Granulation fluid and Pore former on morphology, Mechanical test and Dissolution Rate of microcrystalline cellulose base Alpha-lipoic acid pellet formulation on improving cardiovascular performance

Líquido de granulación y formador de poros sobre morfología, prueba mecánica y velocidad de disolución de la formulación de pellets de ácido alfa lipoico a base de celulosa microcristalina para mejorar el rendimiento cardiovascular

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Abstract

Background: Slow conversion and dissolution of microcrystalline cellulose (MCC) extrudates is a weakness for water-insoluble drugs. This study aim was to determine the growing holes of the granulation liquid affect the physical and chemical properties of alpha-lipoic acid (a lipophilic substance) and its effect on improving cardiovascular performance.

Methods: Pellets containing alpha-lipoic acid, MCC and forming pores were prepared using a non-aqueous granulation liquid by extrusion-spheroidization method, and the micrometric and mechanical properties and drug release of alpha-lipoic acid with effects on cardiovascular function were investigated. The entire formulation of the produced medicinal compounds had pellets of appropriate spherical shape and size.

Results: The dissolution power and elastic modulus of the pellets change with the addition of cavitation agent and granulating liquid, and the dissolution rate of alpha lipoic acid. When the pore agent and the new granulation liquid are used together, the creation of a more porous matrix, faster dissolution, and a significant increase in the solubility of the drug, all lead to an increase in the dissolution rate of the drug and a better effect of the drug on the function of the target organ, and improve the function of an organ such as cardiovascular. Combined modification of these factors increased the disintegration of hydrophobic drugs.

Conclusion: new extrusion-spheronization technique can be used to enhance the solubility of alpha-lipoic acid in the form of multi-particle dosage in improving drugs effect on cardiovascular performance and this technique can also be used with other medications that are not very water-soluble.

Keywords: Alpha-lipoic acid pellets, Dissolution rate, Pore former, drug solubility, granulation fluid, cardiovascular performance.

Resumen

Introducción y antecedentes. La lenta conversión y disolución de los extruidos de celulosa microcristalina (MCC) es una debilidad de los fármacos insolubles en agua. El objetivo de este estudio fue determinar que los agujeros de crecimiento del líquido de granulación afectan las propiedades físicas y químicas del ácido alfa lipoico (una sustancia lipófila) y su efecto en la mejora del rendimiento cardiovascular.

Métodos. Se prepararon gránulos que contenían ácido alfa lipoico, MCC y que formaban poros utilizando un líquido de granulación no acuoso mediante el método de extrusión-esferoidización, y se investigaron las propiedades micrométricas y mecánicas y la liberación de fármaco del ácido alfa lipoico con efectos sobre la función cardiovascular. Toda la formulación de los compuestos medicinales producidos tenía gránulos de forma y tamaño esféricos apropiados.

Resultados. The dissolution power and elastic modulus of the pellets change with the addition of cavitation agent and granulating liquid, and the dissolution rate of alpha lipoic acid. When the pore agent and the new granulation liquid are used together, the creation of a more porous matrix, faster dissolution, and a significant increase in the solubility of the drug, all lead to an increase in the dissolution rate of the drug and a better effect of the drug on the function of the target organ, and improve the function of an organ such as cardiovascular. Combined modification of these factors increased the disintegration of hydrophobic drugs.

Conclusión. Se puede utilizar una nueva técnica de extrusión-esferonización para mejorar la solubilidad del ácido alfa lipoico en forma de dosis de múltiples partículas para mejorar el efecto de los fármacos sobre el rendimiento cardiovascular y esta técnica también se puede utilizar con otros medicamentos que no son muy solubles en agua.

Palabras clave: Gránulos de ácido alfa lipoico, velocidad de disolución, formador de poros, solubilidad del fármaco, líquido de granulación, rendimiento cardiovascular.

