SOP : USP Dissolution Instrument Calibration or PQ

Key Words: Dissolution Tester Calibration
OQ
PQ
Suitability Test
Calibrator Tablets
Test Medium Preparation
UV VIS Spectrometer
Cells (Cuvettes)

Introduction:

This text is designed to form the basis of an SOP for the PQ or Performance Qualification of a dissolution bath using USP ST tablets (calibrator tablets). Prior to this test, it is necessary to perform an OQ on the specific instrument to be tested as an unsatisfactory mechanical status of the instrument will have a bearing on the performance of the dissolution characteristics of the equipment in general. Just as a guide, please see Table 1 below for an idea as to the source and size of errors presented by various mechanical failures.

Table 1: Factors affecting the PQ results:

Type	Rating	influence degree
Temperature	not too significant	linear
Speed	**significant**	**10-30%**
Vibration	**significant**	**20-50%**
Centricity	reasonable	± 5-15%
Dissolved Gas	**significant**	**± 50%**
Media pH	reasonable	± 5-10%
Media Contamination	**significant**	**± 20-45%**
Sampling Position	not too significant	1-3%

Generally, the OQ will allow the operator to have a good overview of the mechanical status of the instrument prior to starting a PQ suitability test with tablets. These tests (apart from checking the operation of peripheral features such as bath illumination and function light operation) will provide tests for the capacity and stability of the heating system, the pumped water flow rate, the stability of the tool rotation speed, the centring of the tools in the dissolution vessel, the wobble at the end of the tool shaft and the depth of the tool with respect to the base of the vessel itself. Characteristics such as tool wobble and accuracy of tool rotation speeds are well documented and clearly laid out in the USP guidelines.

Assuming that the OQ has provided a satisfactory status for the instrument under test, the PQ can move on to the tablet testing stage.

General Description:

The following unit processes have to be undertaken during the procedure of an automated Dissolution System:

1. Fill vessels with medium.
2. Qualify pump flow rate
3. Qualify blank at each cell position (automatic system)
4. Qualify standard at each cell position (automatic system)
5. Flush system: check background adsorption values.
6. Check blank at independent Spectrometer if required (for manual sampling)
7. Check standard at independent Spectrometer if required (for manual sampling)
8. Perform the USP test with appropriate tablets.
9. Take samples after 30 minutes (automatic program)
10. Take samples after 30 minutes (manual sampling option)
11. Measure manual samples in independent Spectrometer (if required)
12. Tabulate AU values and then calculate percentages.

Details of the above:

1. Fill vessels with medium:

    a) The medium has to be selected according to the test that is to be done. This is either Phosphate Buffer, pH 7.4 for Salicylic Acid or Demineralised water or Prednisone.
    b) Select the volume to be dispensed: 900g for Salicylic Acid or 500g for Prednisone. The tolerance of the dispensed weight is ± 1%.
    c) Both media must be deaerated according to the USP Specification.
    d) Once the volume has been dispensed the tests should be started as soon as possible, if the USP test is to be done.
    e) Turn the pump on and wait for the fresh blank to flow through the system and return to the dissolution bath. Note the time taken for this to happen. This value has to be used in the Method set up for the final analysis as flushing time previous to the measurement

2. Qualify pump flow rate:

    a) Once the liquid is flowing back into the dissolution vessel, measure the flow rate. This can be done using a graduated 10ml cylinder.
    b) Adjust the tension on any channel which shows a marked difference in flow rate and if the tube is beyond this, then replace the whole set of peristaltic pump tubes.

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3. Qualify blank at each cell position (automatic system).

    a) If necessary, initialise the Spectrometer and if a cell changer carousel is fitted, click on the position normally reserved for the blank (this is normally position 7 using an 8 cell changer).
    b) Now select and enter a wavelength: 242nm for Prednisone and 296nm for Salicylic Acid.
    c) Do an AUTO ZERO of the spectrometer and wait. A series of 0000's should be displayed in the appropriate display.
    d) Move the cuvette selector to the position normally reserved for the standard (this maybe position 8 for an 8 cell changer).
    e) Record the "Blank" value of the media at this position.
    f) Select cell positions 1 through 6 (the sample positions) and record the Blank values.
    g) With reasonably matched cells, the absorption values should be in agreement within ± 0.00XX units at each position.
    h) If this is not the case, the cells have to be inspected and the windows examined for any surface contamination, either inside or outside.
    i) When replacing cells, please be careful to tighten but not over tighten the screw thread connectors.

