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Different trends for preparation of budesonide pellets with enhanced dissolution rate

Fatemeh Soltani [a], Hossein Kamali [b], Abbas Akhgari [b,a], Hadi Afrasiabi Garekani [c,a], Ali Nokhodchi [d,*], Fatemeh Sadeghi [a,b,*]

[a] Department of Pharmaceutics, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[d] Pharmaceutics Research Laboratory, Arundel Building, School of Life Sciences, University of Sussex, Brighton, UK

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ABSTRACT

The current research attempts different approaches to overcome the poor dissolution of budesonide (a poorly water-soluble drug) from pellet formulations. Various methods such as liqui-pellet (LP) and pellets made of solid dispersion (SDP) were employed and compared to conventional pellets (CP). In SDP method, budesonide:PVP solid dispersion was prepared followed by extrusion-pelletization. Solid dispersion of budesonide-PVP was also layered to the surface of placebo pellets (LSDP). In LP technique, budesonide dispersed in PEG 400 was mixed with Avicel or Avicel:lactose and was extruded-spheronized. Pellets were evaluated for their shape, size, mechanical properties and dissolution rate. The pellets made by LSDP method were significantly harder than CP or PSDP. LP with a loading factor greater than 0.34 was very soft compared to CP and SDP. Pelletization of budesonide SD (PSDP) did not have a tremendous effect on the dissolution enhancement of budesonide compared to CP whilst LSDP showed faster drug release. In conclusion, the layering of budesonide solid dispersion on placebo pellets (LSDP) was the most promising approach for the production of pellets with the highest dissolution rate so that more than 80% of the drug was released within the first 5 min. Also this formulation had proper mechanical properties. This method has the capability to overcome the poor dissolution of budesonide associated with the pellet containing Avicel, and could be employed for the dissolution enhancement of other poorly water-soluble drugs in pellet form.

1. Introduction

One of the glucocorticoids with an effect on a wide range of human organs is budesonide [1–3]. According to the currently available protocols, oral budesonide is the second-line treatment of ulcerative colitis [4,5]. Budesonide is a highly hydrophobic drug (log p of 3.2) with low water solubility (28 μg/mL) and is classified as a BCS class II [6]. Since the slow dissolution rate of budesonide might lead to insufficient drug concentration at the target sites, therefore, attempts to increase its dissolution rate to deliver enough concentration of the drug to the inflamed tissues is worth considering.

Nowadays, there are several methods for increasing the dissolution rate of poorly water-soluble drugs. Nanosuspension, micronization, self-emulsifying products, co-grinding, amorphization, liquisolid technology, liqui-pellet technology as well as solid dispersion [7–14]. Microemulsions, nanosuspension and nanoporous microparticles approaches have been employed by researchers to increase budesonide dissolution rate [15–17]. These approaches could hardly be commercialized for budesonide due to their costs as well as complicated scale-up processes. Furthermore, the probable aggregation of the nano-sized drug particles in the stomach upon administration of dosage form may hamper the benefits of nanonization. Amongst the methods mentioned above, solid dispersion (SD) systems and liquisolid technology have been the most widely used methods with the potential for industrial application.

Solid dispersion systems which contain molecular dispersion of the active pharmaceutical ingredient (API) within an inert amorphous or crystalline carrier have been increasingly implemented.

* Corresponding authors at: Department of Pharmaceutics, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran (F. Sadeghi); Pharmaceutics Research Laboratory, Arundel Building, School of Life Sciences, University of Sussex, Brighton, UK (A. Nokhodchi).

E-mail addresses: a.nokhodchi@sussex.ac.uk (A. Nokhodchi), sadeghif@mums.ac.ir (F. Sadeghi).

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The mechanisms proposed for increasing dissolution rates of drugs in SD systems include decreased drug particle size, changes in crystallinity of drug as well as increased wettability [18]. PVP is widely used as a hydrophilic carrier in SD systems due to its good water solubility [19–21]. It is noteworthy that PVP with T_g value of 154 °C, could prevent drug mobilization and recrystallization during a long storage time [22]. Solid dispersions can be prepared with different methods such as melting (fusion), solvent, melting– solvent or hot-melt extrusion (HME) method [23]. Despite, the use of HME in SD preparations is simple, solvent-free (cost-effective and environmentally friendly) and easy to scale up [24], some researchers demonstrated that solid dispersions prepared via the solvent evaporation method, showed higher dissolution compare to those prepared via hot-melt extrusion method [25].

Liquisolid technology is also a cost-effective approach that is associated with an uncomplicated scale-up process [26]. In liquisolid formulation, a liquid medication (drug dissolved or dispersed in non-volatile solvent) is mixed with excipients (carrier and coating materials) to make a dry, non-adherent, free-flowing and compressible powder mixture. The main mechanisms involved in the improved dissolution rate of the drug from liquisolid systems could be the existence of the drug partially or completely in a molecularly dispersed state, increased surface area, improved aqueous solubility, or enhanced wetting properties [26,27]. In liquisolid systems, microcrystalline cellulose (Avicel) and silicon dioxide (Aerosil) are employed as carrier and coating materials, respectively.

Multiparticulate dosage forms (such as pellets) have shown promising results in enhancement of dissolution rate of class II drugs [28,29]. Rapid onset of action and faster drug release could be expected from multiparticulate dosage forms due to their smaller size and high surface area, less residence time in the stomach, as well as rapid and homogeneous distribution in GIT [30].

Liqui-pellets which benefit from the advantages of both liquisolid technology and multiparticulate dosage forms are considered as the novel solid oral dosage form [13,31] that could potentially increase the dissolution rate of the drugs [32]. The most important benefit of liqui-pellets over liquisolid systems is the lack of need to achieve free-flowing powder thereby providing an opportunity for higher liquid medication load.

The purpose of the current study was to investigate and explore combined methods of solid dispersion system-pellets (solid dispersion pellets (SDP)) or liquisolid technology-pellets (liqui-pellets (LP)) to enhance the dissolution rate of budesonide and to develop fast release budesonide pellets. In this regard, conventional budesonide pellets (CP) were also prepared for comparison purposes.

2. Materials and methods

2.1. Materials

Budesonide was obtained from Jaber Ebne Hayyan Pharmaceutical Company (Tehran, Iran). Lactose monohydrate (Merk, Germany), Avicel pH 102 (Merck, Germany), polyvinylpyrrolidone (PVP K30) (Rahavard Tamin, Iran), polyethylene glycol 400 (PEG 400) (Dr. Mojallaly, Iran), colloidal silicon dioxide (Aerosil 300), (Evonik Industries AG, Hanau, Germany), and sodium lauryl sulfate (SLS) (Scharlau, Spain) were used. All other reagents and solvents were of analytical grades.

