Methods of Synthesis and Technology of Drug Manufacture

Toxicological Study of Radiosterilized Medicinal Preparations

I. V. Berezovskaya, V. L. Tal'roze, and V. I. Trofimov

Radiosterilization is quite widely used today in the manufacture of articles for medical purposes, primarily those of a polymeric nature [1, 2]. A number of advantages of this method (the possibility of sterilization of manufactured articles in ready-made packaging, the high reliability of sterilization, the feasibility of continuous processes, the ease of monitoring the effectiveness, the large amount of experience in the operation of equipment, the high level of safety technique, etc.) [3] make it possible to regard it as extremely promising also for the sterilization of medicinal preparations. Ionizing radiation is used to a small extent in a number of countries for the sterilization of medicinals, primarily powdered medicinals [4-6]. However, it has not yet found extensive application in this area, evidently for two principal reasons. The first and objective reason consists in the fact that injection preparations (primarily dilute aqueous solutions), for which the problem of the development of new methods of sterilization is particularly urgent in connection with the high requirements for their microbial purity, undergo appreciable changes in their properties at the absorbed doses of radiation that ensure their sterility [7, 8].

It should be noted that significant advances have recently been made in the development of methods for the stabilization of injection solutions with respect to the action of radiation. For example, programmable freezing of solutions is a rather general method for increasing the radiostability of injection preparations [9, 10], and the chief obstacle can therefore be regarded, in principle, as having been eliminated. The second reason for the rather slow incorporation of radiation methods is the widely held opinion regarding the increased hazards of irradiated articles (not only medicinals but also, for example, food products). The fact that, upon the whole, the mechanisms and effects of radiochemical transformations have been studied more fully by far than the results of the effects on the same systems of other factors that are customarily (and also without any special foundation) regarded as safe, a consequence of which was the establishment of a large number of products of radiolysis of virtually any chemical compound, evidently serves as the only basis for the existence of this sort of fallacy (the fact that this is a fallacy will be proved below).

However, an increase in the toxicity of a system still does not arise from the presence of a great number of radiolysis products (and dozens of them are detected in the irradiation of some compounds), since the toxicity is not determined only by the specific harmfulness of one or another substance but rather by its concentration in the system. A consequence of the very fact of the formation of a large number of products that are basically relatively harmless is that the amounts of individual potentially harmful products are small. In addition, it is known that significant detoxification of harmful substances occurs in the organism, and the toxicity that is displayed in experiments in vitro is very often absent in investigations in vivo. On the other hand, in those cases in which sufficiently detailed studies of the effects of other methods of treatment (including thermal treatment) are made, one observes the formation of just as many products as in radiolysis.

The aim of this paper is to evaluate the possible toxicological hazard in the radiation treatment of drugs for sterilization purposes and to compare it with the hazard involved in traditional thermal methods of sterilization. This problem is virtually solved today for food products, and it is necessary to pose it again as applied to medicinal preparations, especially because of the specific character of the demands made for their safety and the ways in which they are used.
Any method of sterilization can be used when the following three conditions are strictly observed: assurance of high reliability of the sterility, retention of the pharmacological activity of the preparation, and the absence of an increase in both the acute toxicity and the manifestation of toxic side effects.

For this reason, the discussion of the problems of a possible increase in the toxicity of preparations is meaningful only when the first two of the conditions enumerated above are satisfied. Since any effect on microorganisms of necessity leads to one or another change in the parameters of drugs, the retention of biological activity after sterilizing action should be understood to mean destruction of no more than a few percent of the starting substance, because this is precisely the accuracy in the determination of the percentages of the components of a drug by both physicochemical and biological methods, as defined by the State Pharmacopoeia of the USSR (10th edition, 1968). In conformity with the information set forth above, let us estimate (on the basis of data on the amounts of possible radiolysis products formed in the process of radiosterilization in the case of decomposition of no more than 1% of the starting substances) how high the danger of an increase in the toxicity of a preparation is after sterilization as compared with its starting toxicity. Of course, in most general form, there is no sense in making precise calculations of the expected change in the toxicity of a preparation after irradiation in view of the breadth of the nature of the chemical compounds used as medicinals, although this can be done in individual specific cases. Only an estimate of the upper limit of the amounts of potentially dangerous compounds (radiolysis products), which can be achieved quite simply, is reasonable.

The degree of decomposition of medicinals will below if the indirect effect of the radiation [11], i.e., the interaction of biologically active compounds with the active products of radiolysis of other components of the drug, such as water in the case of aqueous injection solutions, is excluded in the system being irradiated. In the case of the direct action of radiation, i.e., in the case of decomposition of molecules of some or other components of the preparation as a result of the absorption of radiation energy by these molecules, the number of products of radiolysis of the k-th component of the system is defined in the case of small absorbed doses by the expression \( N_k = D \sum G_{ik} \eta_k \), where \( G_{ik} \) is the radiochemical yield in the formation of the i-th product from the k-th component, \( D \) is the absorbed radiation dose, and \( \eta_k \) is the electronic fraction of the k-th component (\( \sum \eta_k = 1 \)). Radiation doses of 10-50 kGy are required in virtually all actual cases for reliable sterilization [12]. The typical value of the overall yield of products \( \sum G_i \approx 4-6 \) molecules per 100 eV \( \sim C_{ea} \) — the yield in the decomposition of the starting substance. However, an extensive set of products, the principal of which are molecular \( H_2 \), \( CO_2 \), light hydrocarbons, and other compounds [13], which do not present a serious danger with respect to increasing the toxicity [14], usually develop as a result of irradiation of organic compounds. Typical values of radiation yields of products that could be hazardous range from 0.01 to 0.1 molecule per 100 eV.

From the indicated \( C \) and \( D \) values one readily finds that the overall amounts of products formed in radiosterilization (with assurance of retention of the biological activity of the preparation) range from \( 10^{-3} \) to \( 10^{-2} \) g (from 1 g of the preparation), and, of this amount, \( 10^{-6} \) to \( 10^{-4} \) g may be potentially hazardous.

If one considers preparations in which the filler (water in injection solutions, and starch and sugar in tableted drugs) constitutes the bulk of the mass, the overall toxicity is the sum of the toxicities of the products of radiolysis of the filler and a small amount of the drug. It has been demonstrated quite convincingly experimentally that the products of radiolysis of water and solid fillers are relatively harmless to the organism [15-18]; this means that the principal source of potentially toxic compounds in the radiolysis of virtually all drugs may be biologically active substances (usually in concentrations of 0.01-10%). Thus the amounts of hazardous substances formed in dilute solutions and solid preparations with low percentages of biologically active substances (at a drug concentration of, for example, 1%) will be even lower and will amount to \( 10^{-8} \) to \( 10^{-6} \) g (in 1 g of the irradiated preparation) in the general case. The estimates obtained are in complete agreement with the published data that indicate that the amounts of potentially hazardous additives that humans may ingest daily when irradiated food is consumed are 2 to 20 mg [19] (from 1.7 kg of products at a dose of 10 kGy). It is interesting to note here that, according to the data of Shubert [19], humans daily ingest from food up to 5 g of substances that are harmful to the organism.