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Brief/Technical Note

Comparison of Dissolution Profiles for Sustained Release Resinates of BCS Class I Drugs Using USP Apparatus 2 and 4: A Technical Note

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INTRODUCTION

In vitro dissolution specifications are established to ensure batch-to-batch consistency while pointing out any potential problems with *in vivo* bioavailability among different drug products (1). At early stages of formulation development, *in vitro* dissolution testing provides guidance on optimizing drug release from formulations. While at later stages, it may be employed as an indicator of the *in vivo* performance of drug products to potentially reduce the number of bioavailability/bioequivalence studies. An established IVIVC can be further used to set meaningful dissolution specifications that take clinical consequences into account in the hope of facilitating regulatory approvals of post approval changes. Among the different *in vitro* systems available for testing, USP Dissolution apparatus 4 offers a viable option for carrying out dissolution of novel dosage forms (2,3). USP Dissolution apparatus 4 is helpful in: testing robustness of the formulation with respect to the variations in the intralumenal environment, maintaining sink conditions for the poorly soluble drugs (4,5) and non tedious method to change pH of the dissolution medium (6).

USP Dissolution apparatus 4 has been extensively studied for the prediction of *in vivo* performance of orally administered dosage forms like amoxicillin capsules (7), paracetamol (8), carbamazepine (9), danazole capsules (10), spironolactone (11). It is the method of choice for extended release and poorly soluble drugs. Point to point correlation of *in vitro* release data using flow through cell apparatus is established for monolithic extended release formulations of highly permeable isosorbide-5-mononitrate (12). Similarly, good *in vitro in vivo* correlation was reported for vincamine extended release formulations (13). The development of flow through cell came about as an attempt to provide controlled hydrodynamic environment and renewable stream to the sample and has proven to be a useful tool in determining the *in vitro* release of the extended release formulations.

Extended release formulation can be formulated using polymer (14), lipids/waxes (15), ion exchange resins (16) *etc.* Ion exchange resins have recently been gaining importance in pharmaceutical industries in the manufacturing of extended release formulations. IER are water insoluble, cross-linked polymers containing salt forming groups in repeating positions on the polymer chains. IER form a complex with the drug through weak ionic bonding. Drug release from resinate depends on pH and electrolyte concentration within the gastrointestinal tract. With basic drugs, strong cationic exchange resins (sulfonic acid) yield strong drug resin bonding resulting in slower elution of drug from resinates and this principle has exhibited the potential of resins as sustained release agents (17,18). The presence of released drug and ion exchange resin with free active sites has a significant effect on the further release of drug from resinate. This effect will be more pronounced while dealing with BCS class I drugs. Butler *et al.* (6) has mentioned the usage of USP Dissolution apparatus 4 particularly for drugs with low solubility as it can maintain the sink condition, independent of drug solubility. Hitherto there are no reports in the literature that cite the necessity of maintaining sink conditions while performing *in vitro* release of sustained release resinates of highly soluble drug. Release data based on a well thought out test is of tremendous value in selection of right formulation. Therefore, the present work was focused on studying the effect of USP Dissolution apparatus 2 and 4 on the *in vitro* release of drug from resinates of BCS class I drugs.

MATERIALS AND METHODS

Materials

Ciprofloxacin hydrochloride, ofloxacin was gifted by Cipla Ltd., Mumbai. Ofloxacin was gifted by Alkem Laboratories, Mumbai. Verapamil hydrochloride was gifted by Suven Life Sciences, Bangalore. Diltiazem hydrochloride was gifted by GC Chemie and Cipla Ltd. Indion® 244 was obtained as gift sample from Ion Exchange (India) Ltd, Mumbai. USP

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Dissolution apparatus 4 was provided by Electrolab Ltd. All the chemicals and reagents used were of analytical grade and were purchased from s.d. fine chemicals, Ltd, Mumbai.

