Pharmaceutical Development and Technology, 2010; 15(2): 184–191

informa
healthcare

RESEARCH ARTICLE

Influence of water uptake, gel network, and disintegration time on prednisone release from encapsulated solid dispersions

Darío Leonardi and Claudio J. Salomon

Area Tecnología Farmacéutica, Departamento Farmacia, Facultad de Cs. Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario. IQUIR (CONICET). Suipacha 531, 2000, Rosario, Argentina

Abstract

Prednisone is considered the glucocorticoid of choice for anti-inflammatory and immunosuppressant effects. However, its very low aqueous solubility can compromise oral bioavailability. Changes in the dissolution of a prednisone-PEG 6000 solid dispersion into capsule were investigated by addition of pregelatinized starch. Physical state of prednisone:PEG 6000 was analyzed by X-ray diffractometry, and scanning electron microscopy. Capsule formulations containing prednisone-PEG 6000 and pregelatinized starch showed superior dissolution properties (> 95% in 60 min) when compared with reference capsules without disintegrant (< 45% in 60 min). Water uptake and disintegration time were directly correlated with pregelatinized starch amount. The morphology of prednisone-PEG 6000 particles with disintegrant was analyzed by SEM, showing a novel surface structure. Thus, solid dispersions of a poorly water soluble drug combined with a disintegrant were confirmed as a valid approach to the improvement of drug dissolution.

Keywords: *Water uptake; disintegration time; drug dissolution*

Introduction

Nowadays, the dissolution characteristic of poorly water-soluble drugs represents a great challenge to the pharmaceutical industry because it is the rate-limiting process in the absorption of these compounds after oral administration.[1] One technique that can be applied to increase the solubility and drug dissolution rate is the formation of the solid dispersions.[2] Even though more than 800 papers have been published dealing with polymeric dispersions, there is still limited knowledge about the successful design of solid dosage forms containing solid dispersions.[3] Further formulations of these systems into tablets and capsules involve a right selection of the excipients, based on the functionality or the type of dosage form in which they are used.[4,5] In this context, the influence of disintegrant agents on drug dissolution from those oral systems remains unclear and sometimes controversial.[6–9] Prednisone is usually considered the oral glucocorticoid of choice for anti-inflammatory or immunosuppressant effects.[10,11] Orally, it is prescribed in association with antibiotics to treat pneumonia in patients with acquired immunodeficiency syndrome (AIDS)[12] and, also, reduce the rate of hospitalization among children with asthma, resulting in a less expensive treatment.[13] However, paediatric patients usually may vomit or refuse to swallow medication, due to the bitter taste associated with prednisone.[14,15] One alternative to oral prednisone is the parenteral route of administration, but usually can be labour-intensive and time-consuming for the medical staff and painful for the patient. Thus, it can result either in significant failure in steroid therapy or in the patient not receiving steroids at all.[16] Therefore, attention should be focused on a well-designed prednisone formulation capable of avoiding the described drawbacks. In this work, the development of prednisone-PEG 6000 hard gelatine capsules with lactose as filler and pregelatinized starch (PS) as disintegrant was carried out. Solid dispersion systems were prepared by kneading, solvent evaporation, and fusion

Address for Correspondence: Dr Claudio J. Salomon, Faculty of Biochemical and Pharmaceutical Sciences, Pharmacy, Rosario, 2000 Argentina. E-mail: csalomon@fbioyf.unr.edu.ar

(Received 06 March 2009; revised 22 April 2009; accepted 29 May 2009)

ISSN 1083-7450 print/ISSN 1097-9867 online © 2010 Informa UK Ltd
DOI: 10.3109/10837450903085434

methods and compared with the corresponding physical mixtures in terms of drug dissolution rates and morphology and surface of particles. The influence of PS on capsules swelling behavior, network gel formation, particles surface, disintegration times and drug dissolution rate was evaluated. The morphology and surface of the particles were studied using scanning electron microscopy (SEM); and X-ray powder diffraction (RXPD) were used to investigate possible interactions between the components. To our knowledge, the correlation between swelling, capsule contents evaluation and disintegration time to improve prednisone dissolution have not yet been reported.

Materials

Prednisone (Hainan Zhongxin Chemical Co Ltd, Haikou, China), PEG 6000 (Aldrich Chemical Co, Milwaukee, USA), lactose (Foremost Whey Products, Baraboo, USA) were purchased. Pregelatinized starch (Starch 1500®) was kindly donated by Colorcon (West Point, USA). All the other reagents purchased were either pharmaceutical or analytical grade.

Methods

Preparation of solid dispersions and physical mixtures

Kneading method (KM)
Prednisone, PEG 6000 and distilled water at 1:1:0.1 ratios (w/w) were kneaded for 10 min in a glass mortar. The wetted mixture was dried in an oven at 40 ± 0.5°C until it reached constant weight.

