DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 8, pp. 901–908, 2004

Effect of Formulation and Process Variables on the Release Behavior of Amoxicillin Matrix Tablets

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ABSTRACT

The sustained release of amoxicillin is desired to be confined to the upper gastrointestinal tract to treat certain kind of infections. In vitro dissolution, at pH 1.2, of amoxicillin sustained release tablets has been studied varying the proportion of Carbopol 971P NF and sodium alginate as well as the ethanol/water proportion in the granulation fluid. M_t, the amount of drug released at time (t) and defined in terms of the total drug released over a long time period (M_{inf}), was described by $M_t/M_{inf}=kt^n$. Matrices with increasing proportions of sodium alginate showed increasing values of the exponent indicative of the release mechanism (n) and increasing release constant values (k). This is attributed to a drop in the coherence of the polymeric matrix with increasing alginate proportions that produces an increasing polymer relaxation and erosion. Decreasing Carbopol 971P NF proportions reduce the amount of dissolved polymer during granulation, producing a lesser obstruction of amoxicillin dissolution. Alginate proportions of 80% produce near zero order release profiles. Granules obtained with increasing ethanol proportions showed increasing release constant values and a minor change in the exponent (n) values. This is considered a result of lower polymer dissolution during granulation that allows a lesser matrix coherence and a greater amoxicillin dissolution. Alginate matrices granulated with different ethanol/water proportions showed no significant changes in the amoxicillin release profile. There is a trend toward increasing floating times with increasing Carbopol 971P NF proportions.

Key Words: Sustained release; Amoxicillin; Carbopol 971P NF; Sodium alginate; Granulation liquid.

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DOI: 10.1081/DDC-200034594
0363-9045 (Print); 1520-5762 (Online)

INTRODUCTION

The convenience of administering a single dose of medication, which releases active ingredient over an extended period as opposed to the administration of a number of single doses at regular intervals, has long been recognized in the pharmaceutical art. However, oral sustained release formulations can be disadvantageous in that certain classes of active ingredients are poorly absorbed during passage through the gastrointestinal tract due to their physicochemical properties and/or favorable sites of absorption. In view of these considerations, some medicaments are not open to conventional sustained release formulations if they are not retained in a given part of the gastrointestinal tract, for instance the stomach.[1]

Hydrophilic matrix tablets are systems attractive from economic as well as from the process development points of view. Different types of polymers are used to control the release of drugs from this type of dosage forms. The use of mixtures of polymers represents a potential way of achieving required release properties.[2] Mixtures of different polymers have been used to give different viscous efficiencies.[3–5] Mixtures of nonionic and ionic varieties led to formulations of hydrosoluble active principles with zero-order release profiles.[6–10] Mixtures of different proportions of polymers with different permeation characteristics can provide a wide range of release rates of a drug by changing the diffusivity of the drug through a polymer barrier.[11]

Swellable matrices may modify their dissolution pattern and dissolution rate on addition of a second polymer to the matrix. The resulting effect is a consequence of the second polymer solubility and the physicochemical interactions between the polymers in an aqueous medium. Moreover, the addition of insoluble polymers to hydrophilic swellable matrices modifies the dissolution profiles, increasing or reducing the release rate, according to their proportion and type of adhesive interaction with the hydrophilic swellable polymer.[12]

Carbopol 971P NF is one of the polymers of the carbomer series. These polymers readily hydrate, absorb water and swell quickly. Their hydrophilic nature and highly crosslinked structure renders them suitable for use in controlled release drug delivery systems.[13]

Aqueous dispersions of Carbopol polymers have an approximate pH range of 2.8–3.2. Carbomer molecules are tightly coiled in the dry powder state. When disperse in water the molecules hydrate and uncoil slightly, increasing the viscosity of water. However, to achieve the highest viscosity the molecule must be completely uncoiled. This occurs by neutralizing the polymer with a suitable base. Carbopol 971P NF has a semi-enteric behavior, providing slow release in the stomach but quickly releasing the drug as the pH rises in intestinal tract. Carbopols feature extremely rapid efficient gelation characteristics.[14]

Alginates are natural polysaccharide polymers. At low pH hydration of alginic acid leads to the formation of a high-viscosity ''acid gel'' due to intermolecular binding. Under acidic conditions (e.g., in the stomach) swelling of alginates scarcely occurs. A drug is likely to be release by diffusion through the insoluble matrix. Under neutral conditions, alginates swell and the drug release depends on the swelling and erosion processes.[15] After gelation, the water molecules that are physically inside an alginate matrix are still free to migrate and to be replaced by other water molecules.

