Towards a better understanding of thermally treated polycarbophil matrix tablets for controlled release

Sara Baldassari a, Paola Cirrinicone a, Giorgia Ailuno a, Giuliana Drava a, Silvia Arpicco b, Gabriele Caviglioli b a

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A B S T R A C T

Polycarbophil (POL), a polyacrylic acid cross-linked with divinyl glycol, is widely used in semisolid and solid dosage forms. When undergoing a thermal treatment in the range 120–160 °C, POL shows interesting morphological modifications, related to changes in physical properties, such as swelling of the powder granules, or hardening and matrix formation if included in the composition of a tablet. Thermal analysis conducted on POL highlighted a thermal event (Z) that can be correlated both to the shrinking of the powder granules and to the matrix formation in compacted POL powder. Modulated differential scanning calorimetry (MDSC) allowed to distinguish, inside event Z, an irreversible process overlapping with a reversible glass transition, attributable to the volatilization of residual solvents identified, through a complex TGA-FTIR-GC-MS interface, as acetate esters used for the polymer production as very fine powder. A specific interaction between acetates and POL, capable of stabilizing the polymer chains in a given conformation, was highlighted. The molecular rearrangement of the POL chains, following the volatilization of the solvent-stabilizers, is therefore ascribable to a loss of energetic stability of this material, which justifies the shrinking phenomena in the granules of the powder and the matrix formation when POL is compacted.

1. Introduction

A recent study on FDA approved products has shown that oral delivery remains the most appealing route and solid dosage forms the most used. Among solid dosage forms, conventional or modified drug release tablets are the most widely employed for orally administering drugs to adult patients (Zhong et al., 2018), thus justifying the never dormant vitality of research and innovation for the different aspects of these dosage forms.

Paramount medicinal products are formulated in tablets, some of which incorporating sophisticated drug-delivery mechanisms, as Viekira XR®, used to treat hepatitis, Spritam®, a tablet produced by 3D printing, and Rybelsus®, the first oral tablet containing a peptide to treat diabetes (Timmins, 2021); also biotech drugs can be formulated in oral tablets, for example Infliximab in the treatment of inflammatory bowel disease could reduce side effects related to systemic exposure (Gareb et al., 2021).

The characterization of tablet formulations has been enriched with new techniques as high-resolution real-time magnetic resonance imaging (MRI) (Quodbach et al., 2014) or terahertz pulsed spectroscopy and imaging (Al-Sharabi et al., 2020; Bawuah and Zeitler, 2021) and modelling-aided approaches are becoming essential tools in pharmaceutical tablet development (Cid et al., 2020; Han et al., 2018; Yang et al., 2018; Zhao et al., 2018). From the manufacturing perspective, with respect to the conventional methods, which have the merit of easy scale-up, innovative methods such as 3D printing (Norman et al., 2017), melt extrusion deposition 3D printing technology (Zheng et al., 2021) or ultrasound-assisted compression (Millán-Jiménez et al., 2017) are being implemented. New materials for tabletting are also another crucial investigational area but, in spite of the extensive research into material design for drug delivery published worldwide, very few new products are employed in manufacturing; anyway, well-known excipients have recently been better characterized and sometimes their use has been repositioned (Luo et al., 2021; Si et al., 2021; Tran et al., 2021; Wan et al., 2020).

Modified drug release tablets occupy the largest share market for oral...
route with respect to other dosage forms, with a stable increasing trend (Zhong et al., 2018), and among them matrix tablets are predominant, as also testified by the numerous articles published on the subject (Elgaied-Lamouchi et al., 2021; Naiserová et al., 2018; Nigusse et al., 2021; Vrbanc et al., 2021).

In this context, for some years our research has been focused on combining unconventional tablet excipients with alternative manufacturing procedures, in order to achieve specific drug release modification.