Fusion method (FM)
A mixture of prednisone:PEG 6000 (1:1 ratio w/w) was heated in a closed Teflon container in an oil bath at 80°C and stirred repeatedly during 10 min. The mixture was cooled at room temperature and dried in an oven at 40 ± 0.5°C until it reached uniform weight.

Solvent evaporation method (SM)
At 1:1 ratio (w/w), prednisone was dissolved in 1 mL of ethanol, and the polymer was dissolved in 2 mL of water. The solutions were mixed under magnetic stirring for 30 min and the solvents were evaporated under reduced pressure.

Physical mixture (PM)
Prednisone and PEG 6000 (1:1 ratio) were mixed for 5 min with mortar and pestle. The powder was dried in an oven at 40 ± 0.5°C until it reached uniform weight. All the samples were sieved through a 420 μm mesh and stored in a desiccator at room temperature.

X-ray powder diffraction (XRPD)
Data collection was carried out in transmission mode on an automated STOE Powder Diffractometer STADIP (Darmstad, Germany). Samples were enclosed between two polyacetate films held together by double sided adhesive tape. Data acquisition and evaluation was performed with the STOE Visual-Xpow package, Version 2.75 (Darmstad, Germany).

Scanning electron microscopy (SEM)
Morphology of prednisone:PEG 6000 systems were investigated by means of an AMR 1000 Scanning Microscope (Amray, USA). Samples were previously sputter-coated with a gold layer in order to make them conductive. Pictures were taken at an excitation voltage of 20 Kv and a magnification of 550×.

Prednisone capsules
Prednisone:PEG 6000 solid dispersion prepared by SM was formulated in hard gelatine capsules, as shown in Table 1. Prednisone and PEG concentrations were kept constant at 6.70% (10 mg) and magnesium stearate at 1.0% (1.5 mg). The remaining part of the formulations consisted of variable amounts of PS and lactose. All the components were manually blended in a mortar for 10 min. Thereafter, the powders were dried in a hot air oven at 40°C for 3 h, sieved through a screen of 420 μm, and dried again. Then, powder mixtures were filled by hand into hard gelatine capsules size 0. Also, reference capsules (CC) without PS were prepared for comparison.

Dissolution studies

Dissolution studies of prednisone from solid dispersions and capsules were performed according to the method described in USP XXIV using apparatus 2 (Hanson Research, SR8 8-Flask Bath, Ontario, Canada) with the paddle rotating at 50 rpm in 500 mL of degassed distilled water, at 37°C. SD powders containing 10 mg of prednisone were dispersed on the surface of the dissolution medium while capsules were introduced in the flask and the time 0 was recorded. At different time intervals, 5 mL samples were withdrawn through a filter. The amount of released prednisone was determined by UV analysis at 244 nm. It was found that PEG 6000 and PS did not

Table 1. Composition of prednisone-PEG6000 SD capsules.

Composition[a]	C 10	C 20	C 30	C 40	C 50	CC[b]
Prednisone (mg)	10	10	10	10	10	10
Lactose (mg)	113.5	98.5	83.5	68.5	53.5	128.5
PS (mg)	15.0	30.0	45.0	60.0	75.0	—
PEG 6000 (mg)	10.0	10.0	10.0	10.0	10.0	10.0

[a]All capsules contain 1.5 mg Mg Estearate; [b]CC means reference capsules without PS.

interfere with the assay at this wavelength. The results presented are mean values of three determinations.

Disintegration time

Disintegration time of capsules was determined with an apparatus (UC-21 Disintegration Test System, Hanson Research, Ontario, Canada) according to USP testing standards. Disintegration media was degassed distilled water at 37°C. Six capsules were tested per batch.

Water uptake studies

To understand the functional contribution of each pharmaceutical excipient to the swelling of prednisone capsules, water uptake studies were performed. Weighed capsules (W_0) were placed in the dissolution medium, degassed distilled water at 37°C. At different interval times (60 s), each capsule was withdrawn from the medium and blotted to remove excess water and then weighed (W_1). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. Percentage increase in weight due to absorbed liquid or water uptake was estimated at each time point from following equation:

$$\%\ \text{Weight change} = \frac{W_1 - W_0}{W_0} \times 100$$

Capsules content images

Examination of the swollen capsules was carried out using a digital camera Olympus SP 350 (Tokyo, Japan) equipped with zoom lens 3× (38–114 mm, Tokyo, Japan). Photo imaging was performed on capsules formulated with 30%, and 50% of PS, and compared with CC. The capsules were immersed in degassed distilled water at 37°C without agitation, and after 15 min were removed and gently dried by removing the excess surface water by means of filter paper. Then, the capsules were opened and the content photographed.

