ABSTRACT: A basket stirrer for testing the dissolution rate of solid pharmaceutical preparations such as tablets and capsules. Passage means is provided through the drive plug which forms a closure at the upper end of the generally cylindrical screen basket to break the air or fluid lock which otherwise introduces errors in the routine laboratory use of this type of equipment by preventing proper fluid drainage from the basket when it is raised out of the testing solution at the end of a test, or proper circulation of the fluid through the basket during the test.
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PHARMACEUTICAL TESTING INSTRUMENT

BACKGROUND OF THE INVENTION

Basket stirrers are employed in routine laboratory testing to determine the dissolution rate of various solid pharmaceutical preparations, including both tablets and capsules, in suitable extraction solutions, as for example in the standard U.S.P. simulated stomach juice. Detailed methods of conducting such tests and specifications for the apparatus employed therein are outlined in 1969 publications of the American Pharmaceutical Association's Drug Standards Laboratory, the United States Pharmacopoeia (U.S.P.), and the National Formulary.

The conventional basket stirrer employed in such testing includes a generally cylindrical basket of 40 mesh stainless steel screen that is approximately 1 inch in diameter and 14 inches long, closed at the bottom also with 40 mesh stainless steel screen, and open at the top for insertion of the pharmaceutical preparation that is to be tested. A solid closure of stainless steel is removably attachable in covering relationship over the top of the basket as by means of spring clips or threaded connection, and this closure has a stainless steel drive rod projecting coaxially upwardly therefrom which is adapted to be engaged in a stirrer chuck for rotation of the assembly during the conventional testing procedure.

A serious problem in the use of equipment of this type is that unless extreme care is used in removing the basket from the solution at the completion of a test, there will almost invariably be an air or fluid lock in the upper portion of the basket which prevents the basket from draining. This is caused by the relatively high surface tension of some solutions in combination with the small apertures of the 40 mesh screen. This results in inaccuracy in the test results because a portion of the fluid is lost from the main body of the solution and is accordingly not a part of the material analyzed to obtain the final test results. This problem is particularly difficult to cope with when basket stirrers are employed in connection with automated cycled pharmaceutical testing equipment, wherein the stirrer cannot be manually tilted or shaken in an attempt to break this air or fluid lock.

This surface tension lock has also been found in many instances to have an adverse effect on the test results by preventing proper circulation of the fluid during rotation of the basket in the solution, with a resultant variation in the fluid exchange through the basket, which in turn affects the dissolving capability of the solution proximate to the tablet or capsule that is being tested.

One prior art attempt to avoid this problem was to combine a surface active or wetting agent in the testing solution, but this is generally undesirable as an answer to the problem because such surface active or wetting agents also tend to affect the rate at which some tablets or capsules will undergo dissolution.

Another prior art attempt to solve this problem involved changing the surface characteristics of the screen employed in the stirrer by etching, which will somewhat improve the fluid flow through the screen. However, this has the disadvantage of reducing the corrosion resistant characteristics of the screen material.

SUMMARY OF THE INVENTION

In view of these and other problems in the art, it is an object of the present invention to provide a basket stirrer for testing the dissolution rate of pharmaceutical preparations such as tablets and capsules, wherein the otherwise solid drive plug forming a removable closure for the top of the basket is provided with passage means therethrough which, by equalizing the pressure between the inside and outside of the basket, will break the air or fluid lock in the upper portion of the basket and thereby permit substantially full fluid drainage from the basket when the basket is removed from the testing solution, and will allow substantially unrestricted fluid exchange through the basket screen during the testing.

Another object of the invention is to provide a basket stirrer of the character described wherein the passage means provided through the otherwise solid or imperforate drive plug forming a closure at the top of the basket has a cross-sectional area that is substantially larger than the individual cross-sectional area of the screen mesh holes in the basket, so as to readily break the air or fluid lock otherwise established by the fine screen mesh, but not so large as to allow any substantial part of a tablet or capsule to pass therethrough.

In the preferred form of the invention the passage means for breaking the air or fluid lock is a hole extending through the drive plug in a direction substantially parallel to the axis of rotation of the basket so as to minimize or substantially completely avoid any centrifugal pumping effect from the passage means. While one or more of such holes may be provided through the drive plug, it has been found that at least one such hole is required having a minimum diameter no less than about 1/16 millimeters, and preferably at least about 2 millimeters; while at the other end of the scale it has been found that the maximum diameter allowable for such holes is about 4 millimeters, and that it is preferred no hole have a diameter greater than about 3 millimeters. This will assure that the air or fluid lock will be broken and that there will be proper circulation and exchange of fluid, while at the same time particles of pharmaceutical preparation being tested cannot escape through such hole or holes in such dimension as to materially alter the test results. If the hole or holes have cross sections that are other than round, then the maximum area range will correspond to the area of a circular hole having a diameter from about 1/16 to about 4 millimeters, and the preferred area range will correspond to the area of a circular hole having a diameter of about 2 to about 3 millimeters.

