https://doi.org/10.31925/farmacia.2022.6.18 **ORIGINAL ARTICLE**

INNOVATIVE METHODS FOR THE CHARACTERIZATION OF A NOVEL PHARMACEUTICAL ADHESIVE FOR 3D PRINTING DRUGS

IULIAN SARBU [1#], ANCUȚA CATALINA FIȚA [2]*, VIOLETA POPOVICI [3#], DUMITRU LUPULIASA [2], MIRELA ADRIANA MITU [2], VIOREL STEFAN BIRMAN [2], EMMA ADRIANA OZON [2]

[1]*Zentiva S.A., 50 Theodor Pallady Blv., 032266, Sector 3, Bucharest, Romania*
[2]*Department of Pharmaceutical Technology and Biopharmacy, Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, 3-6 Traian Vuia Street, Sector 2, 020956, Bucharest, Romania*
[3]*Department of Microbiology and Immunology, Faculty of Dental Medicine, "Ovidius" University of Constanta, 7 Ilarie Voronca Street, 900684 Constanta, Romania*

**corresponding author: catalina.fita@umfcd.ro*
[#]Authors with equal contribution.

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Abstract

3D printing has emerged in the technological context of prototyping. It offers the advantage of producing a unique, individualized object in a noticeably short timeframe and at a relatively low cost. Classical mass production methods provide a meagre price *per* unit delivered only if that product is made in large quantities. Hence, the cost of designing and executing models and templates divided by the number of units is low. The 3D printer does not need a fixed mold for producing drugs; it only uses data from mathematical software that can be adapted to different needs. This paper aims to address the lack of adhesion of the drug to the glass bed of the 3D printer. The adhesion to the glass bed of 3D printed parts is one of the most widespread current problems of 3D printing. This paper proposes the development of an adhesive to solve the problem of poor adhesion while maintaining the characteristics imposed by the rigors of the pharmaceutical field. Screening results showed that the polymer that, after complete drying, still maintains a sticky surface useful for adhesion was PVP. The other polymers did not readily dissolve in alcohol solutions, or they did not present any stickiness after drying, or the formulations were hard to dry (water-based formulations). The selected polymer was polyvinylpyrrolidone (PVP) for final formulations, and different concentrations and alcohol solutions were tested. Viscosity, spray pattern, and push force were investigated for each container spray with different formulations. The correlation between quantitative composition, the solvent used, and viscosity was evaluated to select the best overall formulation.

Rezumat

Imprimarea 3D a apărut în contextul tehnologic al prototipării. Oferă avantajul de a produce un obiect unic, individualizat într-un interval de timp semnificativ scurt și la un cost relativ scăzut. Metodele clasice de producție în masă oferă un preț slab pe unitate livrată numai dacă acel produs este fabricat în cantități mari. Prin urmare, costul de proiectare și execuție a modelelor și șabloanelor împărțit la numărul de unități este scăzut. Imprimanta 3D nu are nevoie de o matriță fixă pentru producerea medicamentelor; folosește doar date din software-ul matematic care pot fi adaptate la diferite nevoi. Această lucrare își propune să abordeze lipsa de aderență a medicamentului la patul de sticlă al imprimantei 3D. Aderența la patul de sticlă a pieselor imprimate 3D este una dintre cele mai răspândite probleme actuale ale imprimării 3D. Lucrarea de față propune dezvoltarea unui adeziv care să rezolve problema aderenței slabe păstrând în același timp caracteristicile impuse de rigorile domeniului farmaceutic. Rezultatele screening-ului au arătat că polimerul care, după uscarea completă, menține încă o suprafață lipicioasă utilă pentru aderență a fost PVP. Ceilalți polimeri nu s-au dizolvat ușor în soluții de alcool sau nu au prezentat nicio lipiciitate după uscare sau formulările au fost greu de uscat (formulări pe bază de apă). Polimerul selectat a fost polivinilpirolidona (PVP) pentru formulările finale și au fost testate diferite concentrații și soluții de alcool. Vâscozitatea, modelul de pulverizare și forța de împingere au fost investigate pentru fiecare pulverizare din recipient cu formulări diferite. Corelația dintre compoziția cantitativă, solventul utilizat și vâscozitatea a fost evaluată pentru a selecta cea mai bună formulare globală.