Results

Dissolution studies of solid dispersions

It is well known that prednisone is slightly soluble in water.[17] To explore the influence of the preparation method on drug dissolution profile, prednisone-PEG 6000 solid dispersions (1:1 ratio) were prepared by different techniques. Release rate profiles were plotted as the percentage of prednisone dissolved from PM and solid dispersions versus time (Figure 1). In all cases, PM and solid dispersions exhibited faster dissolution rates than the intact drug. The dissolution rate of pure drug was very low: 13% in 10 min. In comparison, dissolution rate of prednisone from PM was 42% in 10 min. Samples prepared by both KM and FM showed a great increase in the dissolution of drug: 51 and 53% of drug are dissolved in 10 min, respectively, while SM was the most suitable technique to improve drug dissolution rate, and 76% of this corticosteroid was dissolved in 10 min. Based on these results, SM system was selected for further development of prednisone-PEG 6000 hard gelatine capsules.

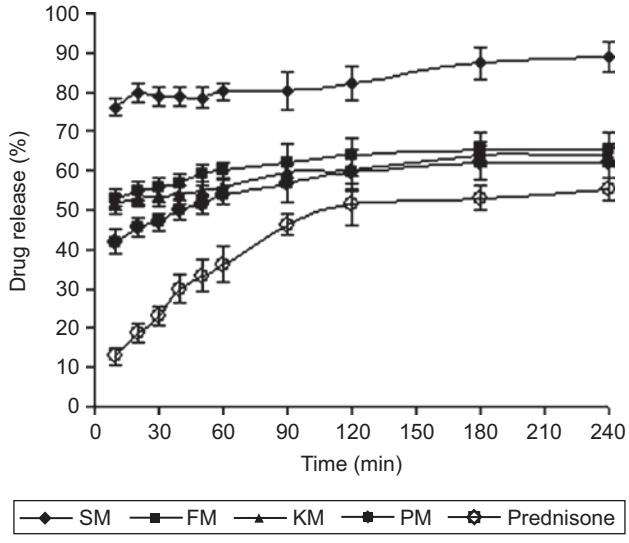

Figure 1. Dissolution profiles of prednisone alone and from prednisone:PEG 6000 physical mixture (PM), kneading (KM), fusion (FM), and solvent evaporation (SM).

Scanning electronic microscopy

Figure 2 illustrates the SEM micrographs of pure materials, PM, and KM, SM, and FM particles. PEG 6000 (a) exists in a mixture of smooth surfaced particles (100–300 μm), mixed with few microparticles (20–40 μm), while prednisone (b) existed as small irregular particles (10–20 μm).[18] In the PM (c) both the drug and the polymer maintain their original morphology and size. Both KM (d) and FM (f) exhibited particles of irregular shape which was similar to PEG 6000 particles. In contrast, in the SM technique (e), semispherical particles were clearly observed.

X-ray diffraction

Figure 3 shows the powder X-ray diffraction patterns of prednisone, PEG 6000, PM and solid dispersions. PEG 6000 revealed two distinct peaks at 19 and 23° 2θ, characteristic of its crystallinity.[19] Prednisone was characterized by two prominent diffraction peaks in the range of

