysing this powder as if it were a mixture sample. This powder is placed directly in a flask to verify that the method performs the extraction and quantification correctly. For this analysis, UV spectroscopy will be used as well as potentiometry (iodometry) using silver nitrate as titrant. The tablets corresponding to three times of the compression process are taken, thus having a sample of the beginning, middle and end of the operation (Table 5).

Table 5
Comparative test of analytical method.

Sample	UV Spectroscopy	Potentiometry
Beginning	109.5%	106.1%
Middle	108.3%	104.81%
End	99.8%	86.97%

These results allow us to draw the following conclusions:

- There are appreciable differences between the results obtained by one method and the other, this variation ranging from a minimum of more than 3% to a maximum of almost 13%. Obviously, these differences can mean that the same mixture can be considered suitable or not suitable de-pending on the analytical method used.
- It can be verified that in the three mixtures analysed, the result provided by the spectroscopic method is always higher than that provided by potentiometry.
- Both methods respect the trend of the results despite the difference between them, the samples with high (beginning) and low (final) values are the same with both analytical methods.
- The tests must be repeated on new mixtures with both methods to verify, with a larger population of data, if these divergences between them continue to exist.

In addition to these tests, various studies have been carried out to improve the mixing indices between powders with important rheological differences and therefore with a tendency to segregation, proving that continuous mixing usually gives better results for this type of product than continuous mixing lots (Oka et al., 2017). The number of turns of the mixer will be used as a parameter when defining the mixing process instead of the mixing time, since it constitutes a more objective criterion that will facilitate the subsequent scaling of the process to different equipment (Landin et al., 1996). In this case, 3.5 kg of mixture is prepared, and a prior centrifugal sieving of the premix is introduced with the idea of trying to improve the distribution of the active ingredient within the mixed product (Vanarase and Muzzio, 2011). Various tests are carried out with different processes and the results are evaluated based on the homogeneity in active principle achieved. The analysis is carried out by UV spectroscopy as indicated by the Pharmacopoeia method (Ph. Eur., 2023).

For mixing, a Glatt TR-120 centrifugal sieve is used, equipped with sieves of different mesh sizes and a Bachiller V-shaped mixer of adequate capacity with the quantities to be mixed.

Fig. 3 schematically shows the process adopted to achieve better homogeneity results. (MgS: Magnesium stearate; MCC: microcrystalline cellulose; Phs: phosphate).

For the sampling of this mixture, five samples will be taken each time at two different times, at time 0 or initial and at 72 h. The five samples that are taken are obtained from different heights and according to the pattern with respect to the equipment showing in Fig. 4.

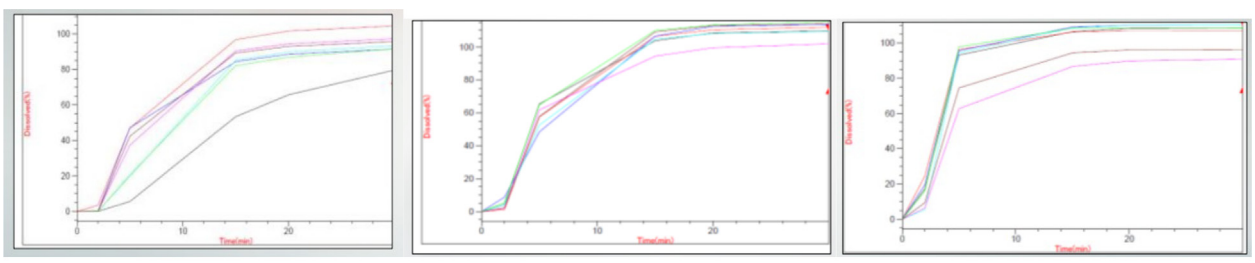

Fig. 2. Dissolution test for mixtures A, B and C.

