ELSEVIER

International Journal of Pharmaceutics 216 (2001) 127–135

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Effect of disintegrants with different hygroscopicity on dissolution of Norfloxacin/Pharmatose DCL 11 tablets

J. López-Solís [a], L. Villafuerte-Robles [a,*]

[a] *Pharmacy Department, National School of Biological Sciences, National Polytechnic Institute, Prol. M. Carpio y Plan de Ayala CP 11340, D.F. Mexico*

Received 24 August 2000; received in revised form 4 January 2001; accepted 4 January 2001

Abstract

This paper reports the effect of disintegrant hygroscopicity on dissolution of tablets obtained by compression at 85 MPa of mixtures of Norfloxacin and different proportions of a disintegrant (Starch 1500®, PVP XL 10® or Croscarmellose sodium®) and a diluent (Pharmatose DCL 11®). Dissolution behavior was evaluated according to USP 23, apparatus 2 (paddle) at 50 rpm and using 750 ml acetate buffer solution of pH 4, at 37°C, as medium. Norfloxacin added of increasing proportions, in a given range, of each disintegrant or the diluent increased the drug dissolved. Addition of increasing proportions of Pharmatose DCL 11 to Norfloxacin with 5% of the high hygroscopic Starch 1500 reduced the dissolution improvement effect of Pharmatose DCL 11. Addition of 5% Pharmatose DCL 11 to tablets of the middle hygroscopic Croscarmellose sodium and Norfloxacin slightly reduced the Croscarmellose sodium dissolution promoting effect, while addition of 15% Pharmatose DCL 11 to tablets of the low hygroscopic PVP XL 10 and Norfloxacin showed no inhibition but potentiated substantially the dissolution of Norfloxacin. These effects were attributed to competition for the available water in the tablet and to different water consume, for dissolution or hydration, by the diluent and the disintegrants. © 2001 Published by Elsevier Science B.V.

Keywords: Norfloxacin; Dissolution; Disintegrants; Hygroscopicity; Lactose

1. Introduction

A drug given in an orally administered tablet must undergo dissolution before it can be absorbed and transported into the systemic circulation. For many drugs, dissolution must be preceded by disintegration of the tablet matrix (Roche-Johnson et al., 1991). For tablets dissolution, it is necessary to overcome the cohesive strength introduced into the mass by compression. Therefore, usual practice to incorporate a disintegrant will induce this process. The term disintegrant is used to refer to a substance that is added to a tablet formula for causing the compressed tablet to break apart when placed in an aqueous environment (Visavarungroj and Remon, 1990). Although disintegration is frequently considered a prerequisite for drug dissolution, it in no manner

* Corresponding author. Fax: + 52-5-3963503.

E-mail address: lvillaro@bios.encb.ipn.mx (L. Villafuerte-Robles).

0378-5173/01/$ - see front matter © 2001 Published by Elsevier Science B.V.

PII: S0378-5173(01)00584-1

assures that a drug will dissolve and hence have the potential for satisfactory bioavailability. Therefore, it is important to examine the effectiveness of a disintegrant in the context of how the rate of dissolution of a drug from a tablet is affected (Gordon et al., 1991).

Among disintegrants, several types acting by different mechanisms may be distinguished. Disintegrants that enhance the action of capillary forces in a rapid uptake of aqueous liquids and those that swell in contact with water are considered the more important. These mechanisms include factors like deformation of particles, capillarity, heat of wetting, particle–particle repulsion and hydrogen bond annihilation (Caramella et al., 1987). Some other, less common, act by melting at body temperature, releasing gases to disrupt the tablet structure and those, which destroy the binder by enzymatic action (Banker, 1990).

For disintegrants like starches it is widely accepted a mechanism of inducing water uptake in the tablet, more than the swelling action formerly ascribed to it. However, the hydration of hydroxyl groups may contribute the starch particles to move apart. Some disintegrants propagate capillary effects but also swell and/or dissolve to further enhance disintegration behavior (Banker, 1990).