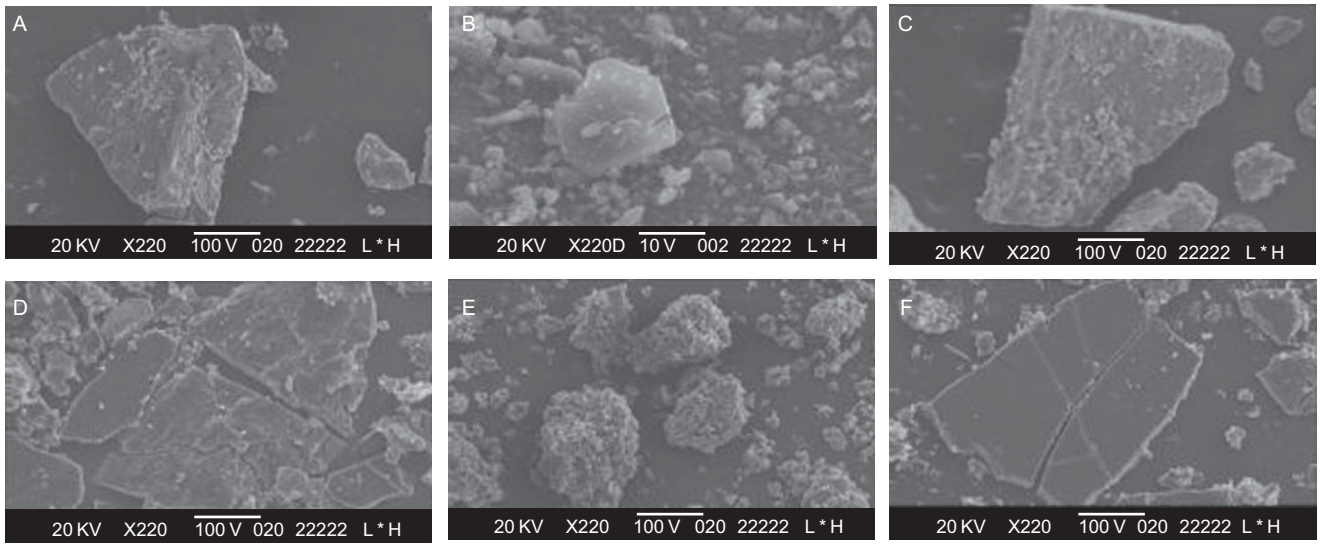

Figure 2. Micrographs of PEG 6000 (a), prednisone (b), PM (c), KM (d), SM (e), FM (f).

10–30° 2θ. Diffraction patterns of prednisone in PM and solid dispersion systems prepared by different method were similar to those of the pure drug.

Water uptake of the capsules

Water uptake study of the formulations and SEM observation of the capsule powders were performed. Changes in weight, characteristic of water uptake and further swelling, were observed from the beginning of the assay. As shown in Figure 4, CC filled with lactose (85%) exhibited a water uptake, probably by capillarity, within 10 min, and then reached a plateau, probably due to the fast dissolution of the easily water-soluble filler. Capsules containing the highly swellable PS (10–50%) showed water uptake behaviour similar to CC, within 10 min. Then, it was observed a considerable increase on water uptake in a linear relationship with the PS amount. These results are supported by the evidence showed in Figure 5 and then discussed.

Evaluation of capsules content

Prednisone-PEG 6000 capsules formulated with variable amount of PS were immersed in degassed distilled water during 15 min, then the capsules were carefully opened and the content was examined (Figure 5). Both the water uptake assay and this evaluation were done without applying any agitation process. As a consequence, the weight gain was measured without seen any degradation or rupture of the shells, avoiding the leakage of the capsule content. Upon exposure to aqueous media, CC exhibited a wetted powder, with particles adhered to the capsule wall, but no gel-like structure was observed. In contrast, a mixture of wetted powder and a viscous gel layer into the inner core was formed when PS was added (30%). Following this trend, when 50% of PS was used, all the powder content was transformed into a gel, due to a stronger PS sorption of water. Also, it was observed a deformation of the shell due to the pressure exerted by the gel forming structure.

To elucidate the influence of PS on the morphology and surface of solid dispersion particles, SEM photomicrographs of the capsules content were analyzed upon contact with degassed distilled water during 15 min. The powder was carefully removed from the capsules, dried and photographed. As seen in Figure 6, particles from CC formulations presented a prismatic shape with a regular and flat surface. On the other hand, a drastic change in the shape and aspect of particles from prednisone-PEG 6000 capsules with 30% and 50% of PS were observed.

Disintegration of the capsules

Capsule formulations (Table 1) fulfilled the USP pharmacopoeia requirements regarding disintegration time (< 30 min). As expected, CC disintegrated completely in 2–3 min, while capsules formulated with 10% and 50% of PS disintegrated in 4.5 and 7.5 min, respectively. Usually, PS is used in solid dosage forms up to 10%; however, larger amounts of this excipient have been used previously to improve drug dissolution of poorly soluble drugs.[20] Thus, in this case, variable amounts of PS were used in order to evaluate its influence on capsule disintegration when combined with PEG 6000 solid dispersions. Table 2 shows the relationship between disintegration time and dissolution of prednisone from PEG 6000 capsules at 30 min (Q_{30}) and 60 min (Q_{60}), respectively. The results clearly showed that the dissolution rate of prednisone was greatly influenced by the