Alginic acid is practically insoluble in alcohol and in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight, and in acids when the pH of the resulting solution becomes lower than 3. Alginic acid dissolves in solution of alkali hydroxides. Sodium alginate is also practically insoluble in alcohol. Alginic acid or the alginates react with gastric acid to form a viscous gel, often termed a raft, which floats on top of the gastric contents, opening the opportunity to make a buoyant formulation with an increased residence time in the stomach. Another potential approach to extend the gastrointestinal residence time is to prepare a bioadhesive drug delivery system. Alginate is demonstrated to have excellent bioadhesive properties.[16]

Considering the properties of the above-mentioned polymers, the aim of this work is the investigation of the effects of polymer composition and granulation fluid on the release profile of amoxicillin from a potential floating matrix tablet.

MATERIALS AND METHODS

Materials

The pharmaceutical excipients Carbopol 971P NF, a brand of a synthetic high molecular weight polymer of acrylic acid from B. F. Goodrich Co., obtained from Noveon-México, sodium alginate, natural polysaccharide polymers isolated from brown seaweed, obtained from ISP-Mexico and the drug amoxicillin trihydrate obtained from FERSINSA-Mexico with a potency of 86%, were used as received. The ethanol used for granulation was 96% pure.

Methods

Matrix Preparation

Matrix tablets were produced with 548 mg polymer of varying composition and a fixed quantity of amoxicillin trihydrate of 1017 mg, equivalent to 875 mg of the base. The alginate proportions corresponded to 20, 35, 50, 65 and 80% of the total polymer content. 50 g of the powders corresponding to each formulation were tumble mixed for 20 min. The powder mixtures were moistened in a mortar with a water/ethanol (15:85) solution, kneading with a spatula. The agglomerates were dried at 50°C for 2 hours and size reduced in a mortar. Another series of matrices containing the polymers in a 50:50 proportion were wet granulated with different proportions of ethanol/water. The ethanol proportions corresponded to 70, 75, 80, 85 and 100%. Pure alginate matrices were wet granulated with ethanol/water mixtures containing 70, 85 and 100% ethanol. The weight of granules corresponding to each tablet was compressed in a hydraulic press at 28 MPa during 10 seconds, with punches and die producing 7 mm width and 21 mm length capsule shaped tablets. No lubricant was used in the tablets.

Drug Release

Dissolution studies were performed in triplicate using the USP apparatus 2 at 50 rpm. The medium was 900 ml buffer solution pH 1.2 which was maintained at 37°C. Samples were taken at appropriate time intervals and assayed spectrophotometrically at 272 nm. The dissolution profiles were corrected for the UV-absorption change produced by amoxicillin degradation.[17]

RESULTS AND DISCUSSION

Dissolution of Amoxicillin from Alginate/Carbopol 971P NF Sustained Release Tablets

Dissolution of amoxicillin at pH 1.2 and determined by UV-absorption displays higher values than those corresponding to dissolution without degradation of the drug. Amoxicillin solutions increase their UV-absorption progressively under dissolution conditions. After correction for the UV-absorption increase due to amoxicillin degradation, the real dissolution data can be obtained.[17]

Experimental data were fitted to the power law expression shown in Eq. 1 to examine the kinetics and mechanism of drug release of each formulation:[18,19]

$$M_t/M_{inf} = k*t^n \quad \text{or}$$
$$\ln(M_t/M_{inf}) = n*\ln(t) + \ln(k) \qquad (1)$$

The terms in this equation are as follows: M_t, the amount of drug released at time t; M_{inf}, the total drug released over a long time period. It actually means the drug that can be extracted from the matrix and not necessarily corresponds to the drug content initially loaded; k, the kinetics constant; and n, the mechanism of drug release. The value of n ranges from 0.5 ($t^{1/2}$ dependence, generally referred to as Fickian release) to 1 (representing the case II transport which is purely relaxation controlled). The values in between indicate an anomalous behavior corresponding to coupled diffusion/relaxation. When the value of n is greater than that of the case-II transport ($n>1.0$), the release is said to be Super case-II transport.[10,20] In the case of a matrix with cylinder form, n is said to be 0.45 instead of 0.5 and 0.89 instead of 1.0.[21]