Whatever could be the mechanism, to obtain a rapid disintegration a disintegrant force must develop inside the tablet, capable of weakening and breaking interparticle bonds. This is generated by the replacement of solid/air with solid/liquid interfaces (Caramella et al., 1987). The displacement of air by water or aqueous liquids is a wetting process that may lead to hydration of the involved particles. Although hydration of similar particles in a tablet can produce disintegration, different hydration kinetics of particles with different properties will produce greater disruptive shear forces and smaller disintegration times. This means that disintegration could be a function of a given surface of contact between particles with different hydration properties. In the case of calcium phosphate/microcrystalline cellulose tablets, a minimum disintegration time was observed at a cellulose proportion of 68%, which is believed to produce a maximum in the surface of interparticle contact between Calcium Phosphate and microcrystalline cellulose particles (Villafuerte-Robles, 1994).

Among the physical properties of accompanying particles that affect the effectiveness of a disintegrant, the solubility is considered of great importance. The solubility of the major component in a tablet formulation can affect both the rate and the mechanism of tablet disintegration. Water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials will produce a rapidly disintegrating tablet if an appropriate amount of disintegrant is included in the formulation (Roche-Johnson et al., 1991). It has been considered that superdisintegrants had a much greater effect on disintegration time in an insoluble system. However, Gordon and Chowhan considered that the solubility of the tablet material did not inhibit the superdisintegrants from promoting dissolution in direct compression systems (Roche-Johnson et al., 1991). Their research is considered to illustrate a relationship between increasing hygroscopicity of the tablet material and decreasing superdisintegrant efficiency. The superdisintegrants were found to be effective in both the soluble lactose system and the insoluble calcium phosphate system. Moreover, the super disintegrant, when not incorporated in tablets, can behave differently in acidic and neutral dissolution media. Superdisintegrants tended to promote faster dissolution in a neutral pH medium than in an acidic medium (Visavarungroj and Remon, 1990).

The schemes proposed for the disintegration process seemed to provide the same information for insoluble formulations. However, by soluble formulations the disintegration force development could be hindered (Caramella et al., 1987). Moreover, Soluble excipients in a formulation, as lactose, are considered to act as passive disintegrants. It was considered that hydrogen bond annihilation was included in a passive mechanism (Van Kamp et al., 1986).

Although solubility and hygroscopicity of other excipients has been mentioned to affect the efficiency of dissolution promotion of disintegrants, hygroscopicity or water consume of disintegrants

should be also a factor to be considered. Disintegrants with different hygroscopicity or water avidity should be affected in a different magnitude by soluble excipients, in their efficiency to promote dissolution. This expectation arises from the fact that the quantity of water penetrating the tablet is limited. The soluble excipient will compete for the available water, consuming it partially, leaving only a part of the total water penetrating the tablet for the deployment of the disintegrant activity.

The aim of this work is the study of the effect of different hygroscopicity disintegrants and a soluble excipient on the dissolution of Norfloxacin tablets, as a first approach to study this circumstance related to drugs with different solubilities.

2. Materials and methods

2.1. Materials

Norfloxacin was kindly provided by C.A.F.E.T. – Mexico. The pharmaceutical excipients Pharmatose DCL 11 (spray dried lactose), PVP XL 10 (crosslinked polyvinylpyrrolidone), Croscarmellose sodium (crosslinked sodium carboxymethylcellulose) and Starch 1500 (pregelatinized starch) were obtained of pharmaceutical quality from Helm de Mexico and were used without further treatment.

2.2. Methods

2.2.1. Mixtures

Corresponding quantities of sieved excipients and Norfloxacin were weighed and mixed for 15 min in a twin shell blender rotating at 15 rpm. The effects of the following variations in tablet formulations on the dissolution rates were examined.

2.2.1.1. Mixtures with individual excipients. Starch 1500 was added to Norfloxacin at proportions of 4%, 8%, 12% and 16% (w/w); PVP XL 10 at proportions of 2%, 4%, 6% and 8% (w/w) and Croscarmellose sodium at proportions of 1%, 1.5%, 2%, 2.5%, 4% and 6% (w/w). Pharmatose DCL 11 was added to Norfloxacin at proportions of 5%, 15%, 25%, 35%, 45% and 55% (w/w). All tablets of these series contained 400 mg Norfloxacin and variable weight, according to the proportion of the added excipient. These and all following powder mixtures were compressed with flat-faced punches, 12.7 mm diameter, for 10 s on a hydraulic press at a compaction pressure of 85 MPa.