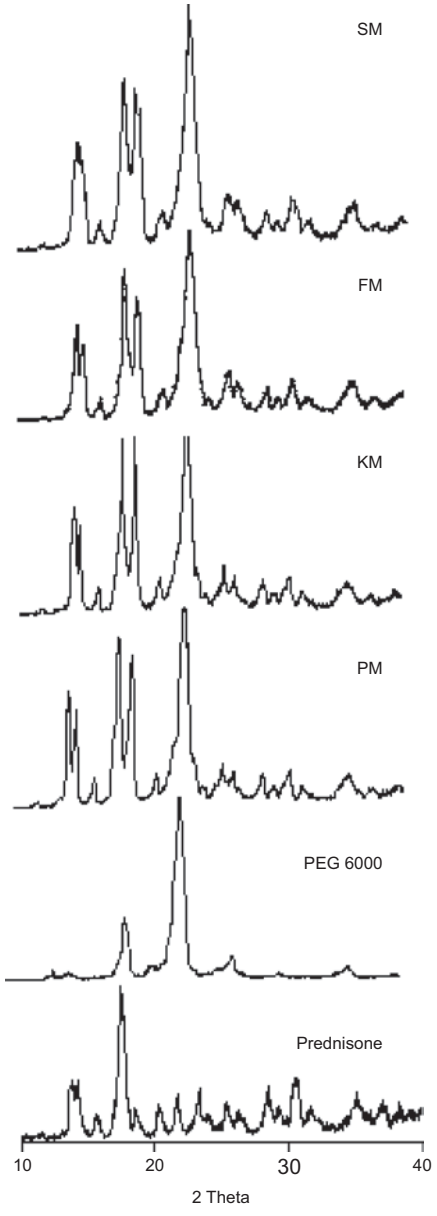

Figure 3. X-ray powder diffraction patterns of prednisone, PEG 6000, PM, KM, FM, SM.

disintegration time of the capsule shell. Moreover, it is confirmed that the behaviour of excipients in capsules is very specific and totally different compared with these additives applied to tablets.[21]

Dissolution studies of capsules

Figure 7 shows the dissolution profiles of prednisone from capsules formulated with 10% (C 10), 30% (C 30), and 50% (C 50) of PS in comparison with a reference formulation (CC), formulated only with lactose (85%). CC released only 28% in 10 min and 56% in 60 min, despite the high amount of the filler. Similarly, drug release from C 10 was 25% in 10 min and 52% in 60 min. C 30 showed

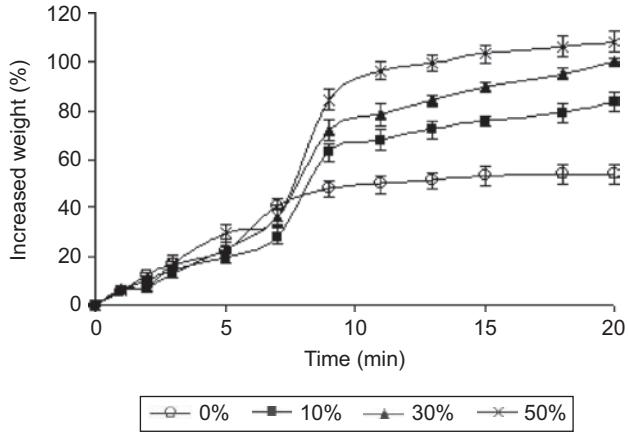

Figure 4. Water uptake in degassed distilled water (37°C) of reference capsule (CC) and capsules with 10%, 30%, and 50% of PS.

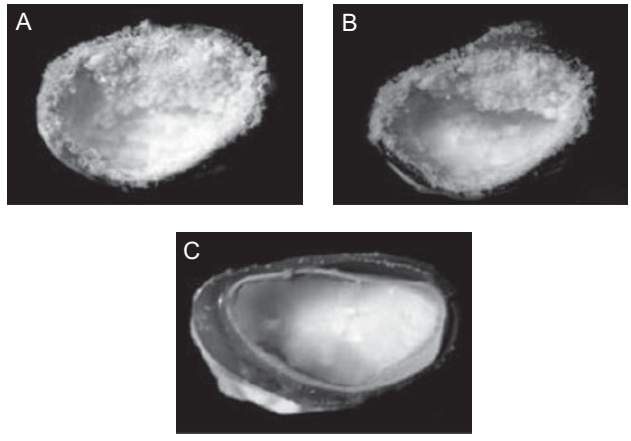

Figure 5. Content images of reference capsule CC (a), and capsules with 30% (b), and 50% (c) of PS, after 15 min in contact with degassed distilled water (37°C).

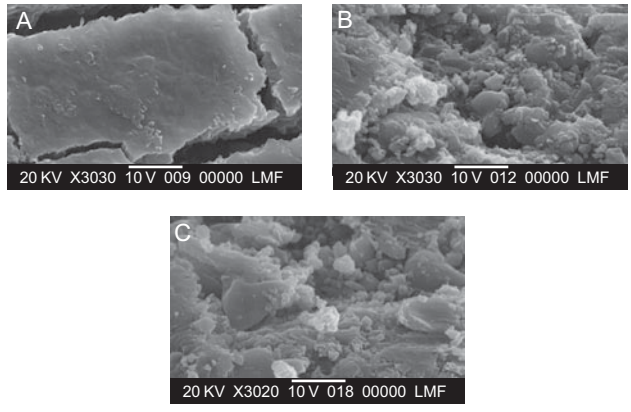

Figure 6. SEM micrographs of particles of reference capsule CC (a), and of capsules with 30% (b), and 50% (c) of PS, after 15 min in contact with degassed distilled water (37°C).