Keywords: 3D printing, printlets, pharmaceutical 3D printing adhesive

Introduction

The idea of more individualized pharmacotherapy [1] has been developed for many years, but its significance has never been higher than it currently is [2]. The need to create personalized medicine [3] through the rational use of drugs by patients [4] in the correct dose is a subject of intense discussion since the heterogeneous nature of diseases [5] is the source of difficulties in the therapeutic intervention [6]. The therapy failure [7] or therapeutic effects

limitations [8] are some of the reasons for changing the dosage form as well as the dose of the active substance, especially for individual age groups [9]. Therefore, the implementation of three-dimensional printing (3D printing) [10], also known as additive manufacturing (AM) [11] or rapid prototyping [12], can become extremely useful in the development of personalized therapy [13] regarding medication design [14] and preparation [15]. The AM involves manufacturing technologies characterized by material deposition as "layer-by-layer" to fabricate three-dimensional drugs under digital control (computer-aided design model or scan). This innovative strategy can fetch many advantages to drug formulation, allowing drug individualization according to the patient's age, body weight, and lifestyle [16] by adjusting the dose and dosage forms [17]. The obtained 3D printed tablets (printlets) [18] are individualized to the patient's therapeutic needs (*e.g.*, dosage, drug combination, and drug release profiles) and preferences (*e.g.*, shape, size, texture and flavour) using various manufacturing processes. Moreover, it appears to be particularly beneficial in producing orphan drugs manufactured for small groups of patients [19].

The designed objects' scalability [20] causes the simplicity of preparing drugs with different doses, so the calculated material consumption can control the dose during the resizing of the printed object already at the design stage. The relatively low cost and production of dosage forms with different dosages are the significant short-term advantages of drug series [21]. These 3D printed drugs are obtained using various techniques and grouped into 3 main categories: printing-based inkjet systems, extrusion-based deposition systems, and laser-based writing systems [22]. The common aspect of the methods belonging to the first group consists in using a post-treatment heating of the obtained three-dimensional drug to eliminate solvents and other impurities; hence, these 3D printed medicines are very fragile and irregular [23]. The second type avoids the limitations of the previous one. It implies the mixing of drugs and polymers until 3D printing. The mixture is passed through a nozzle that performs, layer by layer, the three-dimensional pharmaceutical product. For this reason, the extrusion-based deposition systems are known as nozzle-based ones, containing two types of printings considering the used materials: Fused Deposition Modelling (FDM) with melted components, and Pressure-Assisted Microsyringes (PAM), without heating. The third category is a laser-based writing system (stereolithography, SLA) based on a localized photopolymerization under ultraviolet radiation occurring in a bath with liquid oligomers, monomers and photoinitiators [24].

The initial phase of any 3D printing process involves developing the formulation through the previously mentioned Computer-Aided Design (CAD). CAD software converts the 3D printed file into a stereo-lithography file (STL) that possesses the necessary information for the spatial geometry of the pharmaceutical product before printing. The STL file is portioned into different pieces [25]; one is the slice file (SLI), prepared for uploading to the 3D printer for printing through one of the previously described techniques. The printer bed is an essential component [26] of the whole assembly. Substantial improvements have been made over time [12], and many materials [27] were chosen from which the printer beds were designed [28]. One of the biggest problems facing drug 3D printing is the adhesion [11] of the 3D printed object to the printer bed [29, 30]. While printing the object's first layer, we are dealing with a contraction of the polymer material from the printer bed [31]. To improve the adhesion of the first layer, most users select different adhesives [11] to prevent the print parts from lifting from the printer bed surface. This phenomenon is due to the insufficient adhesion of the polymer molecules to the bed's surface and the polymer's volume contraction when it cools. Polymers such as Hydroxypropyl methyl-cellulose (HPMC), Polyethylene glycol (PEG), Poly-vinylpyrrolidone (PVP), and Methylcellulose (MCC) are used in AM processes as the powder or substrate contribute to obtaining an optimum adhesion [11]. It is essential to mention that there are currently no adhesive formulations that correspond to pharmaceutical industry standards. Therefore, the present study aims to formulate, develop and characterize a pharmaceutical adhesive for 3D printing drugs.