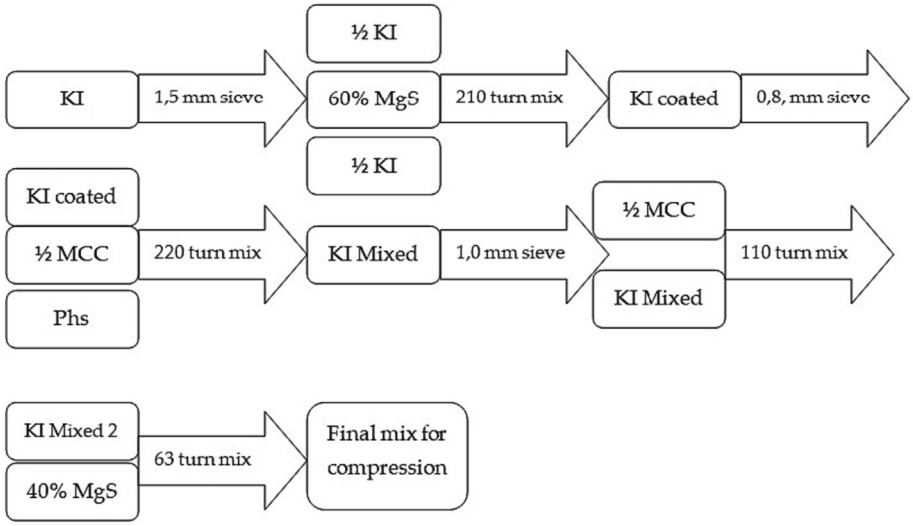

Fig. 3. Mixing process scheme.

From each of the samples taken in the equipment, two subsamples will be taken for analysis, each of which will be subjected to a test with measurements in triplicate. The value for each subsample will be the arithmetic average of the triplicates carried out in the repetitions and the value for each sample will be the arithmetic mean of the results obtained for both subsamples. All these tests are carried out by UV spectroscopy (Table 6).

The large number of samples analysed, and the data obtained allows us to obtain a reasonably broad view of the composition of our mixture at different points in it. It can be determined that the results in general give an idea that we are dealing with a random mixture in which values with a certain deviation are obtained but whose average value is very close to the objective value (Harnby, 2000). Of the entire set of samples, only one value below the specification is obtained (sample M2 at time 0) and one value above (sample M4 at time 72), the deviation being very low in the first case and considerable in the second. As in previous tests, there is no trend in results dependent on time or the sample area, since the highest and lowest values are obtained in a disordered way.

The fact that in sample 5 at time 72 the lowest value is obtained for all the samples at that time allows rejecting the idea that KI secretes over time and tends to deposit in the lower area of the mixing equipment. However, and although they are not excessive values, the highest values tend to be found in the middle zone (Samples 3 and 4), although except in one of the cases, they are not data outside the specification. With acceptable mean values for this mixture and considering that perhaps in order improving the process it would be necessary to resort to techniques for homogenizing the size of the particles such as granulation, we are faced with a mixing process that could be valid for obtaining tablets. It would suffice to see if tablets that meet the dissolution test are obtained from a random mixture as we have. For this, it would be necessary to prepare a significant amount of mixture for compression and subject many the tablets obtained to a dissolution test, to evaluate if there are fluctuations of the active ingredient in them that are equivalent to those observed in the mixture (Zatloukal, 2004). Prior to the next phase, different parameters of the mixture are determined to assess its suitability to be compressed (Table 7).

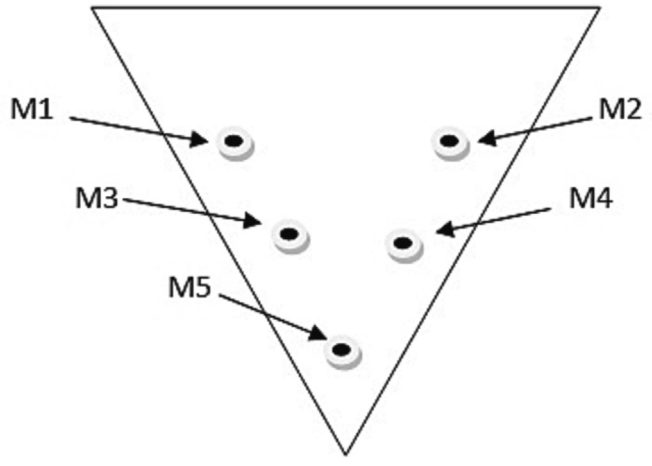

Fig. 4. Sampling pattern on V mixer.

3.3. Compression process

For the compression of the mixture in a pilot batch, a Kilian RTS 21 compression machine with low production capacity is used. The hopper is manually fed with the product, since the use of the pneumatic transport system can cause the separation of the particles, something that we must avoid at this stage (McGlinchey et al., 2000). It is guaranteed that the hopper is always full, since as the product is consumed and the height of the dust column decreases, variations in the weights of the tablets can occur (Hildebrandt et al., 2020). The first compression tests of this mixture are aimed at evaluating the behaviour of the product during the process and establishing the quality parameters that the tablet must meet according to the objective set for the medication:

3.3.1. Tablet appearance

The compression tools will be round, flat EU-D type punches, 13 mm in diameter and the upper one with a double groove. This double groove will facilitate the subsequent division into up to 4 parts for the adequate dosage for the different age windows. These tools therefore condition the shape and size of our tablet and the specifications set in this regard. The tablet obtained must be white, without breaks, stains or defects, round, with a flat surface, 13 mm in diameter and with a double X-shaped groove on one side.