Complexation of Drugs with Ion Exchange Resins (19)

Verapamil hydrochloride, ciprofloxacin hydrochloride, ofloxacin and diltiazem hydrochloride were complexed with strong cation exchange resins *i.e.* Indion® 244 (Divinyl benzene cross-linked with polystyrene having $–SO_3H$ functionality) in different ratios using batch process. The process was optimized with respect to ratio of drug: resin, time of stirring and volume of complexing medium. The degree of complexation was determined by analysing the quantity of drug in filtrate using UV spectrophotometry.

Characterization of the Resinate by Differential Scanning Calorimetry

The complexation between drug and resin was confirmed by recording thermal behaviour of drug, resin and resinate using Differential Scanning Calorimetry. Perkin Elmer Differential Scanning Calorimeter equipped with Pyris 6 software was used for the study. Approximately 5.0 mg of sample was loaded into an aluminium pan, hermetically sealed under nitrogen and run at a scanning rate of 10 °C/min over a temperature range of 30 to 400 °C in a dynamic nitrogen atmosphere. An empty sealed Aluminium pan was used as reference.

USP Dissolution Apparatus 4

The assembly (Fig. 1) consists of a reservoir containing the dissolution medium, a pump that forces the dissolution medium upwards through the vertically positioned flow-through cell, and a water bath. The pump usually has a flow rate delivery capacity between 4 to 16 mL/min, with typical flow rates of 4, 8 and 16 mL/min. The bottom cone of the cell is filled with small glass beads of about 1 mm diameter and with one bead of about 5 mm diameter positioned at the apex to protect the fluid entry tube, whereas a glass fiber filter is positioned at the inner top of the cell and was attached to stainless steel (SS316) coil that helped in maintaining temperature of the dissolution medium. The pump was separated from the dissolution unit in order to shield the later against any vibrations initiating from the pump.

In Vitro Release Studies

USP Dissolution Apparatus 2

The resinate (weighed complex equivalent to 500 mg of ciprofloxacin, 400 mg of ofloxacin, 120 mg of verapamil hydrochloride and diltiazem hydrochloride) was transferred to 900 mL of dissolution medium pH 1.2 buffer. The temperature of the medium was maintained at 37±0.5 °C. The paddle was rotated at 50 rpm. Aliquots were taken at intervals and analyzed by UV spectrophotometry. All experiments were performed in triplicate.

USP Dissolution Apparatus 4

Resinate was transferred to small cell (12 mm i.d.) with temperature maintained at 37±0.5 °C. Buffer pH 1.2 was passed through the cell at a constant rate of 4 mL/min. Fluid exiting from the cells was collected in a beaker. It was analyzed for drug content by UV spectrophotometry. All experiments were performed in triplicate.

RESULTS AND DISCUSSION

Complexation of Drugs with Ion Exchange Resins

Ciprofloxacin hydrochloride, ofloxacin, verapamil hydrochloride and diltiazem hydrochloride were successfully complexed by Indion® 244. Complete complexation was achieved at the end of 3 h. The resin exhibited complete loading of the