Within this subject, in 2013 we described a matrix tablet able to control drug delivery obtained by submitting direct compressed tablets containing polycarbophil (POL) and ethylcellulose (EC) to thermal treatment in the range 120–160 °C, which generates a swellable and unerodible matrix, with modifications of the tablet mechanical properties that make it able to sustain a tunable drug release for a long time, by an anomalous transport mechanism (Caviglioli et al., 2013). This study, which led to the development of new technologies exploiting the matrix thus obtained (Caviglioli et al., 2021; Caviglioli et al., 2018), indicated that POL is the hydrophilic matrix forming component, while EC, the lipophilic component, by acquiring plasticity during thermal matrix consolidation, is essential for controlling drug release.

As the experimental results ruled out that the matrix formation was caused by a chemical modification of the components, we hypothesized that the thermal treatment induced a physical modification of the cross-linked polycarboxylic acid, without investigating it.

In this article, based on new experimental evidences, we propose a possible mechanism explaining the thermal matrix formation, whose clarification may be of interest in the perspective of developing new technologies for health and pharmaceutical use.

2. Materials and methods

2.1. Materials

Polycarbophil (Noveon AA1) was supplied by Lubrizol (Wickliffe, USA). Other materials or solvents used were of analytical or HPLC grade.

2.2. Preparation of POL tablets

13 mm diameter and 300 mg POL tablets were prepared using an oledynamic Carver press, applying two different values of compaction force (2200 N × 1 min and 8800 N × 1 min).

2.3. Thermal treatment of POL powder and tablets

The thermal treatment of accurately weighed powder samples or tablets was carried out in glass tubes or in 40 mesh metal baskets, respectively, using the oven of a HP 5890 series II GC (Hewlett-Packard, Santa Clara, USA). The oven was heated at 30 °C/min, or lower heating rate, up to the treatment temperature, ranging from 120 ± 1 °C to 160 ± 1 °C, and was maintained under isothermal conditions for selected treatment times, ranging from 5 to 30 min. The oven temperature was then immediately reduced to 30 °C by the oven forced air cooling system.

2.4. Powder sieving

The POL powder was sieved through 63, 125, 250, 710 μm certified sieves (Giuliani, Torino, Italy) by a vibratory sieve shaker (AS200 Retsch GmbH, Haan, Germany).

2.5. Swelling study

The swelling behaviour of the POL tablets was studied using a dissolution bath (Premiere 5100 Distek, North Brunswick, USA) equipped with USP apparatus II. The tests were performed on 6 tablets at 37 ± 0.1 °C, with the rotation speed set at 50 rpm. The swelling medium was 700 mL of 0.05 M phosphate buffer at pH 7.2.

At each defined time t, the tablets were withdrawn from the medium, drained on a stainless steel wire net for 30 s and weighed. The swelling index (SI) was calculated according to the following equation:

\[ SI = \left( w_t - w_0 \right) / w_0 \times 100 \]  

with \( w_t = \) tablet weight at time t and \( w_0 = \) initial tablet weight, corresponding to the weight after thermal treatment in the case of treated tablets.

The swelling profile of thermal treated or untreated tablets was obtained by plotting SI vs. time up to 28 h.

2.6. Powder shrinking study

Granule shrinking was studied with a Nikon Alphaphot-2 YS-2 microscope equipped with a hot stage cell (FP82HT Mettler Toledo, Greifensee, Switzerland) and a 3 Mpixel live resolution digital microscopy camera (2300 Moticam, Motic, Hong Kong). Image analysis and measurements were performed with Motic Images Plus 2.0ML software. The hot stage was calibrated for temperature by measuring the melting point of standard benzoic acid and caffeine. The samples, about 1 mg each, were placed on a microscope slide and heated from 30 °C to 260 °C at different heating rates. Images of the granules were captured every minute and shrinking was calculated as the percentage of residual cumulative granule planar surface (RCGPS) with respect to the size measured at the initial condition of 50 °C.