Materials and Methods

Formulation of an adhesive based on pharmaceutical polymers in alcoholic solutions

Analytical balances Kern Adb 200-4, a DLAB OS40-Pro Overhead propeller mixer, Berzelius beakers, and stainless-steel spatulas were used to obtain the adhesive formulations.

Previously screening tests were made with HPMC, HPC, HEC and PVP as polymer and Purified water, ethanol and isopropyl alcohol as a solvent. Screening results showed that the polymer that, after complete drying, still maintains a sticky surface useful for adhesion was PVP. The other polymers did not easily dissolve in alcohol solutions, or they did not present any stickiness after drying, or the formulations were hard to dry (water-based formulations). The selected polymer was polyvinylpyrrolidone (PVP) for final formulations, and different concentrations and alcohol solutions were tested.

The alcohol solutions were added to the Berzelius beakers, the mixer propeller was inserted into the solution, and the mixer was turned on and brought to high speed.

The rule of 2/3 was used. A propeller with a diameter of 2/3 the size of the beaker was used to ensure the proper mixing. The propeller was set to the lowest point in the cup to provide the maximum vortex head and the least down spaces, ensuring high shear stress and optimum homogenization. When the alcohol solution formed a cone (vortex) deep enough to touch the propeller on the bottom of the Berzelius beaker but insufficient enough to include air bubbles, the powdered polymer was added. The polymer was poured over the alcoholic solution into the vortex cone so that large agglomerations did not form in the suspension. After obtaining a uniform suspension of PVP in alcohol, the mixer speed was reduced, and the polymer was allowed to swell until a clear solution was obtained. Different concentrations of PVP in alcohol were used to cover a wide range of polymer viscosities and concentrations. Concentrations of 5%, 10% and 15% PVP were used in isopropyl alcohol, ethyl alcohol, and a stoichiometric mixture of isopropyl alcohol and ethyl alcohol. Each solution was weighed to 50 g and packaged in PET bottles fitted with a spray cap. The volume of the PET bottles used was 100 mL.

Physicochemical analysis of adhesive

Viscosity

A Fungilab SMART rotational viscosimeter was used to determine viscosity. The solution of each formula was brought into an appropriate Berzelius beaker. The instrument was set for analysis, and the viscometer rotor was immersed in the solution. Different rotor speeds (three speeds: 25, 50 and 100 rpm) were selected to analyse the solution's dynamic viscosity.

Sprayer downforce measurement

The required push force of the sprayer was measured to ensure optimal use. A high strength indicates complexity to use, leading to user discomfort. Each spray bottle was placed on a technical scale, Kern EMB 5.2K1, with a maximum capacity of 5.2 kg and a readability of 1g so that we could record the force required for spraying. The digital display of the balance was videotaped with a 12-megapixel 60 fps video camera (Figure 1) to record the required pressure. The sprayer was operated consecutively with force directed downwards on the bottle, and stopping at the end of the stroke was avoided in order not to record erroneous values. Each formula was actuated 2-3 times before measurement so that the dosing pumps were primed and free of air bubbles. Four maximum values were recorded for each applicator, and average forces were calculated.

Measuring the area of the adhesive spray pattern

This study's important aspect is obtaining a uniform film on the printer bed. The ideal product should form a uniform film on the entire surface of the bed from the fewest applications from 15 - 20 cm. To be able to select an ideal formula, a 'spray-pattern' test was performed for each bottle of adhesive solution. This test is frequently employed to set sprayer parameters in pharmaceutical tablet film machines. In this case, the solution was applied by tilting the bottle at 90 degrees and spraying the solution on a white sheet on a contrasting background. The halo obtained by spraying 5 puffs was immediately marked (Figure 2).