2.2.1.2. Mixtures of Starch 1500 and Pharmatose DCL 11. Maintaining a fix concentration of 25% of Pharmatose DCL 11 and variable quantities of Norfloxacin to adjust to 100%, Starch 1500 was added at concentrations of 4%, 8%, 10% and 16% (w/w). In the same manner, maintaining a fix concentration of 5% Starch 1500, Pharmatose DCL 11 was added at proportions of 5%, 15%, 25%, 35% and 45%. Tablets of these series were adjusted to a total constant weight of 400 mg.

2.2.1.3. Mixtures of PVP XL 10 and Pharmatose DCL 11. Maintaining a fix concentration of 15% of Pharmatose DCL 11 and variable quantities of Norfloxacin to adjust to 100%, PVP XL 10 was added at concentrations of 2%, 4%, 6%, 8%, 10% and 12%. In the same manner, maintaining a fix concentration of 10% PVP XL 10, Pharmatose DCL 11 was added at proportions of 5%, 15%, 25%, 35% and 45%. Tablets of these series were compressed with a total constant weight of 400 mg.

2.2.1.4. Mixtures of Croscarmellose sodium and Pharmatose DCL 11. Maintaining a fix concentration of 5% of Pharmatose DCL 11 and variable quantities of Norfloxacin to adjust to 100%, Croscarmellose sodium was added at concentrations of 1%, 2%, 4% and 6%. In the same manner, maintaining a fix concentration of 2.5% Croscarmellose sodium, Pharmatose DCL 11 was added at proportions of 5%, 15%, 25%, 35% and 45%. Tablets of these series were compressed with a total constant weight of 400 mg.

2.2.2. Dissolution studies

Dissolution studies were determined according to the described method in USP 23, apparatus 2 (paddle) at 50 rpm. The dissolution medium described by the USP 23 corresponds with 750 ml Acetate buffer solution of pH 4, maintained at 37°C (USP 23-NF 18, 1995). Although the volume and composition of the medium are not common, these are the conditions specified in USP 23. Filtered samples of dissolution medium, taken at different times, were determined for their Norfloxacin content through ultraviolet absorption at 276 nm. The results were normalized taking as 100% Norfloxacin the final concentration obtained for each trial, after total dissolution of tablets. This was obtained using 100 rpm during 15 min after 1 h dissolution. Dissolution studies were performed in triplicate for tablets of each different mixture of Norfloxacin and excipients and the results registered as an average. The highest dissolution that could be obtained from Norfloxacin tablets corresponds with 0.546 mg/ml. This concentration is about 175 times lower than the estimated solubility at pH 4.0 (Stefancich et al., 1984). Given this solubility (97 mg/ml) the dissolution was always carried out under sink conditions.

3. Results and discussion

3.1. Dissolution curves

Although many direct compressed tablets follow a cube root plot, in many cases dissolution curves are S-shaped. It has been suggested to treat these dissolution data using a Weibull function (Carstensen, 1996). The relationship between the undissolved fraction or the fraction of solid remaining Norfloxacin ($1-f_{diss}$) and the time (t) is described with an equation based on this distribution:

$$\ln\,(-\ln(1-f_{diss}))\ =\ \text{Slope}\times\ln\ t+\text{Constant} \quad (1)$$

Fig. 1 shows the dissolution profile of Norfloxacin from tablets containing 16% of the disintegrant Starch 1500, as an example of the application of the above-mentioned equation to describe the Norfloxacin dissolution process. The regression line is calculated with Eq. (1) and represented as

$$\ln(-\ln(1-f_{diss}))\ =\ 1.530\times\ln\ t-5.8219$$

$$r^2=\ 0.9966$$

As can be seen, this equation properly describes the dissolution process obtaining determination coefficients, in most of the cases, greater than 0.99 and properly fitting the regression of the experimental points.