Figure 1 shows the corrected dissolution profiles of amoxicillin (1017 mg) from alginate/Carbopol 971P NF (548 mg) matrix tablets. The cumulative dissolution

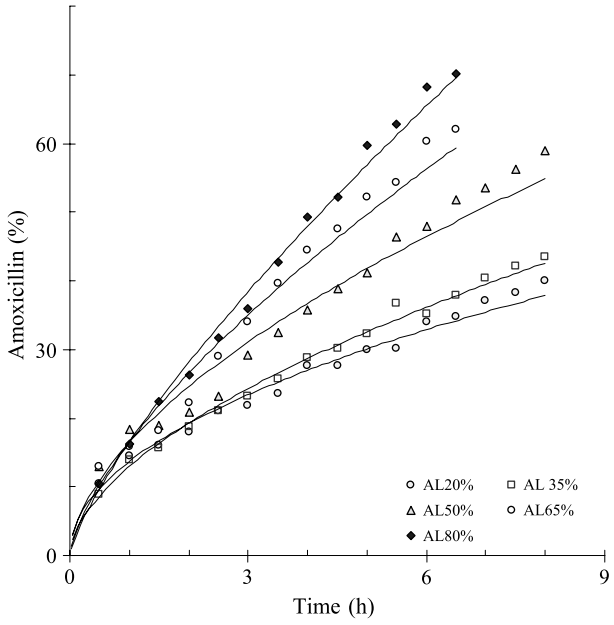

Figure 1. Effect of the sodium alginate proportion on the amoxicillin (1.017 g) sustained release profile from matrices containing different proportions of Carbopol 971P NF and sodium alginate (0.548 g).

curves were calculated correcting the experimental data for the changes produced by amoxicillin degradation.

Effect of Polymers Proportion on the Amoxicillin Release Profile from Matrix Tablets

As can be seen in Fig. 1, an increasing proportion of alginate in the polymeric portion of the matrix tablets produces faster amoxicillin dissolution. Figure 2 shows a trend toward an increasing amoxicillin release rate, expressed as percent amoxicillin dissolved after 3 hours, with increasing alginate proportions.

The increase of release rate produced by increasing proportions of alginate is attributed to a drop in coherence of the matrix. During granulation, Carbopol 971P NF, by partially dissolving in the granulation fluid is likely to increase the coherence of the granules and potentially restricts the dissolution of the amoxicillin particles by coating their surfaces. Moreover, the better Carbopol 971P NF distribution allows a faster hydration and a greater coherence of the matrix in contact with an acid medium.

The hypothetical drop in coherence of hydrated matrix tablets with increasing alginate proportions is reflected on greater exponent (n) values. These greater exponent (n) values correspond to matrices with more emphasis of matrix relaxation and erosion on the release mechanism. Figure 3 shows a clear trend toward increasing exponent (n) values as the alginate matrix proportion increases. At low alginate proportions, beginning with a matrix with a drug release controlled by diffusion, the release mechanism moves progressively, through an anomalous process, toward a relaxation and erosion controlled process. Matrices containing 80% alginate show a near zero order release mechanism.

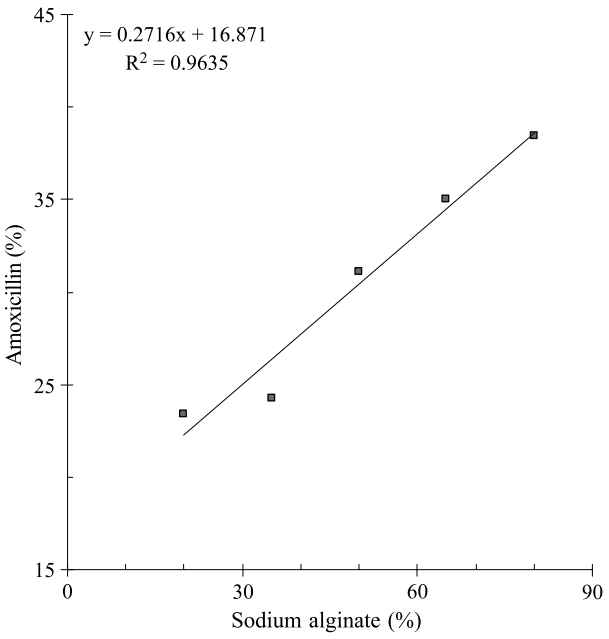

Figure 2. Effect of the sodium alginate proportion on the amoxicillin released after 3 hour from matrices containing Carbopol 971P NF and sodium alginate.