2.2. Preparation of budesonide:PVP K30 solid dispersion

To find out the optimum ratio of budesonide:PVP K30 (API:PVP) in solid dispersion formulation to achieve the best dissolution, various ratios of drug:PVP (1:1, 1:2, 1:4) were prepared by a solvent evaporation method. Certain quantities of budesonide and PVP K30 were dissolved in the 10 mL of ethanol and then the solutions were transferred into Petri dishes (at equal volumes). The Petri dishes were transferred to an oven (40 °C) for the removal of the solvent. The SD film was then separated and milled using a mortar and pestle and passed through a 100-mesh sieve (150 μm) and was kept in a desiccator until further use. The physical mixtures of budesonide and PVP K30 with the same ratios as above were also prepared by mixing sieved fractions of the drug and PVP K30 (<150 μm) using a mortar and pestle.

2.2.1. Dissolution studies of budesonide:PVP K30 SD

Dissolution of SD samples and physical mixture of budesonide-PVP K30 was performed in an automated dissolution tester (Pharmatest, PTWS 3E, Germany) utilizing the USP Apparatus II (paddle). The bath temperature and paddle speed were set at 37 °C and 75 rpm, respectively. The dissolution media was 750 mL of distilled water containing 0.25 %w/v sodium dodecyl sulfate (SDS). The specific weight of samples corresponding to 9 mg budesonide was added to the vessels. Samples were collected through sintered filters using a peristaltic pump (Alitea, Sweden) at predetermined time intervals and were analyzed at 246 nm using a multi-cell transport spectrophotometer (Shimadzu, UV/1204, Tokyo, Japan). The concentration of budesonide was determined based on the calibration curve obtained for budesonide at this wavelength. For each formulation, the dissolution was performed in triplicate.

2.3. Determination of budesonide solubility in different solvents

Saturated solubility of budesonide was examined in several liquid vehicles (PEG 400, propylene glycol, Tween 80, and glycerol) to select the cosolvent with the highest capability to dissolve budesonide for preparation of LPs. To this end, excess budesonide powder was added to 10 mL of each liquid vehicle and was shaken at 60 rpm for 72 h at room temperature (Heidolph Instruments, MR Hei-Tec, Germany). The samples were then centrifuged at 3000 rpm for 30 min (Pars Azma, CE05, Iran). The supernatant was then separated and filtered through a syringe filter (pore size 0.22 μm). The concentration of budesonide in each sample was determined using a UV spectrophotometer (UNICO, UV2150, USA) at 246 nm. Each test was performed in triplicate.

2.4. Preparation of budesonide conventional pellets (CP)

The formulation of conventional pellets is shown in Table 1 (CP1-CP3). Extrusion-spheronization was used to produce pellets. All powdered components, including the drug and excipients, were mixed for 20 min using a kitchen mixer (FUMA, Fu-1877 Hand Mixer, Japan). The mixture was then turned into a wet mass by the addition of distilled water (Table 1). The wet mass was fed through an axial screw extruder (Dorsa Tech, EX-01, Iran) with flat sieves of 1 mm aperture size and extruded in 100 RMP at room temperature. The extrudates were then rounded for 5 min in a spheronizer (Dorsa Tech, EX-01, Iran) equipped with a cross-hatched friction plate rotated at 1200 rpm. The pellets were dried for 24 h at 40 °C in an oven and sieved to collect the pellets in a size range of 850–1180 μm.

2.5. Preparation of budesonide solid dispersion pellets

2.5.1. Preparation of pelletized solid dispersion of budesonide (PSDP)

The solid dispersion of budesonide:PVP K30 at 1:2 ratio was prepared according to the method described above (Section 2.2). The obtained solid dispersion formulation was mixed with lactose, Avicel and PVP K30 (Table 1) followed by the addition of water to get a wet mass. The wet mass was subjected to extrusion-spheronization

Table 1
Compositions of different pellet formulations.

Formulation	API (%w/w)	PVP K30 (%w/w)	Lactose	Avicel (%w/w)	PEG 400 (%w/w)	Aerosil (%w/w)	Placebo pellet (%w/w)	Lf[b]	R-Value[a]	Water (mL) per 25 g of formulation	Successful spheronization
CP1	1.5	5	48.5	45	0	0	0	–	–	13	Yes
CP2	1.5	5	68.5	25	0	0	0	–	–	10	Yes
CP3	1.5	5	78.5	15	0	0	0	–	–	5	Yes
PSDP	1.5	5	68.5	25	0	0	0	–	–	10	Yes
Placebo pellets	0	2	20	78	0	0	0	–	–	15	Yes
LSDP	1.5	3	0	0	0	0	95.5	–	–	0	Yes
LP1	1.5	5	0	42.76	48.5	2.12	0	1.17	20	5	NO
LP2	1.5	5	0	42.76	48.5	2.12	0	1.17	20	2	NO
LP3	1.5	5	0	46.32	44.8	2.28	0	1	20	5.5	Yes
LP4	1.5	5	0	68.28	21.72	3.40	0	0.34	20	13	Yes
LP5	1.5	5	23.16	23.16	44.8	2.28	0	1	20	1	NO
LP6	1.5	5	18.52	27.74	44.8	2.28	0	1	20	1.8	NO
LP7	1.5	5	15.44	30.88	44.8	2.28	0	1	20	1.8	NO
LP8	1.5	5	11.58	34.74	44.8	2.28	0	1	20	2.8	Yes
LP9	1.5	5	25.66	25.66	39.5	2.56	0	0.8	20	2	Yes

[a] R-Value is the ratio of the carrier to coating material.
[b] Lf is the weight ratio of the liquid medication to carrier.

to obtain pellets (PSDP). The formulation components for these pellets are shown in Table 1 and pellets were made by extrusion/-spheronization procedure as described in Section 2.4.

2.5.2. Preparation of layered budesonide solid dispersion pellets (LSDP)

First of all placebo pellets with high Avicel content were prepared using the extrusion-spheronization process to produce robust pellets for the layering process. The excipients used in the preparation of placebo pellets (Table 1) were mixed for 10 min, and then a sufficient quantity of water was gently added to the mixture to form a wet mass. The wet mass was fed through an axial screw extruder and the extrudates were rounded using a spheronizer as described in Section 2.4. The pellets were dried for 24 h at 40 °C in an oven. In this method, a certain amount of PVP K30 was dissolved in 100 mL ethanol, followed by the addition of budesonide to the ethanolic solution to obtain drug:polymer ratio of 1:2. This solution was then sprayed onto 100 g of placebo pellets in a Wurster column fluid bed coater (Haltingen-Binzen, UNI-Glatt, Germany) at a rate of 8 mL/min utilizing an atomizing pressure of 2 bars via a 1 mm aperture spray nozzle. The layering process was performed under the inlet temperature of about 33 °C and outlet temperature of about 28 °C. At the end of the layering process, the pellets were dried for 24 h at 40 °C in an oven.

