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Original Article

EFFECT OF COMPONENTS AND DEPOSITION ON TECHNOLOGICAL PERFORMANCE OF IBUPROFEN TABLETS

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ABSTRACT

Objective: This work evaluated the influence of the technological properties of polyvinylpyrrolidone (PVP), calcium phosphate (CP) and cross-linked sodium carboxymethylcellulose (CC) as well as the deposition of a solid dispersion, through the solvent evaporation method, on the technological parameters that define the properties of ibuprofen tablets.

Methods: The powder flow rate through an orifice, bulk volume and tapped volume of powders, tablet hardness, disintegration time and dissolution profile of the tablets were determined on individual components, their physical mixtures, granules obtained by deposition and solvent evaporation, and tablets obtained at different compaction pressures.

Results: The very poor flowability of CP and the high compactibility of PVP were transferred to the powder mixtures, which showed poor flowability, and ibuprofen tablets with twice the compactibility. The tablets disintegration was high with a low proportion of CC (0.5%), but decreased linearly by increasing the proportion of the disintegrant up to 10%. At the same time, the dissolution of the drug after 30 min increased from 3% to 80%. The agglomeration of CP through the deposition of an alcoholic solution of the drug and PVP improved the flow properties and tripled the hardness of the tablets. However, the dissolution after 30 min decreased from 80% to 18%.

Conclusion: The physical mixture was the best option to improve the dissolution, while the deposition on an adsorbent, of a solid dispersion of drug-PVP, was the best option to improve the compactibility and flow properties.

Keywords: Calcium phosphate, Croscarmellose sodium, Drug deposition, Ibuprofen tablets, polyvinylpyrrolidone, Solid dispersion, Technological performance

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INTRODUCTION

The development of a pharmaceutical product involves compliance with the specifications of the desired product, the satisfaction of the requirement of a certain minimum stability and the fulfillment of the requirements that allow a fluid production process in the manufacturing. These requirements include compliance with product parameters such as compactibility, powder flowability, tablet disintegrability and dissolution rate.

Tablets that require rapid disintegration include superdisintegrants. The choice of these disintegrants depends, among others, on the water solubility of the drug and the excipients of the tablet. Water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally disintegrate if an appropriate amount of disintegrant is included in the formulation [1].

The development of fast disintegrating tablets includes the use of super-disintegrants that allow their disintegration after putting them in contact with the biological fluids. Super-disintegrants allow a quick action, which is beneficial in cases of acute pain [2].

The choice of the excipients is dependent of their physical and chemical properties and their technological functionality. This includes tests that address the chemical composition, tests that address the physical form of the materials, and tests that address their performance or functionality within the formulation and manufacturing process [3].

With respect to the paradigm of QbD, the variability of a pharmaceutical product is a function of the variability of the input variables. The determination of a formula, manufacturing operations, process parameters and product quality attributes can be defined as a function of the properties and technological performance of the materials. For the design of an effective product, it is necessary to have the ability to link the properties and technological performance of the materials to the functionality of the product [4].

Among others, the specific values of the technological properties of the excipient identify its functionality. These specific values allow the establishment of statistical parameters that determine how to use an excipient. These properties are also used to identify materials, for quality control purposes [5].

Ibuprofen is used to reduce fever and treat pain or inflammation caused by many conditions such as a headache, toothache, back pain or minor injuries. The main problems with ibuprofen are its low solubility in biological fluids, gastric irritation and a short half-life of 2 h. The use of fast disintegrating tablets would help to improve the rate of dissolution and therefore the absorption [6].

To improve solubility, a number of methods have been employed, including solid dispersions, prodrugs, inclusion complexes and microcapsules [7].

A low aqueous solubility, as well as an inadequate dissolution rate of the drugs, is frequently overcome using amorphous systems. However, the high energy of the amorphous form is thermodynamically unstable, causing a return to the crystalline form with the consequent loss of solubility [8].

Solid dispersions can be used to stabilize an amorphous system. In the case of flutamide, an increase in dissolution was attributed to the amorphization of the drug during the preparation of the solid dispersion [9].