Introduction

The breakdown of drugs in the digestive system is a stimulus that determines the speed of absorption of drugs in the form of immediate release [1, 2]. An eight-carbon organosulfur fatty acid called lipoic acid is produced from caprylic acid (also known as octanoic acid) [3, 4]. ALA is a biopharmaceutical categorization system (BCS) that is lipid-soluble [5-7]. BCS II has a low in vivo solubility, is not gastrically stable, passes the hepatic barrier, has a bioavailability of just approximately 30%, and has a brief half-life [8]. ALA is less absorbed after various meals. The blood-brain axis can be crossed by ALA [9]. Distal symmetrical polyneuropathy (DSP) and type 2 diabetes both include neuropathic symptoms and problems that can be effectively treated with ALA [10, 11]. This medication's intestinal absorption is subpar. Several techniques have been employed to speed up the dissolution and subsequent oral absorption of poorly soluble medicines, including micronization, salt creation, cyclodextrin complexation, solid liquids, and solid formation [12]. Due to the increased surface area, the combination of drug formulations in multiparticulate doses has recently been employed as a method to enhance the rate of drug disintegration [13]. Due to its biological and technological benefits, such as reduced gastrointestinal discomfort, decreased chance of dosage emptying, improved flow rate, decreased fragility, smaller particle size distribution, and simplicity of encapsulation, pellets have garnered increased interest among the multiparticulate oral forms [14]. The preferred approach for the commercial manufacturing of dense spherical pellets has been spherical extrusion [15]. The most often employed auxiliary and palletizing material in the manufacture of pellets using the ring extrusion method has been MCC with suitable rheological characteristics in the wet condition [16]. However, this substance has some application patterns, such as its usage as an adjuvant, particularly when making pellets with medications that aren't very water-soluble. The reduction in the rate of drug degradation is the major drawback of employing MCC in pellet form. Pellets are compressed during drying, which reduces porosity and prevents deterioration. Its poor disintegration rate is mostly due to this mechanism [17]. Pellet formulation components typically contain a medicine, a filler or assistance in pelleting, and, if necessary, other materials such as adhesives and lubricants. To attain the appropriate wet mass qualities, some excipients may need to be modified. To enhance the rate of dissolution of pharmaceuticals in pellet formulations, MCC has been replaced with soluble excipients such as low-molecular-weight lactose and chitosan [18], pectinic acid [19], or PEG or extra-processed MCC [20]. Furthermore, supersolvent substitution in the pellet structure has recently been employed to resolve the difficulty associated with the usage of MCC [21]. Most researches have shown that the deformation of the components used to make the pellets may have a significant effect on the shape, size, size distribution and other physical and mechanical properties of the pellets and hence affect the processes mentioned above. To present this study in order to investigate the effect of pore-forming agent and granulation liquid alone or in combination on the dissolution of alpha-lipoic acid when used in the extrusion-spheronization process, on the effectiveness of therapeutic interventions in improving and the appropriate effect of the drug on cardiovascular performance.

Materials and methods

Material

MCC from Darupakhsh (Tehran, Iran), polyethylene glycol (PEG) 200 and (Merck, Darmstadt, Germany), HPMC 6cp from Darupakhsh (Tehran, Iran), croscarmellose from Darupakhsh (Tehran, Iran), and sodium dihydrogen phosphate from Merck (Darmstadt, Germany) were utilized in this investigation.

Preparation of pellets

Table 1 shows the several formulations of pellets containing 30% alpha-lipoic acid. After mixing the drug and MCC powders for 10 minutes in a planetary mixer, granulating solutions including ethanol, hydroxypropyl methyl cellulose, and water were added until a wet mass was created, and lastly, PEG200 as a pore-forming agent was added. At 100 rpm, the wet mass was fed through an axial screw extruder (Dorsa, Iran) with a 1 mm screen. The extruded mass was rounded for 3 minutes in a spheronizer (Dorsa, Iran) using a cross-hatched plate at 1000 rpm. The pellets were dried for 15 hours at 40°C in a standard oven (Memmert, Germany) and then stored in firmly sealed containers.

Sieve analysis and yield of pellets

The pellets were sieved using a sieve shaker (Erweka, Germany) for 10 minutes using a nest of standard sieves (1700, 1400, 1180, 1000, 710, 500, and 335 m). The pellets retained on each sieve were weighed, and the data obtained was used to generate a frequency distribution. The size range of 710–1400 m was determined to be suitable, and the weight of pellets in this range is given as palletization yield.

