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RADIOPHARMACEUTICAL KITS

H. L. Atkins, M. D.

Medical Department
Brookhaven National Laboratory
Upton, N. Y. 11973

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RADIOPHARMACEUTICAL KITS

Slide 1

The idea of "kits" for formulation of radiopharmaceuticals arose soon after the introduction of generator produced short lived radionuclides, in particular technetium-99m. When the ^{99}Mo-^{99m}Tc generator became a standard feature of hospital Nuclear Medicine practice it was necessary to manufacture one's own radiopharmaceuticals in order to extend the utility of ^{99m}Tc to more than brain and thyroid imaging. Therefore, methods were developed for rapid and simple synthesis of various labeled compounds which would be clinically useful.

However, as some of these compounds became popular, there was a further development by commercial suppliers to first, develop reliable and simple kits to enable the user to produce his own radiopharmaceutical such as technetium-sulfur colloid and then, as the use became more regular and predictable, to supply the finished radiopharmaceutical on a daily basis. This was a welcome evolution of the supply of useful radiopharmaceuticals since the user was then relieved of responsibility for quality control of the product or for following detailed procedures with the chance of significant error.

There is still a very well defined need for rapid and simple kits to assist the physician practicing Nuclear Medicine. In some areas delivery of radiopharmaceuticals on a regular daily basis can be uncertain and there is a great reliance on use of generators or an extraction system. For such institutions, kits are a necessity if adequate service for patients is to be maintained. In addition, certain preparations must be available on an emergency basis, e.g. a lung scanning agent. Cost may also be a factor for some preparations which are seldom used and therefore not supplied on so regular a basis by the manufacturers.

Slide 2 The most important aspect of kits is simplicity. Ideally they should be one step procedures. Examples of the ultimate in simplicity are the kits for manufacture of ^{99m}Tc-DTPA and ^{99m}Tc-polyphosphate. The complexity of preparation has been put in the vial prior to receipt by the user and the only procedure required is to add pertechnetate in the appropriate volume. The fewer the steps, the less chance for error or contamination.

Another aspect which is particularly important in less seldom used products is a long shelf life. If the manufacturer supplies kits in sets of 6 or 8 vials and only one or a few are used prior to the expiration date, it can be rather expensive to use the particular radiopharmaceutical. The use of lyophilized materials is an advantage since their shelf life is considerably extended. They are less likely to undergo degradation with time and are unlikely to be contaminated bacteriologically.

Since the degree of chemical manipulation available to the user may be limited, the labeling efficiency of the kit reaction must be very high, ~95% or better in order to avoid further processing to remove free radionuclide. It almost goes without saying that the product must be useful and serve a definite clinical need.

Slide 3 There are a number of factors to be considered in the development of a useful kit, some of which may not be obvious to the user, but which can be sources of difficulty. Adjustment of pH can sometimes be critical. It is difficult for the user to monitor pH and he must trust to the proper combination of reagents as set out by the manufatturer. This is not always simple when small volumes and high concentrations of radioactivity are desired.

As suggested above, a high efficiency of labeling is essential. Should there be excessive amounts of free radionuclide, the quality of the examination may be severely compromised. For instance, free technetium can cause excessive localization in the stomach when using technetium-sulfur colloid for liver and spleen scanning. Measurement of glomerular filtration rate with ^{99m}Tc-DTPA may be highly inaccurate if the binding of technetium is incomplete.

For rapid dynamic studies, a small bolus of activity may be required. Most kits require specified volumes of radionuclide solution to be added. When several solutions are added in a reaction vial, the final product may have a concentration much lower than the initial radionuclide solution. This suggests another advantage of lyophilized kits; there is no further dilution when radionuclide is added.

Following addition of radionuclide and formation of the final product, the radiopharmaceutical may be used for several patients but not necessarily immediately. The stability of the product in vitro over a period of several hours should be ascertained since breakdown can occur. This might be true for instance with ^{99m}Tc-DTPA. The SN-DTPA is stored under nitrogen or in a vacuum. This condition is altered when pertechnetate is added and breakdown can occur with time with formation of labeled products which are different from the original.

Stability in vivo is also an important factor. Some ^{99m}Tc-colloid preparations break down rather rapidly in vivo. This not only affects the quality of the examination, but alters the dosimetry appreciably.