Table 6
Homogeneity results* at t = 0 and t = 72.

Sample	results at t = 0		results at t = 72	
	Subsample average(mg)	Sample average (mg)	Subsample average(mg)	Sample average (mg)
M1 1	60.4	66.95	63.1	63.45
M1 2	73.5		63.8	
M2 1	62.3	57.40	67.2	62.50
M2 2	52.5		57.8	
M3 1	79.1	70.10	71.5	69.05
M3 2	61.1		66.6	
M4 1	62.4	67.05	85.1	86.30
M4 2	71.7		87.5	
M5 1	60.7	68.60	50.8	59.85
M5 2	76.5		68.9	
Average t = 0		**66.02**		**68.23**

* Triplicate.

Table 7
Galenic determinations of the selected mixture.

N° of samples	Test	Result
2	Angle of repose	29.5°
5	Bulk density	0.566 g/mL
5	Tapped density	0.672 g/mL
5	Carr index	15,38
5	Haussner index	1.18
10	API proportion	92.825%
1	Humidity	3.4%

3.3.2. Mass of the tablet

Mass of 535 mg of which 65 mg correspond to the active principle. Although the references that we find in the different Pharmacopoeias are broader, the tendency when establishing our specifications will always be much more restrictive than what the bibliography indicates, especially if, as is the case, the product is it allows. This allows us to have an important margin of safety in compliance with the specification when the finished product is subjected to the relevant quality control and provides us with an important margin in the event of detecting deviations by agents external to the process itself, such as changes in the granulometry of a raw material or technical dysfunctions in a machine. For this reason, a margin is established for the control of the average mass of the tablets of ± 3% and in the case of individual mass, the value of T1 (warning limit) is established at ± 3% and the value of T2 (alert limit) at ± 6%.

3.3.3. Hardness of the tablet

The hardness will be fundamentally determined by the pressure exerted by the punches on the powder to be compressed (Monedero et al., 2008). The fact of introducing a tablet of a large relative size with respect to the dose implies a significant proportion of excipients, which in turn improves the compressibility of the mixture at the cost of diluting the active ingredient. In our case, when focusing on a direct compression process, it is important to obtain a mixture that responds well to the pressure exerted by the tableting machine, resulting in tablets of sufficient hardness. From the first tests it was possible to verify that the different mixtures admitted pressure very well and could generate highly hard tablets. In our case, it is estimated that the product allows us to work in a wide range of hardness values, which is why a specification is established that considers two fundamental aspects: establishing a minimum hardness value that guarantees the integrity of the tablet in the phases later in the manufacturing process. Without sufficient hardness, the tablets deform or break at this stage, rendering them unusable for conditioning. On the other hand, we must establish a maximum hardness value that contemplates the necessary divisibility of the tablet in half, and this in turn also in half to have a quarter tablet as complete as possible to administer to children and infants. It must be considered that the tablet administration process will be carried out in potentially dangerous situations and speed is essential, so the division of the tablet should be done easily and, if possible, without the need to resort to any type of tool. For all the above, it is determined that the hardness specification is 5–8 kp.

3.3.4. Thickness

It must be adequate so that the tablet is not too thick to enter the blister pocket with some clearance, but at the same time not too thin so that two tablets can lodge in the feeding ramps of the blister packer, causing jams in the blister pack itself, or even getting to accommodate two tablets per alveolus which in turn would result in sealing problems. It is determined that a suitable range for a 13 mm tablet weighing 535 mg without the mentioned problems being 3.40 to 3.75 mm.

3.3.5. Disintegration

The disintegration was defined as one of the critical parameters to consider, since it will have a great relationship with the speed at which the KI reaches its place of action in the organism, which in the situation for which it has been designed the tablet is crucial. In the equipment to measure the disintegration visually, it has been possible to verify that high disintegration speeds are obtained, achieving in some cases a practically instantaneous disintegration. In more sophisticated equipment equipped with a reading lens (those used in the tests whose results have been previously exposed) longer times have been obtained, although in some cases and as indicated, attributable to the adhesion of aggregates of insoluble particles to the reading lens. Despite this, this equipment has reflected very good times in the disintegration, which have gone from a few seconds to a maximum of 3 or 5 min. Most of the results obtained with the product and the technical requirements for this product due to its objective, support the establishment of a specification for disintegration of less than one minute for all the tablets submitted to the test, which is a value well below the specification found in the Ph. Eur. (2023).