Study on morphology of pellets

A light microscopic image interpretation was used to examine the design and surface of the pellets. To lessen the influence of shadows in picture processing, 30 pellets of each formulation were put on black backdrops, and a high-cold light source was employed. The image analyzer was made up of a computer system linked to

a color video camera (Sony, Japan) and an 8.5-magnification stereomicroscope (ZSM-1001-3E, Iran). Scion image analysis software (Scion Image for Windows, Release Beta 4.0.2) was used to examine the digitized images. The balls' area (A), perimeter (Pm), and ferrite diameter were measured, and two form factors were derived [16, 22]:

Aspect ratio (AR) = dmax/dmin (1)

Sphericity = 4πA/Pm2 (2)

where dmax and dmin were the longest and shortest Feret diameters measured, respectively.

Scanning electron microscopy (SEM)

SEM was used to analyze the morphology of the surface of the pellets. The pellets were mounted on an aluminum stub, sputter-coated with a thin coating of silver using a sputter coater (Polaron, UK) in an argon environment, and then inspected using a SEM (LEO1455 VP, UK).

Mechanical tests

The crushing strength (CS; force required to shatter the pellets) and elastic modulus (EM) of 15 pellets (710-1000 m size fraction) were evaluated using universal testing equipment equipped with a 1 kN load cell (WDW, China). The upper moveable plate was programmed to move at 1 mm/min. A computer system connected to the device was used to generate CS, EM, and force-displacement graphs.

Friability

The friability test determines the mechanical and physical strength of the pellets. A friability test device (CJY-300B, KangPu, Hunan, China) with ten grams of pellets was spun at 25 rpm for four minutes. The pellets were then removed, dusted, and precisely weighed to determine the weight reduction.

Disintegration test

Pellets were disintegrated at 370.5 °C in 0.1 N hydrochloric acid (HCl) using a disintegration test device (Model DT3, SOTAX, Switzerland) without discs. At the bottom of the disintegration tube, a 500-m mesh fabric was put. Each pellet formulation was tested with 100 milligrams. The end point was chosen as the period for pellet breakup.

Analysis of ALA Content

1 gram of pellets was ground into a fine powder using a pestle. The powder that resulted was accurately weighed and dissolved in 50 mL of methanol. A milliliter of the aforesaid solution was then diluted to 25 mL and filtered using a 0.45 mm filter. An HPLC technique described below was used to determine the ALA content in the filtrate.

Quantitative Determination of ALA by HPLC Method

A HPLC technique was used to determine the amount of lipoic alpha acid in the pellet, and the relative standard deviation for successive injections of the standard solution was kept to a maximum of 2.0%. Phase of mobility: Methanol: 0.005MP hosphate solution: acetonitrile (1160:920:180). Use the phosphoric acid solution to get the pH to 3.0-3.1. Then filter and degas the mixture. Chromatography conditions include the following: injection volume: 20 microliters, UV detection at 215 nm, flow rate: 1.2 mL/min, and column temperature: 35 °C.

Dissolution studies

Three precisely weighed samples (n=3) containing 300 mg of alpha-lipoic acid were put through a dissolve test in a USP apparatus II revolving at 50 rpm utilizing automated dissolution testing equipment (Pharma Test, Germany). The dissolve medium was a 900-mL phosphate buffer solution with a pH of 7 and a temperature of 37 °C. Samples were automatically collected at regular intervals and measured using an HPLC chromatography technique at 215 nm.