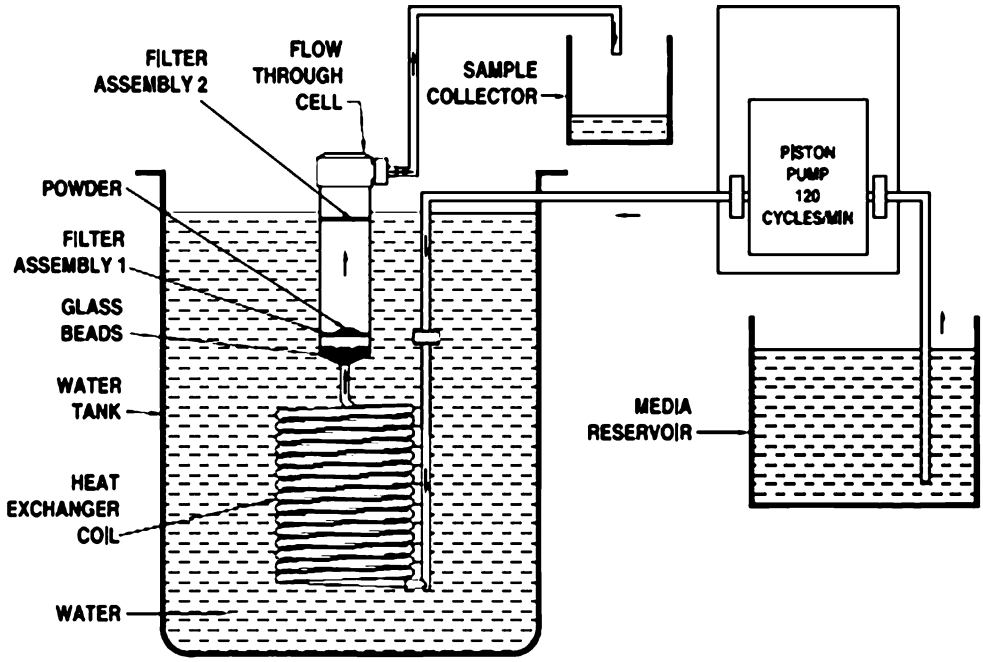

Fig. 1. Schematic diagram of USP dissolution apparatus 4

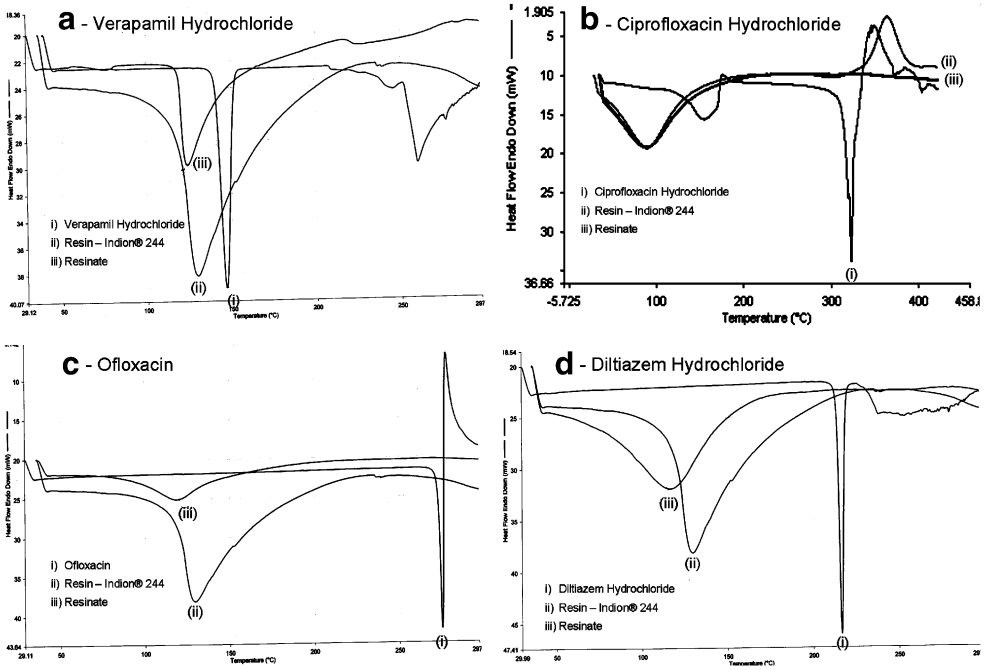

Fig. 2. a–d DSC thermograms of drugs, resin and resinates

drug, which was confirmed by analyzing the concentration of the uncomplexed drug in the filtrate.

