Laura Soumoy and Jean-Daniel Hecq*

Automated Compounding of Intravenous Therapy in European Countries: A Review in 2019

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Abstract: Automated compounding systems appeared on the market during these last 15 years as an alternative for manual compounding of intravenous (IVD) drugs. A literature review was conducted on reconstitution of IVD. The following methods were identified: manual, semi- automatic and automatic. A classification was carried out in three categories: automatic syringes, peristaltic pumps, and compounding doses robots. The number of compounding robots is increasing. A table describes the different features of each device. The ampuls cannot be supported by these robots. Large doses vials improve the time of reconstitution compared to current dosage vials. Advantages of automated preparation are: higher consistency of process and products, higher accuracy of products, Integrated digitized processing, precise, complete documentation, reduced effort and wrist injuries, reduced personnel requirement, increased worker satisfaction. Disadvantages of automated preparation are: risk of failure/down time, dependency on power supply, software (updates), high investment costs/high maintenance costs, specialized personnel with additional training, decreased worker satisfaction (early adopter), complexity when products are switched or added, potential for new errors. This review allows the potential user to know the current availability on the market.

Keywords: aseptic compounding, Centralized intravenous admixtures services, compounding automation, robot

Introduction

In hospitals, the major part of the drugs is administered by intravenous way. This practice, though routine, remains dangerous. The majority of the reconstitution of injectable drugs are carried out right before the administration to the patient by the nursing staff. The risks and errors related to the preparation and the administration of injectable drugs are numerous. The standardization then the centralization of the preparations and reconstitution by the hospital pharmacy make it possible to reduce these various risks and errors.

***Corresponding author: Jean-Daniel Hecq,** Department of Pharmacy, CHU UCL Namur, site Godinne - 1, avenue Therasse, Yvoir, Belgium, E-mail: jean-daniel.hecq@uclouvain.be
Laura Soumoy, Department of Pharmacy, CHU UCL Namur, site Godinne - 1, avenue Therasse, Yvoir, Belgium,
E-mail: laura.soumoy@uclouvain.be

Parenteral nutrition

From an historical point of view, it is at the end of the Seventies that become the preparation of the mixtures standardized under horizontal laminar airflow hood of binary mixtures (amino-acid + glucose) or of ternary mixtures (amino-acid + glucose + lipids) [1]. The first Isolators in hospital pharmacies were introduced in the middle or at the end of the eighties.

The incentives taking in charge these preparations are an increase in the microbiological quality of the end product, possibilities of contamination being brought back from 18 to 2, an increase in the physicochemical quality of the end product, mixtures of parenteral nutrition containing to 50 different molecules and a lightening of the nursing team workload.

The improvement of the microbiological quality of the end product was shown in particular by Miller et al in 1971 who noted that the contamination of the solutions of perfusion resulted from a weak aseptic technique rather than of an aseptic lack of environment [2].

Recently, in a systematic review of 59 references, Larmené-Beld et al 2019, concluded that significantly higher contamination rates were found for the preparation of parenteral medication in clinical environment compared to pharmacy environment [3].

Cytotoxics

It is during the Eighties that Hospital Pharmacies started to deal with the reconstitution and the preparation of anticancer doses of chemotherapy. These doses are carried out under vertical laminar airflow hoods or in isolators. The incentives are identical to the precedents. With these 3 elements is added the protection of the manipulator towards the harmfullness of the handled products [1].

Centralized Intravenous Additive Services (CIVAS)

Beside the mixtures of parenteral nutrition and anti-cancer cures of chemotherapy, there remains an important quantity of injectable medications, in particular antibiotics, anti-emetics and pain treatment. The incentives to take charge of these various medications are identical to the precedents. One 5th element is added which is the economic aspect. Indeed, the preparation of series of standardized injectable doses is made more quickly, is less expensive in material used for the preparation and is less expensive in labour. The Centralized Intravenous Additive Services (CIVAS) then grew [4].

The standardization of preparation methods in care units [5] allows the serial preparation of parenteral nutrition mixtures [6] of chemotherapy doses [7] and of other injectable drugs [8]. With regard to the number of bags or syringes to be supplied, a mechanization or automation of preparations becomes necessary.

Automation robots have recently come to the market as an alternative for manual compounding of intravenous (IVD) drugs. The aim of this paper was to make a review of manual and automated compounding of IV drugs.