Not only the rate of dissolution but the solubility can be modified with solid dispersions. The aqueous solubility of the drug carvedilol was increased up to 3.5 times in an aqueous solution of PVP K30 at 5% w/v. This was attributed to the fact that the physical mixture increased the solubility and maximized the surface area of the drug that came into contact with the dissolution medium, when the transporter dissolved, while the solid dispersion produced a reduction in the crystallinity of the drug [10].

Similarly, in all aceclofenac-PVP solid dispersions, prepared by the rotary evaporation method, the dissolution rate of the drug was increased. The rate of dissolution increased with increasing PVP content [11].

The aim of this work was the assessment of the influence of the formula composition and the preparation method on the technological parameters that define the tablet properties and the manufacturing behavior of ibuprofen tablets.

MATERIALS AND METHODS

Material

Ibuprofen 38 (IBU) from BASF-USA, calcium phosphate (CP) from DROTASA-Mexico, polyvinylpyrrolidone, PVP-K30 (PVP) from Reasol-Mexico, cross-linked sodium carboxymethylcellulose (CC), croscarmellose sodium, from HELM-Mexico, magnesium stearate from HELM-Mexico, Aerosil 200 from Evonik Degussa-Mexico. All these materials were used as received.

Mixtures preparation

Physical mixtures

In a glass mortar, the components were incorporated one by one while mixing with circular movements of the pestle. Mixture continued with circular movements until completing 20 min. The binary mixtures composition were equal parts of IBU with CP and PVP. The ternary mixture was prepared also with equal parts of IBU, CP and PVP. In every case, 1% of magnesium stearate was incorporated as a lubricant. Moreover, the ternary mixture was added of 0.5%, 1.0%, 3.0%, 6.0% and 10% CC.

Imbibition or deposition on the adsorbent

The corresponding amount of IBU is placed in a mortar, adding ethanol for its complete dissolution. Then, an equal amount of PVP is dissolved. Subsequently, the CP was added and kneaded until it was fully incorporated. The mass was allowed to dry at room temperature for a period of 3 h. Then it was passed through a number 20 mesh. The obtained granules were placed in an oven at 50 °C for 60 min. The dried granules were placed in a V-type blender and the CC, the magnesium stearate and the Aerosil were added. The total amount was mixed at 30 rpm for 40 min.

Bulk volume and tapped volume of powders

The bulk volume of the poured powder was determined with 30 g of the corresponding material. The powder was poured gently through a funnel into a 100 ml graduated cylinder that was mounted on a tapper; recording the volume occupied by the powder (bulk volume-Vo). Once the total volume of powder was recorded, the graduated cylinder was tapped from a height of 1.5 cm, by the tapper at a constant speed of 50 taps per minute. The tapping of the sample was carried out in cycles of 10 taps. The volume occupied by the powder was recorded, repeating the operation as necessary, until obtaining 3 consecutive equal measurements. This was the volume of the tapped powder (Vf). These measurements were repeated five times, sieving the powders through a number 20 mesh after each determination. With these measurements, the compressibility index was calculated. These procedures are similar to those used by other authors, although the equipment and operating conditions are different [12, 13].

Assessment of the flow rate of the powders

Approximately 30 g of each material was placed in a glass funnel with a 7 mm opening that had been blocked. This funnel was placed on a 100 ml graduated cylinder mounted on a tapper. While unlocking the opening of the funnel, the tapper started moving. The powder flowed through the opening in the funnel, falling to the bottom of the cylinder. The time it takes to move the powder through the funnel was recorded. The powder flow rate was calculated by dividing the mass of the sample by the time recorded. The test was repeated 5 times, sieving the powder through a number 20 mesh after each measurement. The average of the 5 repetitions was taken as the powder flow rate.

Tablet preparation

The tablets were obtained by compacting the powders for 20 s at a series of compaction pressures from 27 MPa to 163 MPa. For this purpose, a set of punches and matrix of 12.7 mm in diameter was used. The results recorded are the average of three repetitions.