Figure 1.
The working technique for the determination of the sprayer pressure force

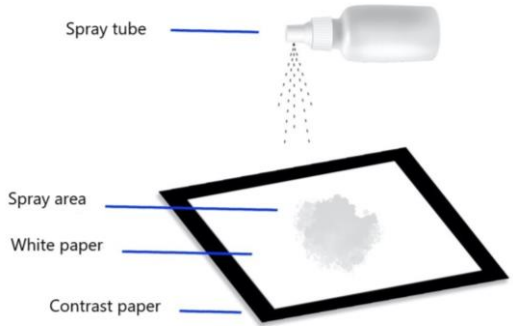

Figure 2.
The working technique for measuring the area of the adhesive spray pattern

Figure 3.
Determination of the mass of solutions applied by spraying

Determination of the mass of solutions applied by spraying

The amount of polymer delivered by each application is also essential in obtaining a uniform coating. The

amount (grams) provided by the actioning of the sprayer was measured by knowing the PVP concentration for each formulation. Thus, 10 puffs of the proposed adhesive were sprayed into a Berzelius Polycarbonate beaker tared on an analytical balance, and the mass of the applied solution was recorded (Figure 3).

Choosing the optimal adhesive formula for use in pharmaceutical 3D drug printing

A Creality Ender 3 (Shenzhen Creality 3D Technology Co, Ltd., Shenzhen, China) FDM (Fused Deposition Molding) 3d printer was used for testing the formulation's performance. The system uses a belt-driven Cartesian XZ-single head, providing a Layer height of 100 - 400 microns with a print precision: of ± 100 microns at a maximum print speed of 200 mm/s. Bed surfaces chosen for the tests were mirror glass and borosilicate glass, especially diamond cut to the bed frame dimensions and bevelled to ensure secure handling.

A 3D object of a lenticular-shaped pill was drawn (Figure 4) in FreeCAD software [24]. The 3D object was exported in a stereolithography (SLA) format [22] and translated into 3D printer G-code using Ultimaker Cura 4.3. software. The tablets were made from polylactic acid (PLA)[32] and printed directly on the printer's glass bed. Without adhesive and support structures used or to improve adhesion to the printer bed in the software (brim, skirt), the tablets did not adhere, and the printing was interrupted.

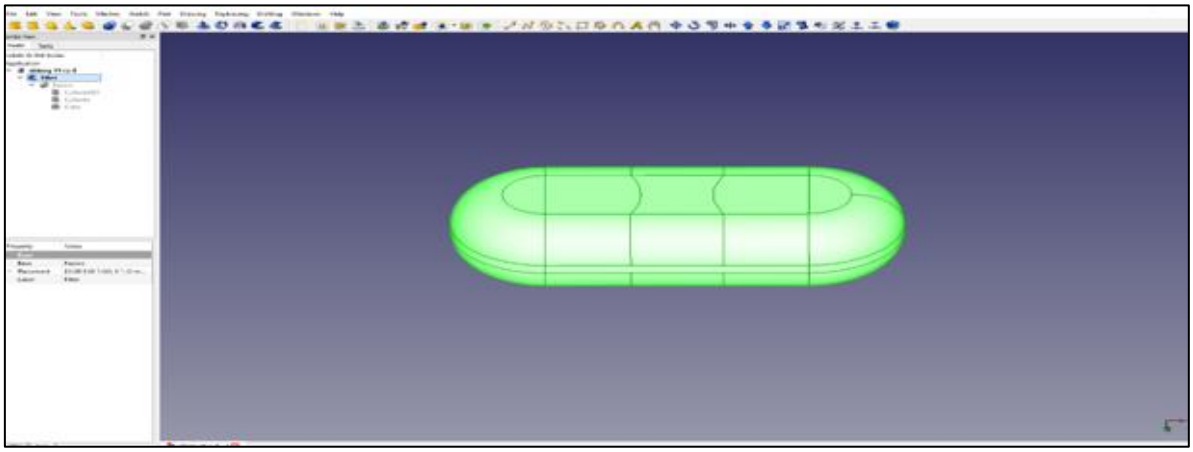

Figure 4.
Printlet 3D design in FreeCAD software

Results and Discussion

Formulation of an adhesive based on pharmaceutical polymers in alcoholic solutions

