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DEVELOPMENT OF A FORMULATION OF SUSTAINED RELEASE POTASSIUM CHLORIDE

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The purpose of this work has been the designing and "in vitro" evaluation of a potassium chloride tablet using a wax matrix.

Carnauba wax, stearyl alcohol and stearic acid were employed to prepare granulates at different drug/wax ratios. From dissolution kinetic studies and technological performances a 75/25 - KCl/carnauba wax granulates was selected. The rheological properties of granulates were characterized and tablets were manufactured employing commun tablets excipients. Also a coating procedure was developed. The coated tablet formulation selected release the potassium chloride according to the USP requirements.

The dissolution kinetics of the potassium chloride from both coated and uncoated tablets fit the Higuchi diffusión model, giving a straight line when the amount dissolved is plotted against the square root of time.

INTRODUCTION

Over the last few years, great advances have been achieved in the development of pharmaceutical dosage forms that release active principles into the body on a time scheduled basis, in order to optimize their effects (1-4). This kind of formulation is very valuable in the case of drugs which, like potassium chloride- can irritate the mucose of the digestive tract. When administered under conventional dosage forms, such drugs may cause ulcerations with severe hemorrhage and perforations (5-8).

In the present work we have studied the formulation, the physical characteristics, galenic properties as well as the release of the active principle "in vitro" of a sustained release potassium chloride tablet, using a wax matrix.

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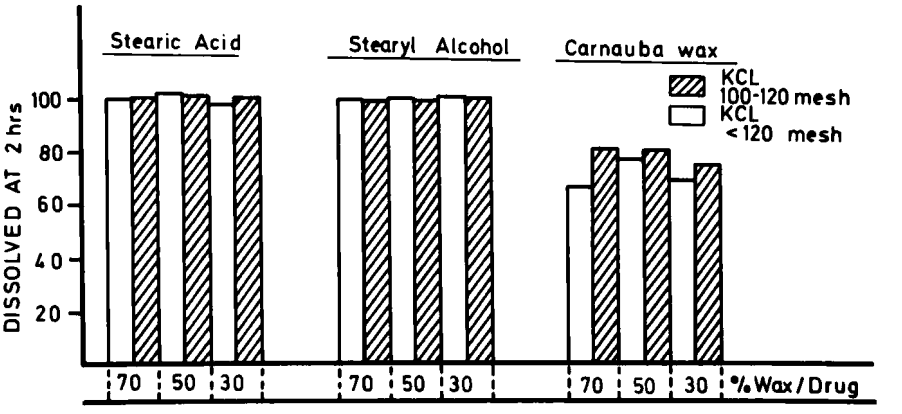

FIGURE 1

Percentage of potassium chloride dissolved at 2 hours, starting from granulates obtained with different waxes at different proportions, using two sizes of drug particles.

Treatment of the Dissolution Data: The treatment suggested by Higuchi and other authors was applied (13-16).

Statistical Analysis: The Student's t test for paired data was used, at a significant level of 0.01 (17).

RESULTS AND DISCUSSION

The granulates homogeneity decreases as the proportion of wax in the mixture augments; in the case of the carnauba wax granulate the coefficient of variation fluctuated between 0.95% (ratio 25/75 wax/drug) and 7.4% (ratio 70/30, wax/drug).

Figure 1 shows the results of the dissolution test, using two sizes of potassium chloride particles. Stearic acid and stearyl alcohol release the whole drug at 2 hours, in the 3 ratios studied as long as carnauba wax retains approximetely 25% of the KCl. There were no differences in the amount of drug dissolved at the different ratios studied. Neither were differences when employing the two sizes of KCl particles in the manufacture of the granulates. However the use of the 120 mesh KCl particles facilitates the manufacturing process. Growing concentrations of the drug were also used until attaining the ratio drug/wax 90/10. The ratio 75/25 presented the best characteristics for technological management and around 100% of dissolved drug was attained at 12 hours.

MATERIALS AND METHODS

Equipments and Machinery:

Excentric machine, Hanseat, Model EI; Excentric machine, Manesty, type F3; Flame Photometer Evans Electroselenium LTP; Six vessels dissolution equipment,

Hanson Research Model 48 300 202 5; Durometer Erweka Apparatebau GmbH Type:TBT/S; Durometer Schleuniger 4M; Friabilometer Erweka Apparatebau GmbH.

