ELECTROLAB
Your Quality, Our Assurance

FAQ for USP Type 4 Flow through dissolution apparatus (EFD-07)

1. How is sampling Performed if sampling is required at intervals of 10, 20, 30 minutes, etc? For how long exactly is it carried out in an open type? Is there a delay account?

Sampling can be performed manually and by connecting the system to an auto-sampler as well. There is provision in the instrument where you can set the time points and sampling will be performed by the auto-sampler automatically as per the set time. In case of open loop configuration, a sample collector splitter does the job of auto-sampling. In case of close loop configuration, a Dx sample collector does the job of auto-sampling. The duration of the test depends on the product type. The Electrolab USP-4 flow through dissolution instrument has a provision of maximum time limit of 999 hr and 59 min. Auto-sampling will take more time in comparison to manual, so to account for the delay, manifold lead time feature has been added, so that the aliquot collection is within the USP range of ± 2 %.

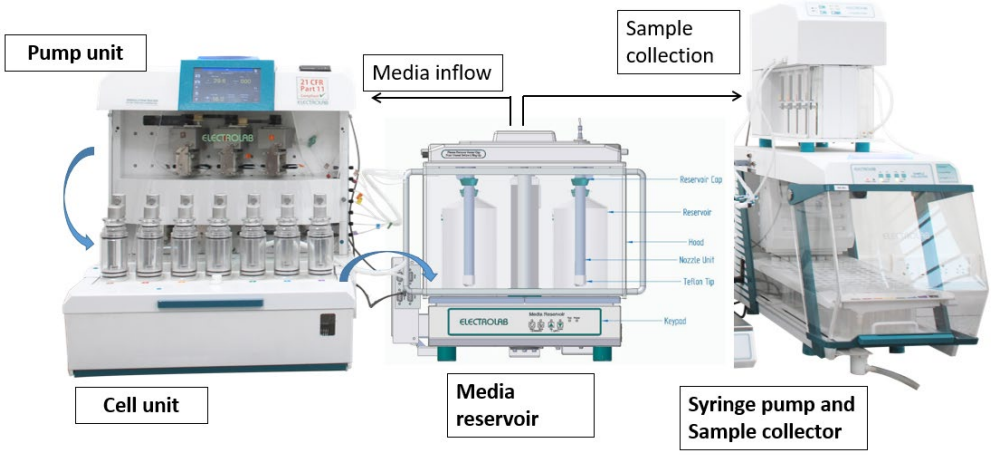


Figure 1 Fully automated closed loop system with automatic sample collection

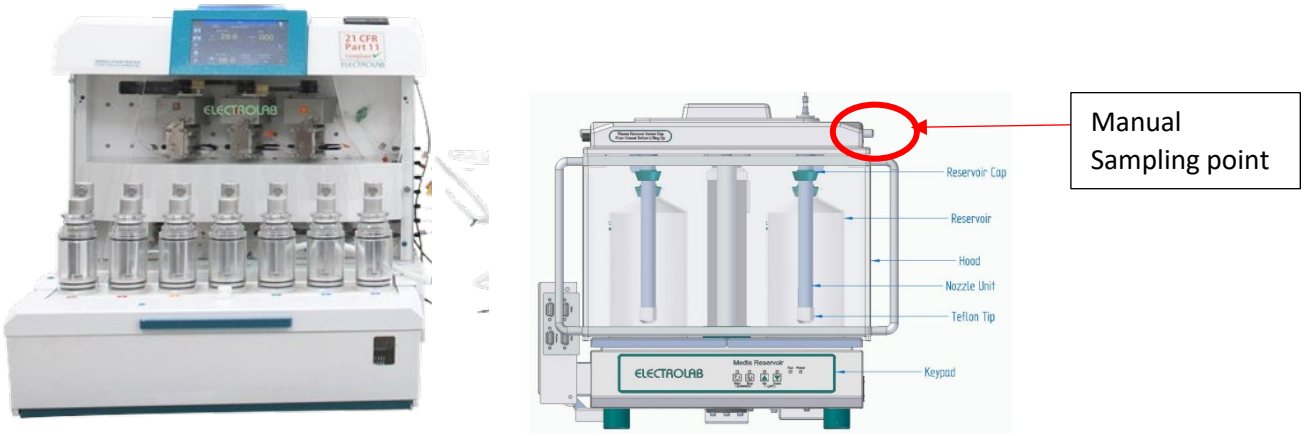


Figure 2 Closed loop system with Media reservoir (Samples can be collected from the media reservoir manually)