Method

A literature review was conducted on reconstitution of IVD. The results of meetings with all automated compounders firms present during congresses of European Association of Hospital Pharmacists in Europe (EAHP) of international congress of French speaking hospital pharmacy (Hopipharm), during the five last years were also collected. These congresses are representative of the European hospital profession. On this basis, the following methods were identified: manual, semi-automatic and automatic. A classification was carried out in 3 categories: automatic syringes, peristaltic pumps, and compounding doses robots.

Results

Automatic syringes

Syringes and needles are classically used for the reconstitution of injectable drugs.

The Multi-AD Fluid Dispensing System® can be considered as the first manual syringe allowing, after adjusting the length of the piston, to manually inject the same amount of solution into series of vials, bottles or bags [9]. This article is currently available at B Braun.

Electric syringes replace manual force by an electric motor and reduce the workload of pharmacy technicians. It can be a device with one (Fagron, Grifols, KRZ, Icumed, Smartcompounders) or more syringes (Hemedis, Icumed).

Autoyec® (Krz) is intended for the upload and download of 50 mL syringes through the use of 3-way stopcocks and allows to fill infusion pumps or other type of syringes of different capacity. It looks similar to the following device, Integra®.

Integra® (Integra) is a modular system made of single compounders which fits existing equipment of the Hospital Pharmacy and which is able to prepare, at the same time, more antitumor therapies.

Gri-fill 3.0® (Grifols) can be used for compounding many types of intravenous mixture, including chemotherapy, and fits inside a standard laminar airflow hood or biosafety cabinet. It is adaptable to different sources of solution containers (vials, bags, bottles) and can be used to fill any empty or partially dispensed destination container. Its evolution, Gri-fill 4®, can receive patients data from the health information system of the hospital.

Smartcompounders Chimio® (Smartcompounders) has a capacity of 10 containers of end products: bags, pumps or syringes. It can handle up to 10 vials of medicines with a maximum of 4 different drugs simultaneously. It can be installed in a LAF or in an isolator.

Otherwise, Diana ACS® (Icumed) is an automated sterile compounder for the accurate, safe and efficient preparation of hazardous drugs; it is a user-controlled automated system for repeatable accuracy. Its evolution, the Diana compounding workflow system®, combines both automated compounding and IV workflow technologies with wireless pharmacist notification to remotely verify each preparation on a handled tablet display. Integrated high-definition cameras let visualize the workflow.

Mibmix Coumponder C12® (Hemedis) may be used for the preparation of TPN for neonatal and pediatric patients. The installation of 4 syringe drivers may be extended to 8, 12 or 16 channels, of different volumes.

Peristaltic pumps

Peristaltic pumps allow to program an automatic filling of vials or a supplementation of pre-filled vials

with a drug solution. The programmable volume is larger than in the case of a syringe. (Added Pharma, Baxter, Healthmark). The peristaltic pump can be integrated in a small (Medxl) or medium-sized filling ramp (Added Pharma) to produce batches of suitable quantities of syringes.

Parenteral nutrition requires the mixing of the contents of different bottles and/or bags to ensure the supply of amino acids, glucose and lipids, but also vitamins and trace elements to the patient. The historical method of compounding these multicomponent admixtures has been to manually use gravity-driven transfers for the large volume additives. Small additives, such as electrolytes, trace elements and vitamins have been added manually and separately with a syringe [10].

The emergence of automated technology has led to potentially improve compounding accuracy with the use of fluid pump technology and software that controls the compounder pump [11].

Currently Exactamix® (Baxter) and Pinacle® (B Braun) compounders were regularly used in the hospital pharmacies. A Kabihelp® (Fresenius kabi), to connect 12, 24 or 36 bottles, is under development.

Robots for compounding

With robotic arm

The use of a robotic arm for preparing doses of i.v. drugs was described in 1989 [12]. Robots were then developed for the reconstitution of cytotoxic or non-cytotoxic medications.

Robots can be distinguished between robots with one or two arms, or robots without arms; some of them dedicated to the production of hazardous drugs, others to non-hazardous intravenous drugs.

One arm

Robots for compounding of intravenous cytotoxic doses

Cytocare® is probably the first robot with a robotic arm put on the market for the preparation of cytotoxic drugs [13].

Originally developed by Health Robotics, this robot has been distributed in Europe by B Braun from 2007 until 2010, when Health Robotics has re-acquired from B. Braun the exclusive marketing, sales, installation, implementation, interface, manufacturing, and technical support European rights. Aesynth in 2014, then Omnicell in 2015 acquired Healthrobotics. Its use has been commented by various authors [14–16].