2.6. Preparation of budesonide liqui-pellets (LP)

To prepare budesonide LP pellets, first of all, budesonide and PVP K30 were dispersed in PEG 400 and then mixed with Avicel powder in a mortar and pestle for 10 min to ensure absorption of the liquid medication by the carrier. Aerosil 300 (as a coating substance) was then added to the admixture and mixed for another 10 min. This mixture was then wetted by adding deionized water bit by bit to produce the desired plasticity for extrusion. The wet dough was extruded and then spheronized as described in Section 2.4. Pellets were subsequently dried in an oven overnight at a temperature of 40 °C. The weight ratio of carrier to coating material (R-value) in all formulations was considered 20 based on a previous study [31]. However, the liquid load factor (the weight of liquid medication to the weight of carrier) and the type of carrier were varied (Table 1). In LP1 to LP4 formulations the influence of liquid load factor (Lf) was investigated, while in LP5 to LP9 formulations the effect of the type of carrier was evaluated.

2.7. Evaluation of pellets

2.7.1. Pellet morphology studies

All formulations that were successfully spheronized were morphologically analyzed using a stereomicroscope (Kyowa, Japan) outfitted with a computer system coupled to a video camera (Sony, Japan). The sphericity and aspect ratio was determined using Image J software (ImageJ 1/50 for windows).

2.7.2. Particle size analysis of pellets

The particle size analysis of all successful formulations was performed using standard sieves (150, 180, 250, 425, 850, 1000, and 1180 μm). Pellets (25 g) were placed on top of the sieves and shaken on a sieve shaker for 10 min (Azmun test, 50410, Iran). For each formulation, the fraction of pellets that remained on each sieve was weighed and geometric mean particle size (dg) and geometric standard deviation (σ) were determined from the plot of cumulative percent of undersize on probability scale versus the log of particle diameter.

2.7.3. Pellet mechanical properties

A Material Testing Machine (Hounsfield, H50KS, England) was used to test the mechanical characteristics of twenty pellets of each successful formulation in the size range of 850–1180 μm. The top movable platen with a 1 kN load cell at a speed of 1 mm/min was used. A computer system connected to the device was used to generate force–displacement graphs (Hounsfield, QMAT, and England). Pellet crushing strengths, yield points and elastic modulus were determined. For statistical comparison of mechanical testing data, a one-way analysis of variance (ANOVA) was performed, considering $p < 0.05$ as significant.

2.7.4. Dissolution studies of the pellets

All dissolution experiments of pellets were performed using USP apparatus I (Pharmatest, PTWS 3E, Germany). The dissolution test was performed for accurately weighed pellets (n = 6) containing 9 mg of budesonide in 750 mL distilled water containing 0.25% w/v SLS, under the basket rotation speed of 75 rpm and at 37 ± 0.5 °C. At varying time intervals, samples were collected using a peristaltic pump (Alitea, Sweden) and analyzed at 246 nm using a multi-cell transport spectrophotometer (Shimadzu, UV/1204, Tokyo, Japan). The dissolution profiles were compared using Eq.1 to get the similarity factor (*f2*):

$$f2 = 50 \times log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(\mathrm{Rt}-Tt)^2\right]^{-0.5} \times 100\right\} \quad (1)$$

Rt and Tt in this equation represent the percentage of budesonide released for the reference and test samples, respectively. The value of *f2* higher than 50 indicates that the dissolution profiles may resemble each other.

2.7.5. X-ray powder diffraction (XRPD)

An X-ray powder diffractometer (GNR; Explorer, Italy) was used for the XRD study. The instrument was operated at 40 kV and 30 mA in the range (2θ) of 5 to 55°. The data were obtained over an angular range from 5 to 55° 2θ using a step size of 0.01° 2θ and step-time of 3 s, with a non-stop mode.

2.7.6. Differential scanning calorimetry (DSC)

A differential scanning calorimeter was used to evaluate the thermal behavior of budesonide in SD and pellet formulations (Mettler Toledo, DSC 822e, Switzerland). An indium standard was used to calibrate the DSC. The samples (3–5 mg) were weighed and transferred into DSC pans, followed by sealing the DSC pans. The samples were performed at a rate of 10 ^{0}C/min across a temperature range of 25–300 °C with a nitrogen flow of 80 mL/min.

3. Results and discussion

3.1. Dissolution studies of Budesonide:PVP K30 solid dispersion

As seen in Fig. 1, the dissolution rate of budesonide was improved significantly in all SDs samples compared to budesonide powder or budesonide-PVP K30 physical mixtures (*f2* values of <50), with almost more than 80% of the drug was released from SDs samples within 5 min. The lack of difference between dissolution profiles of physical mixtures of budesonide-PVP K30 and pure budesonide powder ruled out the increased hydrophilicity of the sample (due to the presence of PVP K30) as the main mechanism for enhancing dissolution rate in SD samples. Therefore the improvement in the dissolution rate of SDs formulation could probably be due to an increase in the surface area of drug particles as they are molecularly dispersed in the solid dispersion formulations [33,34]. A similar enhancing effect of budesonide dissolution rate was reported for solid dispersion formulations of budesonide and polyethylene oxide [35] or poloxamer 188 [6]. Drug release profiles for SD formulations showed that an increase in the amount of PVP in the formulations could not improve the dissolution of budesonide further (*f2* values >50). This indicates that a low concentration of PVP in the solid dispersions (1:1 ratio of drug:PVP) is good enough to reach the highest possible dissolution for budesonide; and a more increase in the concentration of PVP in the sample could not improve the dissolution of budesonide further. Comparing the dissolution profiles of all SD formulations for the first 5 min revealed that SD formulation with a ratio of drug:carrier 1:2 showed the fastest drug release within the first 5 min, therefore, this ratio was selected for further studies.

3.2. Solubility studies of budesonide in different solvents

Budesonide showed the highest solubility in PEG 400 (14.57 mg/mL) and the least solubility in glycerol (0.35 mg/mL), as shown in Table 2. The drug solubility in a liquid vehicle is an important factor affecting drug release from liquisolid systems. The formulation with the greatest solubility in the liquid vehicle should show the fastest drug release as more drug particles would be in molecularly dispersed form in the vehicle, leading to an increase in the surface area of the drug for dissolution [36]. As the PEG 400 demonstrated a better solubilizing ability for the budesonide, it was selected for the production of liquipellets. In addition, it has been shown that the addition of PEG 400 to Avicel based pellets could result in the formation of pellets with sponge-like structure leading to the formation of pellets with lower hardness and higher porosity, hence faster dissolution rate [37,38].