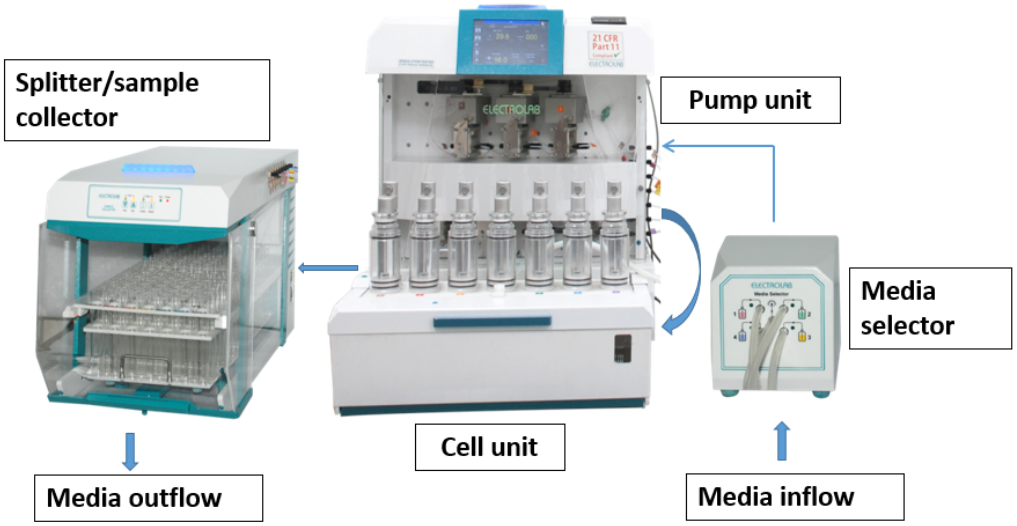


Figure 3 Fully automated open loop system with automatic sample collector splitter

Figure 4 Basic unit (cell unit and pump unit) sample collection is completely manual

2. When developing the cell dissolution test (a new product) what should customer focus on? What should the results be compared with when choosing conditions?

If method is published in Office of Generic drug (OGD) guidance, then same condition needs to be followed. And to achieve discrimination, minor modifications to the OGD media can be done for flow rate, which is the main parameter governing dissolution rate.

If the method is not official in any of the document guidance / pharmacopoeia then based on the evaluation of drug substance characteristic like solubility, particle size, polymorphism, crystallinity, saturation solubility can be determined. It becomes essential to study API (Active Pharmaceutical Ingredient) in-vitro dissolution within Type 4. This in turn can be adopted to the formulation. For specific cases where technical support is required, Electrolab can assist.

3. Is it possible to create an online system, to connect a spectrophotometer?

Yes it is possible.

4. How should the cells be cleaned after the test?

The cells can be cleaned by using laboratory detergent solution. In case of sticky/oily samples, 30% organic solvent (like methanol, IPA) diluted in water can be used to clean the sticky/oily material and immediately rinse with water to remove the organic medium traces. Do not use corrosive solvents like THF.

5. Does the dissolution media have time to heat up to 37 degrees on the way from the tank to the cell, or does the dissolution media need to be preheated?

In Electrolab USP-4 flow through dissolution instrument, there is heat exchanger coil just before the entry to the flow through cell. This heat exchanger coil is always immersed inside the heated water bath. The dissolution medium flows through this heat exchanger coil and then reaches the flow through cell. So preheating of the dissolution medium is not necessary.