3.3.6. Friability

This test is especially important in the case of tablets that are going to serve as a core for coating, since the equipment used for this subject the tablet to significant mechanical wear (Ticó and Miñarro, 2010). As this is not our case, specifications that are as restrictive with respect to the standard as in previous tests will not be applied. Furthermore, friability is an inverse parameter to hardness in such a way that a tablet will be less friable the harder it is. As our tablet gives us the possibility of moving in a reasonably

Table 8
Compression parameters in pilot batch.

Individual mass uniformity		
(T1: 508.57 – 562.11 mg)		**(T2: 481.80 – 588.88 mg)**
Average: 535,34 mg		**Standard deviation: 2,807 mg**
Test	**Result**	**Specification**
Aspect	Pass	White bi-scored and bevelled tablet. Smooth surface without imperfections
Active principle content (UV–Vis)	Pass (98.3%)	90–110% 58.5–71.5 mg
Disintegration test	Pass (30 s min – 7 min max)	6 fully disintegrated units in less than 15 min
Dissolution test	Pass (102%)	> 80% of the dose (52 mg) dissolved in < 45 min. Temperature 37 °C. Speed 50 rpm
Individual mass	Pass	No more than 2 tablets outside of the T1 interval and none outside of T2
Hardness	6.8 kp	5 – 8 kp
Friability	0.29%	Weight loss < 1%

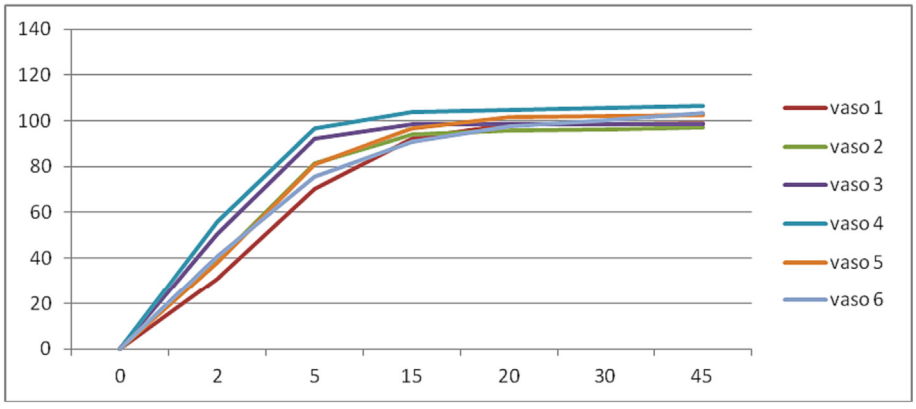

Fig. 5. Dissolution test for the pilot batch with 6 vessels.

Table 9
Comparative between spectroscopy medium.

UV spectroscopy in water			**UV spectroscopy in HCl**	
Sample	**Result (mg)**	**Average sample (mg)**	**Result (mg)**	**Average sample (mg)**
M1 1	68.6	68.6	68.7	68.7
M1 2	68.6		68.7	
M1 3	68.7		68.7	
M2 1	63.4	63.4	63.5	63.6
M2 2	63.5		63.6	
M2 3	63.4		63.6	
M3 1	59.9	59.9	60.0	60.0
M3 2	59.9		60.0	
M3 3	59.8		60.1	
M4 1	61.2	61.2	61.0	61.0
M4 2	61.2		61.1	
M4 3	61.2		61.0	
M5 1	60.7	60.8	60.5	60.5
M5 2	60.8		60.6	
M5 3	60.8		60.5	
Average in water		**62.78**	**Average in HCl**	**62.76**

wide range of hardness, it is a test whose result could be regulated with some ease. For this tablet, it is established that the friability allows a mass loss of up to 1% when performing this test.

Once both the formula and the manufacturing process for our tablet have been established, both conclusions are transferred to the real production scenario in which the final medicine will be obtained. To do this, the scaling of the process must be carried out from the galenic phase to the pilot phase and from there to the final industrial scale, contemplating the equipment that will be used regularly for manufacturing and the final batch size (Natoli et al., 2017). The industrial batch size will be determined by the optimum filling volume of the mixing equipment. The scaling to the pilot level is carried out in a Bachiller MV 200 mixer (200 L/capacity) from which it can be passed to an industrial level to Bachiller MV 400 or MV 600 mixers (400 and 600 L respectively). Finally, it is decided to do the industrial scaling in the MV 400 due to the occupancy rate and workload per line in the production plant 40 kg of mixture are prepared as a pilot test and the compression is started at a speed of 20.000 u/h to observe the behaviour of the product. The parameters maintained during compression are

Table 10
Summary of test results for the stability study.

