Chemistry of Natural Compounds, Vol. 40, No. 3, 2004

MECHANOCHEMICAL MODIFICATION OF 5-NITRO-8-HYDROXYQUINOLINE WITH CELLULOSE, PECTIN, AND β-CYCLODEXTRIN

A. A. Isaev,[1] O. I. Lomovskii,[2] K. G. Koralev,[2] and R. K. Karimov[1]

UDC 66-936.8:[541.18.053:615.453.2

The physicochemical consequences of mechanical treatment of 5-nitro-8-hydroxyquinoline with natural polymers cellulose, pectin, and β-cyclodextrin were studied in order to improve its properties. It was found that particle sizes of the medicinal compound in the agglomerated mechanical-composite materials increased. The particle-size increase of the medicinal compound was avoided by adding a third component differing from 5-nitro-8-hydroxyquinoline by the acid—base properties and containing calcium carbonate.

Key words: 5-nitro-8-hydroxyquinoline, mechanical activation, grinding together with natural polymers.

Formation of molecular complexes of medicinal compounds can both decrease and increase their activity [1]. Treatment of a low-molecular-weight alkaloid such as lappaconitine hydrobromide with cellulose prolongs its action [2]. Mechanical activation of the pure alkaloid leads to rearrangement to the amide of anthranilic acid. Mechanical treatment of mixtures with pectinic acid preserved the alkaloid properties [3].

Effective methods based on mechanochemical treatment are being developed to produce quickly dissolving medicines [4-6].

Mechanical activation of medicinal preparations can selectively modify their properties and form agglomerates with auxiliary components. Particles produced by activation have greater solubility owing to the decreased size and content of metastable or amorphous phases. As a rule, the biological activity is also more apparent [5].

Unfortunately, general recommendations for selecting components of mechanochemically modified preparations have not been developed. The main task of our research is to find the optimal method for preparing 5-nitro-8-hydroxyquinoline with a minimal particle size in the presence of a polymer of plant origin.

We performed an x-ray phase analysis (XPA) of mechanically activated samples and an estimate of the dimensions of the coherent-scattering blocks by measuring the peak broadening in small-angle diffraction patterns.

The dimensions of 5-nitro-8-hydroxyquinoline crystallites (nm) mechanically activated with polymeric matrices are as follows: initial, 45; after mechanical activation without matrix, 55; with pectin, 57; with cellulose, 57; with β-cyclodextrin (β-CD), 60; with (β-CD + $CaCO_3$), 45.

Mechanical activation of mixtures of 5-nitro-8-hydroxyquinoline and polymeric matrices increased the crystallite size and substantially changed the x-ray diffraction pattern (Fig. 1). Reflections in the range $2\theta = 23\text{-}30°$ became stronger. Apparently, these changes are due to an increase of 5-nitro-8-hydroxyquinoline particles and recrystallization of the sample (decreased content of amorphous phase) [6].

It could be that the initial 5-nitro-8-hydroxyquinoline contained a significant amount of a phase with an increased free-energy content. Such phases typically dissolve quickly. Since the assimilation of a medicine by an organism is often limited by the solubility, such a state of the solid preparation typically has distinct biological activity [5].

1) S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (99871) 120 64 75; 2) Institute of Solid-State Chemistry and Mechanochemistry, Siberian Division, Russian Academy of Sciences. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 225-226, May-June, 2004. Original article submitted April 12, 2004.

 0009-3130/04/4003-0266

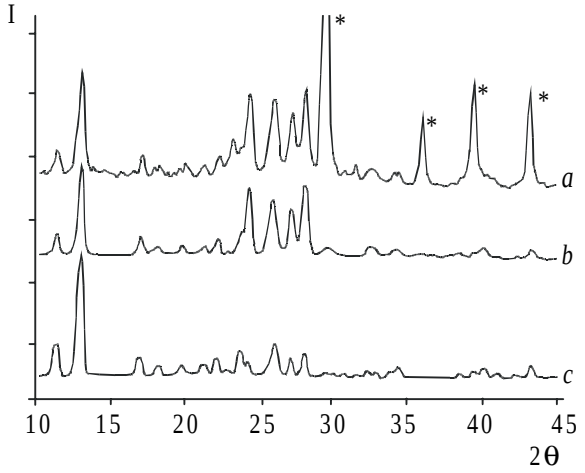

Fig. 1. Change of diffraction of 5-nitro-8-hydroxyquinoline by mechanical treatment: starting 5-nitro-8-hydroxyquinoline (a), mechanically treated (b), mechanically treated with β-CD and $CaCO_3$ (c). *$CaCO_3$ reflections.