Compactibility assessment

The crushing strength or tablet hardness was measured in triplicate; the results were recorded as an average. For this purpose, a tablet hardness tester Erweka TBH30-Germany was used. The procedure consisted of placing each tablet diametrically between two flat surfaces and applying pressure until the tablet breaks. The compactibility profile was described with an equation based on the Weibull distribution [14-16]:

$$ln\left[-ln\left(1-\frac{D}{Dmax}\right)\right] = n * ln\, Pc + I$$

Where D denotes the hardness or crushing strength of the tablet, $Dmax$ the maximum hardness reached, Pc the compaction pressure, n the slope of the curve and I the intersection of the curve.

Tablet disintegration

To measure the disintegration time of the tablets, a TEMSA disintegration tester (TEMSA, Mexico City, Mexico) was used. In accordance with USP's disintegration procedures and using 900 ml of distilled water at 37 ° C. Disintegration tests were performed using the USP-type disintegration apparatus without disks. One tablet was placed in each of three individual tubes of the disintegration tester. The disintegration times of three tablets were determined and their average was recorded.

Tablet dissolution

The dissolution of the ibuprofen tablets was carried out in a type-USP II paddle apparatus. For this purpose, 500 mg tablets obtained at a compaction pressure of 109 MPa were used. The dissolution tester was adjusted to the temperature of 37 °C and 50 rpm. As a dissolution medium, 900 ml of a phosphate buffer at a pH of 7.2 was used. Samples of 8 ml of each of three glasses were taken at different times, recovering the dissolution medium after each sample taking. The amount of dissolved drug was determined by reading the absorbance of each of the samples at a wavelength of 265 nm. The results recorded are the average of three tablets. The procedure was similar to that used by some other authors [17].

RESULTS AND DISCUSSION

Flowability of raw materials

The first part of the development of a pharmaceutical product includes the characterization of the materials used in the formulation. This characterization is useful as a reference of the properties of these materials, in order to control their quality. In addition, the characterization of the raw materials allows the inference of the possible uses of the excipients in the pharmaceutical formulation.

Fig. 1 shows the flow properties of the powder of the materials used in the formulation of IBU tablets. The flow properties of the powder were determined by assessing the flow through an orifice and the compressibility index of the powder (CI). Both parameters agree to show intermediate rheological properties of IBU (CI=29.7%±3.3%), in comparison with those of PVP (CI=6.1%±1.2%) and CP (CI=42.9±0.6%). According to the powder compressibility index, both IBU as well as CP showed unsatisfactory rheological properties. As stated by the scale of flowability of powders, IBU displayed a poor powder flow, while CP showed a very poor powder flow.

The compressibility index was calculated according to:

$$\text{Compressibility index} = \text{CI} = 100 * [\frac{\text{Vo} - \text{Vf}}{\text{Vo}}]$$

Where the volume occupied by a given mass of powder when allowed to settle freely, Vo, is related to the volume of the same mass of powder after sedimentation by tapping, Vf. The latter is obtained after tapping the material until it no longer changes its volume [18].

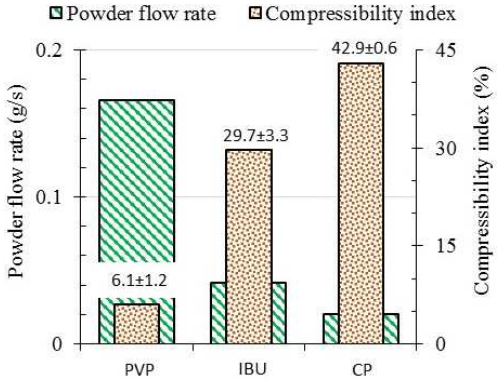

Fig. 1: Flow properties of the powders included in the formulation of ibuprofen tablets: ibuprofen (IBU), polyvinylpyrrolidone (PVP), calcium phosphate (CP), data given in mean±SD, n=5

Compactibility of raw materials

Fig. 2 describes the characteristics of compactibility of the active principle and that of the two excipients to be used. The curves of compactibility showed the increase of the tablet hardness as the compaction pressure increased. The PVP compactibility curve shows the experimental points, their standard deviation and the calculated regression. PVP showed the highest compactibility, followed by CP while IBU showed the lowest capacity to form coherent tablets.