Table 2. Relationship between content of lactose, PS, disintegration time and prednisone dissolution (%) from hard gelatine capsules at 30 min (Q_{30}) and 60 min (Q_{60}).[a,b]

Lactose (%)	PS (%)	Disintegration time (min)	Q_{30} (%)	Q_{60} (%)
85.4	0	2.5 ± 0.2	39.2 ± 2.54	43.5 ± 4.61
75.4	10	4.5 ± 0.1	38.2 ± 4.84	43.2 ± 4.51
65.4	20	5.0 ± 0.6	43.1 ± 0.34	52.1 ± 3.76
55.4	30	5.9 ± 0.3	49.8 ± 2.21	60.8 ± 5.11
45.4	40	6.5 ± 0.4	62.1 ± 4.12	84.2 ± 3.13
35.4	50	7.5 ± 0.7	73.3 ± 0.76	95.4 ± 6.33

[a]All values represent mean ± SD (n = 3); [b]Prednisone and PEG concentrations were kept constant at 6.70%.

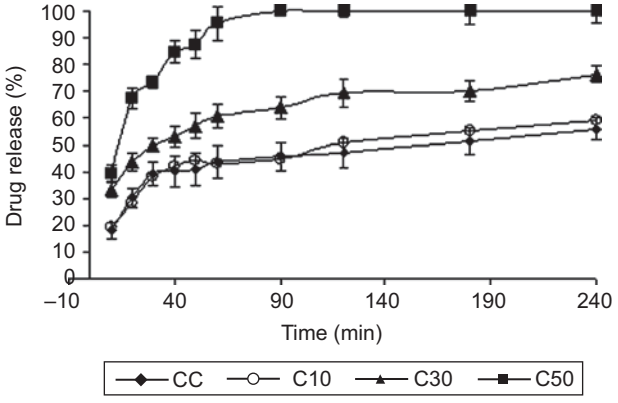

Figure 7. Dissolution profiles of prednisone from reference capsule (CC), and from capsules with 10% (C 10), 30% (C 30), and 50% (C 50) of PS.

a slightly increase on drug dissolution: 38% and 63%, in 10 min and 60 min, respectively. In contrast, a remarkable difference was observed when 50% of PS was used. As shown in Figure 6, C 50 showed a prednisone release rate of 45% in 10 min, and increased up to 100% in 60 min.

Lot reproducibility

Three batches of each formulation were prepared and the dissolution rate of prednisone was evaluated under the same conditions. The resulting drug release profiles from these three different batches showed no significant difference among the release profiles for each set of three batches, indicating that this manufacturing process is reliable and reproducible.

Discussion

Allen et al. described the preparation of glucocorticoids solid dispersions by means of fusion method, at 1:40 drug:carrier ratio.[22] However, both the method and the high concentration of carriers are important disadvantages for preparing convenient dosage forms of administrable size.[2] During dissolution experiments it was noticed that the PM powder sank immediately to the bottom of the dissolution vessel, whereas the pure drug floated for a long period on the surface of the dissolution medium. As a result, it was detected a significant difference on the drug released from PM in comparison with the pure drug, probably due to the improved wettability of the drug and inhibition of particle aggregation by effect of the polymer. Regarding the solid dispersion methods, SM was found to release prednisone in almost quantitative amount in comparison with the other two techniques (KM and FM), as shown in Figure 1. It could be mainly attributed to the particles morphology (Figure 2). Furthermore, SM does not have the problems associated with the FM, such as high melting temperature usually applied and the drug:carrier stability problems associated with it.

SEM micrographs of PM showed that both the drug and the polymer maintained their original morphology and size. The carrier separates drug particles, preventing their aggregation after introduction of the powder to the dissolution medium, leading to higher drug dissolution rates. Micrographs of SM particles exhibited a totally different arrangement between the drug and the carrier in comparison with the pure components, PM, KM, and FM (Figure 2). These differences in the surface, morphology, and particle size could result in different behavior in the dissolution tests, as shown in Figure 1.