3.2. Effect of Starch 1500 on dissolution of Norfloxacin tablets

Starch 1500 is a brand of pregelatinized maize starch being recommended as a disintegrant at proportions of 5–10%. It is considered a hygroscopic material with high water content, loss on drying $\leqslant 15\%$ (Wade and Weller, 1994). The actual loss on drying has been estimated as 10.5%.

The USP 23 calls for Norfloxacin, instead of a complete drug dissolution profile, for a one-point

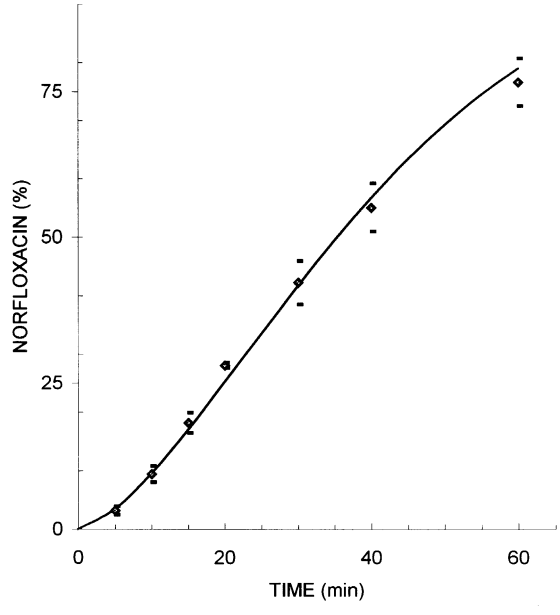

Fig. 1. Dissolution profile of Norfloxacin tablets containing 16% Starch 1500. Experimental points with standard deviation and regression calculated with the equation: $\ln(1-f_{diss})=$ Slope $\times \ln t +$ Constant.

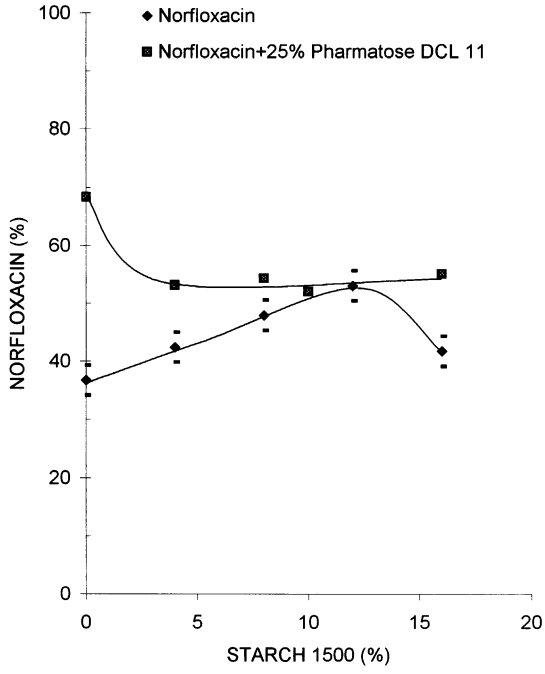

Fig. 2. Effect of addition of Starch 1500 on dissolution, at 30 min, of Norfloxacin and Norfloxacin/25% Pharmatose DCL 11 tablets.

method. In this case, a lower limit of 80% Norfloxacin dissolved after 30 min. Given this circumstance, the effect on dissolution of disintegrants and diluents are expressed in this article as Norfloxacin dissolved after 30 min. This point is calculated with the regression parameters of each dissolution curve and, in this way, this result is supported by all experimental points of each particular dissolution curve.

Fig. 2 shows the effect of different proportions of Starch 1500 on the dissolution after 30 min of tablets of pure Norfloxacin and Norfloxacin/Pharmatose DCL 11. The points in Fig. 2 are experimental and include the average standard deviation observed for individual values. Increasing concentrations of Starch 1500 increase the percentage of Norfloxacin dissolved after 30 min, until a maximum is reached at about 12% Starch 1500. After this maximum, the Norfloxacin dissolved decreases. This behavior can be considered as normal for a substance that acts promoting dissolution and, at the same time, works as a direct compression binder. Starch 1500 can form, under certain conditions, a swollen matrix that restricts the dissolution process. The problem with this type of disintegrants is that they absorb water to produce swelling and disintegration but if the quantity of Starch 1500 is big enough, the matrix does not disintegrate. The result would be a sticky or gelatinous mass similar to hydrophilic sustained release matrices, which resist break up of the tablets. This makes particularly important to optimize its concentration. At the beginning, increasing concentrations of Starch 1500 improve the Norfloxacin dissolution while after a concentration of about 12% the restricting effect begins to be more important.