2.7. Thermal analysis

Differential scanning calorimetry (DSC) was carried out using a DSC-7 instrument managed by Pyris software (Perkin Elmer, Waltham, USA). The instrument was calibrated for temperature and enthalpy with indium and zinc and the samples were crimped in aluminum pans (type Perkin Elmer kit number 0219–0041). Amounts of 3–5 mg of powder, accurately weighed, were heated from 50 to 250 °C at different heating rates while being purged with nitrogen (20 mL/min).

Thermogravimetric analysis (TGA) was performed using a TGA7 instrument (Perkin Elmer, Waltham, USA). The samples (5.0 mg) were analyzed under nitrogen atmosphere, at different heating rates.

Modulated DSC (MDSC) was obtained using DSC 8500 (Perkin Elmer, Waltham, USA) managed by StepScan™ software. Measurements were performed on samples of about 20 mg, with a 2 °C step at heating rate of 5 °C/min, followed by an isothermal step equilibration of ±0.01 mW.

TL9000 Evolved Gas Analysis (EGA) system was used to perform TG-IR-GC/MS analysis on a sample by moving the off gases to the FT-IR (Frontier FT-IR, Perkin Elmer, Waltham, USA) and GC/MS (Clarus SQ 8, Perkin Elmer, Waltham, USA) after their evolution in the TGA. The TG-IR data consist of a sequence of spectra, acquired at intervals of approximately 8 s. The transfer line runs at 350 °C and uses pumps and mass flow controllers to deliver a precise flow of gas to the GC/MS. Chromatography was performed at the following conditions: GC Column Elite-5 MS 30 m × 0.25 mm × 0.25 μm; injector temperature 280 °C; helium as carrier gas; initial oven temperature 35 °C for 3 min, then increased to 290 °C at 10 °C/min, and maintained for 3 min; amu ranging from 15 to 500 m/z; scan duration 0.10 s. NIST was used as MS database.

HyperDSC® was performed on a double-furnace hyper-enabled DSC 8500 (Perkin Elmer, Waltham, USA) with liquid nitrogen cooling at 200 °C/min.

2.8. Weight loss

Tablets and powder were weighed before and after thermal treat-
ment and the weight variation, induced by the treatment, was expressed as weight loss:

\[ \text{weight loss} = \frac{(w_i - w_d)}{w_i} \times 100 \]  

(2)

with \( w_d \) = dry sample weight and \( w_i \) = initial sample weight.

2.9. Scanning electron microscopy (SEM)

For SEM, the samples were placed on a stub using double-sided conducting tape and coated with a thin (approx. 15–20 nm) gold layer by sputtering in an argon atmosphere. The coated samples were examined at an acceleration voltage of 20 kV (Steroscan 440, Leica Cambridge, Ltd., Cambridge, UK).

2.10. Water content determination

Water content was assayed by Karl–Fischer (KF) titration with a DL38 apparatus (Mettler-Toledo, Greifensee, Switzerland) on accurately weighed (50.0 mg) powder samples obtained from tablets ground in a mortar. The titration solution was Hydranal composite 5, standardized with sodium tartrate dihydrate (Merck, Darmstadt, Germany); the titration medium was stirred at 500 rpm with a 30 s dispersion waiting time. The results were expressed as percentage of water contained in the powder sample. The measurements were performed in triplicate.

3. Results

3.1. Thermal treatment of POL

SEM micrographs allowed to observe a clear change in morphology of the POL granules submitted to thermal treatment as compared to the native polymer powder (Fig. 1).

The powder of untreated POL consists of hemispherical structures aggregated to form large “cauliflower” structures; after heat treatment, many of these aggregates resulted to coalesce into larger structures and a reticular design began to be discernible.

3.2. Swelling properties

Physical modifications were evident on compacted POL powder submitted to thermal treatment, as evidenced in the swelling study: when placed in pH 7.2 aqueous medium, POL tablets progressively increased in size, until turning into a transparent gel disc (Fig. 2).

The size increase continued up to 28 h, as shown by the swelling index plot in Fig. 3, a notable result also considering that untreated tablets swelled much less (maximum SI = 100%) and showed erosion signs already at the first sampling time. The swelling properties and resistance to erosion were directly related to the force of compression used in the tabletting process (Fig. 3).