The X-ray diffractometry spectra of prednisone alone showed a typical crystalline pattern. In a similar way, all major characteristics crystalline peaks of the drug appear in the diffractogram of both PM and solid dispersions. Moreover, the relative intensity of these peaks remains almost unchanged. Thus, it can be postulated from these data that there is not amorphization of prednisone. Since the diffractograms of PEG 6000 patterns in all SD systems were very similar, it might indicate the absence of chemical interaction between prednisone and carrier.[23]

Most of the works dealing with solid dispersions describe that wettability, mainly attributed to the carriers, is one of the reason for improved drug dissolution. However, no detailed studies are reported regarding the influence of excipients, used to formulate solid dispersions into capsules or tablets, on the wettability of drug-carrier particles. In agreement with the water uptake evaluation, water penetrated deeply into the capsule, the polymer swelled, and SD granules become more hydrated by the effect of water absorption (Figure 4). That is why SD, which contacts with water for longer time of period, could lead to the improvement of drug dissolution rate.[24] According to these differences, it is postulated that the 'wetted' surface of the carrier increase, and as a consequence, the drug release is improved to a large extent.

By the analysis of the images, the influence of increased amounts of PS on the gel network formation

was clearly observed (Figure 5). While CC (0% PS) did not show a gelling structure, capsules with 50% PS exhibited only a gel network. In addition, the swelling effect of PS increased the 'wetted' surface of PEG 6000 that further assist to enhance prednisone dissolution. These results are very consistent with the results from the in vitro dissolution experiments (Figure 7).

Morphology, size, and surface of particle powders included in solid dosage forms are crucial to understand the drug dissolution behaviour. Indeed, capsule formulations with 30% and 50% of PS exhibited a novel arrangement of the particles, in comparison with the reference formulation (CC). Particles were totally irregular and samples appeared as agglomerates, displaying a quite significant reduction in particle size (Figure 6). From the SEM analysis it can be concluded that PS act as surface-active compound increasing the wettability of drug-polymer particles and, therefore, the drug dissolution, as shown in Figure 7.

In addition, the influence of PS on disintegration time of capsules was clearly observed. CC (0% PS) was rapidly disintegrated, probably due to the fast penetration rate of water into the capsules and a rapid dissolution of lactose (85%). A gelling structure was not formed and, as a consequence, the capsule disintegrated faster than those with PS. As observed in Figure 5, a gel network was created into the capsules formulated with PS, forming a viscous layer that may prolong the disintegration, as described.[20]

Dissolution profiles of prednisone from SD-capsules were performed. Since lactose is freely water-soluble compound, once water is inside the capsule, this filler is dissolved and pores should be formed to facilitate the solvent front penetration to assist drug dissolution. In agreement with the evaluation of capsule contents (Figure 5) and the disintegration times, prednisone release from hard capsules prepared with PS should be controlled by the formation of a hydrated viscous layer around the capsules. Surprisingly, no correlation between disintegration time and dissolution of C 10, C 30 and C 50 was observed, in contrast with previous reports describing a direct relationship between these two parameters.[25] Furthermore, it would demonstrate that the incorporation of excipients with a high aqueous solubility (lactose) is not always an effective tool to increase drug dissolution rates.[26] In this work, it was confirmed that release rate of prednisone was primarily controlled by the rate and extent of water uptake and swelling of the corresponding excipients.[27]

Conclusions

It is concluded that prednisone-PEG 6000 hard gelatine capsules with PS are a very useful alternative to increase drug dissolution rate, using an easy and inexpensive process without any special production equipment. As demonstrated by SEM, the particular surface morphology of the particles offered an explanation of better dissolution rate from its solid dispersion. Water uptake experiments, disintegration time values obtained, and dissolution study confirmed that PS is a suitable additive to increase prednisone release from hard gelatine capsules. Evaluation of capsules contents gave very useful information about the correlation between gel network and drug dissolution rates.