The disintegration of Norfloxacin/Starch 1500 tablets is partial and after 1 h, not all the particles passed the bottom sieve of the disintegrator. This circumstance makes difficult the establishment of any relationship with the dissolution process. Dissolution is supposed to occur from Norfloxacin surfaces in direct contact with the dissolution medium as well as from diffusion through the water filled pores of granules or agglomerates of particles.

As can be seen in Fig. 2, the only addition of 25% of Pharmatose DCL 11 to Norfloxacin tablets increased their dissolution. The drug dissolved after 30 min increased from 36.7% to 68.3%. The supplementary addition to this formula of Starch 1500 decreases the tablet dissolution in an important manner. After addition of 4% of Starch 1500, the drug dissolved after 30 min decreases to values between 53% and 55%. No extra significant effects are observed by higher concentrations of the disintegrant up to 16%. In this case, Starch 1500 acts restricting the Pharmatose DCL 11 effect of improving the dissolution process. This could be attributed to water uptake by starch 1500, reducing in a small amount the availability of water for the Pharmatose DCL 11 dissolution and slowing the rate of water entry. It is supposed that Pharmatose DCL 11 competes with Starch 1500 for a given amount of available water inside the tablet or agglomerates. Moreover, dissolution of Pharmatose DCL 11 may allow accommodation of the swelling Starch 1500 particles, permitting little or no disintegrating force development.

3.3. Effect of Croscarmellose sodium on the dissolution of Norfloxacin tablets

Croscarmellose sodium or cross-linked Carboxymethylcellulose sodium is an excipient used as tablet and capsule disintegrant showing wicking and swelling abilities. Concentrations of up to 5% w/w are recommended as a tablet disintegrant although 2% can be considered as the usual concentration in tablets prepared by direct compression. For capsules, higher concentrations are recommended (10–25%). A loss on drying $\leqslant 10\%$ is considered normal and is a halfway value between that of Starch 1500 ($\leqslant 15\%$) and PVP XL 10 ($\leqslant 5\%$). The actual loss on drying has been estimated as 2.0%. Its efficacy as a disintegrant could be reduced in formulations containing hygroscopic excipients such as sorbitol (Wade and Weller, 1994).

Norfloxacin tablets containing Croscarmellose sodium shows the highest dissolution rates of all tablets studied. As can be seen in Fig. 3, the use of Croscarmellose sodium alone allows the dissolution of 76–100% Norfloxacin after 30 min. In the same way that Starch 1500, Croscarmellose sodium shows a maximum in its improvement of Norfloxacin dissolution, 100% Norfloxacin dissolved after 30 min, at a concentration of about 2.5%. Greater concentrations of this disintegrant decreases progressively Norfloxacin dissolution to 89% with the use of 4% Croscarmellose and then, to 76.5% when using 6% Croscarmellose (Fig. 3). This effect could be explained because of the binding properties of Croscarmellose sodium. By Croscarmellose proportions lower than 2.5%, the dissolution improvement effect is more important, while thereafter the binding properties overcome.

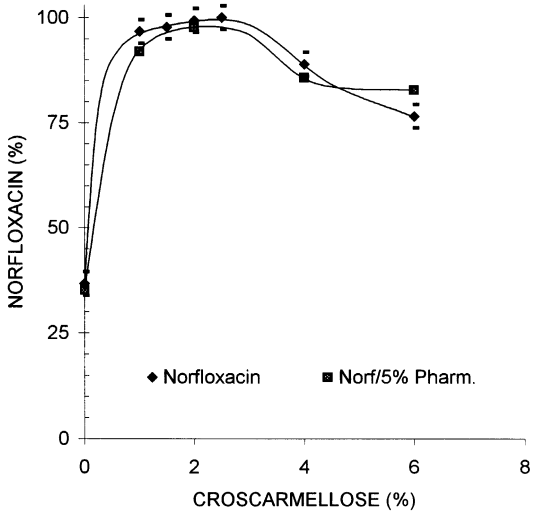

Fig. 3. Effect of addition of croscarmellose sodium on dissolution, at 30 min, of Norfloxacin and Norfloxacin/5% Pharmatose DCL 11 tablets.