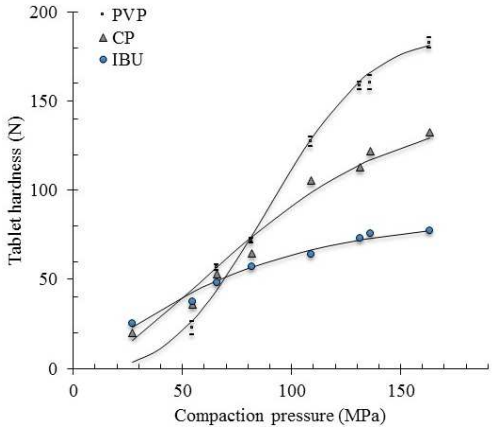

Fig. 2: Compactibility curves of raw materials included in the ibuprofen tablets: ibuprofen (IBU), polyvinylpyrrolidone (PVP), calcium phosphate (CP), data are given in mean±SD, n=3

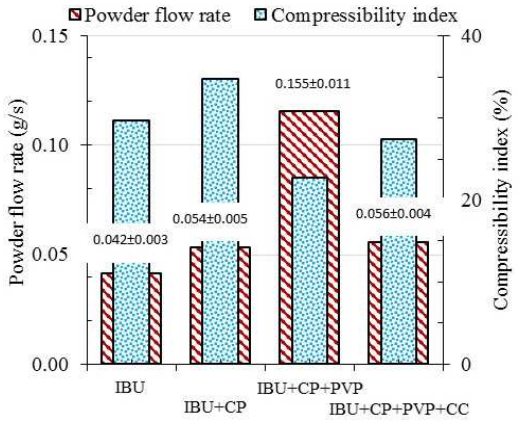

Fig. 3: Effect of formula composition on the flow properties of the powders of ibuprofen tablets: ibuprofen (IBU), polyvinylpyrrolidone (PVP), calcium phosphate (CP), croscarmellose sodium (CC), data given in mean±SD, n=5

Effect of the excipients on the flowability of ibuprofen

Fig. 3 shows the effect of the different excipients on the flowability of the IBU powder. The powder mixtures were composed of equal parts of the components while the CC was added in a proportion of 10%. As can be expected from the data of the excipients, CP increased the compressibility index of IBU, which means a lower flowability of the mixture. The subsequent addition of PVP reduced the compressibility index, improving the flow properties of the mixture. The final addition of CC to the aforementioned mixture again increased the compressibility index of the powder, reducing its flowability, to almost the same level as IBU alone. The poor flow properties of the powder blend generated by an excipient (CP) can be compensated by the addition of a more fluid powder (PVP).

Effect of the excipients on compactibility of ibuprofen

Fig. 4 shows the effect of the different excipients on the poor compactibility of IBU. This fig. displays the experimental points and the calculated regressions. In particular, the curve corresponding to the mixture of IBU-CP-PVP also includes the standard deviation of the experimental points. In all the following figures, the experimental points of at least one curve show their standard deviation. Although CP showed a better compactibility than IBU, its mixture did not appreciably change the compactibility profile. The drug maintained practically the same compactibility profile. However, the addition of PVP to the above mixture showed a considerable increase in the compactibility, due to the greater compactibility of the PVP and perhaps to its plastic behavior during compression. As a cellulose derivative, CC exhibits appreciable compactibility properties, although not as good as those of PVP. After its addition to the previous mixture, CC slightly reduced compactibility of the mixture. The observed effect of the excipients was related not only to its compactibility but also to its compacting mechanism. Blends of brittle materials with plastically deforming materials provide mixtures with greater compactibility.