Results

In order to create a uniform plastic body that remains uniform throughout the extrusion process, the wet body must be appropriately formulated for ring-form extrusion, and the extrudates must not exhibit any evidence of adhesion. For discrete pellets to form without creating a lot of tiny particles, the extrudates need to have the right mechanical makeup and brittle behavior during ringing. For instance, alpha-lipoic acid is prepared by utilizing a basket extruder and a spheronizer with water, ethanol, and mixt. do. with or without the addition of PEG 200 (0–5% w/w) and with a set quantity of CCS (10% w/w). The granulation fluid will consist of ethanol/water and hydroxypropyl methylcellulose (20–35% w/w). Preliminary studies have shown that increasing the concentration of PEG200 as a pore forming agent affects the appearance and properties of the obtained pellets. In the preparation of pellets, all compounds containing HPMC 6cp showed good extrudability, and increasing the binder concentration up to 5% did not cause any problems during extrusion. However, the wet mass's extrudability was reduced, and extrusion was accomplished with some difficulty in the formulation of materials with a greater concentration of HPMCs, and the issue got worse with the addition of more binder polymers [23]. The morphology of pellets containing numerous granulating liquids is shown in images of pellets with various adhesives (figures not shown). When HPMC 6 cps was utilized as the binder, spherical, uniform, and distinct pellets were produced. Additionally, pellet sphericity scores demonstrate a nearly spherical form.

The efficiency of the procedure for various pellet formulations is also stated in (Table 1), along with the percentage of water needed to make the wet body depending on the formulation's dry weight. According to (Table 1) findings, the amount of water needed to create a wet

body reduces as viscosity or binder concentration rises. The formulation without HPMC and ethanol included the largest percentage of water, whereas the formulation with 5% HPMC and 10% ethanol contained the lowest amount of water. Although the amount of water needed to prepare the wet body in formulations including HPMC 6cp reduced as the binder's viscosity increased, the extrusion process was not adversely affected since water was employed as a lubricant during extrusion [24]. The effectiveness of (Table 2) was reduced when HPMC (all three grades) was used in the formulation with an increase in binder concentration or viscosity. In order to create pellets with the narrowest size distribution possible, it is preferable to achieve the ideal formulation and processing conditions. The kind and quantity of the binder among the several pellet constituents are crucial in determining how it will be shaped. According to the size distribution, increasing binder concentration increased the proportion of bigger particles in the final products in all formulations. This was connected to the stronger connections that were created between powders and the higher adhesive properties of polymer binders as their concentration increased. Malipedi et al. 19 also reported that with increasing binder concentration (polyethylene oxide) in the formulation, the average diameter of caffeine pellets increased [1-3].

In contrast, the optimal concentration pore-forming agent (i.e., 5% w/w of PEG 200), which offers an excellent appearance, was employed in additional studies. In accordance with the restriction (values up to 1.2 are generally regarded as acceptable), the aspect ratio of all pellet formulations in (Table 2) is in the range of 1.04–1.07. An aspect ratio of 1.00 implies perfect spherical geometry.

For subsequent processing, such as coating, packing, and/or compression, the pellets' mechanical characteristics are crucial. The findings for the pellets' crushing strength, yield point, and elastic modulus are shown in (Table 3).

Table 1. Composition pellet formulation

Row	Granulation Fluid	Pore Agent	MCC101 %	CC	HPMC	H2O	EtOH	PEG200	ALA
F1	25	10	0	35	0	0	30	100	MIN
F2	25	10	0	30	3	2	30	100	
F3	25	10	5	25	0	5	30	100	
F4	25	10	5	30	0	0	30	100	
F5	25	10	3	25	5	2	30	100	
F6	25	10	0	20	10	5	30	100	MAX
F7	25	10	0	25	10	0	30	100	
F8	25	10	5	25	3	2	30	100	
F9	25	10	3	20	7	5	30	100	

Table 2. physicochemical charactrization of pellet formulation

Row	Residual moisture (%)	Sphericity	Average diameter (m)	ALA content (%)	Disintegration Time (s)	Yield%	crushing strength (N/mm)	elastic modulus (mP)
F1	2.92 ± 0.05	0.79 ± 0.09	1315	94	192	61	2.92 ± 0.05	51±0.6
F2	2.61 ± 0.2	0.80 ± 0.12	1221	95.1	40	79	1.1 ± 0.06	18.953
F3	2.90 ± 0.07	0.68 ± 0.67	1791	93.3	45	71	3.9 ± 0.07	63.751
F4	2.99 ± 0.1	0.82 ± 0.34	1812	92.9	68	67	4.8 ± 0.08	86.352
F5	2.1 ± 0.09	0.83 ± 0.43	1565	93.7	55	78	4.04 ± 0.09	73.1644
F6	2.52 ± 0.3	0.93 ± 0.44	1267	95.5	50	84	0.86 ± 0.10	15.3854
F7	2.71 ± 0.5	0.80 ± 0.31	1202	95.1	58	80	1.22 ± 0.11	21.655
F8	2.90 ± 0.8	0.77 ± 0.46	1711	93.7	54	75	4.25 ± 0.12	76.4575
F9	2.82 ± 0.8	0.90 ± 0.46	1431	93.9	52	77	3.6 ± 0.13	62.748