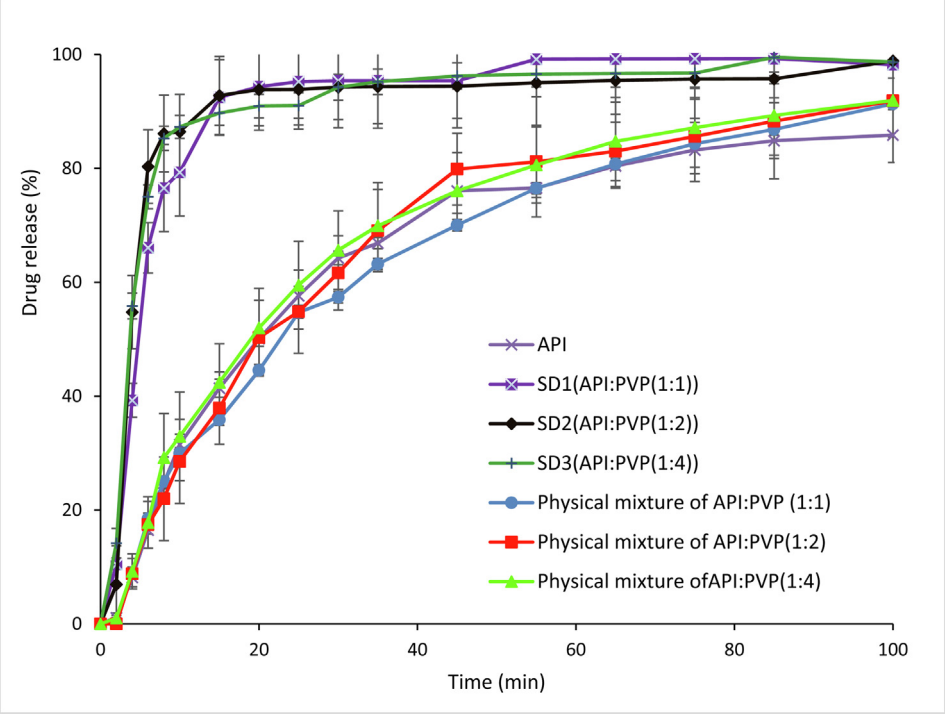

Fig. 1. Dissolution profiles of budesonide (API), physical mixtures and SD samples of API:PVP K30 at different ratios.

Table 2
Solubility of budesonide in various solvents (n = 3).

Solvent	Solubility (mg/mL) ± SD[a]
PG	7.29 ± 0.53
PEG 400	14.57 ± 0.62
Tween 80	1.25 ± 0.10
Glycerol	0.35 ± 0.01

[a] Standard deviation.

3.3. Evaluation of pellet characteristics

As it can be seen in Table 1, all CP and SD formulations were successfully spheronized. Avicel is the most widely used excipient in pellet formulation, due to its ability to provide the essential plasticity for extrusion [39,40]. However, studies have shown that the use of Avicel as the main excipient in pellet formulation could result in incomplete drug release for poorly water-soluble drugs from pellet formulation. Therefore in this study lactose was also used along with Avicel for the production of pellets. The required volume of water in CP formulations (13 mL) decreased with an increase in lactose and decrease in Avicel content (to 10 and 5 mL in CP2 and CP3 respectively). An increase in the amount of water needed for the extrusion process could be due to the high water adsorptive capacity of Avicel [41]. It was observed that the process of extrusion and pelletization became a little bit more difficult with a reduction in the amount of Avicel (compare CP2 and CP3), but this change did not badly affect the properties of wet dough in these formulations. The formulation with even 15% Avicel could also turn into proper pellets. According to Table 1, the required volume of water for granulation of PSDP and CP2 are similar probably due to the same concentration of Avicel used in these formulations.

In accordance with the results shown in Table 1, among liqui-pellets, only formulations LP3, LP4, LP8, and LP9 were successfully converted into pellets. Due to the cohesive property of the extrudate surface, signs of agglomeration were observed for failed formulations during the spheronization process [42]. There seems to be a limit for the amount of liquid vehicle that could be added before the formulation becomes prone to agglomeration [32]. When the Lf was more than 1 (as in LP1 and LP2), the cohesiveness of the extrudate surface was increased, and agglomeration occurred during the spheronization process. Although the required volume of granulation liquid in formulation LP2 was lower, the surface of the extrudates remained excessively cohesive and agglomeration could not be prevented. Agglomeration was also seen when the carrier type was changed from Avicel to a combination of Avicel and lactose in LP5, LP6 and LP7 formulations. As Avicel has a great absorptive capacity for liquids [39], therefore a decrease in the concentration of Avicel would reduce the absorptive capacity of the LP formulation, making the extrudate more susceptible to leakage of the liquid vehicle. This could result in the formation of cohesive surfaces on extrudates leading to agglomeration. It was shown that when the carrier type is a binary combination of Avicel and lactose, the Avicel: lactose ratio should be at least 75:25 (LP8) in order to achieve successful spheronization procedure. It was noticed that by reducing the amount of liquid vehicle (LP9) it was possible to make liqui-pellet, although the concentration of lactose was high.

The microscopic images of the selected oellets (Fig. 2) show the formation of near spherical pellets. As shown in Table 3, the sphericity and aspect ratios for all pellets were around 0.9 and near to 1 respectively. These values are acceptable roundness [43] which is a key element in the case of need for coating [44] or proper filling in capsule filling machines. It has been reported that the electrostatic charge created as a result of contact between non-spherical particles (due to surface roughness) could negatively affect the capsule filling process [45].

The results of particle size analysis (Table 3) show that the mean particles size of all pellets is typically <2 mm which indicates their suitability for considering as multiparticulate dosage form [46]. An increase in the lactose concentration in CPs resulted in the formation of large pellets due to a reduction in brittleness and an increase in the plasticity of the extrudates. The size of pellets in PSDP and CP2 (with the same concentration of lactose) were similar.

An increase in the Lf in the liqui-pellet formulations resulted in the formation of larger size pellets. This effect could be due to the binding and plasticizing effect of non-volatile vehicles which could contribute to the compactness of extrudates and decrease their brittleness [47]. Therefore LP4 with the least Lf showed the smallest pellet size. The results also demonstrate that in liqui-pellets with the same Lf, the size of pellets containing lactose was not considerably different from those without lactose. This demonstrates the importance of the plasticizing ability of the liquid vehicle and shows that the effect of Lf is more pronounced than carrier type on the size of LP pellets.

The mechanical strength of pellets can be characterized by the force necessary to break or deform the pellets. The results of the mechanical test on pellets are depicted in Table 3. It is noticeable that in CP formulations, an increase in the amount of lactose resulted in a decrease in crushing strength and elastic modulus. This also increased the plasticity of pellets. As Avicel can create strong intermolecular bonds [39], with decreasing the Avicel concentration, the number of these bonds decreases. Therefore formulations with a higher percentage of Avicel showed higher crushing strength and elastic modulus. A similar finding with changes in Avicel content in pellet formulations has been reported [48]. Formulations with the same percentage of lactose either in CP2 or in PSDP showed almost similar crushing strength; however, LSDP pellets were more resistant to deformation probably due to the presence of more PVP K30 on the surface of these pellets. The crushing strength and elastic modulus of the LSDP pellets were significantly higher than CP2 or PSDP pellets ($p < 0.05$). This might be either due to the presence of a high amount of Avicel in the placebo pellets [48] and also to the presence of PVP K30 on the surface of these pellets which increases the surface strength of the pellets. It is a known fact that numerous cracks and flaws are formed at the surface of the pellets or even probably inside the pellets which could result in pellet breakage under the load [49]. Applying the drug on the surface of placebo pellets with a strong binder such as PVP K30 could delay load transfer into the pellet matrix. When compared to other pellets, the crushing strength of liqui-pellet with high Lf (LP3) was very low (0.65 ± 0.1 N) but formulation with a lower Lf (LP4) was harder and more resistant to deformation (with crushing strength of (7.03 ± 0.95 N). In general, liqui-pellets made from a combination of Avicel and lactose (as a carrier) were softer and had a lower elastic modulus than those made from Avicel alone ($p < 0.05$). As can be seen, increasing the amount of lactose in the LP formulations resulted in a shift in pellet properties from brittle to plastic (Table 3).