Another and more general object of the present invention is to provide a novel basket stirrer of the character described which, by automatically causing the release of substantially all of the testing solution from the basket when the basket is raised out of the solution at the end of a test, facilitates the laboratory manipulation and use of such equipment, and substantially improves the accuracy and reliability of test results emanating from the use of the equipment.

Further objects and advantages of this invention will appear during the course of the following part of the specification, wherein the details of construction and mode of operation of several embodiments are described with reference to the accompanying drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view illustrating a basket stirrer embodying a presently preferred form of the invention, with the combined drive plug and basket cover illustrated in axially spaced relationship above the basket.

FIG. 2 is an enlarged, fragmentary, axial, vertical section, partly in elevation, illustrating the basket stirrer of FIG. 1 with the combined drive plug and basket cover operatively engaged in driving-covering relationship over the top of the basket.

FIG. 3 is a horizontal section taken on the line 3-3 in FIG. 2.

FIG. 4 is an enlarged, fragmentary, axial, vertical section similar to the upper portion of FIG. 2, but illustrating a basket stirrer embodying a modified form of the invention.

FIG. 5 is a fragmentary, horizontal sectional view taken on the line 5-5 in FIG. 4.

DETAILED DESCRIPTION

Referring to the drawing, and at first particularly to FIGS. 1, 2, and 3 thereof, the basket stirrer assembly illustrated in these FIGS. is generally designated 10, and includes a basket portion 12 and drive structure 14. The drive structure 14 comprises a drive plug 16 releasably attachable in covering relationship over the top of basket portion 12, and a drive shaft 18 projecting axially upwardly from the center of the drive plug 16.
The basket portion 12 of the stirrer assembly 10 includes a cylindrically formed screen 20 which is rigidly supported at its upper end by a ferrule 22 of stepped construction having an annular flange portion 24 which projects radially outwardly from the upper edge of cylindrical screen 20. The ferrule 22 has a cylindrical inner surface 26 and a flat annular top surface 28.

A similar ferrule 30 of stepped construction rigidly supports the lower end of the cylindrical screen 20, and it likewise includes an annular flange portion 32 which projects radially outwardly below the lower end of screen 20. The bottom ferrule 22, in the test results, has a cylindrical inner surface 34 to which a bottom screen disc 36 is annularly secured.

The drive plug 16 is an annular structure having a cylindrically bottom portion 38 slidably engageable within the top ferrule 22, and includes an annular flange 40 which overlies and is adapted to seat flush against the flat top surface 28 of the ferrule 22. In this seated relationship of the drive plug 16 in the top ferrule 22, the drive shaft 12 is substantially coaxial with the basket 12, so that when the drive shaft 18 is rotatably driven during operation of the apparatus, there will be a minimum of "run-out" or eccentricity in the rotational movement of the basket assembly.

The drive plug 16 is releasably secured in this seated operative relationship in the upper end of the basket 12 by means of a plurality of spring clips 42, preferably three in number, mounted in regularly spaced relationship about the flange 40 of the drive plug 16. The spring clips 42 project downwardly and radially inwardly from the flange 40 on the top ferrule 22 of the basket. While this spring clip means is preferably preferred for connecting the basket 12 to the drive plug 16, it is to be understood that other suitable means such as a threaded connection (not shown) may be employed without departing from the present invention.

According to U.S.P. specifications, all materials used in the construction of the basket 12 and drive structure 14 must have the characteristics of type 316 stainless steel or equivalent in corrosion resistance to dilute hydrochloric acid solutions that are sometimes specified for tests with the equipment. The U.S.P. also specifies that the screen material employed in the basket 12 be 40 mesh screen, which has screen apertures of about 0.015 by 0.015 inch, which in millimeters is approximately 0.38 by 0.38, or about 0.145 square millimeters.

Thus, a basket stirrer assembly 10 made in accordance with U.S.P. specifications will have a cylindrical screen 20 and bottom screen disc 36 with screen apertures of approximately 0.145 square millimeter cross section. The diameter of the screen wire employed in screen of this character is approximately 0.010 inch, or about 0.254 millimeter, and the screen apertures constitute only approximately 36 percent of the total surface area of the screen. With this much of the overall surface of the screen constituting the screen wire, and with such small screen apertures, surface tension of the extraction solution in which the stirrer has been immersed during a test tends to cause a strong air or fluid lock to occur in the upper portion of the basket when the basket is removed from the solution, thereby tending to cause inaccuracies in the test results because of loss of a portion of the fluid from the body of the fluid which is subsequently analyzed to determine the amount of the pharmaceutical preparation being tested that was dissolved therein. Such air or fluid lock also has a tendency to limit proper circulation of the fluid through the basket during a test to thereby tend to cause further inaccuracy in the test results.