Assay of Potassium Chloride: Potassium chloride was assayed by flame photometry (9).

Wax Matrices: Stearic acid, carnauba,wax and stearyl alcohol were used in different proportions.

Obtention of the Granulates

Different granulates were obtained, by melting each wax at the appropriate temperature (Stearic acid 70°C, stearyl alcohol 60°, carnauba wax 86°C) in a porcelain capsule. Potassium chloride, previously sieved through a 120 mesh screen, was then added and stirred to achieve a dispersion on an aluminium dish; it was then quickly chilled. The resultant mass was then ground and sieved through a N° 16 mesh.

Properties of the Granulates

Dissolution characteristics were studied. The apparatus N° 2 of the USP XXI was used; bi-distilled water was the dissolution medium and the stirring speed was 50 rpm (10). It was found that the vector that longer delayed the release of potassium chloride was carnauba wax.

A granulometric analysis was carried out, using standard screens; the repose angle and the flow rate, using 20 g granulate and a funnel with a 70 mm long and 6 mm diameter stem, were also determined.

Manufacture and Properties of Potassium Chloride Tablets in Carnauba Wax

In order to work with a granulate whose characteristics would be close to those recommended (11, 12), 65% of the weight of the intial granulate, was separated (sieved through the 16 mesh screen); it was then ground and sieved through the 60 mesh screen and subsequently mixed with 35% of the remaining granulate, thus obtaining the final granulate. The other excipients were then added at the adequate proportions, they were mixed for 5 min, and finally compressed in an excentric machine. Both the hardness and friability of the tablets thus obtained were determined. The same method described for the granules was employed to study the dissolution kinetics of the tablets. A suspension containing Eudragit RS 100, talc, magnesium stearate, titanium dioxide and colorant was employed for coating the tablets.

Dissolution Kinetics of Coated Tablets

In order to select the final formulation, six tablets of each lot were submitted to dissolution test. Samples were drawn after 2 hours and assayed using flame photometry. The formulation selected was submitted to a dissolution kinetic study using experimental conditions described above. Samples were taken at 15, 30, 45 and 60 min and at 2, 4, 6, 8, 10 and 12 hours.

The granulometric study for carnauba wax in the initial granulate (75/25) indicates that the distributions of the granulate presents a higher deviation toward the larger particles; i.e., the fractions retained in the 20 mesh and 40 mesh screens, in contrast with the final granulate which presents a distribution closer to the normal one.

The repose angle was larger in the final granulate than the initial one, although the latter showed a better granulometric distribution. With the addition of colloidal silica (0.25% - 0.5%) and talc (2% - 4%) the initial granulate showed no variation in both parameters. Nonetheless, the final granulates showed an improvement in both parameters when lubricants were added. An optimum flow was obtained using 0.25% of colloidal silica.

We selected two granulates for the manufacture of the tablets (70/30 and 75/25; drug/wax). Six formulations were developed, the types of granulate and the quality and quantity of the excipients were different.

Table 1 shows the results of the dissolution studies carried out with these formulations. Formulation 1 (70/30 drug/wax) presents 68.4% of dissolved KCl at 2 hours; i.e., higher than the limit indicated by USP XXI. Formulation 2 was carried out with the objective of slowing down the dissolution rate; to this end, 0.5% magnesium stearate was added to Formulation 1, which produced a statistically significant delay of the percentage of drug dissolved from hour 2 of the sampling.

In tablets with a very high dose of active principle it is important to reduce the amount of excipients in order to facilitate their deglutition. This is especially advisable in the case of KCl, a compound which prduces irritation in the digestive tract. Formulation 3 was prepared from granulate 75/25, with the same excipients as in Formulation 2; the tablets obtained had a smaller final volumen which, however, released 74.7% of the active principle at 2 hours and showed statistically significant differences in the percentage of drug dissolved at the other times, as compared to those obtained from Formulation 2.