4. Qualify Reference Standard at each cell position (automatic system)

    a) Undo the connection from the dissolution bath output to the input of the peristaltic pump.
    b) If necessary, attach feeder tubes which will allow you to pass standard from a suitable beaker directly into the pump and from there into the cell changer.
    c) Pump the Reference Standard through the system for the flushing (sampling) time that you have entered, say 45 seconds for example.
    d) Stop the pump, and wait for about 5 seconds
    e) Follow the same procedure as above for the Blank, BUT do not press the AUTO ZERO function at cell 7 this time. Record the standard AU values at each of the cells including the blank position. If the standard has been made correctly, then all position's AU's should agree within the range of ± 0.00XX AU.
    f) If some values are too high, then check the cell out. If values are too low, then check the pumping efficiency of the tubing, as some of the standard may be diluted with the blank. Another reason is that the flushing (sampling) time may not be long enough. Extend the pumping time before doing any dramatic changes and retest again.
    g) Run through measurement sequence to qualify the positioning of the cells at the correct orientation to the incident and transmitted light.

5. Flush system: check background adsorption values.

    a) Remove the feeder tubes from the Reference Standard beaker and turn on the pump for about 10 seconds.
    b) Rinse and dry the feeder tubes.

c) Using the same procedure as with loading the Reference Standard, repeat the sequence this time by replacing the beaker of standard with a beaker of Blank medium.
d) Pump this through for double the time needed to load the standard.
e) Recheck the Blank values at each of the cell positions and record them. The agreement should be much as before. Some drift may have occurred with the spectrometer, but the values should still be close to those measured before.
f) Empty the dissolution vessels and clean them out for the next stage.

6. Check Blank at independent Spectrometer if required (for manual sampling).

a) This can be done easily to make sure that any other manually filled cuvette or cell used is giving a reasonable agreement as to the Blank value obtained with the automatic system.
b) Use the instrument Auto Zero function to zero the Blank in the measurement cell. The sample cell should be filled with Blank and this should be zeroed either against another cuvette in the Blank position (in the spectrometer) or against air if another cuvette is not available.
c) In the case of Salicylic Acid, a 1mm sample cell has to be used; the use of a 1mm flow cell adapted to take a female Luer in line connector is a great bonus. Manual 1mm cells are difficult to use and especially hard to flush. The flow-through 1mm cell with the female Luer adaptation allows the easy filling, flushing and successive introduction of samples, without recourse to difficult manipulations or sample dilution by 10 times (if a 10mm cell were to be used).
d) The Blank for the Prednisone test can be run in a 10mm cell.

7. Check standard at independent Spectrometer if required (for manual sampling)

a) Having cleaned and dried the manual cell, place the Reference Standard solution in it and record the value for the standard. This should be in close agreement with the values obtained using the automated system.
b) If the 1mm flow cell adaptation is to be used it is sufficient to blow out the blank with a syringe full of air and flush with standard twice. Record the values.

8. Perform the USP test with appropriate tablets.

a) The vessels must now be cleaned and filled with fresh deaerated medium.
b) Start the automatic sequence as soon as possible after the last vessel has been filled and placed in the dissolution tester.
c) Before starting, check and note the medium temperature in each vessel.
d) Do not use Helium to sparge the medium.
e) For preference, use a degasser which also conforms to the USP methodology and preheats the medium whist degassing it. This minimises the delay before starting the test proper.
f) Store the tablets either in the bottle provided or better in a desiccators prior to the start of the test.
g) Do not handle the tablets or expose them to sources of moisture prior to the test.

h) Wear thin rubber medical examination gloves (powder free) and if necessary pull some of the tablets out on to a clean tissue or better, remove them one by one from the bottle supplied using large tweezers. Today's Tablets come in Blister Packages.
i) In the case of Salicylic Acid tablets and as the tablet quality is so poor, you will have to dedust the tablets prior to use and this can be done using a dry tissue paper (preferably coloured) to the point where the tablets almost start to shine at the surface. At this point the tablet is sufficiently dedusted. If the tablet is not dedusted then the surface powder will dissolve into the medium very quickly and may give a higher than expected apparent dissolution rate.
j) In the case of Prednisone tablets, they seem to be very influenced by dissolved gasses. Although this was more by accident than design, it does highlight the need for effective degassing and a quick start of the test once the medium is dosed and in the bath.
k) In the automatic program the Blanks will be run and recorded in the program architecture and then you will be prompted to drop the tablets.