3.4. Dissolution studies of pellets

The dissolution profiles for CP pellets are shown in Fig. 3A. The figure shows that the release of the drug from CP1 pellets was incomplete within 100 min. CP1 showed the slowest release with the highest amount of Avicel in the formulation (Table 1). It has been reported that the formation of very hard and non-disintegrating Avicel-based pellets via extrusion-spheronization is the main reason for the slow and incomplete release of poolry water-soluble drugs [37,50].

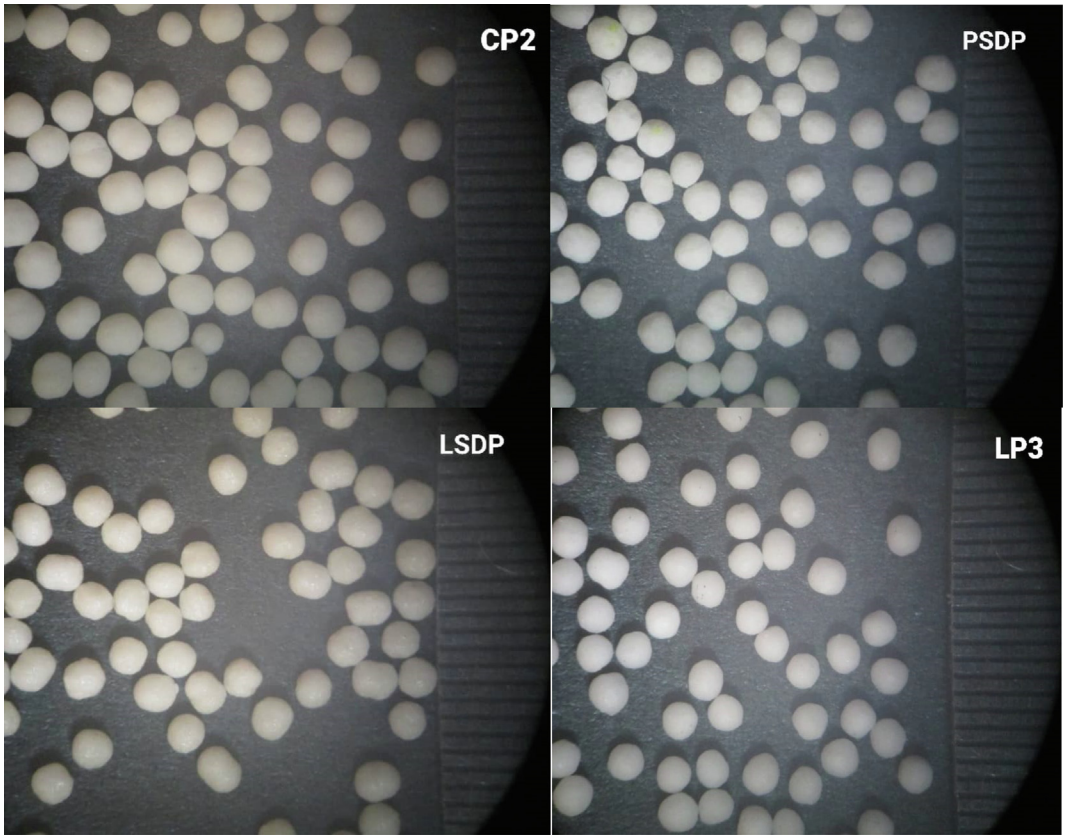

Fig. 2. Images of CP2, PSDP, LSDP and LP3 pellets in size fraction of 1000–1180 μm (8X).

Table 3
The characteristics of pellets.

Formulation	Crushing strength (N)	Yield Point	Elastic Modulus (Mpa)	Aspect Ratio	Sphericity	dg ± σ (μm)
CP1	7.87 ± 1.10	–	1624.0 ± 238.5	1.20 ± 0.20	0.99 ± 0.00	725.6 ± 1.3
CP2	5.93 ± 1.10	–	1145.0 ± 189.2	1.00 ± 0.01	0.99 ± 0.01	1102.2 ± 1.5
CP3	3.27 ± 1.00	–	1068.6 ± 292.0	1.00 ± 0.01	0.99 ± 0.01	1127.4 ± 1.1
PSDP	5.28 ± 0.80	–	1335.0 ± 352. 9	1.00 ± 0.01	0.99 ± 0.01	1121.2 ± 1.1
LSDP	10.50 ± 1.10	–	1961.0 ± 184. 6	1.01 ± 0.05	0.99 ± 0.02	820.7 ± 1.4
LP3	0.65 ± 0.10	–	72.01 ± 3.00	1.02 ± 0.10	0.98 ± 0.05	1163.9 ± 1.5
LP4	7.03 ± 0.95	–	689.70 ± 13.50	1.01 ± 0.06	0.99 ± 0.01	752.2 ± 1.3
LP8	–	0.17 ± 0.02	3.33 ± 1.68	1.00 ± 0.05	0.99 ± 0.01	1171.1 ± 1.4
LP9	–	0.12 ± 0.02	12.85 ± 6.82	1.00 ± 0.06	0.99 ± 0.02	1166.7 ± 1.5

As shown in Fig. 3A, an increase in lactose concentration from 48.5% (CP1) to 68.5% (CP2) resulted in a considerable increase in drug release. A further increase in the amount of lactose from 68.5% (CP2) to 78.5% (CP3) did not show a significant increase in the drug release ($f2$ = 53). It can be concluded that the optimal amount of lactose that can be easily used in the preparation of budesonide pellets to increase the drug release rate was 68.5%. The addition of a higher amount of lactose not only made the process of pellet production more difficult but also led to the formation of pellets with poor mechanical properties of pellets with no positive effect on the dissolution rate.