A greater percentage of magnesium stearate was added to formulation 4 in order to delay the KCl release. Formulations 2 and 4 did not present statistically significant differences in their percentages of KCl dissolved at all sampling times, except at 10 and 15 minutes. Formulations 5 and 6 contain larger percentages of magnesium stearate than Formulation 4 (2.5% and 5%, respectively). Both formulations showed a statistically significant delay in the release of the KCl as compared to Formulation 4.

Coating the tablets was considered convenient. The formulation selected for coating contained:

Potassium Choloride 75%, Carnauba wax 20%, Talc 4.5%, Magnesium stearate 0.5%, Colloidal silica 0.25%.

Figure 2 summarizes the results of the dissolution test for all manufactured lots. All the lots manufactured from formulation D fall within the range established by the USP XXI and the amount of potassium chloride dissolved at 2 hours depends on the volume of coating suspension added. Lot D_1 is the closest to the 35% of drug dissolved required as an average at 2 hours. Studies of dissolution kinetics were carried out using this lot. A good reproducibility of the dissolution at all the times studied was observed: from 2 hours on, the variation coefficients obtained fluctuated between 9.6 and 4.26%. A slow and steady release of potassium chloride was observed, and the whole dosis was released through the 12 hours of the study (Figure 3).

TABLE 1

Dissolution of potassium chloride from 6 sustained release formulations with a carnauba wax matrix. Each value is the mean of six determinations.

TIME	% of KCl Dissolved (± SD)					
	1	2	3	4	5	6
2 min	9.1 (0.25)	9.2 (0.23)	10.0 (0.20)	9.3 (0.46)		
5 min	16.1 (0.36)	16.5 (0.65)	17.3 (0.61)	15.3 (0.30)	10.5 (0.30)	10.1 (1.00)
10 min	23.7 (0.30)	23.1 (0.55)	25.4 (0.98)	21.1 (0.23)		
15 min	28.9 (0.15)	27.6 (0.29)	30.3 (0.52)	26.6 (0.21)	15.7 (3.26)	16.9 (2.63
2 hrs	68.4 (1.47)	57.1 (2.40)	74.7 (1.28)	58.1 (1.04)	53.1 (0.46)	50.2 (0.85)
4 hrs	84.4 (1.06)	71.1 (2.66)	88.9 (3.10)	73.3 (3.69)	70.4 (2.86)	64.7 (1.90)
5 hrs	90.1 (2.07)	77.9 (2.02)	98.1 (1.40)	80.2 (2.28)		
6 hrs	95.1 (0.92)	78.9 (2.60)	99.6 (0.81)	85.2 (0.90)	82.3 (5.46)	73.6 (4.33)
8 hrs					89.6 (0.74)	90.0 (0.95)
10 hrs					92.5 (1.56)	91.3 (2.36)
12 hrs					100.5 (0.95)	101.5 (0.12)

Different coating formulas were tested with varying proportions of the components. Which were designed with letters A, B, C and D. The subscripts to the letter that identifies each formulation indicate small differences in the amount of coating suspension added.