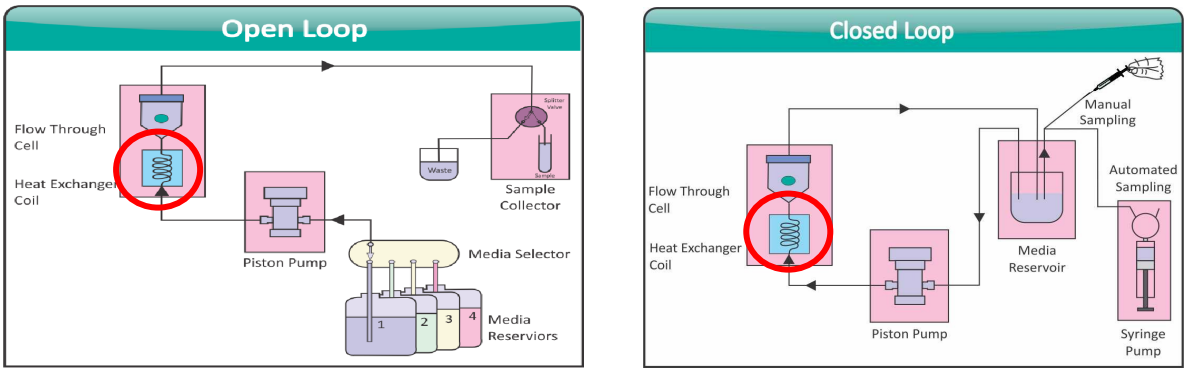


Figure 5 Open and closed loop system schematic diagram

6. When carrying out the kinetics of dissolution, it is necessary for difficult-to-dissolve substances to achieve three times the saturation volume. How does this work in a closed and open loop configuration?

For poorly soluble drugs, yes it is necessary for sink conditions to be maintained. When using a closed loop configuration with Electrolab Media reservoir, the media reservoir, can accommodate maximum of 2 litre for each flow through cell. In case of open loop configuration, there is continuous flow of fresh dissolution medium, so there is no limit to use of volume of dissolution medium.

7. How many cycles does the cell and the device as a whole last on average?

It depends on usage, there is no specific life.

8. In the USP, only 16 and 24 ml/min are regulated. Is it possible to use 32 or 8 or less?

Yes it is possible to use flow rate of 32 ml/min and lesser as well. It depends on the make of the instrument.

9. What are the criteria for choosing the flow rate? What factors should be considered?

Rate of diffusion of drug from formulation needs to be assessed before subjecting drug product for USP type 4 diffusion. And also it is governed by the Biopharmaceutical Classification System (BCS)

Class of the drug. Design matrix of the formulation should be considered for eg. Dispersion, erosion, swelling, etc.

10. Are the open and closed loop configuration different devices? Or is it possible to make both an open and a closed system in one device?

The main unit – i.e. the pump unit and cell unit are common for open and closed configurations. The other units are add-ons to the main unit for automated sampling. For open loop configuration, media selector and sample collector splitter can be connected to the main unit for automated sampling. For closed loop configuration, media reservoir and Dx sample collector can be connected to the main unit for automated sampling.

So it is possible for the main unit to be connected to both – open and closed system.

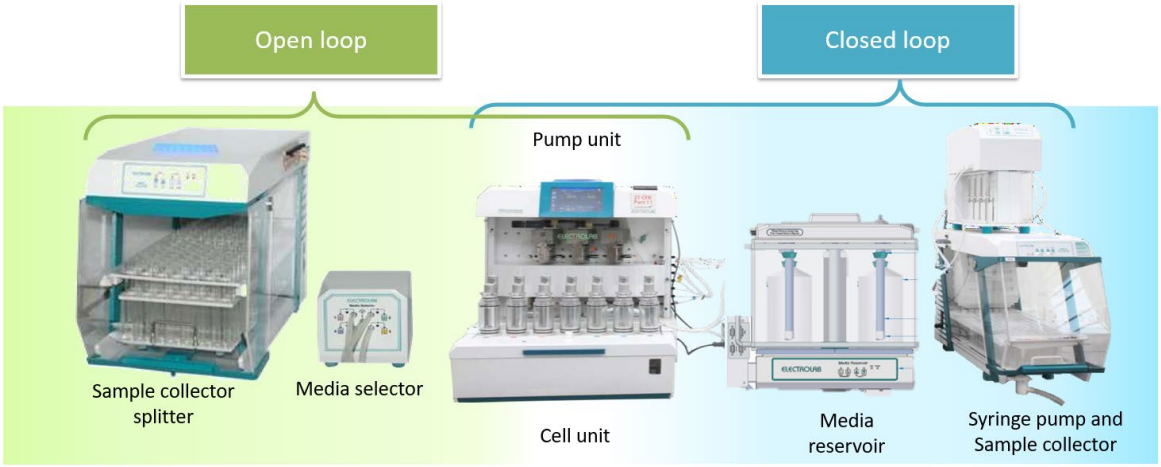


Figure 6 Open and closed loop – full automation

11. Do you have ready-made cases for using a cell for dissolving suppositories? Interested in the reproducibility of dissolution. What is the flow rate most often used for dissolving suppositories? What kind of dissolution media are used?