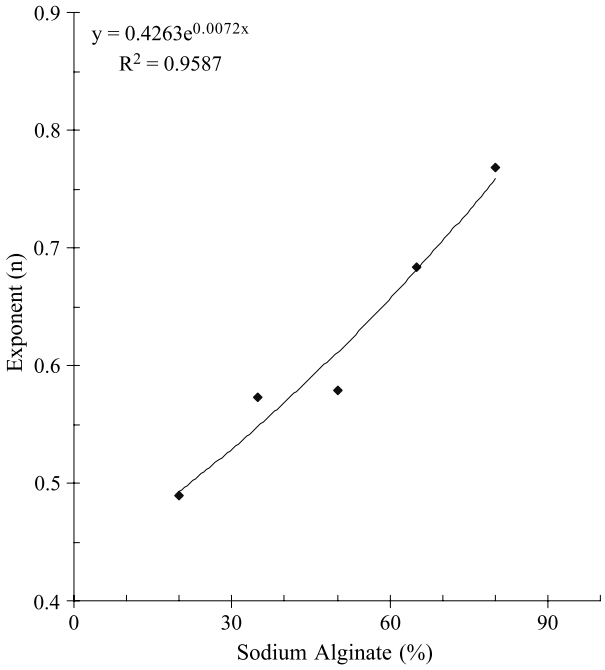

Figure 3. Effect of the sodium alginate proportion on the exponent indicative of the release mechanism (n) of amoxicillin release curves from matrices containing Carbopol 971P NF and sodium alginate.

The above-mentioned treatment of release data according to the power law expression that is shown in Eq. 1 allows the estimation of an average release mechanism. However, the changes in release mechanism taking place during the process are not manifest.

The known Higuchi equation or equation of the square root of time considers the matrix release kinetics with a fixed mechanism, generally referred to as Fickian or diffusion controlled release. The treatment of initial amoxicillin release data fitting the Higuchi equation allows the observation of the part of the dissolution process controlled by diffusion. Figure 4 shows the regression and extrapolation of dissolution profiles that describe the diffusion-controlled part of the amoxicillin dissolution and depicts the contribution of matrix relaxation and erosion to release process.

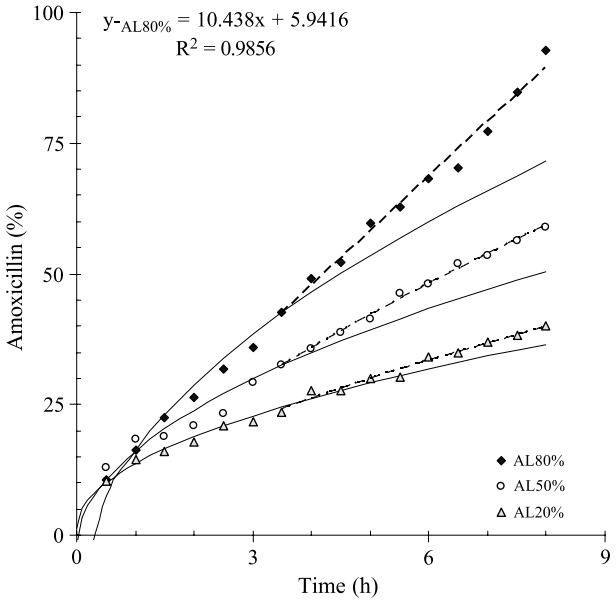

Figure 4. Effect of the sodium alginate proportion on amoxicillin sustained release from matrices containing different proportions of Carbopol 971P NF and sodium alginate.