Acknowledgements

The authors wish to thank to CONICET (Argentina) and National University of Rosario, UNR (Argentina) for financial support. D.L. is grateful to CONICET (Argentina) for a fellowship.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Leuner C, Dressman JB. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50:47–60.
2. Serajuddin ATM. Solid dispersion of poorly water soluble drugs: Early promises, subsequent problems and recent breakthroughs. J Pharm Sci 1999;88:1058–1066.
3. de Waard H, Hinrichs WLJ, Visser MR. Bologna C, Frijlink HW. Unexpected differences in dissolution behaviour of tablets prepared from solid dispersions with a surfactant physically mixed or incorporated. Int J Pharm 2008;349:66–73.
4. Jones BE. Two-piece gelatin capsules: Excipients for powder products, European practice. Pharm Technol Eur 1995;7:25–34.
5. Botzolakis JE, Augsburger LL. Disintegrating agents in hard gelatin capsules. Part I: Mechanism of action. Drug Dev Ind Pharm 1998;14:29–41.
6. Gohel MC, Patel LD. Improvement of nimesulide dissolution from solid dispersions containing croscarmellose sodium and aerosil 200. Acta Pharm 2002;52:227–241.
7. Desai DS, Rubitski BA, Varia SA, Newman AW. Physical interactions of magnesium stearate with starch-derived disintegrants and their effects on capsule and tablet dissolution. Int J Pharm 1993;91:217–226.
8. Bolhuis GK, Zuurman K, te Wierik GHP. Improvement of dissolution of poorly soluble drugs by solid deposition on a super disintegrant. II. The choice of super disintegrants and effect of granulation. Eur J Pharm Biopharm 1997;5:63–69.
9. Sjökvist E. Nyström C, Aldén M. Physicochemical aspects of drug release. IX. Investigation of some factors that impair dissolution of drugs from solid particulate dispersion systems. Int J Pharm 1998;54:161–170.
10. Tischner D, Reichardt HM. Glucocorticoids in the control of neuroinflammation. Mol Cell Endocrinol 2007;275:62–70.
11. Levine AM, Tulpule A, Espina B, Sherrod A, Boswell WD, Lieberman RD, Nathwani BN, Welles L. Liposome-encapsulated doxorubicin in combination with standard agents (cyclophosphamide, vincristine, prednisone) in patients with newly diagnosed aids related non-Hodgkin's lymphoma: Results of therapy and correlates of response. J Clin Oncol 2004;22:2662–2670.

12. Mccomsey CA, Whalen CC, Mawhorter D, Asaad R, Valdez H, Patki AH, Klaumunzner J, Gopalakrishna KV, Calabrese LH, Lederman MM. Placebo-controlled trial of prednisone in advanced HIV-1 infection. AIDS 2001;15:321–327.
13. Becker JM, Arora A, Scarfone RJ, Spector ND, Fontana-Penn ME, Gracely E, Joffe MD, Goldsmith DP, Malatack JJ. Oral versus intravenous corticosteroids in children hospitalized with asthma. J Allergy Clin Immunol 1999;103:586–590.
14. Hutto CJ, Bratton TH. Palatability and cost comparison of five liquid corticosteroid formulations. J Pediatr Oncol Nurs 1999;16:74–77.
15. Mitchell JC, Counselman FL. A taste comparison of three different liquid steroid preparations: Prednisone, prednisolone, and dexamethasone. Acad Emerg Med 2003;10:400–403.
16. Barnett PLG, Caputo GL, Baskin M, Kupperman N. Intravenous versus oral corticosteroids in the management of acute asthma in children. Ann Emerg Med 1997;29:212–217.
17. Ferrari F, Bertoni M, Bonferoni C, Rossi S, Caramella C, Bolhius G. Dissolution enhancement of an insoluble drug by physical mixture with a superdisintegrant: Optimization with a simple lattice design. Pharm Dev Technol 1996;1:159–164.
18. Giovagnoli S, Blasi P, Ricci M, Schoubben A, Perioli L, Rossi C. Physicochemical characterization and release mechanism of a novel prednisone biodegradable microsphere formulation. J Pharm Sci 2008;97:303–317.
19. Özkan Y, Doğanay N, Dikmen N, Işimer A. Enhanced release of solid dispersions of etodolac in polyethylene glycol. Il Fármaco 2000;55:433–438.
20. Gohil UC, Podczeck F, Turnbull N. Investigations into the use of pregelatinised starch to develop powder-filled hard capsules. Int J Pharm 2004;285:51–63.
21. Rowe RC, Sheskey PJ, Weller PJ. Handbook of pharmaceutical excipients. 4th ed. London: Pharmaceutical Press/Washington, DC: American Pharmaceutical Association; 2003.
22. Allen LV, Levinson RS, Martono DD. Dissolution rates of hydrocortisone and prednisone utilizing sugar solid dispersion systems in tablet form. J Pharm Sci 1978;67:979–981.
23. Lin CW, Cham TM. Effect of particle size on the available surface area of nifedipine from nifedipine-polyethylene glycol 6000 solid dispersions. Int J Pharm 1996;127:261–272.
24. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga U, Ohike A, Ibuki R, Higaki K, Kimura T. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine. J Control Release 2005;108:86–395.
25. Sammour OA, Hammad MA, Megrab NA, Zidan AS. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS Pharm SciTech 2006;7:Art. 55.
26. te Wierik GHP, Eissens AC, Bergsma J, Arends-Scholte AW, Bolhuis GK. A new generation starch product as excipient in pharmaceutical tablets III. Parameters affecting controlled drug release from tablets based on high surface area retrograded pregelatinized potato starch. Int J Pharm 1997;157:181–187.
27. Li H, Gu X. Correlation between drug dissolution and polymer hydration: A study using texture analysis. Int J Pharm 2007;342:18–25.