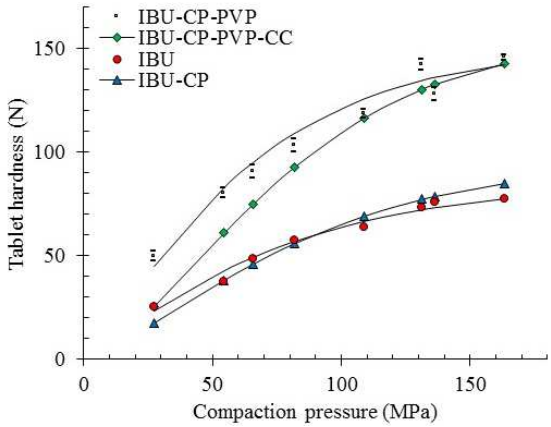

Fig. 4: Effect of formula composition on the compactibility curve of ibuprofen tablets: ibuprofen (IBU), polyvinylpyrrolidone (PVP), calcium phosphate (CP), croscarmellose sodium (CC), data given in mean±SD, n=3

Effect of the excipients on the release profile of ibuprofen tablets

The admixture of equal parts of IBU and CP exhibited the lower dissolution profile. The subsequent addition of PVP, producing mixtures of equal parts of each excipient and the drug, did not better the dissolution behavior. The drug release profile was similar to that of tablets without PVP (fig. 5).

The effect of PVP on the tablet dissolution had been observed earlier in oxytetracycline dihydrate tablets. Tablets that were obtained by wet granulation, with a PVP solution, showed that the increase in PVP concentration in the binder solution decreased the dissolution rate of the tablets [19].

Similarly, the caffeine tablets obtained using a wet granulation method and with PVP contents of 1, 2.5, 5 and 10% showed that the dissolution rate of the drug decreased with the increase in the proportion of the binder (PVP). The fastest dissolution of the active substance took place with the lowest amount of PVP (1% w/w) in the tablet [20].

However, the Addition of CC which is an excipient used as tablet and capsule disintegrant showing wicking and swelling abilities increased importantly the drug dissolution. IBU tablets containing 10% CC showed the higher dissolution rate of all tablets studied. As can be seen in fig. 5, the use of CC allowed the dissolution of approximately 85% IBU after 30 min dissolution.

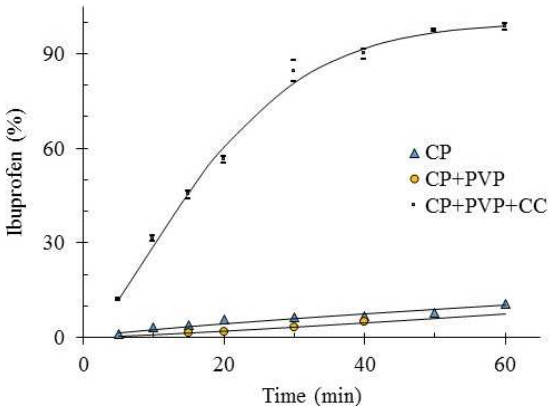

Fig. 5: Effect of formula composition on the dissolution profile of ibuprofen tablets obtained by applying a compaction pressure of 109 MPa: polyvinylpyrrolidone (PVP), calcium phosphate (CP), croscarmellose sodium (CC), data given in mean±SD, n=3

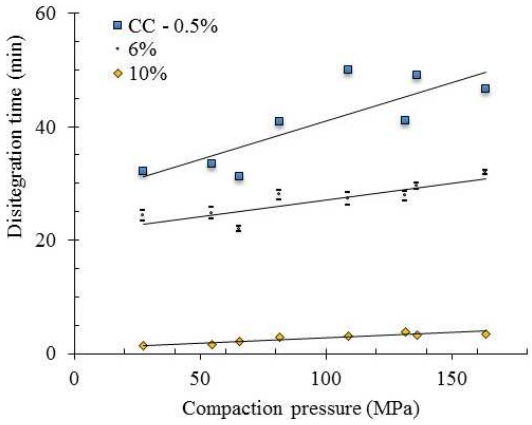

Fig. 6: Effect of compaction pressure and croscarmellose sodium (CC) content on the curve of disintegration time of ibuprofen tablets, data given in mean±SD, n=3

Effect of the excipients on the disintegration profile of ibuprofen tablets

The disintegration test is a test that helps in the optimization of manufacturing variables, such as compression force and dwell time. This test is also a parameter for quality control of the tablets and for checking the consistency between different batches.

In this part of the study, the effect of different compaction pressures and different proportions of the disintegrant CC on disintegration time of IBU tablets was investigated.