FIGS. 1, 2, and 3 of the drawing illustrate the applicant's presently preferred means for breaking this objectionable air or fluid lock in the upper portion of the basket 12. This means is a passage 44 which extends through the drive plug 16 in a direction substantially parallel to the axis of the stirrer assembly 10. The passage 44 is preferably of circular cross section to provide a maximum of cross-sectional area of the passage relative to the surface area in the passage. Applicant has found in experimental testing of this apparatus that the passage 44 must have a diameter of at least about 1 millimeter for sufficiently free flow therethrough to assure that an air or fluid lock will not be established in the upper portion of the basket when the basket is removed from the test solution, and to assure proper circulation of the fluid while the basket is being rotated in the testing solution. On the other end of the scale, the applicant has found in experimental testing that the passage 44 must not have a diameter greater than about 4 millimeters, as particles of the pharmaceutical preparation being tested are likely too large to pass through a passage of any larger cross-sectional dimension, and thereby adversely affect the accuracy of the test. Testing by the applicant has revealed that the optimum and accordingly the preferred range for the size of the axially directed passage 44 is a passage having a diameter of from about 2 to about 3 millimeters. Within this preferred range the applicant has found that regardless of variations of the viscosity and particle size of the pharmaceutical preparation being tested, the air or fluid lock will be broken, and proper circulation of the solution through the basket will occur, while at the same time there will be no escape of particles of the pharmaceutical preparation out of the basket through the passage 44 such as will adversely affect the test results.

The axial orientation of the entire length of the passage 44 in the preferred embodiment of the invention as shown in FIGS. 1 to 3 avoids any radial component of the passage which might otherwise develop a centrifugal pumping action during rotation of the basket when it is immersed in the test solution. Such centrifugal pumping effect would result in an abnormal fluid circulation pattern which would result in the introduction of an error factor in the use of the apparatus. It is also desirable in the preferred embodiment of the invention to have the passage 44 displaced substantially radially inwardly from the cylindrical screen 20, since this causes the passage 44 to be displaced radially inwardly from particles of the pharmaceutical preparation which are centrifugally urged against the cylindrical screen 20 during rotation of the basket in the test solution.

While a single passage 44 has been illustrated in FIGS. 1 to 3, it is to be understood that a plurality of such passages may be employed within the scope of the invention. However, in order for the objectives of the invention to be fulfilled, if there is such a plurality of axially oriented passages 44 disposed through the drive plug 16, at least one of such passages must have a diameter of about 1/4 millimeters or preferably at least about 2 millimeters; while on the other hand no one of such passages 44 may have a diameter greater than about 4 millimeters, and preferably not more than about 3 millimeters.

In the operation of the apparatus shown in FIGS. 1 to 3, the pharmaceutical preparation such as a tablet or capsule, sometimes hereinafter referred to as a "pharmaceutical unit", is placed in the basket 12, and the basket 12 is then engaged with the drive plug as best illustrated in FIG. 2 with the basket coaxially arranged relative to the drive shaft 18, and the assembly is then lowered into a suitable extraction solution, such as the standard U.S.P. simulated stomach juice, inside a standard laboratory resin flask. A support seal of Teflon or rubber is usually engaged over the top of the resin flask as a stopper with the drive shaft 18 projecting upwardly through an aperture therein.

The drive shaft 18 is then operatively connected to a stirrer motor, as by means of a chuck, and the basket is then rotated in the extraction solution at an r.p.m. in the range of from about 20 to about 400 for a specified length of time, both the r.p.m. and the time being determined according to predetermined pharmaceutical unit and extraction solution employed in the test. During such test the solution and the apparatus are normally maintained at a specified temperature by conventional temperature regulating means.
At the end of the specified time, the basket is removed from the resin flask, and the solution is then analyzed for its content of the active ingredient or ingredients in the pharmaceutical preparation. The pressure equalization, and consequent breaking of the air or fluid lock in the upper portion of the basket by the presence of the passage 44, permits substantially the entire volume of the solution to quickly drain from the basket as it is removed from the resin flask without requiring any special care on the part of the operator, and without necessitating tilting or shaking of the basket, and such substantially complete drainage will be reliably effected even with the basket automatically actuated as in automated cycled pharmaceutical testing equipment.