Test	Results		Specification
	Accelerated, 6 months	On going, 12 months	
Aspect	Pass	Pass	White bi-scored and bevelled tablet. Smooth surface without imperfections
Active principle content	Pass (98.4%)	Pass (109.9%)	90–110% 58.5–71.5 mg
Mass variation	Pass (1.7%)	Pass (12.5%)	Variation < 15%
Dissolution test	Pass (97.7%)	Pass (104%)	> 80% of the dose (52 mg) dissolved in < 45 min Temperature 37 °C. Speed 50 rpm
Mass uniformity	Pass	Pass	No more than 2 tablets outside of the T1 (5%) interval and none outside of T2 (10%)

Table 11
Uniformity of unit dose preparations.

	Tablet (mg) Wi	Xi
1	543.7	111.34
2	541.7	110.93
3	543.7	111.34
4	526.6	107.84
5	522.0	106.90
6	532.9	109.13
7	528.4	108.21
8	544.9	111.59
9	542.3	111.06
10	540.3	110.65
	Wm = 536.7 mg	**Xm = 109.9%**

A 109.9 s 1.7 A/Wm 0.205.

checked to verify the specifications that were originally established (Table 8) (See Fig. 5).

In addition, and to evaluate the analytical method, the homogeneity of the mixture is controlled by UV spectroscopy using water and 0.1 N hydrochloric acid, without appreciating a significant difference between both methods and obtaining consistent values in both cases (Table 9).

4. Discussion

After different mixing and compression tests, it can be verified that it is possible to obtain a product that meets the quality criteria that have been established by direct compression. However, to consider that the final work is a success, it must be guaranteed that the tablet can maintain its properties for a sufficient period. For this reason and as a final phase, stability studies are carried out to establish the viability of the drug, according to the ICH guidelines. The results of the accelerated (6 months) and real-time stability study are shown below (Table 10).

Below are the results of the content assessment broken down (Table 11), where Xi: Estimated individual content of active principle of the analysed units. Wi: individual mass of finished product of the analysed units. A: active ingredient content as a percentage of the theoretical value contained in each tablet obtained in the assessment of the finished product. s: Standard deviation. Wm: average of the individual masses of the analysed units. Xm: average of the individual active principle contents of the analysed units.

Based on the above data, it can be concluded that the product shown in Fig. 6, which corresponds to tablets obtained by direct compression, using compatible excipients, quickly and easily acquired by CEMILFARDEF, meets all quality expectations and of expected stability.

The characteristic of being double scored allows the subdivision into four equal parts of the total dose of 65 mg, which responds to the proposed objective, that is, to have a single dosage form, to be used according to the needs of patients of any age, facilitating the control of distribution and replacement inventories and rapid quality production so that the potential user has the product ready to be used at all times in the event of a nuclear incident (Fig. 6).

5. Conclusions

The design and production on an industrial scale of a novel formulation of KI double scored tablets through a direct compression manufacturing procedure, has shown to be viable, compatible with the established quality parameters, and reproducible at scale. The stability study under different conditions has not revealed a reduction in the potency of the drug during the evaluated period, content uniformity results met expectations and fulfil the quality parameters for their packaging, dosage, administration, and stability and short disintegration times, suitable for a dosage form oriented to emergency use. Likewise, it can be verified that the tablet maintains its organoleptic and pharmacotechnical properties during the time studied, which allows continuing the study in longer times and estimating a period of validity for this preparation. In addition, the excipient composition included microcrystalline cellulose, calcium phosphate and magnesium

Fig. 6. A) ki 65 mg dose double-scored tablets b) Final pharmaceutical dosage form.

stearate, which are compatible, meets all quality and stability expectations, all of them are commonly used, cheap and readily available by CEMILFARDEF.

The direct compression manufacturing process meets the two established objectives: employing minimum formulation costs and reducing both the complexity and the time required for its preparation. The active principle is formulated in a dose of 65 mg useful for patients of any age, facilitating the control of distribution and replacement inventories and rapid quality production so that the potential user has the product ready to be always used in the event of a nuclear incident, since satisfactory results were obtained in the divisibility of the tablets into four equal parts of the total dose. However, since potassium iodide is specific against a radioactive species and protects the thyroid, it may be necessary to administer other complementary specific antidotes for complete protection and minimization of risk.

Data availability

The data used to support the findings of this study correspond to the project: "Desarrollo de una forma farmacéutica para uso oral que permita la utilización de azul de Prusia, como agente para decoporación de ^{137}Cs y otras especies radiactivas y tóxicas". PROGRAMA SYP41804 CONTRAMEDIDAS MÉDICAS-EXPEDIENTE 1003220007100. Reference: 150/2020.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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