We have performed dissolution of suppositories using a suppository cell. Flow rate and the dissolution medium can differ from product to product. But if you are considering suppositories then on can start with 16 ml/min. Physiological buffers and buffers containing surfactants can also be used.

12. How is the dissolution medium mixed in a closed system? What additional automatic mixing device is available?

In closed loop configuration, media reservoir has a magnetic bead inside the vessel to stir the dissolution medium for uniform mixing.

13. How do we can make a qualification for USP-4 (tablets exist for USP I and II like prednisolone)?

Currently USP does not specify the mechanical or chemical calibration of USP type 4 dissolution apparatus.

14. Does the device need to be validated at each switch if testing is required at different flow rates?

No. Once the instrument is calibrated and validated for the flow rate, there is no need to validate again

15. What criterion is used to choose between laminar and turbulent flow?

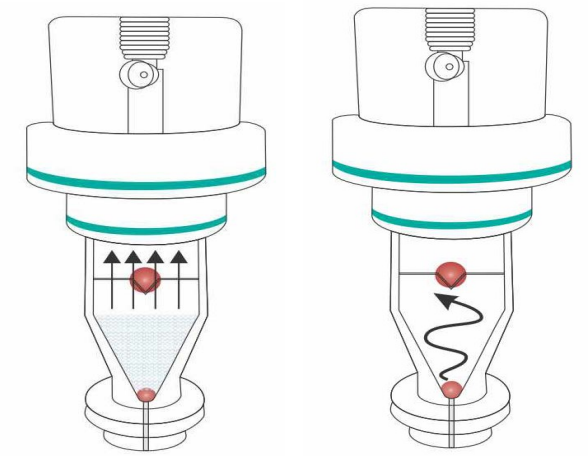


Figure 7 Laminar flow (left) and turbulent flow (right)

In case of laminar flow, the dosage form experiences uniform flow, while in case of turbulent flow, the dosage form experiences greater hydrodynamic turbulence. So depending on the release rate, one can choose between the two.
Design matrix of the formulation should be considered for eg. Dispersion, erosion, swelling, etc.

16. What are the criteria for choosing between a "closed" and an "open" system for solid dosage forms?

The choice of open loop and closed loop is governed by the Biopharmaceutical Classification System (BCS) Class of the drug.

The Biopharmaceutical Classification System (BCS) categorizes drugs into four classes based on their solubility and permeability:
Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability)

17.Is it possible to use USP-4 with liposomal dosage forms?
Yes. The selection of filters is critical in this case.

18. Is it possible to set different flow rates for different cells in the same test?
No, it is not possible set different flow rates for different cell. However you can set different flow rate for different time points.

19. How are liquid forms (suspensions) and emulsions placed and held in the cell?

The cell is placed on the cell unit, ruby bead and glass beads are placed in the cell, and then the liquid formulation is poured into the cell.