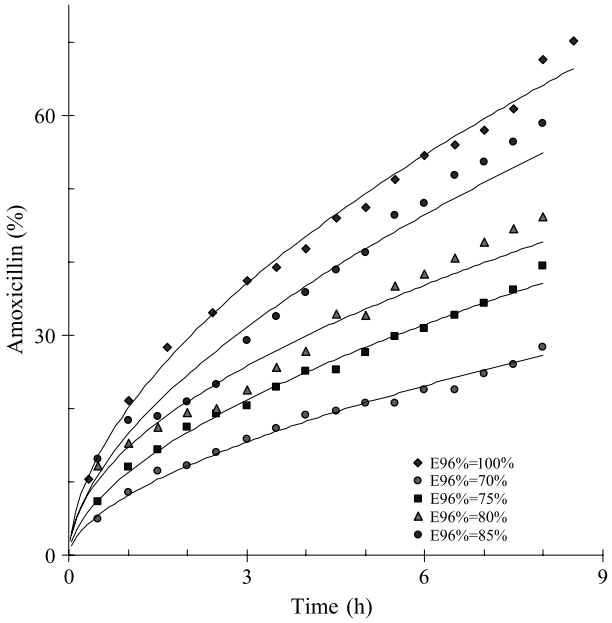

Figure 5. Effect of the ethanol proportion, in mixtures with water used as granulation liquid, on the sustained release profile of amoxycillin (1.017 g) from matrices containing 0.548 g of Carbopol 971P NF and sodium alginate (50:50).

Matrices containing 20% alginate release amoxicillin almost with a diffusion-controlled process. The above-mentioned drop in coherence of the polymeric matrices with increasing alginate proportions is shown here as an increasing separation of experimental points from the extrapolated regression.

Increasing proportions of alginate in the polymeric portion of the matrix increase this separation. Matrices with 80% alginate show an almost lineal release of amoxicillin after a burst effect in the initial stage of about 6%. The regression calculated with the experimental points not fitting the Higuchi or square root equation.

Effect of the Granulation Fluid on the Amoxicillin Release Profile from Matrix Tablets

Figure 5 shows the release profile of matrices containing 548 mg of a fixed proportion of a Carbopol 971P NF and alginate (50:50) mixture and a fixed amoxicillin quantity of 1017 mg/tab.; the regressions are the calculated with Eq. 1. As can be seen, the increase of ethanol in the mixture with water used as granulation fluid increases the release rate of amoxicillin. Figure 6 shows this trend expressed as the amoxicillin dissolved after 3 hours. The increase in release rate produced by increasing ethanol proportions in the granulation fluid is attributed to decreased

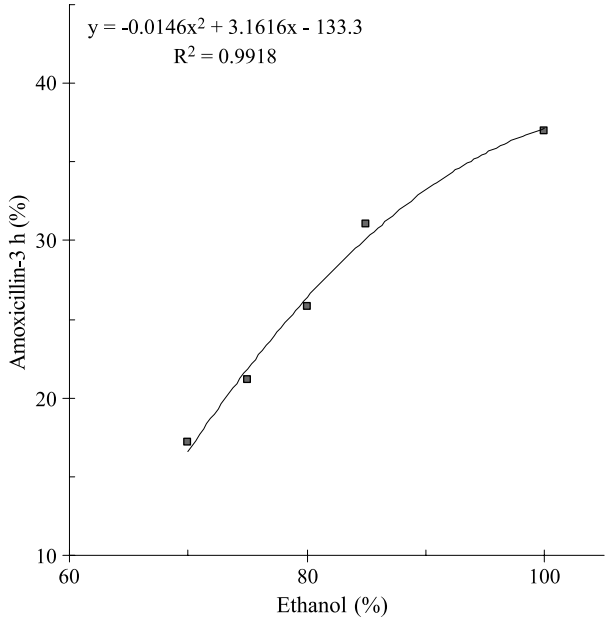

Figure 6. Effect of the ethanol proportion, in mixtures with water and used as granulation liquid, on the amoxycillin dissolved after 3 hours from matrices containing Carbopol 971P NF and sodium alginate (50:50).

coherence of matrices granulated with smaller proportions of water. The Carbopol 971P NF dissolved during granulation increases as the water content of the granulation fluid increases. Moreover, the dissolution of Carbopol 971P NF during granulation allows a more intimate mixture with amoxicillin, obstructing or delaying its dissolution. The granulation with an alcoholic solution of a water-soluble excipient like Carbopol 971P NF will dissolve it in a variable degree, depending on the water proportion of the granulation fluid. Partially dissolved polymer is then distributed on the surface of the undissolved particles. After drying, the dissolved polymer remains as a solid layer deposited around the undissolved particles, in this case amoxicillin and the alginate.

The values of the exponent (n) show an average of 0.578 ± 0.053. It is considered constant. The release mechanism is anomalous and similar to that of the formulation granulated with 85% ethanol in the previous series (0.579).