Table 3. Physicochemical charactrization of pellet formulation

Row	Residual moisture (%)	Sphericity	Average diameter (µm)	ALA content (%)	Disintegratin Time (s)	Yield%	Crushing strengh (N/mm)	Elastic modulus (mPa)
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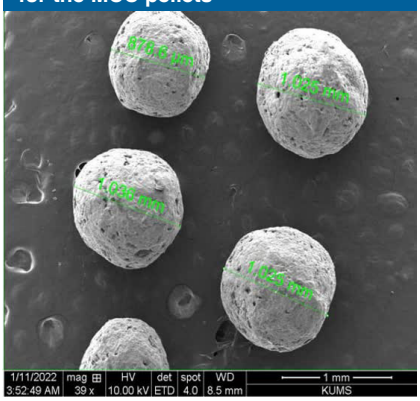
F3	2.90 ± 0.07	0.68 ± 0.67	1791	93.3	45	71	3.9 ± 0.07	63.7
F4	2.99 ± 0.1	0.82 ± 0.34	1812	92.9	68	67	4.8 ± 0.08	86.3
F5	2.1 ± 0.09	0.83 ± 0.43	1565	93.7	55	78	4.04 ± 0.09	73.1
F6	2.52 ± 0.3	0.93 ± 0.44	1267	95.5	50	84	0.86 ± 0.10	15.3
F7	2.71 ± 0.5	0.80 ± 0.31	1202	95.1	58	80	1.22 ± 0.11	21.6
F8	2.90 ± 0.8	0.77 ± 0.46	1711	93.7	54	75	4.25 ± 0.12	76.4
F9	2.82 ± 0.8	0.90 ± 0.46	1431	93.9	52	77	3.6 ± 0.13	62.7

The energy needed to ignite the pellets may be used to establish whether or not they are stable in their mechanical form. Bond sum or break mechanics theories can be used to analyze the reaction of a bullet when it is subjected to such pressure. The focus is centered on how particles link to one another in the idea of bond aggregation and how these bonds break down during the strength test. The spread of tablet fractures during the strength test is the key component of the failure mechanics concept. The breaking strength of the pellets, or mechanical stability, was measured in this investigation, and it was discovered that adding PEG 200 causes it to drop below the level of MCC pellets. These tests identified and reported the buckling strength, or the maximum force needed to shatter the bullets, as well as the elastic modulus of the bullets, which represents their resistance to deformation. All pellets demonstrated a brittle character during mechanical testing, rendering them unsuitable for use in products comprising various grades of HPMC. The breaking strength and elastic modulus of pellets rose as HPMC content increased. According to a number of studies, cellulose-derived substances such as microcrystalline cellulose and HMPC create highly hard granules after being ground with water [25, 26].

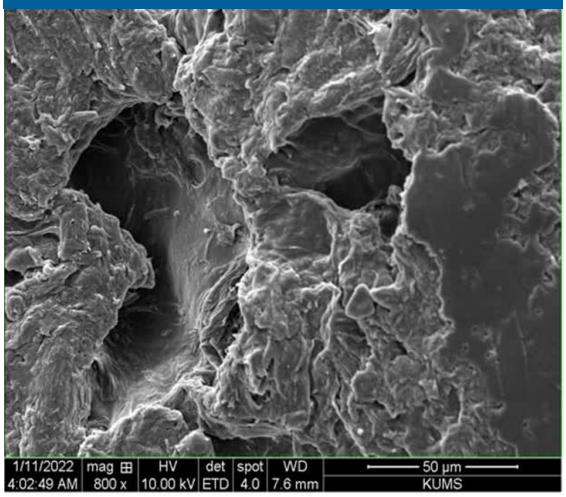
In comparison to the MCC formulation, which is typically not thought of as friable (0-0.2% friability), the pellet formulation with PEG 200 had a higher friability (3% friability). To achieve a high density, it is required to decrease the route between the particles by a sufficient amount to prevent excessive mechanical wear between the particles [27]. Data on pore volume and pore diameter can also be used to support confined density. The pellet formulation with PEG 200 is distinguished by the highest total pore capacity and offers a much larger pressure volume for a given surface area than other formulations. These parameters have such a significant impact on stability and fracture that the capability of these bullets is inferior to that of MCC bullets (Table 2). It has been demonstrated that a solid sample's mechanical strength decreases exponentially with increasing porosity; thus, this is not a surprise. SEM was used to examine the cross-section of several pellets. All pellets had a spherical form, as seen (Figure 1). According to the SEM images, a smooth surface was found for the MCC pellets (Figure 1).