The highest swelling index (5320% after 28 h in phosphate buffer at 37 °C) was obtained using a tabletting force of 8800 N (13 mm diameter, 300 mg weight). By swelling, these thermal treated tablets increased their diameter to more than 48 mm, becoming monolithic cylinders featuring high optical transparency (Fig. 2).

3.3. Powder shrinking

The POL powder, when heated in the thermal range from 120 °C to 160 °C, showed an irreversible granule shrinkage. The shrinking was tracked by hot stage microscopy equipped with a digital camera: during the heating, images of the granules were captured every minute and shrinking was calculated as the percentage of residual cumulative granule planar surface (RCGPS), with respect to the original size at 50 °C.

Fig. 4 shows the shrinking curve, where each point is the mean value computed by observation of differently sized granules submitted to selected isothermal treatments (Fig. 4 right), and the comparison between the shrinking profiles obtained by heating two single granules from two different POL batches up to 250 °C (Fig. 4 left). From these plots we deduced that the shrinkage reaches the maximum value at 160 °C; over 200 °C, the modification in percentage of RCGPS was attributed to the incipient thermal degradation of POL.

The maximum shrinking of the powder granules (Figs. 5-6) is related to the temperature of the treatment applied, within the range 130–160 °C; moreover, the shrinking is neither influenced by the heat rate used to reach the isothermal curing condition, as shown in Fig. 7, nor by the granule size (Fig. 8).

3.4. Thermal studies

A thermal event observed in the DSC trace of POL, occurring around 130.6 ± 0.5 °C and consisting in a change of heat capacity (\( \Delta C_p = 0.45 \pm 0.07 \) J/(g °C)), has been associated to the morphological change occurring in POL powder (granule shrinking) or to the matrix formation in tablets containing POL when undergoing thermal treatment. This event has been attributed, provisionally, to a glass transition and indicated as Z event.

However, while POL shrinkage or matrix formation are irreversible processes that occur only when untreated POL is heated above 120 °C, the Z event is partially reversible, as it is still detectable in the DSC trace of POL samples already submitted to thermal treatment (Fig. 9).

Therefore, the Z event seems to be the combination of a reversible

Fig. 1. SEM micrographs: (a) Untreated POL; (b) POL treated at 150 °C × 15 min.
process, such as a glass transition, and of an endothermic overshoot, often hardly detectable in the DSC trace of untreated POL samples, probably related to the irreversible process.

The Z event is independent on the water content of POL batches: actually, it was still evident in batches completely dried. It is maintained also in POL samples stored at high RH value and after more than two years storage at RT.

TGA (Fig. 10) and HSM observations revealed that the first endothermic peak in the DSC trace of untreated POL was related to the water content of POL, as confirmed by KF water determination, and that POL degradation started over 200 °C. Interestingly, TGA disclosed a tiny weight loss in correspondence of the Z event, always lower than 0.4% (w/w) and present in all the analyzed batches.

By a stepwise MDSC (Drzezdzon et al., 2019; Ford and Mann, 2012; Knopp et al., 2016) (Fig. 11) it was possible to confirm that the Z event resulted from the overlapping of a glass transition (reversible phenomenon) and an irreversible transition.

In addition, also a hyper-DSC (Ford and Mann, 2012) (Fig. 12) performed at 200 °C/min on POL samples allowed to observe two distinct thermal events in untreated POL (Fig. 12 b) and only one (Fig. 12 c) in treated POL attributable to the reversible modification.

By EGA, it was possible to acquire simultaneously the FT-IR spectra (Fig. 13) and GC–MS chromatogram (Fig. 14) of the gas evolved in correspondence of the Z event and of the small weight loss occurring in the range 130–150 °C. It was identified as a mixture of ethyl acetate and isopropyl acetate in a chromatographic area ratio of 95:5.