The effect of adding 5% Pharmatose DCL 11 to Norfloxacin tablets containing Croscarmellose sodium is a slight decrease of dissolution. The modest effect of Pharmatose DCL 11 on the Croscarmellose sodium improvement of dissolution may be explained by a lower hygroscopicity of this substance, compared to Starch 1500. The dissolution improving properties of Croscarmellose sodium seem to be reduced in a magnitude corresponding with its hygroscopicity, which is at the middle of that of Starch 1500 and PVP XL 10. In this case, Pharmatose DCL 11 (5%) inhibited the effect of Croscarmellose sodium while in the case of Starch 1500, this disintegrant inhibited the dissolution improvement effect of Pharmatose DCL 11 (25%).

In most cases, there are many possibilities to combine the diluent and the disintegrants to study their interactions affecting tablet dissolution. In this case, disintegrant concentrations were primarily selected according to pharmaceutical criteria, selecting concentrations suitable or recommended for the best results and some other concentrations around. The reference was the Handbook of pharmaceutical excipients (Wade and Weller, 1994). Although a given and differential concentration of the diluent was selected for each disintegrant according to experience, the effect of different diluent concentrations on each disintegrant is also included to observe this particular effect.

3.4. Effect of PVP XL 10 on the dissolution of Norfloxacin tablets

PVP XL 10 (Crosspovidone) is a water insoluble type of cross-linked polyvinylpyrrolidone used as tablet disintegrant at concentrations of 5–10%,

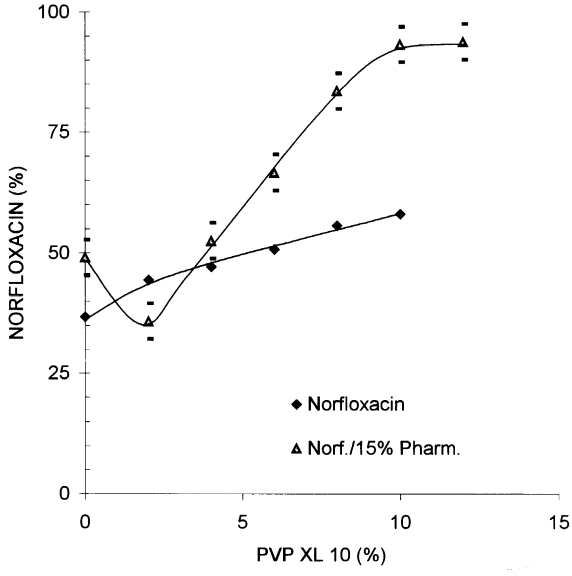

Fig. 4. Effect of addition of PVP XL 10 on dissolution, at 30 min, of Norfloxacin and Norfloxacin/15% Pharmatose DCL 11 tablets.

exhibiting high capillary activity and pronounced hydration capacity with little tendency to gel formation. Its water content is considered $\leqslant 5\%$ (Wade and Weller, 1994). Actually, it has been estimated as 4.7%.

Fig. 4 shows the effect of different proportions of PVP XL 10 on the dissolution after 30 min of Norfloxacin tablets. Increasing concentrations of PVP XL 10 increase the percentage of Norfloxacin dissolved after 30 min. The dissolution of Norfloxacin tablets containing PVP XL 10 is lower than 56% by concentrations of PVP XL 10 $\leqslant 8\%$. In this case and opposed to Starch 1500 and Croscarmellose sodium, the effect of a supplementary addition of Pharmatose DCL 11 (15%) to Norfloxacin/PVP XL 10 tablets is a substantial improvement of their dissolution. The reason for this behavior seems to be the lower hygroscopicity of PVP XL 10, compared to Starch 1500 and Croscarmellose sodium. This lower hygroscopicity allows a better deployment and potentiation of the dissolution improving properties of both components, Pharmatose DCL 11 and PVP XL 10. Presumably, because of a lower consume of water by the disintegrant, leaving inside the tablet more available water for dissolution of Pharmatose DCL 11.