Despite the higher release rate of solid dispersion of budesonide:PVP K30 samples compared to budesonide powder (Fig. 1) when solid dispersion of budesonide:PVP K30 was incorporated in the matrix structure of the pellets (in PSDP), no significant effect on drug release rate was observed compared to CP2 formulation ($f2$ = 54). As both CP and PSDP pellets obtained in this study were non-disintegrating, therefore drug release occurred via diffusion through an inert matrix [37]. Consequently, entrapment of drug:-carrier SD in the matrix of the PSDP pellets prevented the benefits of SD system to appear in these pellets. Whilst in situ SD, the presence of the drug on the surface of placebo pellets (LSDP) significantly boosted the drug release rate so that more than 80% of the drug was released within the first 5 minutes. Solvent evaporation and drug precipitation on the surface of the placebo pellets during the layering technique would probably result in the formation of molecularly dispersed drug particles in PVP K30 at the surface of the pellets [51]. The layering of the drug along with hydrophilic PVP K30 on the surface of placebo pellets enhances the contact area between the budesonide and the dissolution medium as well as the wettability of the pellets, thereby increasing the dissolution rate substantially. Changes in the solid-state of the drug and its crystallinity might also contribute to the dissolution enhancement of budesonide from LSDP which is confirmed by DSC studies in the next section below.

Fig. 3C shows that an increase in Lf in liqui-pellets from 0.34 (LP4) to 1 (LP3) considerably increased the amount of drug released from 60% to 90% ($f2$ = 38.9). Solubilization or molecular distribution

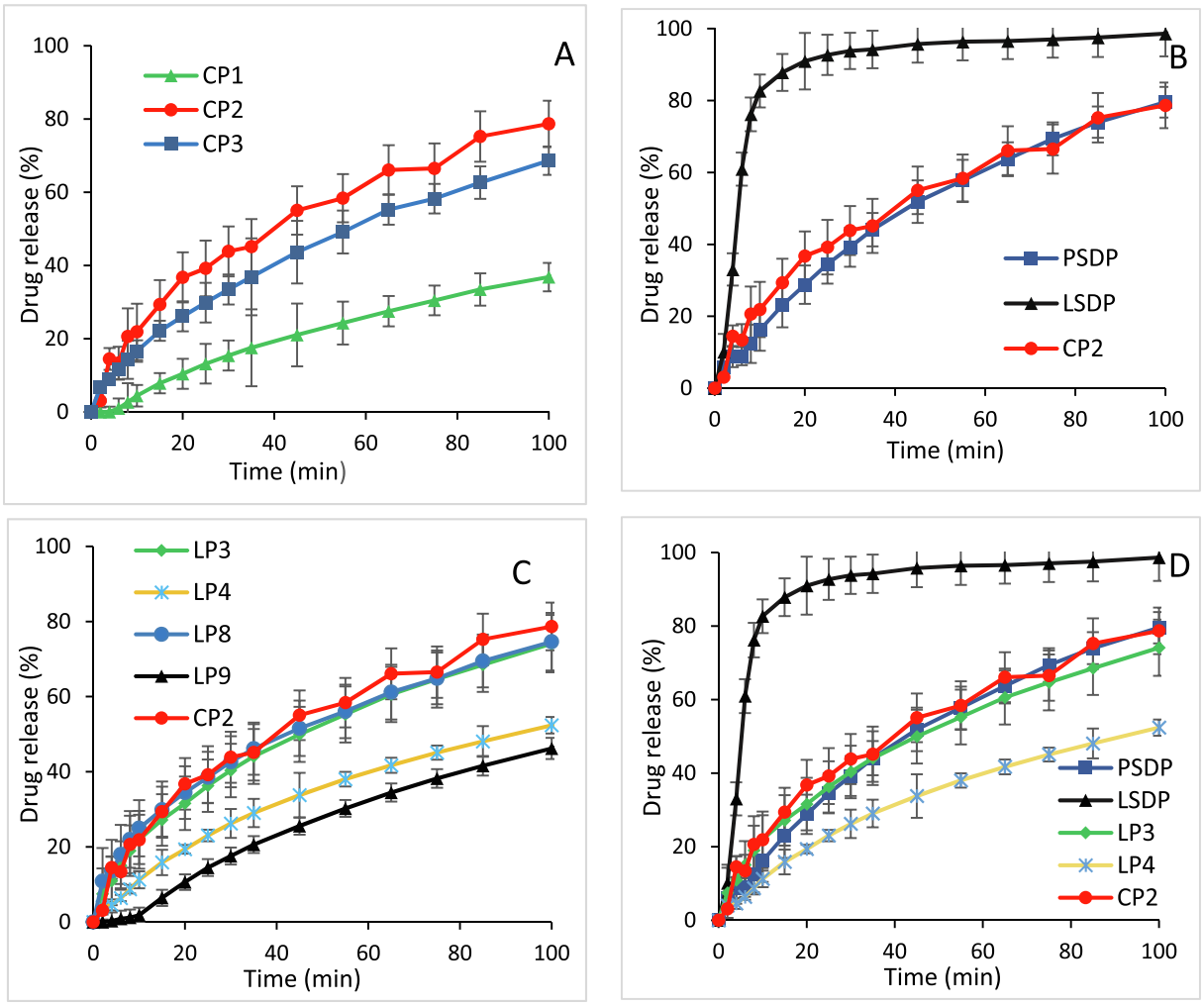

Fig. 3. Dissolution profiles for different pellet formulations A) CP, B) SDP, C) LP pellets and D) comparison of dissolution profiles for pellets with the higher dissolution rate in each category.

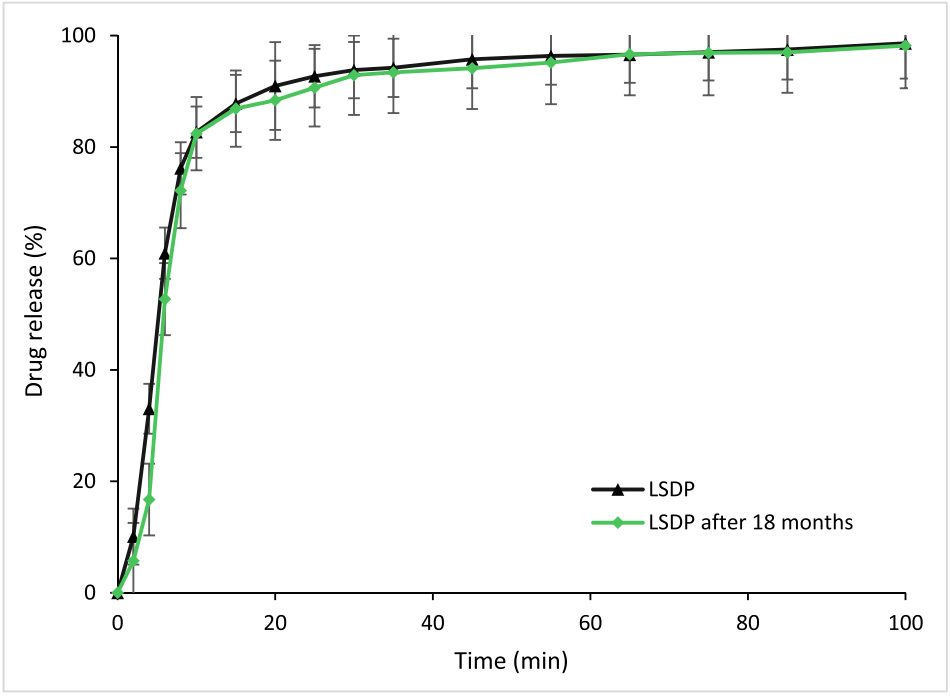

Fig. 4. Dissolution profiles of freshly prepared LSDP and those that were kept in closed container at room temperature after 18 months.