3.5. Tablet drug release profiles

One successful application of the described technology is the preparation of formulations for controlled release of drugs, principally suitable for oral use but potentially applicable to other administration ways such as vaginal. On this purpose, the polyacrylic polymer is mixed with the active substance and other excipients, necessary to decrease the release rate of hydrophilic molecules, such as ethylcellulose; then, the powder mixture is compressed and thermally treated at a temperature higher than 130 °C for an appropriate time. The obtained tablets, if subjected to dissolution test in aqueous medium, result very resistant to erosion and able to control the release of the active with kinetics
approximating zero-order.

In one case we conceived a formulation containing propranolol hydrochloride (20% w/w, BCS Class I), POL (13.3% w/w), EC (46.7% w/w) and dicalcium phosphate (20% w/w). The tablets were treated at 150°C for 15 min and underwent a dissolution test performed in phosphate buffer 0.05 M pH 7.2 for 25 h; untreated tablets were used as controls. As shown in Fig. 15 (left), the two release profiles, initially superimposed, diverged at 10 h, with the treated tablets following zero order kinetics up to the end of the test.

In another batch of tablets propranolol hydrochloride was replaced with gliclazide (BCS Class II), which was mixed with POL (20% w/w), EC (30% w/w) and dicalcium phosphate (30% w/w). In this case (Fig. 15 right) we achieved a modulation of the release rate by changing the thermal treatment conditions: by prolonging the treatment from 5 to 15 min the rate decreases, with kinetics approximating zero order for up to 25 h.

In both cases, the effect of the heat treatment on the formation of the matrix was clearly visible from the swelling of the units for the formation of a compact gel crown (Fig. 16).

4. Discussion

Polycarbophil is a polyacrylic acid cross-linked with divinyl glycol. It
is insoluble in water, but swellable in aqueous medium, and features remarkable bioadhesiveness (Grabovac et al., 2005; Lee et al., 2000; Russo et al., 2016; Singh, 2009).

It is mainly applied as gelling agent on semisolid formulations for local treatments, but it is also employed as excipient in solid dosage forms (Abdelbary et al., 2010; Baus et al., 2019; Biglia et al., 2010; Carelli et al., 1997; Huang et al., 2016; Kenechukwu et al., 2018; Sinka et al., 2019; Yang et al., 2018).

When submitting POL to thermal treatment in the range from 120 to 160 °C, we observed a shrinkage in powder granules and an increase of tablet hardness in powder compacts, possibly due to a sintering process (Mohanty, 2011). Notably, the modifications induced by the thermal treatment influence markedly the swelling properties of POL, which can be exploited, as highlighted in paragraph 3.5, to control the drug release in solid dosage forms (Figs. 15, 16).

The observed powder shrinking is an irreversible process, kinetically...
depending on the temperature of treatment (Figs. 4, 5). The Z event, appreciable in the DSC trace in the thermal range considered, is associated to the above described morphological and functional changes in this cross-linked polymer. This event, characterized by a change of heat capacity much higher than the one normally associated to the transitions of other polymeric excipients, such as cellulose ethers (0.03–0.10 J/(g ◦C)) (Gómez-Carracedo et al., 2003), is attributable to a glass transition often accompanied by a relaxation endotherm. Indeed, a glass transition is often evident in many cross-linked acrylic polymers, like carbopol, at approximately 130–140 ◦C and can be related to the degree of cross-linking (Gómez-Carracedo et al., 2004).

Yet, unlike glass transition of carbopol, the Z event of POL is not influenced by moisture content and is detectable in samples already submitted to thermal treatment. The absence of the Z event in POL calcium salt, and the related changes of rheological and mechanical properties of the polymer, indicate that the event is associated with a change in polymer chain mobility: actually, the calcium salt formation increases the rigidity of the polymeric network, because less than two monomer units remain free between adjacent ionic cross-linkers (Gómez-Carracedo et al., 2004).