Disintegration of Norfloxacin/PVP XL 10 tablets is incomplete at a time of 1 h. Although some tablets disintegrate to particles passing the bottom sieve of the disintegrator tubes, some other tablets disintegrate to particles that remain on the sieve. This situation made difficult to establish any relationship between dissolution and disintegration of the tablets.

3.5. Effect of Pharmatose DCL 11 on the dissolution of Norfloxacin tablets

It is clear from experience that every excipient, like a diluent, has always other properties that contribute to the entire tablet properties. The addition of Pharmatose DCL 11 improves the dissolution of pure Norfloxacin tablets, acting as a dissolving or passive disintegrant. Fig. 5 shows this effect. Increasing concentrations of Pharmatose DCL 11 produce important increases of Norfloxacin dissolved, reaching a maximum of about 80% Norfloxacin dissolved at 30 min, by tablets containing Pharmatose DCL 11 propor-

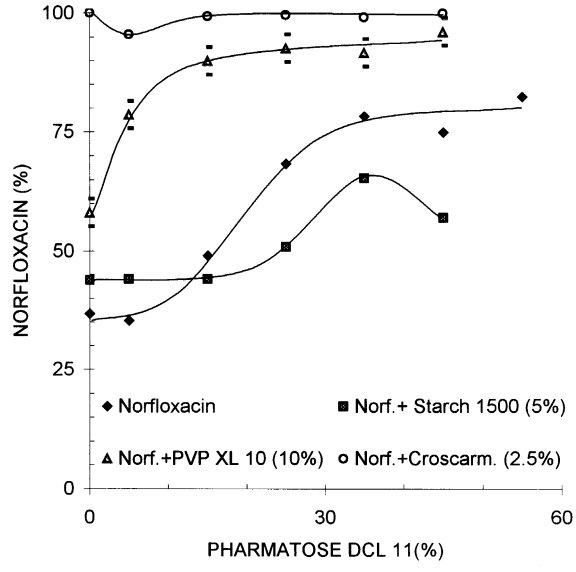

Fig. 5. Effect of addition of Pharmatose DCL 11 on dissolution, at 30 min, of tablets of Norfloxacin and Norfloxacin added of a disintegrant.

tions from 35% to 55%. Tablets of this series disintegrate completely at increasing times as the proportion of Pharmatose DCL 11 decreases. The disintegration times are 37, 38, 44, 45 and 52 min for tablets containing, respectively, 55%, 45%, 35%, 25% and 15% Pharmatose DCL 11. Tablets containing 5% Pharmatose DCL 11 show no disintegration after 1 h but dissolved partially.

Fig. 5 also shows the effect of different proportions of Pharmatose DCL 11 on the Norfloxacin dissolved after 30 min from tablets containing 5% Starch 1500. Tablets containing Norfloxacin and this disintegrant increase their dissolution with increasing concentrations of the diluent but in lower proportion than tablets of Norfloxacin alone. This seems to occur because of competition for the available water. This circumstance impedes the complete deployment of the dissolution improving properties of each individual excipient.

Although 5% Pharmatose DCL 11 inhibits slightly the dissolution improvement effect of Croscarmellose sodium, increasing proportions of Pharmatose DCL 11 allow total dissolution of Norfloxacin (Fig. 5). Croscarmellose sodium (2.5%) recovers and maintains its dissolution improvement effect with increasing proportions of Pharmatose DCL 11.