Renamed I.V. Station Onco®, a new generation is maintained available. I.V. Station Onco® is capable of a broad array of drug transfers, dilutions, and reconstitutions. HEPA air filtering and a negative pressure chamber to reduce compounding errors, improve accuracy, and protect pharmaceutical staff.

Another robot was developed some time later by Loccioni. Apoteca chemo® is a robotic system capable of weighting the active ingredients and solutions, reconstituting powdered drugs, thanks to the use of a dedicated, six way anthropomorphic mechanical arm and actuators, preparing syringes, bags and other final containers while safely loading and unloading the materials and preparations. The first use of this robot was also described [17–19].

Non cytotoxic doses

Omnicell purpose an IV Station robot® dedicated for the preparation of ready to use non-hazardous injectable drugs. (Figure 1). This robot is smaller than the I. V. Station Onco®.

Figure 1: Robotic arm, CHU UCL Namur, Belgium.

It has an ISO 5 positive pressure compounding chamber. The development and use of this robot has been described in a recent symposium [20].

Peters et al modified its function to adapt it to the summary of product characteristics of monoclonal antibodies, to avoid foaming and formation of protein aggregates [21].

Two arms

Robots for compounding of intravenous cytotoxic doses

Compouding robot with two robotic arms are also available at now (Kiro).

The robotic arms of Kiro Oncology® (Grifols) perform separate tasks simultaneously, the movement of disposable items are minimized in the compounding area and the decontamination of hazardous chemicals is realized by self-cleaning. Kiro Oncology® is classified as a class II A2 biosafety cabinet and the compounding are is ISO 5 classified. Deljehier et al describe his use for monoclonal antibodies and anti-infectious sterile drug preparation [22].

The intelligent compounding system (= ICS®, Steriline) is a fully automated robotic solution, controlled by software, which compounds parenteral medication doses into the appropriate final containers within a controlled environment (ISO class 4.8, grade A). It is based on isolator technology and includes a bio-decontamination system with vaporized H_2O_2 sterilization technology; therefore it can be installed in an ISO class 8 (grade D) background environment. The ICS® can handle both hazardous and non-hazardous medications and both patient specific and batch production. The ICS includes state of the art automation and robotics to perform the following tasks without requiring human intervention.

Non cytotoxic doses

IV Icon Twins® (Newicon) is a compounding system for intravenous antibiotics, in a Class II biological safety cabinet. One robotic arm mixes the medicinal substances, after which the other arm draws the reconstituted antibiotic solution into a syringe.

Without robotic arm

Pharma help® (Fresenius Kabi) is available in two configurations, a laminar air flow cabinet and an isolator. The mechanism for dose preparation was developed by Medical dispensing Systems. This multipurpose robot must be dedicated to the reconstitution of cytotoxics, antibiotics, parenteral nutrition and radiopharmacy. Experiences were published with laminar airflow cabinet [23] and isolator [24] for preparation of cytotoxic doses.

Pharmoduct® (Comecer) is an automatic compounding system for the preparation of chemotherapy doses. Pharmoduct® is able to reconstitute, transfer and dilute oncology drugs in order to prepare final dose and multidose bags. The system can manage more than 300 different drugs. It is equipped with a rotating carousel. The transfer of liquid is ensured by peristaltic pump.

Equashield® Pro (Equashield) is the first ever closed system drug compounding robot, using Closed System Transfer Devices (CSTDs) for hazardous drugs. It uses a multi-station compounding system.

The Table 1 describes the different features of each device. Automated compounders are listed in alphabetical order. The initial as well as the final containers are mentioned. The Table 2 gives the links to the website of the different suppliers.

Table 1: comparative table of automated compounders.

Name	Vendor	Source solution containers				Destination container			
		Bottle	Bags	Ampuls	Syringe	Bags	Syringes	Elastomeric pumps	Infusors
Apoteca	Loccioni	Yes	Yes	No	No	Yes	Yes	No	No
Autoyec	Krz	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
Baxa Repeater pump	Baxter	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
Aseptic Smart Coumponder	Added Pharma	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
Cytocare	Omnicell	Yes	Yes	No	No	Yes	Yes	No	No
Diane ACS	Icumed	Yes	Yes	No	No	Yes	No	Yes/No	Yes/No
Equashield Pro	Equashield	Yes	Yes	No	No	Yes	No	No	No
Exactamix 2400	Baxter	Yes	Yes	No	Yes	Yes	Yes/No	Yes/No	Yes/No
Gri-fill 3.0	Grifols	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

(*continued*)

Table 1: (*continued*)