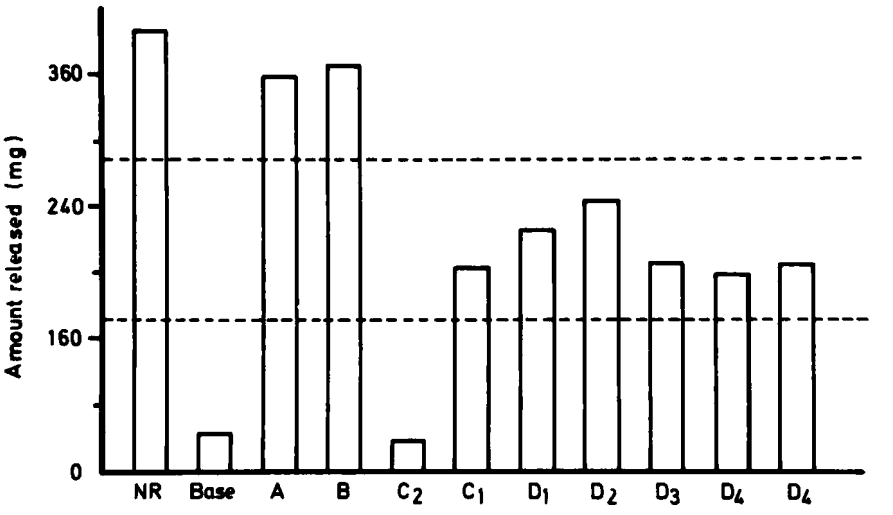

FIGURE 2

Amount of potassium chloride dissolved at 2 hours from uncoated tablets (NR) and from different formulations (A, B, C, D) of coated tablets. The subscripts indicate slight variations in the manufacturing method (see text). Segmented lines: maximun and minimum indicate quantities stipulated in USP XXI.

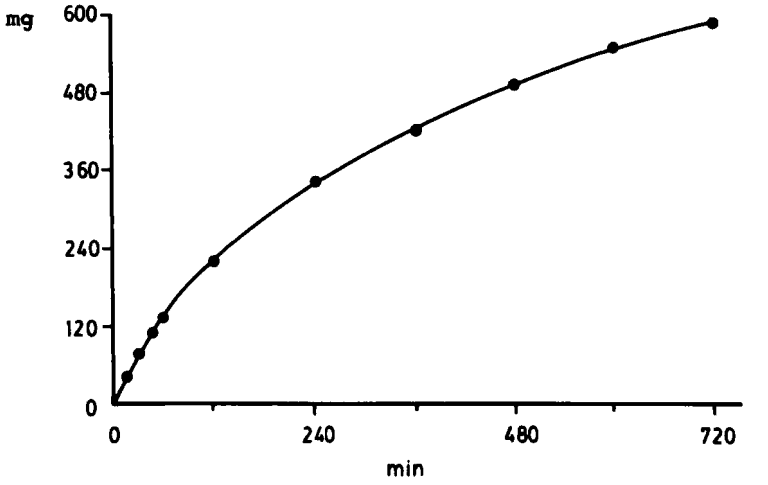

FIGURE 3

Dissolution profile of KCl from a 600 mg sustained release tablet designed in this work.

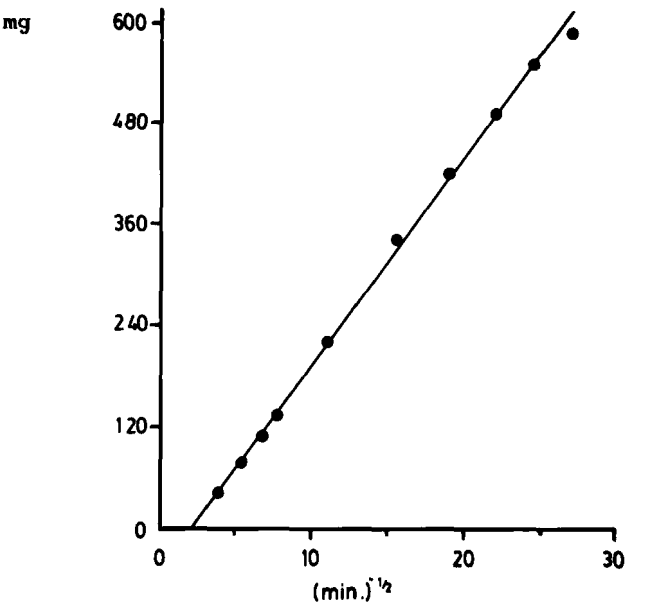

FIGURE 4

Amount of potassium chloride dissolved versus $\sqrt{t}$ for the sustained release formulation designed.

Figure 4 shows the profile of the amount dissolved Q versus $\sqrt{t}$ for the final formulation. A straight line is obtained whose correlation coefficient is 0.9992. This would indicate that the mechanism of release of the drug corresponds to a diffusion process (13).

In addition, it was found that the behaviour of the uncoated tablets also adjust to the same diffusional model proposed by Higuchi: when plotting dissolved quantity against the square root of the time, a straight line is obtained with a correlation coefficient of 0.991.

These results which indicate a satisfactory "in vitro" performance, suggest the convenience to start "in vivo" studies to characterize its behaviour in the body.

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