Nine formulations were prepared, with increased PVP concentrations, from 5% to 7.5% and 10%. The remaining 95%, 92.5% and 90% were attributed to isopropyl-alcohol (F1, F4 and F7), ethanol (F2, F5 and F8), and both alcohols in equal percent (F3, F6 and F9). All nine formulations (F1-F9) are shown in Table I.

Table I
Adhesive formulations and quantitative and qualitative composition

Formulation	% PVP	%Isopropyl-alcohol	% Ethanol
F1	5	95	0
F2	5	0	95
F3	5	47.5	47.5
F4	7.5	92.5	0
F5	7.5	0	92.5
F6	7.5	46.25	46.25
F7	10	90	0
F8	10	0	90
F9	10	45	45

Viscosity Measurement

The viscosity values augment directly proportional with %PVP. The highest viscosity values note the exclusive presence of isopropyl-alcohol in correspondent formulations-generally, the viscosity decrease when the rotor speed increase from 25 to 100 RPM. Only the F7 and F9 have the lowest viscosity at 50 RPM. The results are registered in Table II.

Sprayer downforce measurement

The data obtained are registered in Table III. The lowest sprayer downforce values are obtained for F3 (1943 g), F8 (1955.5 g), and F4 (1955.8 g).

Table II

The viscosity of obtained formulations

Formulation	Composition			Viscosity (CPs) at different rotor speeds (RPM)		
	%PVP	% Isopropyl alcohol	% Ethanol	25 RPM	50 RPM	100 RPM
F1	5.00	95.00	0.00	20.00	19.5	18.00
F2	5.00	0.00	95.00	21.6	16.7	13.7
F3	5.00	47.50	47.50	19.57	18.14	15.90
F4	7.50	92.50	0.00	23.69	23.12	22.72
F5	7.50	0.00	92.50	19.14	18.9	17.35
F6	7.50	46.25	46.25	22.29	21.00	19.80
F7	10.00	90.00	0.00	28.46	27.06	28.41
F8	10.00	0.00	90.00	24.21	22.80	21.60
F9	10.00	45.00	45.00	24.82	24.28	24.43

Table III

Sprayer downforce measurement

Formulation	Composition			Sprayer downforce (g)				
	%PVP	% Isopropyl alcohol	% Ethanol	Pressing 1	Pressing 2	Pressing 3	Pressing 4	Mean ± SD
F1	5.00	95.00	0.00	3268	3278	2437	2278	2815.3 ± 532.5
F2	5.00	0.00	95.00	2247	2051	2268	1768	2083.5 ± 231.9
F3	5.00	47.50	47.50	2468	2008	1897	1400	1943.3 ± 438.4
F4	7.50	92.50	0.00	2038	2269	1653	1863	1955.8 ± 261.5
F5	7.50	0.00	92.50	1802	2609	2898	1798	2276.8 ± 563.0
F6	7.50	46.25	46.25	2171	2143	2070	1929	2078.3 ± 108.2
F7	10.00	90.00	0.00	2138	1788	2663	2739	2332.0 ± 450.4
F8	10.00	0.00	90.00	1696	1448	2227	2451	1955.5 ± 463.3
F9	10.00	45.00	45.00	1409	2674	2356	2441	2220.0 ± 557.4

Measuring the area of the adhesive spray pattern

After drying the solution, the axes of each pattern were measured, and the spray area was calculated. An ideal design must have a constant appearance with an oblong shape so that short applications in a few points can uniformly cover the entire printer bed. Figure S1 from Supplementary Material presents the spray patterns obtained by spraying the formulas and plotting them for area calculation.