Pharmatose DCL 11 increases the dissolution of Norfloxacin/PVP XL 10 tablets (Fig. 5). Opposite to Starch 1500 and Croscarmellose sodium, tablets with PVP XL 10 show no negative effect on dissolution but potentiation after addition of Pharmatose DCL 11. However, concentrations of Pharmatose DCL 11 greater than 15% increase only slightly the Norfloxacin dissolved after 30 min. The greatest effect is provided by concentrations up to 15% Pharmatose DCL 11. This circumstance gives an idea about a predominance of water absorption by the disintegrants, leaving the rest of water for dissolution of the diluent.

4. Conclusions

It is clear from the experiments that the factors affecting the dissolution of Norfloxacin tablets include both the disintegrant and the diluent. Physically, the interaction between the disintegrant and the diluent is considered to be due to competition for the available water. When the water uptake is high in both formula components, as in mixtures of Starch 1500/Pharmatose DCL 11, the result is a mutual inhibition of their dissolution improvement activities. The use of a less hygroscopic or less water avid disintegrant like Croscarmellose sodium allow a more effective deployment of its dissolution improvement properties in presence of a dissolving diluent like Pharmatose DCL 11. Croscarmellose sodium experiences only a modest effect of inhibition, compared to a more hygroscopic disintegrant like Starch 1500. In the same way, the use of a disintegrant with much lower hygroscopicity or much less water avidity like PVP XL 10 allows a more effective deployment of its dissolution improvement properties. PVP XL 10 allows a better deployment of the dissolution improvement properties of dissolving diluents like Pharmatose DCL 11. As a result, Pharmatose DCL 11 does not inhibit this disintegrant but potentiates its dissolution improvement activity.

Improvement of drug dissolution through disintegrants cannot be made without considering the interaction with water of the major components of the formula. High hygroscopic or high water avid disintegrants will be inhibited by other high water consuming formula components. On the other hand, low hygroscopic or less water avid disintegrants will be potentiated by passive dissolving disintegrants like Pharmatose DCL 11.

References

Banker, S.G., 1990. Modern Pharmaceutics, second ed. Marcel Dekker, New York, pp. 372–379.

Caramella, C., Colombo, P., Conte, U., La Manna, A., 1987. Tablet disintegration update: the dynamic approach. Drug Dev. Ind. Pharm. 13 (12), 2111–2145.

Carstensen, J.T., 1996. Modeling and Data Treatment in the Pharmaceutical Sciences. Technomics Pub. Co., Lancaster, PA, USA, pp. 55–56.

Gordon, M.S., Rudradaju, V.S., Dani, K., Chowhan, Z.T., 1991. Effect of the mode of super disintegrant incorporation on dissolution in wet granulated tablets. J. Pharm. Sci. 82 (2), 220–226.

Roche-Johnson, J., Wang, L.H., Gordon, M.S., Chowhan, Z.T., 1991. Effect of formulation solubility and hygroscop-

icity on disintegrant efficiency in tablets prepared by wet granulation, in terms of dissolution. J. Pharm. Sci. 80 (5), 469–471.

Stefancich, G., Artico, M., Corelli, F., Massa, S., 1984. 1-Ethyl-6-fluoro-1,4-Dihydro-4-Oxo-7.(1H-Pyrrol-1-YL)-Quinoline-3Carboxylic acid, a new Fluorinated Compound of Oxacin Family with high broad-Spectrum Antibacterial Activities. Il Farmaco. Ed. Sci. 40 (4), 237–248.

USP 23-NF 18, 1995. The United States Pharmacopeial Convention, Inc. Rockville, MD, USA, pp. 1791–1793.

Van Kamp, H.V., Bolhuis, G.K., Kussendrager, K.D., Lerk, C.F., 1986. Studies on tableting properties of lactose. IV. Dissolution and disintegration properties of different types of crystalline lactose. Int. J. Pharm. 28, 229–238.

Villafuerte-Robles, L., 1994. Efecto de la concentración de fosfato de calcio sobre la desintegración de tabletas de celulosa microcristalina tipo 102. Rev. Mex. C. Farm. 25 (3), 16–21.

Visavarungroj, N., Remon, J.P., 1990. Crosslinked starch as a disintegrating agent. Int. J. Pharm. 62, 125–131.

Wade, A., Weller, P.J., 1994. Handbook of Pharmaceutical Excipients. American Pharmaceutical Association, Washington, USA.