9. Take samples after 30 minutes (automatic program)

a) The program has to be constructed such that samples of the dissolved active are taken after an interval of 30 minutes. Both tests for all types of tools used (Apparatus 1 and 2) require the same sampling conditions.
b) As the sampling is done automatically, the sampling ferrules will either be in the solution permanently or will be lowered into the solution prior to sampling (PHARMA TEST EPE system).
c) Sampling will start at the 30 minute interval less the time entered in for sample line prefilling (flushing), e.g., 45 seconds.
d) The instrument will then go through the measurement sequence and record the displayed values in the results protocol.
e) There will be an automatic calculation of the percentages of active dissolved.
f) If any of the values fall outside the specified range, then the whole test must be repeated until either the failures are eliminated.
g) The instrument has been declared unfit for use pending mechanical parameter investigation. Or the media was improperly deaerated (often the reason for failures). The USP criterion for tablet test failure and the pattern of repeat tests is clearly laid out in the relevant guide.

10. Take samples after 30 minutes (manual sampling option)

a) When sampling manually, be aware that dry filter elements at the end of the sampling ferrules may be one of the reasons for differences between manual and automatic measurements.
See the addendum: Differences between automatic and manual measurements.

11. Measure manual samples in independent Spectrometer (if required)

    a) Manually taken samples should be filtered in line and not centrifuged or filtered later as undissolved active will continue to dissolve, so if attached to particulate matter such as residual excipients.
    b) These samples may then be transferred to a test tube for further analysis.
    c) Record all results in an appropriate table and calculate the percentage dissolved active.

12. Tabulate AU values and then calculate percentages.

    a) Suitable tables for recording the AU values and the resultant percentages are available from PHARMA TEST.
    b) Automatic calculations cannot be adjusted unless the file containing these adjusted values is saved under a different file name.
    c) Manual samples may yield different values to those obtained automatically. Again, refer to the addendum text at the end of this SOP for alternative reasons for these differences.
    d) Values can be calculated manually according to the calculation formulae which can be seen in the accompanying test for this SOP, available from PHARMA TEST.

Differences between Automatic and Manual Measurements.

We have also to ask ourselves why these occur? This is a often seen phenomenon and is therefore not unusual. There are several reasons:

a) Has the automatic method itself been validated?

b) Has each component of the automatic system been validated? This applies also to the Pump and the Spectrometer as to the ability of the pump to produce a similar flow rate through each of the tubes and deliver a sample which is representative of the vessel from which it came at the same time in each of the flow cells.

c) Has the Spectrometer been validated as to its condition. If yes, then was it with the cell changer (probably not). If it was validated with the sample changer, was it validated with the cells in it. What was the medium with which the cells were validated in conjunction with the spectrometer. In the case of the USP materials, i.e., the standard Prednisone solution for example, then each of the cells should be validated first with demineralised water for the Blank and then validated with the standard solution so that each position can be evaluated for the 100% dissolved active solution and that the transition from Blank to 100% solution shows no effects of carryover. If carryover is detected, then maybe the pumping system is at fault (insufficient volume pumped through the system) so that there is a significant mixing of the blank and the 100% solution. In the USP test this would easily have an influence on the final result as there is only one measurement point between 0% and the final result.

d) There is also an effect known as occlusion. This is highlighted in the attached Question and Answer form from the Dissolutions Solutions Network page available from the internet. Occlusion is a point on the dissolution profile at which the drug substance is no longer released into the medium. Some drug substance may be reabsorbed onto the excipient material during the automatic sampling sequence. This could happen with material which is filtered out is held at the filter surface through which the solution to be analysed has to pass.

e) There can also be adsorption of the material at the filter surface, especially if the filter is dry. This is the case with manual sampling where each of the filters is dry. In the automatic system the filter is immersed and therefore wet from the start of the measurement cycle and is certainly wet at the end of the 30 minutes measurement period.

f) There is then the time lag between the automatic sampling which is synchronous and the manual sampling which is consecutive. For manual testing a staggered start option with the Dissolution Bath is preferable. Although this is only a small time difference, the manual sampling from the vessels is more realistic than the automatic sampling as the automatic sequence starts about 30 to 40 seconds prior to the 30 minute sampling time. Therefore solution in the cuvettes is “younger” than that in the manual sampling syringes.

g) There is also position of sampling. In our experience the filter position for manual sampling is not as repeatable as that with automatic sampling, especially with a 500ml volume where the space between the top of the tool and the surface is only a couple of cm.

h) Pump tubing quality. This has more or less been outlined in points (b) and (c).