The alternative form of basket stirrer assembly illustrated in FIGS. 4 and 5 is generally designated 10a, and includes drive structure 14a having a drive plug portion 16a and the drive shaft portion 18a. The drive plug 16a has a cylindrical bottom portion 38a thereof and a radially outwardly projecting annular flange portion 40a to which spring clips 42a are attached. The basket 12 employed in the alternative form 10a of the invention is the same as the basket 12 employed in the preferred embodiment of FIGS. 1 to 3, and the drive plug 16a is engaged in the top ferrule 22 of the basket 12 as best illustrated in FIG. 2.

In the alternative form 10a of the invention shown in FIGS. 4 and 5, the air or fluid lock is broken by means of a passage 44a which is in the form of a groove extending in the axial direction in the periphery of the cylindrical bottom portion 38a of plug 16a, and thence radially outwardly in the lower generally flat annular surface of the flange 40a of drive plug 16a to the periphery of flange 40a. Accordingly, the passage 44a is defined within the drive plug 16a, but between the drive plug 16a and the top ferrule 22 of the basket 12.

The passage 44a, while being generally U-shaped in cross section, nevertheless has a cross-sectional area within the range specified for the passage 44 in the preferred form of the invention shown in FIGS. 1 to 3. Accordingly, the passage 44a has a cross-sectional area at least as great as that of a circular passage having a diameter of 1 1/2 millimeters, and preferably as great as a circular passage having a diameter of about 2 millimeters; while the passage 44a has a cross-sectional area no greater than a circular passage having a diameter of about 4 millimeters, and preferably no greater than a circular passage having a diameter of about 3 millimeters.

It is to be noted that although the axially directed portion of the passage 44a communicates with the inside of the basket 12 further radially outwardly than the passage 44 of the preferred embodiment, it is nevertheless displaced somewhat radially inwardly from the cylindrical screen 20 of the basket, whereby particles of the pharmaceutical preparation being tested which are centrifugally urged against the screen 20 will not tend to pass into the passage 44a. As compared with the passage 44 of the preferred embodiment of FIGS. 1 to 3, the passage 44a of the alternative embodiment of FIGS. 4 and 5 does have the disadvantage of having a portion thereof that is oriented generally in the radial direction, which will tend to establish some centrifugal pumping effect. This effect can be minimized by employing only a single one of the passages 44a, and this effect is quite small as compared to the adverse effect of the air or fluid lock that is overcome by the presence of passage 44a, so that the test results will be much more accurate with the passage 44a than without it.

While the instant invention has been shown and described herein in what are conceived to be the most practical and preferred embodiments, it is recognized that departures may be made therefrom within the scope of the invention, which is limited neither to the details disclosed herein, therefore not to be limited to the details disclosed therein.

I claim:

1. A pharmaceutical dissolution rate testing instrument which comprises a generally annular screen basket adapted to receive a pharmaceutical unit to be tested, said basket having an open upper end through which the pharmaceutical unit is introduced into the basket, a generally annular drive plug removably attached to the upper end of the basket generally coaxial of the basket and forming a closure over said upper end of the basket, and a drive shaft rigidly connected to said drive plug and extending upwardly therefrom generally coaxially of the drive plug and basket, said drive shaft being rotatable so as to rotate the drive plug and basket during a dissolution rate test, said drive plug having pressure equalizing passage means extending therethrough providing communication between the inside and outside of the basket, said passage means including at least one passage having a cross-sectional area substantially greater than that of the individual screen apertures of the basket.

2. A pharmaceutical testing instrument as defined in claim 1, wherein said passage means includes at least one passage having a minimum cross-sectional area at least as great as that of a circular passage having a diameter of about 11/2 millimeters.

3. A pharmaceutical testing instrument as defined in claim 2, wherein said passage means includes no passage having a minimum cross-sectional area greater than that of a circular passage having a diameter of about 4 millimeters.

4. A pharmaceutical testing instrument as defined in claim 1, wherein said passage means includes at least one passage having a minimum cross-sectional area at least as great as that of a circular passage having a diameter of about 2 millimeters, but no passage having a minimum cross-sectional area greater than that of a circular passage having a diameter of about 3 millimeters.

5. A pharmaceutical testing instrument as defined in claim 3, wherein said passage means is substantially straight and oriented substantially parallel to the axis of the drive shaft, drive plug and basket.

6. A pharmaceutical testing instrument as defined in claim 5, wherein said basket includes a generally cylindrical screen sidewall, and said passage means is offset substantially radially inwardly relative thereto.

7. A pharmaceutical testing instrument as defined in claim 6, wherein said passage means comprises a single passage having a substantially circular cross section.

8. A pharmaceutical testing instrument as defined in claim 3, wherein said passage means comprises a peripherally located notch in said drive plug.