Figure 1. Smooth surface was found for the MCC pellets



Internal smoothing of MCC bullets showed holes inside the bullets. This may be a result of the rotational tensions present during ringing. Bullets have cavities because their smooth edges fold into one another like a flower [28]. For pellets containing PEG 200, a pinhole structure was seen inside the pellets (Figure 2). These results are in line with those of the mechanical test, which showed that the PEG 200 and CCS pellets have greater pinholes and a lower fragmentation strength than the MCC pellets.

Figure 2. More porous structure inside the pellets



Pellet decomposition

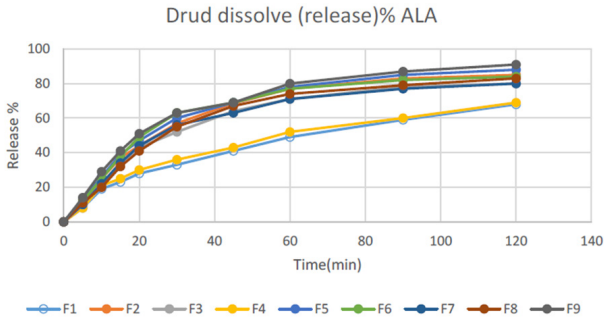
For medications with low solubility, in particular, MCC pellets typically do not melt, leading to poor and sluggish drug distribution. Many attempts have been made to address this issue by reducing the MCC pellets' dissolving time using a nonionic surfactant. The composition of the pellets had an impact on the dissolving time of all composite materials in this investigation, as indicated in (Table 2). This could be because pore-forming and polymer binder work together synergistically. No matter how much CCS (10% w/w) was used, the mixture of HPMC 6c, PEG 200, and water/ethanol demonstrated the quickest dissolving time. The pellets broke up into tiny bits very instantly (within 5 seconds). The enhanced strength and the pellets' capacity to be melted by the polymer glue do not support the findings. These variations may have an impact on how well drugs dissolve since breaking apart pellets into smaller pieces can enhance the dosage by supplying more surface area for drug breakdown and cross-linking structure [29]. Large holes and high porosity make it easier for water to quickly permeate the pellet, causing the bonds to fall apart and the pellet to be destroyed [30]. The findings of this investigation unequivocally demonstrate that the pellet formulation with a hole-hole structure (Figure 1) and a high pore capacity disintegrates extremely fast.

The use of an alcoholic solution as a granulation fluid resulted in a high porosity of MCC pellets, but the disintegration time of the pellets was still delayed, as dem-

onstrated by Schroeder and Klein [31] and Nicholson and Alderborn [32]. This demonstrates that the content of the pellets as well as the granulation liquid affect how easily the pellets dissolve. The breakdown of the bonds during deterioration is presumably made easier by the makeup of the component pores. MCC pellets without pores did not exhibit this behavior [21].