MDSC (Ford and Mann, 2012) allowed to establish that the Z event consists in two overlapped phenomena and the deconvolution of this complex transition highlighted that the total heat flow measured was due to a change in specific heat capacity combined with an irreversible enthalpic event. While the reversible event was related to the above cited glass transition, the irreversible enthalpic event had to be elucidated.

At the temperature corresponding to the Z event, the irreversible phenomena, specifically morphological changes as powder shrinking or hardening in the tablet, are accompanied by a very small weight loss (≤ 0.4% w/w). In fact, the weight loss is no longer measurable in samples already submitted to thermal treatment and is therefore related with the irreversible enthalpic event; the thermal coincidence of Z event with the weight loss supports the hypothesis of a causal relationship between them.

To study the nature of the weight loss, we submitted different batches of POL, as such or thermally treated, to EGA, analyzing simultaneously the gas evolved during a TGA measurement by means of connected FT-IR and GC–MS instruments.

The gas evolved during the weight loss occurring in the range 130–150 ◦C, in correspondence of the Z event (Fig. 10) was identified by IR (Fig. 13) and MS spectra comparison (Fig. 14), as a mixture of ethyl acetate and isopropyl acetate in a chromatographic area ratio of 95:5.

This result was validated by submitting an untreated POL powder sample to residual solvent extraction at room temperature followed by GC–MS analysis, which revealed the presence of the acetates in the aforementioned ratio, allowing to exclude the formation of ethyl acetate and isopropyl acetate induced by the thermal treatment.

We have linked the presence of the residual solvent to the manufacturing procedure used, as reported in a patent (Sehm, 1992), which describes a method to obtain POL as powder with average particle size of less than 10 μm, without grinding. In this patent, the inventors disclose the use of alkyl acetates, and in particular ethyl acetate, as reaction solvent, to avoid the formation of a solid chunk. This drawback occurred with a previous procedure performed in aqueous medium, where it was necessary to grind the final product, a dried chunk, to obtain the powder with the desired particle size.

In this useful manufacturing procedure, acetate solvent plays a fundamental role in the production of the polymer in the powder state. To date, the presence of solvent traces in this polymer was simply considered from the point of view of the quality of the product, especially for pharmaceutical use. In fact, USP43-NF38 POL monograph reports that ethyl acetate content must not exceed 0.45% w/w.

These considerations highlight a specific interaction between acetates and this polyacrylic polymer, capable of stabilizing the polymer chains in a given conformation. The modification undergone by POL during the thermal treatment could be due to a molecular rearrangement of the POL chains, following the volatilization of the acetates at temperatures above 130 ◦C. The residual solvent, enclosed in powder granules, might act as a physical stabilizer of the polymeric molecular...
Fig. 12. Hyper DSC traces obtained at heating rate of 200 °C/min: (a) Untreated POL sample; (b) Dried POL sample; (c) Thermal treated POL sample.

Fig. 13. TGA-FTIR-GC–MS interface analysis: IR identification of ethyl acetate in evolved gas corresponding to the weight loss occurring at 150 °C during TGA of a POL sample.
structure. At the temperature close to the glass transition, the acquired chain mobility favours the release of the solvent as a vapour, which justifies the shrinking phenomena observed in the powder, while after compaction the matrix formation could be explained by the increased chain mobility combined with the plasticizing effect of the acetate vapour evolved by the material. As a matter of fact, POL powder, that has already undergone complete shrinking by thermal treatment, loses irreversibly the ability to form the matrix by compaction and subsequent heat treatment. Moreover, it has been demonstrated that a thermally treated POL powder sample, if soaked in ethyl acetate, does not recover the irreversible enthalpic event, suggesting that the specific interaction between the POL chains and the acetates occurs only in the course of the polymer synthesis.

Several authors have applied heat treatments (Azarmi et al., 2005; Azarmi et al., 2002; Kubova et al., 2017; Zhang et al., 2016) causing sintering phenomena to pharmaceuticals but, to the best of our knowledge, this mechanism appears unique in its specificity. It should be emphasized that, with the conventional analytical methods currently available, the amount of residual solvent responsible for the described
event is too low to perform a better characterization of the specific molecular interactions in a cross-linked, and therefore amorphous, polymer.