The number of doses that can be prepared from each kit is a major factor in cost. Aside from the consideration of in vitro stability, one must be aware of the concentrations of reagents and radionuclides that are possible or permissable. It is assumed that administration of the entire contents of a vial to one patient is safe and does not exceed dangerous levels. Excessive administration of chelating agents could cause cardiac irregularities or tetany. This is extremely unlikely, however, with the quantities used in available kits.

There is still room for error in formulation of radiopharmaceuticals from kits. Some require heating such as in formation of ^{99m}Tc-sulfur colloid. Duration and degree of heating and time for mixing and reactions to occur can be critical and affect particle size and quality of the product.

Careful attention should be directed toward the expiration date. Not only may there be decomposition of the components, the changes for contamination with bacteria become greater with time. Some kits (e.g. technetium-iron hydroxide) have rather short term utility. Those utilizing lyophilized materials have a rather long useful shelf life. However, for materials which must be kept under vacuum or in nitrogen, a slow leak can develop in the vial and the quality of the contents thus endangered. It may be well to set an arbitrary expiration date on each kit received in order to assure safety and quality.

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Most of the pitfalls and problems associated with the use of kits have already been alluded to. The manufacturers can only assume responsibility to a certain point. A critical need is for rapid, accurate quality control testing of the product prior to administration. to the patient. This is especially important in products where there

may be a relatively high potential risk such as lung scanning agents, or where a certain degree of instability is frequently found. As of today, it is highly unlikely that kit products are tested by the user prior to patient administration in the average community hospital, or even in major teaching hospitals, for that matter.

While the kits may be supplied sterile and free of pyrogens, contamination can be introduced by the user. The risk is higher when there are several steps to the procedure or when there are multiple administrations from a single preparation.

Contamination of stored vials may occur, especially if stored under a vacuum where the pressure relationships are favorable to the introduction of air or organisms. Gelatin is a good growth medium for bacteria and is best avoided in kits as a stabilizer. Severe complications may occur if pH adjustments are required and are not carried out accurately. The result may also be a product with undesirable metabolic properties.

The product should be examined for the presence of particulate material. This may be due to impurities in the vial, in the eluate of the generator or can be caused by precipitation of products formed in the reaction. These can alter the distribution of radioactivity or, more rarely, cause adverse reactions. The problem of dilution has already been discussed.

SLIDE 5 Commercially available kits are primarily for technetium-99m radiopharmaceuticals. At least one of these radiopharmaceuticals, technetium-sulfur colloid, can also be supplied ready made by pharmaceutical manufacturers. This form rather than the kit, is more practical in larger departments that use the colloid preparation daily. It may work out to be less expensive and relieves the user

of the responsibility of preparing the material. For smaller departments using the colloid only intermittently, the kits are more practical.

One problem which has arisen in the application of colloid kits is the use of generator versus extracted technetium. The presence of impurities such as alumina can affect the quality of the product.

Particle size is affected by degree of heating and stabilization material. Some of the newer kits using tin as a reducing agent such as the Medi-Physics tin hydroxide or Diagnostic Isotopes phytate are more simple to prepare and do not require heating.

A variety of kits is available for bone imaging. These include polyphosphate, diphosphonate and pyrophosphate. As of this date none has been approved for general use, but are under clinical investigation. All appear simple to use and effective.

Several agents for lung scanning using short-lived radionuclides exist. The 3M company albumin microspheres have a rather low labeling efficiency and are rather complicated to prepare. Ultrasonication, heating and rinsing are required. The main advantage is accurate control of particle size.

The instant lung aggregate of Medi-Physics is somewhat more simple to prepare. Its disadvantages are the necessity of using very high concentration of pertechnetate (0.5 - 0.7 ml) and incubation is 30 minutes. The labeling is sensitive to the presence of oxidants.

Another simple kit for lung scanning is ^{99m}TcFeOH (Diagnostic Isotopes). Some patients have experienced a "flushing" reaction, probably due to the iron. There is also some concern about long-range retention in the lungs and particle size control. Personal experience is limited, but satisfactory.

For renal studies (and brain imaging) ^{99m}Tc-DTPA kits are available in liquid (Diagnostic Isotopes) and freeze dried (CIS) preparations. These are modeled after the Eckelman and Richards method, the first of the "instant" kits, developed at Brookhaven. This is probably the most simple kit for the user, a one stage procedure. However, for the manufacturer, the problem is more complex. The material must be stored under vacuum or in nitrogen, else it may be unstable.