The surface area was calculated after measuring the length and width of the pattern by applying the following formula:

$$A = \frac{\pi}{100} \times \frac{L}{2} \times \frac{W}{2}$$

where: A = aria (cm^2), L = length (mm), W = width (mm).

Determination of the mass of solutions applied by spraying

It can be seen that regardless of the viscosity and polymer concentration, the mass of the sprayed solution *per* each spray puff is constant for all formulations (116 - 112 mg). This highlights that more polymer reaches the bed's surface as the PVP concentration increases. Therefore, F1 - F3 corresponds to 5.15 - 5.80 mg PVP, F4-F6: 8.03 - 8.55 mg PVP, and F7-F9: 11 - 11.2 mg PVP. On the other hand, it was observed that ethanol-based alcoholic solutions (F2, F6 and F8) generated a pattern with a more uniform ovoid appearance and managed to provide the highest amount of polymer on the spray-coated surface (Table IV).

Table IV

Spray area obtained for each formula and amount of polymer

Formulation No.	%PVP	%Isopropyl alcohol	%Ethanol	Solution/10 spray puff (mg)	Solution/1 spray puff (mg)	Polymer/1 spray puff (mg)	Length pattern (mm)	Width pattern (mm)	Pattern Area (cm^2)	Polymer layer (mg/cm^2)
F1	5.00	95.00	0.00	1160.00	116.00	5.80	95.00	52.00	38.78	0.75
F2	5.00	0.00	95.00	1030.00	103.00	5.15	98.00	54.00	41.54	0.62
F3	5.00	47.50	47.50	1060.00	106.00	5.30	110.00	70.00	60.45	0.44
F4	7.50	92.50	0.00	1140.00	114.00	8.55	118.00	75.00	69.47	0.62
F5	7.50	0.00	92.50	1100.00	110.00	8.25	119.00	48.00	44.84	0.92
F6	7.50	46.25	46.25	1070.00	107.00	8.03	156.00	48.00	58.78	0.68
F7	10.00	90.00	0.00	1100.00	110.00	11.00	134.00	67.00	70.48	0.78
F8	10.00	0.00	90.00	1110.00	111.00	11.10	136.00	54.00	57.65	0.96
F9	10.00	45.00	45.00	1120.00	112.00	11.20	178.00	56.00	78.25	0.72

Choosing the optimal adhesive formula for use in pharmaceutical 3D drug printing

Having the maximum concentration of PVP in the solution, F8 revealed a low viscosity compared to 10% isopropyl alcohol-based solutions. Apart from the average solution viscosity, F8 scored the best in the squeeze test, having compressive forces comparable to less concentrated solutions. Moreover, F8 presented the most uniform pattern and the highest concentration of PVP *per* cm^2 of application.

Therefore, a layer of F8 solution was applied to the printer bed. Ten sprays were required to obtain a thin and uniform film of liquid on the glass surface of the bed. An ideal product should form a uniform film on the entire surface of the bed from the fewest applications from a distance of 15 - 20 cm.

After the quick drying of the solution, the printing of the test tablets was started. Even if no other special settings were used to improve adhesion in the CURA software, printing was performed without any problems. The first layer sat evenly on the polymer film, and the tablets immediately adhered to the printer bed. After printing was completed and the equipment cooled down, the printer bed with the tablets was removed and analysed.

It can be seen that the first layer adhered uniformly to the printer's bed; there were no raised corners, and the tablets did not have any "warped" appearance (Figure 5a). The tablets easily detach from the printer bed after cooling, which means that they will ensure comfortable use for the user, who will not be forced to use sharp tools (sharp stainless-steel spatulas or knives) and thus reduce the risk of injury (Figure 5b).

(a) (b)

Figure 5.
(a) Printlets adhered to the printer bed;
(b) Printlets detached from the printed bed

To obtain a pharmaceutical adhesive, a polymer already existing in the pharmaceutical industry was chosen considering the following: be inert, not interact with active substances, to be well-established use, to provide good adhesion before and after drying; to be soluble in both organic and inorganic solvents; to form a transparent film; not to have a characteristic pregnant taste and smell [33].