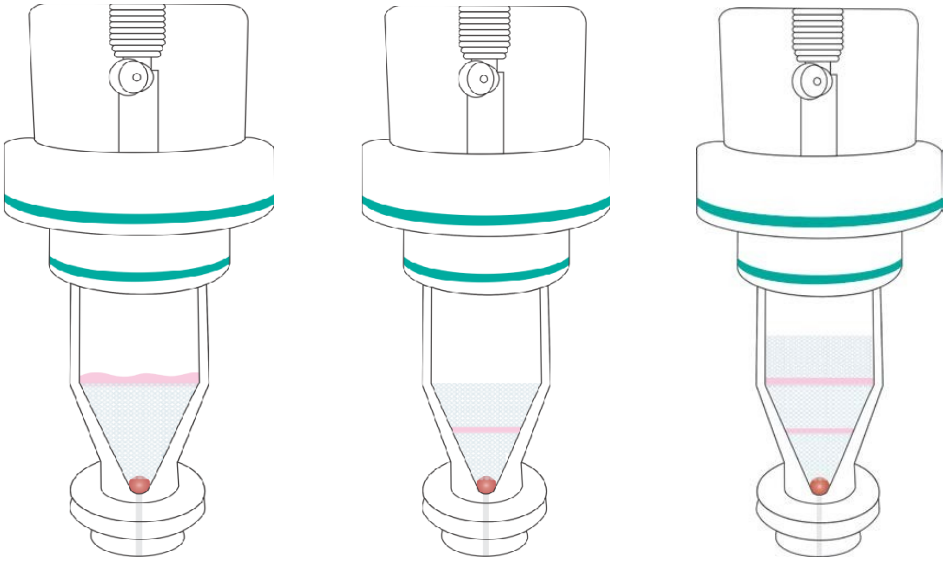


Figure 8 Dosage positioning for liquids (Onto the glass beads, sandwich layer, double sandwich)

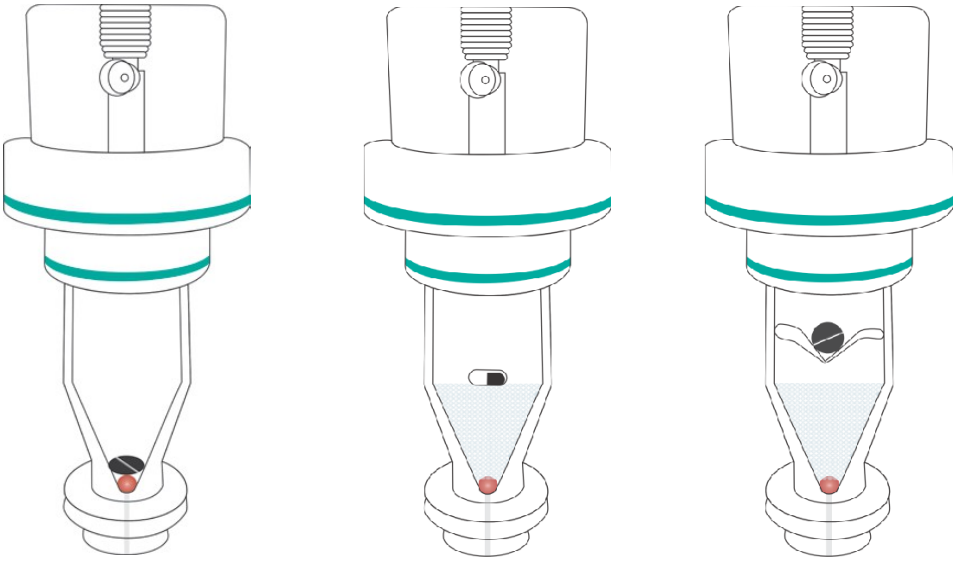


Figure 9 Dosage positioning for solids (with ruby bead, with ruby bead and glass beads, with tablet holder)

20. What regulates the number of beads in a cell?

If the number of beads are increased, then the impact/force with which the medium is flowing inside the cell is less in comparison to that when the amount of glass beads is less. So if you want to formulation experience less turbulence then, you can increase the quantity of glass beads.

21. Are the beads needed to maintain laminar solvent flow?

Yes. The beads are necessary to maintain the laminar flow inside the flow through cell.

22. For closed loop system, the EMR glass bottles are available in the sizes 100 mL, 500 mL, 1000 mL and 2000 mL as per the quote. Are 5L bottles available? And respective heating station?

Yes, EMR glass bottles are available in sizes 100ml, 500ml, 1000ml and 2000ml. Also we can supply different size of bottles based on requirement. However we would like to understand requirement of 5L bottle to serve you better. EMR is having individual heating for each glass bottle placed and temperature is controlled with high accuracy by Main unit and all records are printed on test report for each time point.

23. We anticipate use of organic solvents in certain percentage in our media like- n-octanol, PEG-400, propylene glycol, n-butanol etc. Please comment on the compatibility with the system.