Fig. 6 shows the relationship between the compaction pressure and the disintegration time of the tablets containing different proportions of the disintegrant and equal parts of CP, PVP and IBU, added with 1% magnesium stearate. The points in fig. 6 are experimental and include, in the case of the formula containing 6% CC, the observed standard deviation for the individual values. These tablets were obtained by direct compression of the powder mixtures. As can be seen in the graph, there is a linear tendency to increase the disintegration time as the compaction pressure increases. This occurred in all the different formulations studied that contain different proportions of the disintegrant.

Fig. 7 shows a linear relationship between the proportion of CC in the formulations and the disintegration time of the tablets. The tablets studied were obtained by direct compression at a compaction pressure of 109 MPa.

The progressive increase in the proportion of the disintegrant gradually decreased the disintegration time of the tablets. This tendency was maintained at all the used proportions of the disintegrant. This occurred even though other studies have found an increase in the disintegration time of the tablets after exceeding a threshold proportion of 2 % CC for CP tablets. This threshold was attributed to the fact that increasing the amount of CC in the formulation also increased the hardness of the tablets [21]. In the same way, it was observed that increasing concentrations of the disintegrant Starch 1500 increased the percentage of Norfloxacin dissolved after 30 min, until a maximum is reached at about 12% Starch 1500. After this maximum, the dissolved Norfloxacin decreased. This behavior was considered as normal for a substance that acts promoting disintegration and, at the same time, works as a direct compression binder [22].

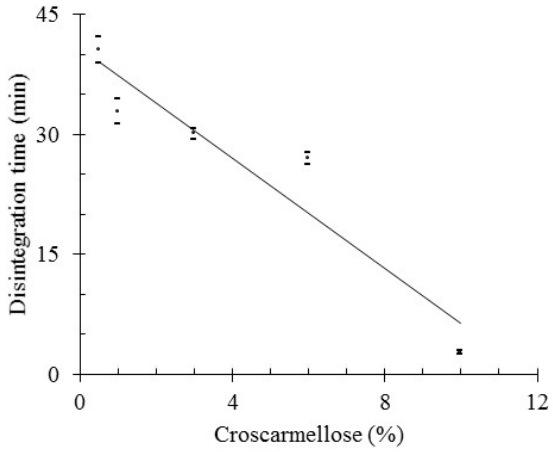

Fig. 7: Effect of croscarmellose sodium content on the disintegration time of ibuprofen tablets compacted at 109 MPa, data given in mean±SD, n=3

Effect of the excipients and processing on the flowability of ibuprofen

During the early stages of development of a pharmaceutical product, it may be important to understand the influence of the processing technique on the performance of the solid dispersion to ensure the selection of a suitable formulation and processing technique.

The flow properties of the mixture of equal parts of IBU, CP or PVP, added of 10% CC (fig. 3) could be improved by including an agglomeration operation. This operation included the formation of a solid dispersion of the drug. An alcoholic solution of the drug and PVP was embedded or deposited on CP, with and without subsequent addition of Aerosil. The solid dispersions were prepared by the solvent evaporation technique.

It can be observed in fig. 8 that the agglomeration by imbibition or deposition of solutions of IBU-PVP on CP decreased the compressibility index of the powder of the physical mixture. The addition of Aerosil, after the deposition of the solution, further decreased the compressibility index of the physical mixture.

Correspondingly, the powder flow rate of the physical mixture increased after preparation of the solid dispersion by imbibition or deposition on CP, increasing even more after deposition on CP plus the subsequent addition of Aerosil.

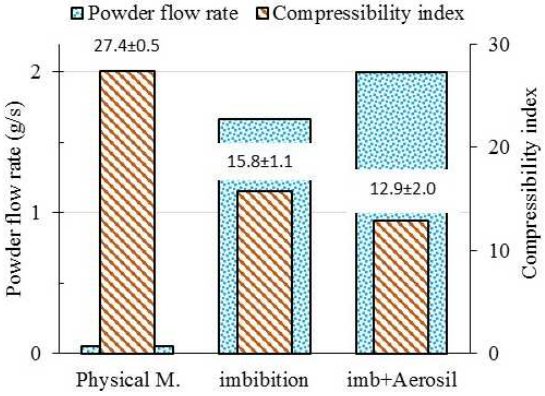

Fig. 8: Effect of preparation method and formula composition on the flow properties of powders of ibuprofen tablets, data given in mean±SD, n=5

Solid dispersions of furosemide showed similar results. The formulation of the solid dispersion included furosemide with polyethene glycol 6000 and microcrystalline cellulose as the adsorbent. The powders of the solid dispersions showed an angle of repose that gradually decreased as the proportion of the adsorbent increased [23].