The Tablets

The Tablet tests are designed to be done with both Baskets (USP Apparatus 1) and Paddles (USP Apparatus 2). If a dissolution tester is set up for one particular test only then the instrument must be so marked on the USP test sticker and then the instrument may then be tested for either paddles or baskets. The Test Tablets themselves fall into two categories: disintegrating and non-disintegrating. The disintegrating Tablets are made of Prednisone plus normal fillers and bulking agents and are currently produced with an active concentration of 10mg (as of LOT N). The non-disintegrating Tablets are made up of pure Salicylic Acid and are currently produced with an active concentration of 300mg (as LOT O).

One Tablet is used in each of the 6 vessels to be calibrated. Generally, both tools (Apparatus 1 and 2) are used for both tablet tests. This means four tests have to be performed. The current “Lot” must be used and this applies to the standards also. Both the Tablets and the Reference Standards should be stored as per the description outlined in the USP guidelines. The drying guidelines for both Tablets and standards are also to be found on the container labels, and will generally require the use of a desiccator for some time prior to the start of the test.

The vessels themselves have to be scrupulously clean and contain no apparent flaws or aberrations. Glass can chip, plastic vessels can be scratched (shows only when dry!).

Internal undesirable features such as dimples at the base of the dissolution vessel will cause the tablet to race around and give a (generally) too high dissolved active measurement.

Once the solutions have been carefully loaded into the dissolution vessels, then the Tablets should be taken as directly as possible from the bottles or the storage point in the desiccator and introduced into the dissolution vessel. Tablets should not be allowed to lie around prior to use, especially if they are left resting on vessel covers and the like which are close to sources of moisture.

The preparation of the medium should follow the guidelines as indicated in the calibration certificates, which are delivered with every lot of calibrator tablets. Some helpful hints are included under the heading of Test Medium Preparation below.
Tests may be started in either a staggered (manual sampling) or synchronous manner (automated systems). Sampling should be made as per the USP guidelines, i.e., half way between the top of the tool and the surface of the medium itself, at least 1cm away from the wall of the vessel.

Automatic measurement methods have to be qualified and may give quite different results from manual measurement methods with syringe and filter. The reasons for this are many. Automated methods must be validated. The USP test gives good results using manual sampling and measurement, provided that all other systematic error sources have been eliminated. A reasonable series of checks to eliminate any problems revolve around the efficiency of sample transportation from the dissolution tester to the measurement device, which is normally a UV VIS Spectrometer (or possibly a Fraction Collector). The most obvious and often encountered problem is that of tubing on peristaltic pumps. Almost nobody relieves the pressure on these tubes when the device is out of use and the life expectancy is therefore very limited. In these cases, the tubing can be split and / or the tubing so squashed, that the pumping efficiency is greatly reduced, so that sample is not correctly transported from the tester to the measurement device.
The answer is of course to qualify the pump and make sure that delivered volume rates are as exact as possible from channel to channel. This can be easily checked and technically should be done before the start of every estimation in order to validate the pumping efficiency. You also may use a Piston Pump which is absolutely precise and requires less qualification work. Small leaks of either liquid out, or air in, are another source of error. Adsorption of active material on either the tubing walls or on the filter have also been responsible for low estimations. This can easily be overlooked as more often than not these test materials fall out of the scope of the normal products measured on the instrument. Sometimes filters may become clogged. It is our experience that 10µ polypropylene filters are not so prone to clogging. However, these filters should be wetted and have liquid pumped around the system through them (with Blank medium for example) in order to eliminate entrapped air in the filter membrane itself. Whatever the sampling method, samples should always be taken through a filter and never be centrifuged after sampling. Also be aware of sample carry over, especially if the quartz flow through cells in the spectrometer have been qualified with a standard solution and not efficiently flushed.
Lastly some ideas about the tools themselves. These should be qualified in terms of their depth relative to the bottom of the dissolution vessel. Additionally, we have found that starting with the paddles (Apparatus 2) with say Prednisone and then installing the baskets (Apparatus 1), doing the two tests for Prednisone and Salicylic Acid with the Baskets and then reinstalling the Paddles for the last test reduces the qualification time required for the

tools as well as allowing the most effective use of medium preparation devices such as the PT-DDS. See picture below

The PT-DDS Medium Pre-heater and Degasser Unit.