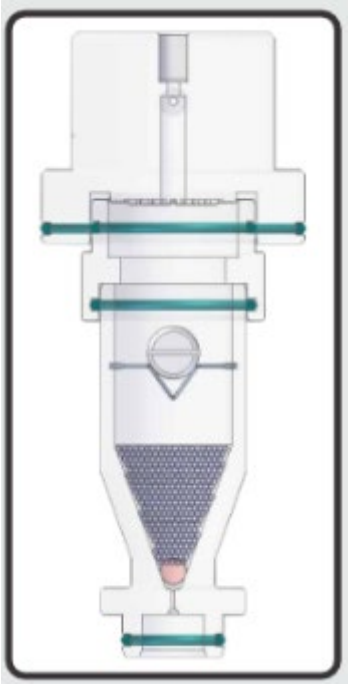
Organic solvents like n-octanol, PEG-400, propylene glycol, n-butanol at concentrations of 10% or lower will be compatible with all type of cells. Our application team can assist you for any application with higher concentration use case of organic solvents.

24. Our operating pH range would be majorly pH 1.2 to 6.8. Any issues that you foresee?

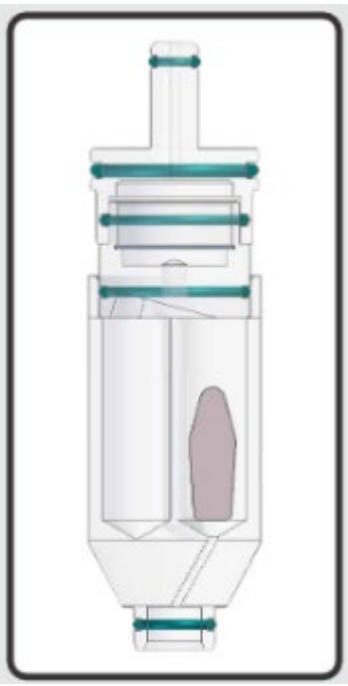
pH range of 1.2 to 6.8 is commonly used in our instrument. Our instrument can be operated in pH range from 1.2 to 7.4.

25. Can normal tablet cells 12mm/22.6mm be used for soft gel capsules or liquid-filled capsules?

Normal tablet cells 22.6mm can be used for soft gel capsules or liquid filled capsules if it is not having oily properties. For soft gel capsules or liquid-filled capsules with oily properties it is recommended to use suppository cell which is designed for specific application. This cell is described in Ph. Eur. And has special two chambered design which blocks lipidic excipients from the suppository/soft gelatin capsules to allow only the dissolution media to pass up to the filter. Refer below pictures of 22.6 mm cell and suppositories cell.



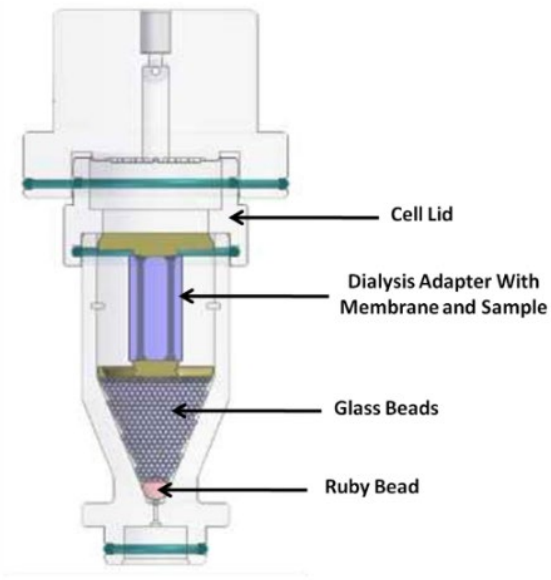
22.6 mm Cell



Cells for suppositories and Soft gelatin capsules

26. Can dialysis membranes be used in place of filters in cells?

Yes, there is possibility to use dialysis membrane in place of filters in cell. We have dialysis adapter which can be used in to separate the drug sample from the dissolution media and can be used for nanoparticles, microspheres, micro suspensions and injectable etc. Refer below picture to understand dialysis adapter in 22.6mm cell.



We commonly use glass fiber filters and Nylon/PVDF filters in the filter unit.

27. What is the range of flow rate that we can operate the instrument with?

The range of flow rate that is operated in the instrument is 2 ml/min to 32 ml/min.

28. How do you record the temperature of the dissolution medium?

The individual cell temperature is recorded and displayed by the instrument.

In case of closed loop configuration, a media reservoir is connected to the main unit. The media reservoir has 8 positions, one vessel for each cell and the 8th vessel for replenishment medium. Each vessel has probe dipped in the dissolution medium using which the temperature is monitored, controlled and recorded.