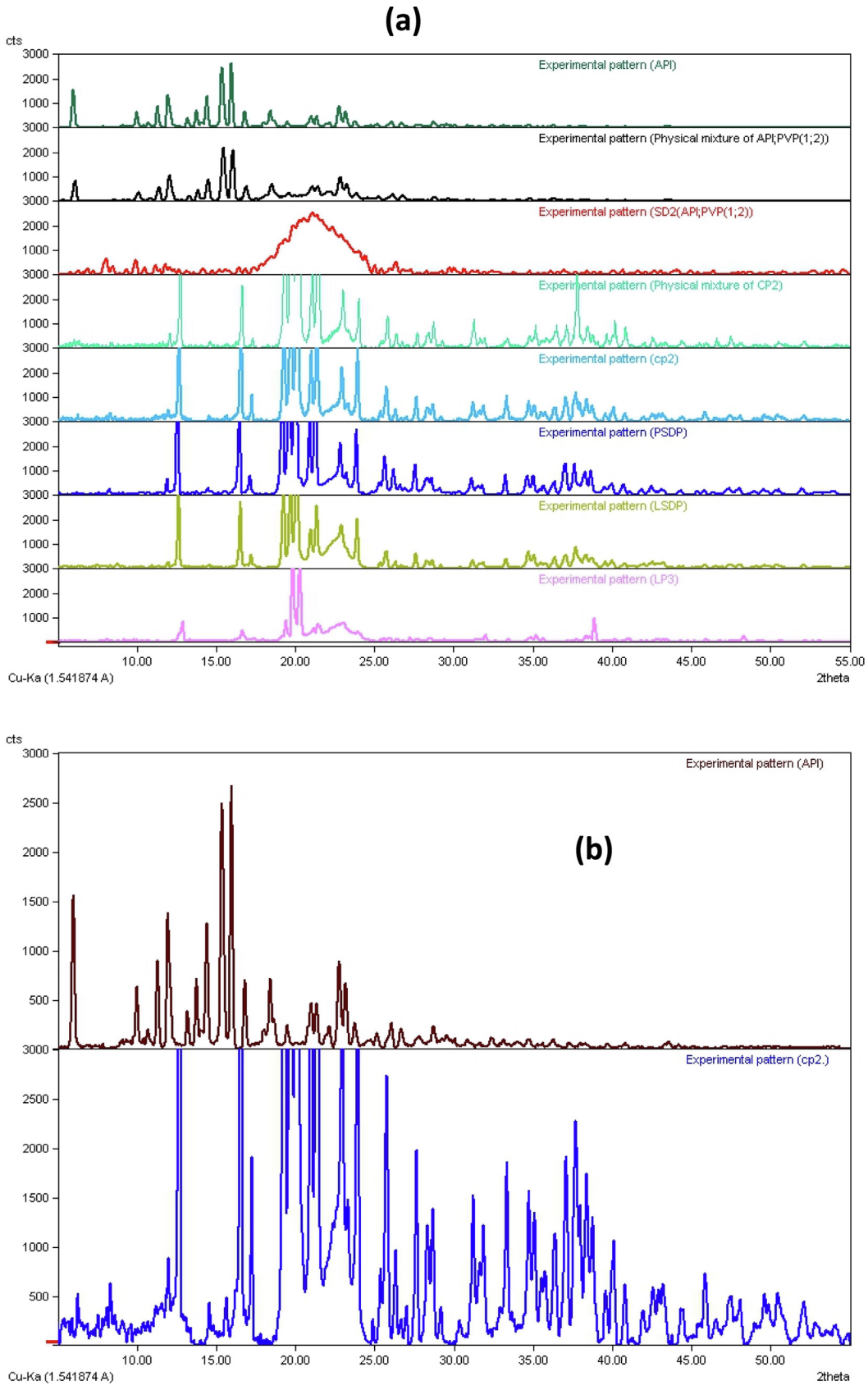

Fig. 5. XRPD spectra of different samples (a). XRPD spectra of budesonide and CP2 pellets on a larger scale (b).

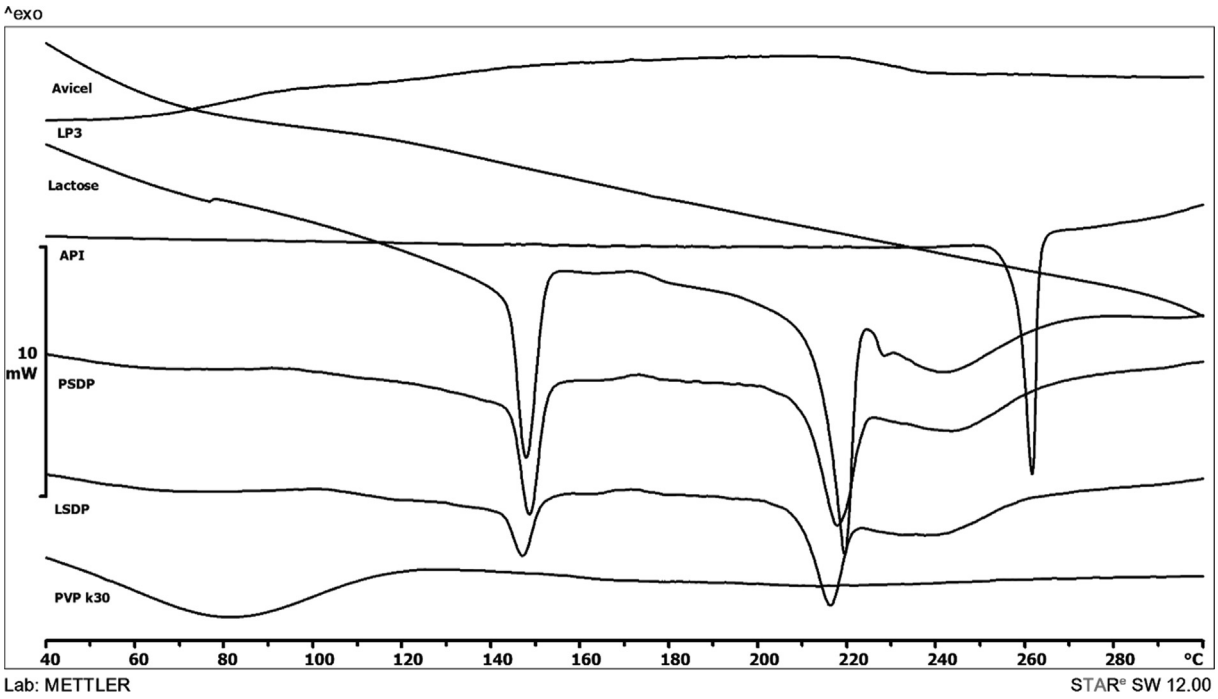

Fig. 6. DSC thermograms for budesonide, excipients and selected pellet formulation.