Figure 7 shows that matrices containing only amoxicillin and alginate, and granulated with different proportions of ethanol and water, show no significant changes in their release profile. This could be expected, considering that Carbopol 971P NF is the only polymer affecting the release profile by its dissolution during granulation with alcoholic solutions.

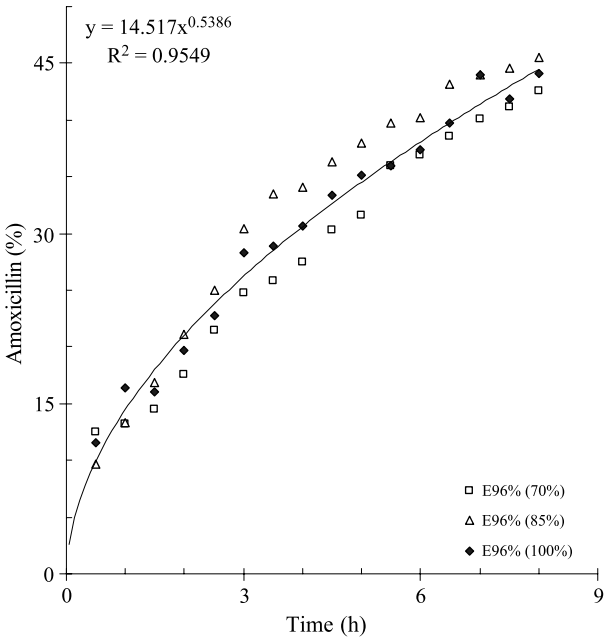

Figure 7. Effect of the ethanol proportion, in mixtures with water used as granulation liquid, on the release profile of amoxicillin (1017 mg) from sodium alginate matrices (548 mg).

Table 1. Flotation time of different amoxicillin formulations. Matrix tablets containing different proportions of carbopol 971p nf and sodium alginate granulated with ethanol/water mixtures.

Granulation fluid (%-ethanol)	Carbopol 971P NF (%)	Flotation time (h)
85	80	4.5
85	65	4
85	50	4
85	35	3.5
85	20	3.5
100	0	3
85	0	3
70	0	3.5
100	50	3.5
85	50	3.5
80	50	4
75	50	4

Floating Behavior of Alginate/Carbopol 971P NF Matrix Tablets

Matrices of the first series, with varying proportions of the two polymers, floated from the very beginning. Although after about 1 hour the matrices were still floating, they began to go under the surface of the liquid. In a time of about 4 hours, the matrices went down to the bottom of the dissolution vessel (Table 1). There is a trend toward increasing floating times with increasing Carbopol 971P NF proportions. It seems that the rapid gelling properties of Carbopol 971P NF seal the tablets keeping the air inside. Matrices containing 80% alginate float for 3.5 h while matrices containing 20% alginate float for 4.5 h.

Matrices granulated with different ethanol/water proportions show a minor trend toward increasing floating times with increasing water content in the granulation fluid. Matrices of amoxicillin/alginate show negligible changes in the floating behavior due to increasing water or ethanol proportions in the granulation fluid.

CONCLUSIONS

Release curves obtained from tablets containing amoxicillin and Carbopol 971P NF/sodium alginate

mixtures show increasing values of the exponent indicative of the release mechanism (n) and increasing release constant values (k) as the alginate proportion increases. This is attributed to the water solubility of Carbopol 971P NF and its partial solubilization during granulation. Increasing Carbopol 971P NF proportions deposited on amoxicillin particles allow a higher restriction of the dissolution process and a greater coherence of the gelled matrix. A drop in matrix coherence produced by increasing alginate proportions moves the release mechanism from diffusion toward relaxation/erosion. The use of increasing proportions of ethanol in mixtures with water used as granulation fluid increases the release rate of amoxicillin due to lesser dissolution of Carbopol 971P NF during granulation and consequently, a lesser restriction of amoxicillin dissolution. The change in proportions of ethanol and water seems to maintain unaltered the release mechanism when the Carbopol 971P NF/alginate proportions are constant. Because of the above-mentioned explanations, alginate/amoxicillin matrices granulated with different proportions of ethanol/water maintain unchanged their dissolution profile. The flotation properties of about 4 hour has to be improved to guaranty a sufficient residence time in the stomach to release the complete amoxicillin content.

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