One of the pharmaceutical industry's most-known and used polymers is polyvinylpyrrolidone (PVP), also known as povidone [34]. Povidone is a fine, white to creamy-white coloured, odourless or hygroscopic, almost odourless powder [35]. Polyvinylpyrrolidone is characterized by its K-value [36], a function of the average molecular weight, the degree of polymerization and the intrinsic viscosity [37]. The viscosity was measured for aqueous PVP solutions [38] with K-values ranging from 92.1 to 95.4 and with concentrations from 2 to 3 weight percent. A correlation was determined that relates solution viscosity to the K value and weight percent PVP, which is particularly useful in its use as a photoresist in manufacturing high-resolution display screens [39]. Povidones with K values equal to or less than 30 are manufactured by spray drying and appear as spheres [40]. Povidone K-90 and higher K-value povidones are manufactured by drum drying and appear as slabs [40]. Povidone darkens to some extent on heating to 150°C, with reduced aqueous solubility. It is stable to a short cycle of exposure to heat around 110 - 130°C; steam sterilization of an aqueous solution does not change its properties [41]. Aqueous solutions are susceptible to mould growth [42] and therefore require the addition of appropriate preservatives. Povidone can be stored under normal conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place [43].

The solvent had to meet the attributes mentioned above (inert, odourless, tasteless, frequently used) and slight evaporation. Although ideal for such use, water would result in high drying times [38]. Thus, isopropyl alcohol, ethyl alcohol and a stoichiometric mixture of them were chosen for the solvent. In addition to the attributes mentioned above (inert, odourless, tasteless, frequently used), the solvent must also have slight evaporation. Although ideal for such use, water would result in high drying times. Thus, isopropyl alcohol, ethyl alcohol [35], and a stoichiometric mixture were chosen for the solvent.

The adhesive formulation viscosity is essential to its role as an adhesive and the application method. A low viscosity will prevent the formation of cohesive particles, which will be airborne and will not reach the support. Also, a low viscosity will jeopardize the shape of a uniform polymer film on the printer bed, the construction of small adhesive spots, with a damaged appearance and role [44]. On the other hand, a too-high viscosity would mean too much cohesion, forming large particles that would be difficult to spray. Experiments before this work observed that at concentrations of 15 - 25% when pressing the spray head, the solution is no longer scattered in tiny drops but rather in the form of a concentrated jet that is not evenly distributed on the printer bed. Also, at high viscosity, the pressing force on the sprayer head would be too high, making the use of the adhesive cumbersome for the user.

The required push force of the sprayer was measured to ensure optimal use. High pressure indicates the difficulty to use, leading to user discomfort.

We would generally expect an increase in compressive force with increasing polymer concentration and an increase in the dynamic viscosity of the solution.

However, it can be observed that the pressing force does not increase linearly with the polymer concentration. On the contrary, the highest forces were recorded in the more dilute solutions, especially in the solutions obtained based on isopropyl alcohol.

It is noted that the addition of ethyl alcohol decreases the force required for spraying. The probable cause is the slightly lubricating effect of the polymer on the piston inside the applicator. Also, isopropyl alcohol, although widely used in the technical and pharmaceutical fields, is known to attack the pistons' silicone o-rings (seals). From these considerations, we can conclude that it is preferable to use an ethanol-based solution to prevent the applicators from sticking and malfunctioning during the product's life. Moreover, after analysis of the obtained data, it was deduced that F8 represents the ideal candidate for testing.

Conclusions

Our study showed that the polymer that, after complete drying, still maintains a sticky surface useful for adhesion was PVP. The other polymers did not easily dissolve in alcohol solutions, or they did not present any stickiness after drying, or the formulations were hard to dry (water-based formulations). The selected polymer was polyvinylpyrrolidone (PVP) for final formulations, and different concentrations and alcohol solutions were tested. Viscosity, spray pattern, and push force were investigated for each container spray with different formulations. The correlation between quantitative composition, the solvent used and viscosity was evaluated to select the best overall formulation.

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Conflict of interest

The authors declare no conflict of interest.

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