In order to avoid recrystallization accompanied by an increase of crystallite size and a decreased content of a phase with a high free-energy value, an additional component that reacted with 5-nitro-8-hydroxyquinoline more extensively than the polymer was added to the system.

Weak organic acids are known to be readily neutralized by bases during mechanochemical treatment and to form with them stable surface complexes. The product of such transformation is less likely to agglomerate compared with the starting compound and can be stabilized as a neutral or weakly acidic matrix of the polymer.

According to XPA, a metastable form of 5-nitro-8-hydroxyquinoline can be "fixed" in a matrix consisting of β-CD and $CaCO_3$. Mechanical activation of such compositions did not increase the 5-nitro-8-hydroxyquinoline crystallites.

It can be hypothesized that the activity of mechanocomposites consisting of 5-nitro-8-hydroxyquinoline, β-CD, and $CaCO_3$ will not decrease because of formation of a more stable crystalline form during preparation of tablets and will have a long shelf-life.

Thus, mechanical treatment of mixtures of a medicinal compound with solid auxiliary compounds (polymers, matrices, diluents) forms mechanocomposites, agglomerated particles that typically have improved properties. In certain instances, the mechanocomposites are small particles of individual phases with a well-defined phase interface. The ability to form mechanocomposites is apparently determined by the ratio of the reactivity of the medicine and the auxiliary compound.

The relationship of the acid—base properties of the two phases is of prime importance. If the components of the mechanocomposite differ widely in acid—base properties, mechanocomposites are readily formed. However, this process readily proceeds further to complete chemical reaction between the components, which is not always desirable.

Similar properties of the medicinal and auxiliary compounds can lead to a different undesired consequence, i.e., crystallization and increased particle size of the medicinal compound. Apparently, such a situation occurs upon mechanical treatment of 5-nitro-8-hydroxyquinoline with the most common pharmacopeic polymers cellulose, pectin, and β-CD.

The results showed that in this instance addition of a third component can solve the problem if it is more likely to react with the medicinal compound, in our instance, $CaCO_3$.

EXPERIMENTAL

We used reagent grade 5-nitro-8-hydroxyquinoline (VFS 42-578-76, test production of ICPS, AS RUz) and pectin (TU 10-03 RUz 72-91, test production of ICPS, AS RUz), cellulose (Reakhim, TU 6-09-10-1051-75), and β-CD (ICN).

Mechanical treatment of mixtures of 5-nitro-8-hydroxyquinoline—matrix (1:1) was performed in a planetary centrifugal grinder AGO-2 (ISSCM, SD, RAS, Russia) with water cooling. The mechanical-treatment conditions were as follows: rotation

frequency of the steel reactors 630 rpm (acceleration of grinding bodies 200 m/s^2), mass ratio of grinding bodies and reagents 20:1. The grinding bodies were steel spheres of 5-mm diameter.

REFERENCES

1. S. S. Khalikov, G. P. Zhuravleva, and P. P. Larin, *Khim. Prir. Soedin.*, 303 (1995).
2. S. S. Khalikov, T. Yu. Pominova, and Kh. N. Aripov, Intern. Conf. Modern Problems of Polymer Sci., Tashkent, Uzbekistan (1995), 185.
3. S. S. Khalikov and Kh. N. Aripov, *Oxid. Commun.*, 321 (1995).
4. S. S. Khalikov, A. P. Kutlymuratov, E. L. Kristallovich, N. D. Abdullaev, M. A. Khodzhaeva, T. Sadikov, and Kh. N. Aripov, *Khim. Prir. Soedin.*, 556 (1995).
5. O. I. Lomovskii, *Periodical Collection of Scientific Works "Treatment of Disperse Materials and Media*," Odessa (2001), Vol. 11, 81.
6. G. L. Ivashchenko, *Mendeleev Commun.*, **1**, 3 (2003).
7. A. M. Dubinskaya, *Khim.-Farm. Zh.*, **23**, 755 (1989).