Effect of the excipients and processing on compactibility of ibuprofen

In solid dispersions obtained by spray drying of a drug with PVP VA64 (1:2), it was observed that at any porosity of the tablets, the ground physical mixture showed a higher tensile strength compared to the solid dispersions. This was attributed to the loss of lattice and weaker forces between the glassy particles in the solid dispersions [24].

In contrast to the above, fig. 9 shows a greater compactibility of the mixtures obtained by the process of imbibition or deposition of a solution of the drug and PVP on CP, to obtain a solid dispersion. It is noteworthy that the tablets obtained with the solid dispersions behaved plastically, avoiding an accurate determination of their tensile strength. The tablets deformed slowly before breaking or simply reached the measurement limit of the hardness tester and did not break at all.

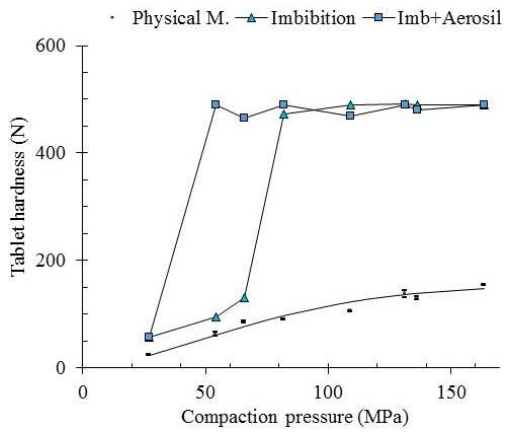

Fig. 9: Effect of formula composition and preparation method on the compactibility curve of ibuprofen tablets, data given in mean±SD, n=5

In the present case, it is considered that the material exposed to the compression forces is the PVP since it covers the adsorbent material. Therefore, the compaction capacity of the tablets can be referred to this material, which, as seen in fig. 2, has a high compaction capacity. However, the higher tensile strength of current tablets can also be attributed to the fact that PVP was mixed with a material such as CP that breaks up during compression. CP is widely fragmented, improving the filling of the empty spaces during compression, which leads to an optimum use of the compaction force [25].

The use of a combination of a material that deforms plastically with another that fragments should guarantee a greater compactibility. It seems that the mixture can have advantages over the individual materials. The inclusion of Aerosil in the formulation increased the previous effect facilitating the sliding of the particles during compression.

Effect of the excipients and processing on the release profile of ibuprofen tablets

It has been reported in the literature that the combination of a hydrophilic polymeric vehicle such as PVP could improve the solubility as well as the dissolution rate of poorly water-soluble drugs. The solid dispersions of IBU with PVP (1:1 and 1:2) showed a higher saturation solubility compared to pure IBU. The *in vitro* dissolution profiles of solid dispersion samples also showed greater dissolution than that of pure IBU. The solid dispersions of IBU with PVP showed a dissolution of approximately 65% after 60 min [26].

The greater dissolution of IBU was attributed to greater wettability due to the higher level of hydrophilicity obtained with the use of the polymeric vehicle. In addition, the results suggested that the greater dissolution of IBU from the solid dispersion was also due to the presence of the drug in an amorphous state, compared to the pure drug, where the drug was present in the crystalline state.

With vehicles other than PVP, it was observed that the rate of dissolution of IBU tablets was improved by the solid dispersions obtained with urea. The results of the characterization of the solid dispersions suggested that IBU partially precipitated in crystalline and amorphous forms after the preparation of the solid dispersion [27].