Name	Vendor	Source solution containers				Destination container			
		Bottle	Bags	Ampuls	Syringe	Bags	Syringes	Elastomeric pumps	Infusors
Gri-fill 4.0	Grifols	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
ICS	Steriline	Yes	Yes	No	Yes	Yes	Yes	No	No
Integra	Integra	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
IV Icon twin	Newicon	Yes	Yes	No	No	Yes	Yes	No	No
IV Station	Omnicell	Yes	Yes	No	No	Yes	Yes	No	No
IV Station Onco	Omnicell	Yes	Yes	No	No	Yes	Yes	No	No
Kiro	Grifols	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Medimix	Fagron	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
Medoc VMC	Icumed	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
Mibmix	Hemedix	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
Multi Add Fluid dispenser	B Braun	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
Pharmahelp	Fresenius Kabi	Yes	Yes	No	No	Yes	No	No	No
Pharmassist	Healthmark	Yes	Yes	No	Yes/No	Yes	Yes	Yes	Yes
Pharmoduct	Comecer	Yes	Yes	No	No	Yes	Yes	No	No
Pinacle	B Braun	Yes	Yes	No	No	Yes	No	No	No
Praxifill	Medxl	Yes	Yes	No	No	No	Yes	No	No
Smartfiller	Added Pharma	Yes	Yes	No	No	No	Yes	No	No

Yes/No = technically: Yes/pratically: No

Table 2: Vendors and related website.

Vendor	Website
Addedpharma	https://www.addedpharma.com/aseptic-smart-compounding/smartfiller-syringe-filling-machines)
Baxter	http://www.baxtermedicationdeliveryproducts.com/pharmacy-workflow/repeater.html
B. Braun	https://www.bbraun.com/en/products/b2/pinnacle-compounder.html)
Comecer	https://www.comecer.com/pharmoduct-automatic-compounding-system/
Equashield	www.equashield.com
Fagron	file:///C:/Users/Administrateur.000/AppData/Local/Microsoft/Windows/INetCache/IE/U8B9ND8Q/tharban-imf.pdf
Fresenius kabi	https://www.fresenius-kabi.com
Grifols	https://www.grifols.com/en/results?q=gril-fill
Healthmark	http://www.healthmark.ca/2-7-11-PharmAssist_fr.html?ProduitID=73
Hemedis	www.hemedis.com
Icumed	http://www.icumed.com/products/specialty/tpn-compounding-systems/medoc-vmc-(pc-based).aspx
Integra	http://ospedaliera.eurospital.it/en/172/INTEGRA/OVERVIEW
KRZ	https://www.krz.es/fr/produits/electro-pharmacie/23/autoyec-50-sc
Loccioni	https://www.loccioni.com/en/
Medxl	https://www.medxl.com/praximed-system/
Medical dispensing system	www.medicaldispensing.nl
Newicon	https://newicon.fi/pharmacy-automation-in-a-hospital/compounding-system
Omnicell	www.omnicell.com/us/en_us/products/iv-station-onco-hazardous-compounding-robot
Smartcompounders	https://www.smartcompounders.com/chemo-2/
Steriline	www.steriline.it

Discussion

Common points are that the ampuls cannot be supported by these robots and that large dosages vials improve the time of reconstitution compared to current dosage vials.

The panel of the material described is very extensive, ranging from the mechanized syringe to the “plug and play” production robot. The purchase prices are obviously not comparable, the uses either. Some devices can be installed in a laminar air flow cabinet or an

isolator. Others contain all the material in the appropriate ISO environment. The robots will be installed in a class C or a class D, according to the specifications of the manufacturer.

Advantages of automated preparation are: higher consistency of process and products, higher accuracy of products, integrated digitized processing, precise, complete documentation, reduced effort and wrist injuries, reduced personnel requirement, increased worker satisfaction.

Disadvantages of automated preparation are: risk of failure/down time, dependency on power supply, software (updates), high investment costs/high maintenance costs, specialized personnel with additional training, decreased worker satisfaction, complexity when products are switched or added, potential for new errors [25].

This work is intended to be a review of compounding material in the broad sense of the term, available in Europe. However, devices may have escaped our attention and, in another side, the number of compounding robots is regularly increasing. We invite the reader to send us any new material available or launched on the European market.

Conclusion

This review is intended to be exhaustive, without favoring any supplier and to guide colleagues who want to automate their pharmaceutical reconstitutions and productions. However, devices may have escaped our attention and, in another side, the number of compounding robots is regularly increasing. If the reader has additional information, we obviously include it in a future review.

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