(Figure 3) depicts the model of the ALA breakdown process derived from the formulation of several pellet components. Because the MCC pellets did not disintegrate, drug degradation from them was sluggish (only 37% of the medication dissolved in 120 minutes) [33]. This is possibly because MCC shrank throughout the drying process, producing pellets that were denser and less perforated [34]. The chemical degrades more quickly when linked to PEG 200 (Figure 3). Generally speaking, PEG200 has been utilized as a carrier to speed up the dissolution of various medications that aren't very water-soluble [35]. In this study, PEG 200 serves as a piercing agent in the composition, and due to its re-formation during drying, it produces sponge-like matrix pellets [32]. The resulting pellets are less durable than pellets with MCC, and as a result, the rate of drug degradation increases noticeably when these perforated pellets degrade in the environment. This might create a water-absorbing environment that would speed up medication dissolution while also enhancing drug absorption. (Table 2) shows the findings on the apparent variation in the crushing power and breaking time of the pellets. As indicated in (Figure 3), adding a polymeric binder with PEG 200 to the formulation resulted in quick drug absorption, particularly at the beginning of it.

Figure 3. Decomposition process for different compounds



Discussion

It was determined in this study to utilize the perforation agent and PEG200 solvent and its water-soluble nature in the composition of pellets and the surface of pellets in order to enhance and improve the rate of decomposition of water-insoluble alpha-lipoid acid. Compared to the pellet composition without PEG, it has been shown that using PEG up to 5% in the pellet preparation process makes it easier to empty the wet body and to extrude and ring the pellets. The outcomes revealed that adding PEG 200 to the mixture had no effect on the pellets' average diameter. With PEG added to the pellet structure, the ratio of the pellets' diameters and rings remained unaltered (P>0.05). Therefore, after adding PEG to the surface of the pellets, the stability in swelling and the elastic modulus of the pellets both decreased noticeably, suggesting the formation of pellets. (P 0.001) It is malleable and flexible. The pellet formulation of PEG200 revealed a dissolving pattern that indicated it contained 5% PEG200, which accelerated the drug's rate of dissolution. Both the decrease in the pellets' ability to harm themselves, which makes it easier for water to enter their structure, and the water solubility of PEG, which creates more holes for drug release, were blamed for the rise in the disintegration rate. These results led to the conclusion that it was necessary to look into the impact of both PEG200 (as a pore-forming agent and water-soluble component) and non-aqueous granulation liquid in the composition of the pellet in order to look into various methods for these materials. PEG200 and non-aqueous granulation fluid were used to replace 25% of the MCC in the pellet formulation in order to modify the degradation rate. In spite of an increase in the crushing power of the pellets in certain instances, the breakdown pattern for several compounds in (Figure 3) revealed that the increase in binder concentration led to a considerable drop in the MDT level (P=0.01) and an increase in the drug release rate. HPMC dissolve in water upon contact with the dissolving media, leaving holes in the matrix pellet structure. PEG200 and non-aqueous granulation fluid were used to replace 25% of the MCC in the pellet formulation in order to modify the degradation rate. In spite of an increase in the crushing power of the pellets in certain instances, the breakdown pattern for several compounds in (Figure 3) revealed that the increase in binder concentration led to a considerable drop in the MDT level (P=0.01) and an increase in the drug release rate. HPMC dissolve in water upon contact with the dissolving media, leaving holes in the matrix pellet structure. These holes make it easier for water to enter the pellet structure and for the soluble medicine to discharge outside the pellets. Faster drug release is achieved by increasing the binder concentration, which creates more pores for drug release. Additionally, Abbaspour et al. demonstrated that lowering the MDT of pellets made from Eu-

dragit RS by increasing the binder content from 1 to 5% by weight. Similar to this, Dukic-Ott et al., [30] showed that piroxicam was released more slowly in pellets containing 4% w/w HPMC than those containing 7% w/w HPMC.

Conclusions

The findings of this study showed that a new extrusion-spheronization technique can be used to enhance the solubility of alpha-lipoic acid in the form of multi-particle dosage in improving drugs effective on cardiovascular performance and that this technique can also be used with other medications that are not very water-soluble. This study showed that the internal smoothing of MCC balls shows cavities inside the balls, which can be effective from the rotational stresses present during ringing, which will ultimately affect the final performance of the interventions.

According to the results obtained from this research, microcrystalline cellulose can be introduced as an important raw material for the production of water-insoluble drugs with a very high added value of microcrystals, which has many uses in various pharmaceutical industries.

Conflict of interests

The author has no conflicts of interest to disclose.

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