As shown, the technology applied to POL/EC tablets resulted suitable for achieving extended drug release, coming alongside widely used matrices, including polysaccharides or cellulose ethers, as methylcellulose or hydroxypropyl methylcellulose (HPMC), and might represent an advantageous alternative to these technologies, to overcome some of their drawbacks. For example, it is acknowledged that HPMC performance can be affected by incompatibilities with drugs, electrolytes and other small molecules; specifically, incompatibilities have been reported with small aromatic moieties present in many drug molecular structures (e.g., non-steroidal anti-inflammatory, bronchodilator, anti-Parkinsonian agents) (Banks et al., 2014). Another peculiar aspect of this methodology is the remarkable mechanical resistance and, therefore, low erosion of the gel layer in the swollen matrix.

On the other hand, like all technologies, this one is not devoid of limitations: the main one is it can be applied only to non-thermally agencies in the public, commercial, or not-for-profit sectors. In other words, in gaseous form. A consequent change in polymer chain conformation, with small aromatic moieties present in many drug molecular structures (meth)acrylates on dissolution behavior of very soluble drug from hypromellose polymer. Adv. Drug Deliv. Rev. 57, 1713–1723. Hansen, M.R., 2017. Predicting oral disintegrating tablet formulations by neural network techniques. Asian J. Pharm. Sci. 12, 336–342. Huang, W., Zhang, N., Hua, H., Liu, T., Tang, Y., Fu, L., Yang, Y., Ma, X., Zhao, Y., 2016. Preparation, pharmacokinetics and pharmacodynamics of ophthalmic therosensitive in situ hydrogel of betaxolol hydrochloride. Biol. Photocancer. 83, 107–113. Kenechukwu, F.C., Attama, A.A., Ibezin, E.C., Nnamani, P.O., Umeyor, C.E., Uronnachi, E.M., Gugu, T.H., Momoh, M.A., Ofokansi, K.C., Akpa, P.A., 2018. Surface-modified mucosal microgels as a controlled release system for microneedle arrays to improve localized treatment of vulvovaginal candidiasis. Eur. J. Pharm. Sci. 115, 358–375. Knopp, M.M., Loberg, K., Elder, D.P., Rades, T., Holm, R., 2016. Recent advances and potential applications of modulated differential scanning calorimetry (mDSC) in pharmaceutical development. Eur. J. Pharm. Sci. 87, 164–177. Kubova, K., Pecek, D., Haseroxová, K., Doležel, P., Pavelková, M., Vysoulj, J., Muselík, J., Vetchy, D., 2017. The influence of thermal treatment and type of insoluble poly (meth)acrylates on dissolution behavior of very soluble drug from hypromellose matrices evaluated by multivariate data analysis. Pharm. Dev. Technol. 22, 206–217. Lee, J.W., Park, J.H., Robinson, J.R., 2000. Biodegradable-based dosage forms: the next generation. J. Pharm. Sci. 89, 865–885. Luo, Y., Hong, Y., Shen, L., Wu, F., Lin, X., 2021. Multifunctional role of polyanvypyrrolidone in pharmaceutical formulations. AAPS PharmSciTech 22, 34. Millan-Jiménez, M., Galdón, E., Ferrero, C., Caraballo, I., 2017. Application of ultrasound-assisted compression in pharmaceutical technology. Design and optimization of oral sustained-release dosage forms. J. Drug Deliv. Sci. Technol. 42, 119–125. Mohanty, C., 2011. Sintering technique in pharmaceutical sciences: a brief review. Int. J. Pharm. Technol. 3, 799–806. Naisarova, M., Kubová, K., Vysoulj, J., Pavolová, S., Vetchy, D., Urbanová, M., Brus, J., Vysoulj, J., Kulich, P., 2018. Investigation of dissolution behavior HPMC/
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