Efficient bulk degassing of medium can provide enough ready to-go-solution to suffice for both tests so that re-aeration time is kept to a minimum and temperature equilibration periods are eliminated, which can also reduce the cost per analysis.

Medium Deaeration:

This is a really common problem. The effects are really noticeable with the Prednisone test. Although previous lots based around the 50mg tablets were generally well behaved, the newer 10mg formulations have shown up (an accidental) sensitivity to poorly deaerated media. Excessive degassing (a curious term referred to in some private correspondence) will yield too low results and inadequate degassing will yield too high results. The general feeling is that the inter tablet variation within the overall stated ranges can be quite large anyway and this is very much dependent on the particular bottle as well as the tablet storage conditions.

Another tip is to avoid excessive heating. If you follow the directions in the accompanying USP literature then heating to 41°C will possibly (depending on the “manipulations” involved) lead to a medium temperature in the vessel of about 39.5°C. This will require about 1.5hrs to equilibrate to the 36.5° to 37.5°C operational range and the media is nearly re-aerated again. The use of a lower target temperature of say 38.5°C may prove beneficial. Some people have also turned on the paddles (for example) in order to try and speed up the temperature equilibration. The net effect here is to help nature re-establish what we have just tried to eliminate, i.e., aeration. Excessive pouring or decanting techniques from a great height will also add to the “folded in” air. There is also a general movement away from alternative “established” deaeration techniques. The use of Helium (which does not really degas as it

rather replaces nitrogen and oxygen with helium) is really frowned upon now and several multinational sites have been sent warning letters to desist with this practise, so this is a good time to switch. The use of ultrasound is also now not recommended.

It is well to remember that although most media is re-aerated after about one hour (especially with paddle rotation) it is the effect in the opening time frame of the measurement that shapes the dissolution rate and hence the profile; this applies even for slow release products where the release profile may be collected over a period of 12 hours for example. Apart from anything else, poorly deaerated media can be easily spotted as tablets will collect bubbles around them and restrict the surface area in contact with the medium and baskets will have large sections of their mesh blocked with trapped air. Tapping the shaft of the basket holder is not advised as a remedy!

Other Observations:

During the lifetime of the Lot M Prednisone tablets, the ranges had to be extended for both the paddles and the baskets. The baskets were extended (at 100RPM) from 88% to 91%. The paddles had the limit dropped from 28% (at 50RPM) to 23%. This brings out a very important difference between the “European” and “US” designed instruments, as the drop in the limit for the paddle test was principally to incorporate baths of European manufacture. Most US bath manufacturers have large gantries from which the tools are suspended, so that the locking chucks and the bearings (i.e., the paddle supports) are quite removed from the paddle tool itself. This means that the European models have less detectable wobble at the tool end; therefore the greater wobble on US models will give a larger dissolved active profile than those of European manufacture where the tool is very much closer to both the supporting bearing and chuck, resulting in lower dissolution levels for the same tablet. Hence the change.

It has been found that the deaeration of dissolution medium can effect the results of a dissolution test in either higher or lower profiles. Besides the time consuming manual method which is recommended using a 0.45 micron filter, drawing a vacuum and stirring through the entire process. The PHARMA TEST Media Deaeration and Dosing System PT-DDS offers continuous medium circulation under vacuum and heating up to max. 60°C. It has been proven to be a very efficient method. Dosing is controlled by using a built-in electronic load cell which can be calibrated against a 1 kg standard weight.