Contrasting with the higher dissolution from the above-mentioned solid dispersions, fig. 10 shows the dissolution profile of IBU tablets containing equal parts of PVP, CP and IBU, added of 10% CC. The release profile of the physical mixture attained almost 100% dissolution of the drug after 60 min. The tablets obtained from solid dispersions deposited on CP showed a dissolution after 60 min of 46%, while the tablets obtained from a solid dispersion deposited on CP plus the subsequent addition of 2% Aerosil showed a similar dissolution profile, the drug dissolved after 60 min was 42%.

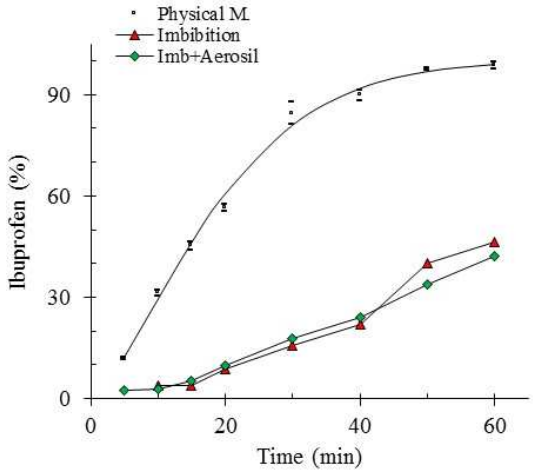

Fig. 10: Effect of formula composition and preparation method on the dissolution profile of ibuprofen tablets, data given in mean±SD, n=3

The processing of the physical mixture to deposit an alcoholic solution of the drug and PVP on CP or on CP plus the subsequent addition of Aerosil did not produce an increase in the dissolution of the drug from the tablets, but a decrease.

A similar situation was observed with solid dispersions of valsartan with HPMC. The solid dispersions showed film formation during the preparation. The formation of such a film made it difficult to release the drug from the formulation [28].

Similarly, tablets of solid dispersion formulations of the anti-HIV drug UC 781 with HPMC 2910 showed a slow dissolution process due to the gelation of the polymer. The drug was released slowly as HPMC 2910 dissolved in the medium. In this case, 90% of the drug dissolved after 4 h [29].

Although a higher dissolution rate of the solid dispersions of ibuprofen in PVP has been observed, this has been observed in samples in powder form [26]. Currently, the compaction process had a negative influence on the dissolution. The tablets obtained showed a high mechanical strength and behaved plastically, which significantly increased the disintegration time (fig. 11). The tablets obtained with solid dispersions formed a matrix of PVP that rather dissolves instead of disintegrating.

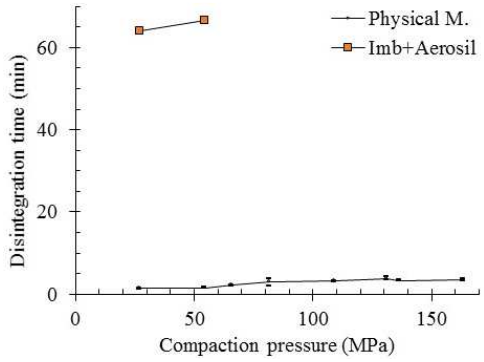

Fig. 11: Effect of formula composition and preparation method on the curve of disintegration time of ibuprofen tablets, data given in mean±SD, n=3

CONCLUSION

The characterization of the technological properties of the materials is useful to control their quality and allows the inference of their possible uses in the pharmaceutical formulation.

The technological properties of the materials are transferred to their powder mixtures and their tablets. The poor technological properties of a material can be compensated by adding another with better functionality.

The progressive increase in the proportion of CC up to 10% linearly decreased the disintegration time of the tablets, although other studies have found an increase in the disintegration time of the tablets after exceeding a threshold proportion of the disintegrant.

Unlike other reports, the formation of a solid dispersion of IBU-PVP, by imbibition or deposition on an adsorbent, did not improve the dissolution but deteriorated it. This was attributed to a significant increase in the compaction capacity of the agglomerated material, forming a matrix of PVP that dissolves rather than disintegrates.

The physical mixture was the best option to improve the dissolution, while the deposition of a solid dispersion of IBU-PVP on an adsorbent was the best option to improve the compactability and flow properties.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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