We tried out one manufacturer's kit in the developmental stage on mice to compare with our previously obtained results. All the mice promptly died! The reason was the use of the pentasodium salt rather than the calcium trisodium salt of DTPA. While that amount of DTPA would not have proved fatal to a human being, it was a result that did not inspire confidence.

This is an example of what sometimes can happen when the manufacturer changes the formulation. It can be done in error, or to suit a particular purpose and the results are not always anticipated.

Another renal agent is ^{99m}Tc-iron ascorbate. This is provided by two manufacturers (Squibb, Philips-Duphar) and is useful for imaging the renal cortex. Unfortunately the Squibb product was originally called technetium-DTPA since the DTPA was used as a stabilizer. This has caused the misapplication of the pharmaceutical for glomerular filtration measurements.

Kits for labeling human serum albumin with technetium have not achieved widespread use. None appears completely satisfactory as yet. Among these is the use of the electrolytic process in pre-packaged form.

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It is highly probable that iodine-123 will be available in adequate supply in the not too distant future. While the T 1/2 is sufficiently long that the supplier can provide most radiopharmaceuticals labeled with ^{123}I it may be desirable to be able to label some compounds at the site of use. This might be particularly true for agents which are used at irregular intervals, for only one patient at a time and for emergency use. A lung scanning agent would be one such radiopharmaceutical.

A short-lived radiopharmaceutical could be useful for renal function studies. In patients with renal transplants and poor renal function, a long-lived radiopharmaceutical is not well excreted and can deliver a high radiation dose as well as building up a high background for sequential studies which are often required. While ^{99m}Tc-DTPA can be useful in this kind of situation, it is not as renal-specific as orthoiodo hippurate, the latter being more sensitive in detecting poorly functioning renal tissue.

Of course, any radiopharmaceutical which serves a clinical need could be useful in kit form, particularly if a satisfactory agent is not now available. One such agent might be for pancreas scanning. The material now in use, ^{75}Se-selenomethionine, is expensive. If it is ordered for a specific examination and not used for one reason or another, it can be rather costly.

A satisfactory, inexpensive lung scanning agent is not yet commercially available. One of the major problems here is quality control of particle size.

One area of need for which commerical suppliers cannot supply a finished product is the labeling of some of the patient's own tissue such as

red blood cells. In this situation a kit would be ideal. A kit method for ^{99m}Tc labeling erythrocytes is under development at our laboratory. If successful, this would be a useful method for imaging blood pools such as heart, major vessels, placenta, etc. and for use in cardiac dynamics and splenic function and imaging procedures. A kit would then make ^{99m}Tc-RBC available for every Nuclear Medicine laboratory.

Other blood products could also be useful when labeled. These include white cells for localization of inflammatory conditons and platelets for thrombus detection.

In summary, radiopharmaceutical kits fulfill a definite need in the practice of Nuclear Medicine. They make available, usually at reasonable cost, short-lived radionuclide labeled radiopharmaceuticals to laboratories where complex chemical manipulations are not feasible. This improves the quality of health care and at the same time can reduce radiation dose to the patient populations.

Still to be solved is the question of quality control. It would be useful if simple, standard procedures could be developed for each type of kit which would allow rapid testing prior to use.

Radiopharmaceutical Kits

A. Indications

1. For use with radionuclides of short T½
2. Where source of radionuclide is at site of use
3. Where delivery of radiopharmaceuticals is unreliable
4. For emergency use
5. Where cost may be a factor, particularly for seldom used preparations

Radiopharmaceutical Kits

B. Components of an ideal kit

1. Simplicity; one step procedure
2. Long shelf life
3. High labeling efficiency
4. A useful product

Radiopharmaceutical Kits

C. Factors to consider

1. pH adjustments
2. Percent unlabeled radionuclide
3. Volume and concentration of final products
4. Stability *in vivo* and *in vitro*
5. Number of dose administrations per kit
6. Time, temperature criticality
7. Expiration date

Radiopharmaceutical Kits

D. Pitfalls and problems

1. Quality control
2. Sterility
3. Contaminants
4. pH
5. Particulate material
6. Dilution

Radiopharmaceutical Kits

E. Presently available kits

1. Liver agents
2. Bone agents
3. Lung agents
4. Kidney agents
5. Blood pool agents

Radiopharmaceutical Kits

F. Desirable agents

1. ^{123}I kits
2. Agents for renal function
3. Agents for pancreas imaging
4. Less costly, more effective lung scanning agents