Picture # 1: left hand side vessel shows non-deaerated medium while the right vessel is deaerated

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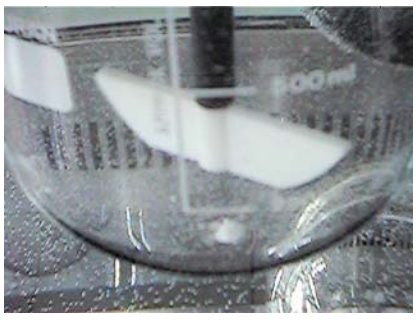

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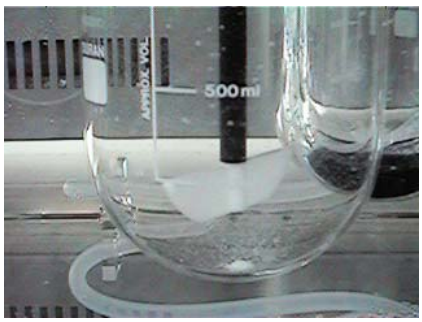

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Picture # 2: again shows non deaerated media, a lot of non-dispersed particles float on top of the medium, while within deaerated media (Picture # 3) these particles are floating throughout the whole medium.
Picture # 4: a USP calibrator tablet (Prednisone) inside non-deaerated medium, the medium is not clear and a lot of non dispersed particles float arround the stirrer.
Picture # 5: shows also a USP calibrator tablet from the same batch but inside deaerated medium, it's visible that the medium is clear and a lot less non dispersed particles float around. All pictures have been taken at the same time.

Test Medium Preparation:

The solutions which you should prepare for the tests are as follows:

1. Prednisone: Demineralised Water:
This has no real preparation except that it should be filtered to 0.45µ. It may then be treated using the pre-heating and circulation method with the additional application of vacuum. In our experience the level of vacuum for successful results is around the 500mB level. In the case of the DDS, the vacuum will switch itself out at this point and then keep the vacuum applied throughout the heating and circulation cycle (to remove any extra gas which may come out from the medium as a function of circulation and reduced pressure. The DDS 2 will prepare about 25 litres of demineralised water in about 35 minutes. The total requirement for the standard test is about (min) 16 litres.

2. Salicylic Acid: Phosphate Buffer, pH7.4
This is a pH 7.4 ± 0. 05 solution of Phosphate buffer, which is 0.05M in strength. It is made up by weighing out approximately 67.7g ± 0.5g of potassium dehydrogen orthophosphate and 15.6g ± 0.5g of sodium hydroxide pellets into a large container using a balance accurate to two decimal places. Add 10 litres of water, filtered to 0.45 µ, and mix thoroughly to dissolve all the material before transferring to the degassing device. You will need approximately 15 to 20 litres of this medium. The pH should be measured and recorded for the PQ protocol.

Standard Solution Preparation:

1. Prednisone: in demineralised water:

With the advent of the 10mg test tablet and a test volume of only 500ml, the Reference Standard has to be carefully made. In order to minimise errors we have found that 10mg weighed out into a clean, dry 100ml volumetric flask is a reasonable start. This is well within the scope of a five place balance. The weight should be recorded for the PQ protocol. If you attempt to disperse and then dissolve the Prednisone directly in a small quantity of water, then there will be some small amount of agglomerated product floating around in lumps. The addition of a small amount of Ethanol (AR or analytical grade) will help to disperse the powder into finer particles and then the business of dissolving will be achieved over a shorter period of time. You are allowed to add up to 2% of Ethanol as a function of the total volume according to USP rules. Once the powder has dissolved, then make up to the mark, agitate for a few more minutes and then take an aliquot of 10ml and make up to 50ml with demineralised water in a volumetric flask. This will now give a standard which will represent exactly the 10mg of Prednisone in 500ml of water required as the 100% standard. The typical absorbance for this product in a 10mm path length cuvette will be around 0.84 AU. This is within the limit of the AU range recommended for a standard which is about 1.0 AU. Dilution of this Reference Standard should be made in order to be within approximately 10% of the expected sample values.
The solution should always be made freshly on a daily basis. The adsorption value for this Reference Standard solution will increase day by day if left at room temperature.