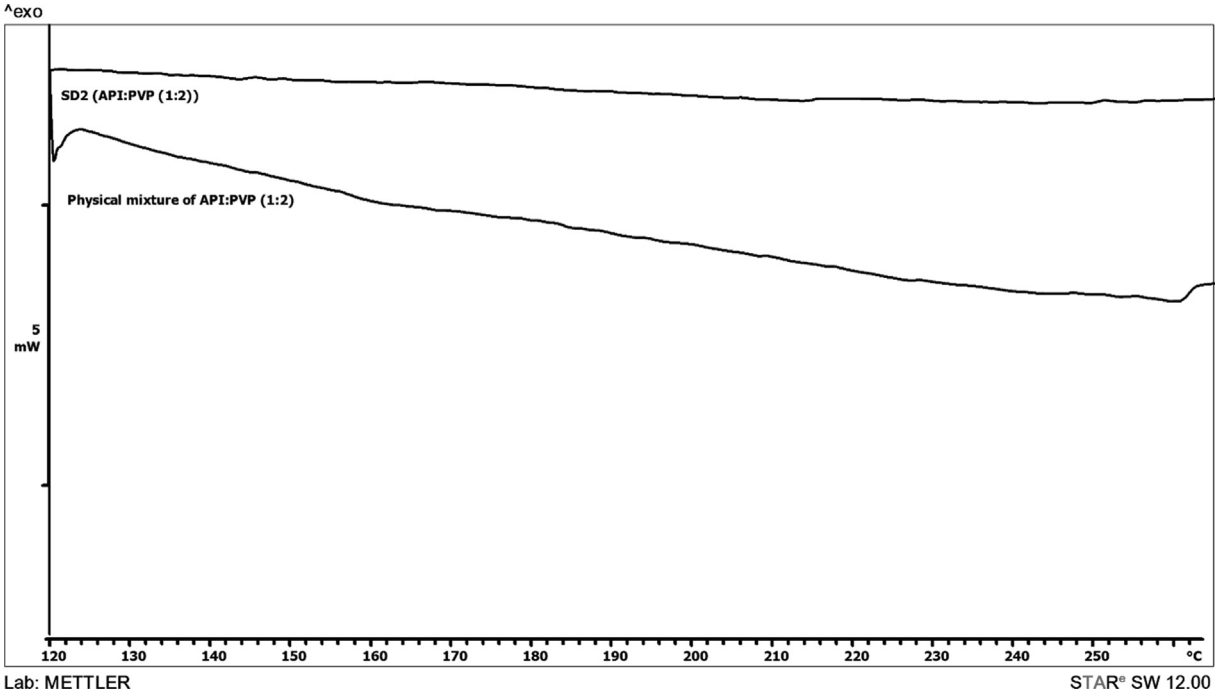

Fig. 7. DSC thermograms for physical mixture and SD system of budesonide:PVP K30 at 1:2 ratio.

of more drugs could be accounted for these results [36]. It is thought that the PEG 400 at the surface of pellets dissolves faster [13] and therefore drug molecules could move out easily via the pores generated as a result of PEG 400 dissolution. Unlike CP pellets, changes in the Avicel:lactose ratio from 100:0 (LP3) to 75:25 (LP8) had no significant influence on the drug dissolution profiles in liqui-pellets (f2 = 82.7). The results also showed that LP9 formulation released the drug substantially slower than LP3 (f2 = 33.5). This might imply that in liqui-pellet formulations, the Lf had a greater influence on the dissolution profile than the carrier type. Even though LP3 showed the fastest release rate among all liqui-pellets, LP4 had better mechanical properties. The release profile of LP4 was slower than that of CP2 (f2 = 35), indicating that the impact of adding a liquid vehicle to the pellet formulation to

increase the drug release rate may be achieved by increasing the concentration of lactose in the formulation of conventional pellets.

Fig. 3D demonstrates that, among the formulations, LSDP pellets, which are formed by the layering method, showed the fastest drug release. Similarity factor showed that the release profiles of CP2, PSDP, and LP3 were similar ($f2$ = 71.7 & $f2$ = 69.9). As it can be seen in Fig. 4, the drug release profile of LSDP pellets that were kept in closed containers at room temperature for 18 months showed no significant difference compared to freshly prepared pellets ($f2$ = 67.80) which indicates that these pellets were stable at room temperature at least for 18 months.

3.5. X-ray powder diffraction (XRPD)

Fig. 5a shows XRPD pattern for different samples. Budesonide showed characteristic peaks at 2θ of 5.99, 11.95, 14.42, 15.36 and 15.96 indicating its crystalline nature. These data were in agreement with published data elsewhere [52]. In the physical mixture of API and PVP K30 the main diffraction patterns of budesonide are visible whilst in SD sample of API and PVP K30 the peaks related to the drug are absent indicating the huge reduction in crystallinity of the drug. In pellet samples only a peak at an angle of 2θ 5.99 could be considered for comparison due to the overlap of most of the API peaks (at an angle of 2θ more than 10) with lactose peaks present in pellet formulation [53]. In CP2 pellets the API peak at an angle of 2θ 5.99 could be observed (Fig. 5b) which indicates the crystalline nature of the drug, however, this peak is absent in PSDP, LSDP and LP3 pellets which could be due to reduced crystallinity of drug in these samples.

3.6. Differential scanning calorimetry

DSC thermograms of budesonide, all excipients used in the preparation of pellets and the selected pellet formulations are shown in Fig. 6. For a better comparison of DSC traces, the thermograms of physical mixture and SD system of API: PVP K30 at 1:2 ratio are shown in a separate figure (Fig. 7) to avoid overcrowding DSC traces in a single figure. Budesonide showed a sharp endothermic peak at around 261 °C corresponding to its melting point [54,55] indicating its crystalline nature. In the DSC thermogram of PVP K30 a broad endothermic peak at around 80 °C corresponds to absorbed moisture [56] and in the lactose thermogram, the endothermic peaks observed at 148 °C and 220 °C are related to dehydration and the melting point of lactose respectively [57]. In Fig. 7 a peak related to the melting of the drug could be observed in the thermogram of the physical mixture of budesonide: PVPK30 which is small due to the dilution with a high amount of PVP K30 (1:2). The peak for budesonide melting disappeared in SD system indicating the reduced crystallinity of budesonide in SD system and confirming XRPD studies. The melting peak for budesonide in thermograms of SDP and LP pellet formulations (Fig. 6) is also absent indicating the reduction in crystallinity of budesonide which might contribute to the enhanced dissolution rate in these pellet formulations.

4. Conclusions

The results showed that among the methods used to prepare budesonide pellets the preparation of SD pellets by layering method was the most effective method in enhancing the dissolution rate of budesonide. In the case of budesonide pellets, liqui-pellet formulations were not very promising as they were mechanically weak which made them unsuitable for further processing with no considerable difference in drug release rate compared to conventional pellets.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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