2. Salicylic Acid: in phosphate buffer:

Once again, it is really important to get the Reference Standard right. The 100% dissolved active is 300mg in 900ml. This gives a concentration of 333.4mg in a litre. As the Reference Standard is supplied in 125mg lots, then we suggest that you take a 33.34mg amount weighed into a clean, dry 100ml volumetric flask. Again, the use of Ethanol is recommended in order to first disperse the material in order to get a better rate of solvation. As the extinction coefficient for this moiety is fairly large and the concentration quite high, we have to employ either a dilution stage (typically by 10) or we can use a 1mm flow-through cell in our measurement spectrometer. Using a manual fill 1mm cell is not the easiest thing to do and the threat of substantial carryover from one sample to the next is very significant. Therefore we can advise, based on a positive experience, that you can successfully employ a flow through 1mm cuvette (cell) with a syringe female luer line connection at one end of the Teflon tubing for sample injection and the other end placed in a beaker to collect waste or reclaim the sample. The advantage of this system is that :

1. there is no need for dilution,
2. no need for difficult manipulations of a conventional 1mm path length cell, and
3. easier cell flushing and sample introduction, greatly cuts down the analysis time.

The typical adsorption for this concentrated standard is 0.82 AU. Again the Reference Standard should be diluted to be within approximately 10% of the expected sample values. As with all solutions, each Standard should be clearly labelled as to its contents, the date of preparation, the expiry date and the operators name or initials.

Buffers and aqueous media prepared with the PT-DDS Medium Preparation instrument, can have all of the above information as well as target temperature, deaeration time with and without vacuum, buffer expiry date and buffer batch number entered directly in to the pre-programmed method parameters, which can later be printed out as part of the results protocol.

Allowable errors: a 1% error in the weight of medium dispensed is allowed.

Sampling:

Samples should be taken by the use of an in line filter attached to the end of a stainless steel tube which has been suitably formed to accept a filter at on end and a female Luer socket at the other (which allows a syringe to be attached).

Special precautions:

The Salicylic Acid tablets are very dusty and often stuck together. If the tablets are placed in the dissolution medium as they stand, then you will run a risk of obtaining a high value for the dissolution results after 30 minutes. De-dust the tablets prior to dropping them in the dissolution vessel by gently rubbing them with a clean dry (non-abrasive) paper towel until you almost “shine” them up. If you have a chipped or cracked tabled which has to be discarded, try rubbing one of these with a green or blue paper hand towel and just see how much comes off. Well worth the experiment!

Procedure:

Prednisone: This test requires 500g of pre-heated, degassed medium, per vessel. Tablets may be taken straight from the Bottle or Blister in which they were supplied and added to the dissolution vessels. These are fast disintegrating types and will first sink to the bottom of the vessel. Make sure that the tablet is located directly under the blade of the paddle so that it forms a mount directly under the base of the paddle itself. The basket test at 50rpm will allow almost none of the tablet mass to be released from basket itself.

1. A paddle speed of 50 RPM should be selected on the dissolution tester for this test using Apparatus 2
2. A basket speed of 50RPM should be selected on the dissolution tester for this test using Apparatus 1.
3. The absorbance of each sample and the standard should be measured at 242nm. Set the UV Spectrometer accordingly.
4. Each test is run for 30 minutes.
5. A total of six tests must be run.
6. Any failure on any station means a re-run of another 6 tests.
7. The tests can be started simultaneously or can have a staggered start to facilitate easier sampling (10 to 20 seconds between drops).
8. Use the following equation to calculate the percentage dissolved active:

$$\%\text{dissolved} = \frac{\text{AU Sample}}{\text{AU Standard}} \times \frac{\text{Wt. of standard used (mg)}}{10} \times 100$$

Salicylic Acid: This test requires 900g of pre-heated, degassed medium, per vessel. Tablets may be taken straight from the Bottle ob Blister in which they were supplied and added to the dissolution vessels. These are non-disintegrating types and will first sink to the bottom of the vessel. Make sure that the tablet is located directly under the blade of the paddle or in the case of the basket, stays within the confines of the floor of the basket and does not float.

1. A paddle speed of 100 RPM should be selected on the dissolution tester for this test using Apparatus 2
2. A basket speed of 100RPM should be selected on the dissolution tester for this test using Apparatus 1.
3. The absorbance of each sample and the standard should be measured at 296nm. Set the UV Spectrometer accordingly.
4. Each test is run for 30 minutes.
5. A total of six tests must be run.
6. Any failure on any station means a re-run of another 6 tests.
7. The tests can be started simultaneously or can have a staggered start to facilitate easier sampling (10 to 20 seconds between drops).
8. Use the following equation to calculate the percentage dissolved active:

$$\%\text{dissolved} = \frac{\text{AU Sample}}{\text{AU Standard}} \times \frac{\text{Wt. of standard used (mg)}}{33.34} \times 100$$

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