Characterization of the Complex by Differential Scanning Calorimetry

DSC thermogram of verapamil hydrochloride, ciprofloxacin hydrochloride, ofloxacin and diltiazem hydrochloride showed one endothermic peak of fusion, having a peak maximum of 146.7, 323.28, 276 and 216.49 °C respectively. DSC thermogram of the resin showed one endotherm of fusion, having a peak maximum of 128.38 °C. DSC thermograms of resinates of verapamil hydrochloride, ciprofloxacin hydrochloride, ofloxacin and diltiazem hydrochloride showed one endothermic peak of fusion, having a peak maximum of 122.5, 93.12, 119.24, 115.87 °C respectively. Thus, disappearance of the drug

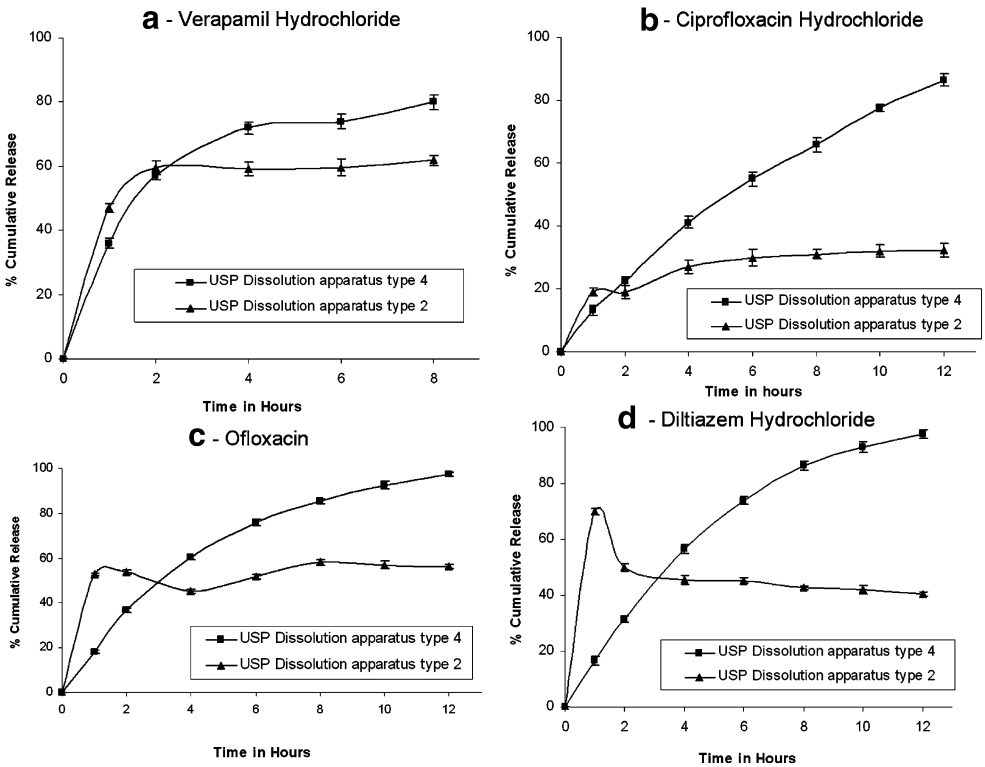

Fig. 3. a–d Comparison of release profiles using USP apparatus type 2 and type 4

peak in the DSC thermograms confirmed complete complexation between drug and resin (Fig. 2).

In Vitro Release Studies

USP Dissolution Apparatus 2

The *in vitro* release of all four drugs was studied by carrying out their dissolution in USP Dissolution apparatus 2. It was observed that in all cases the release of drug from resinates was less than 60%. The Fig. 3 illustrated that after 2 h there was no drug release. In addition, the Fig. 3b, c and d demonstrated a decrease in drug release after 1–2 h. Such decrease in an *in vitro* release system could occur only due to re complexation of released drug with free active sites of ion exchange resin. However, the said phenomenon will not occur *in vivo*, especially for BCS class I drugs, due to the maintenance of sink conditions.

After 2 h, equilibrium was established between bound and unbound drug, which was exhibited by a plateau in the drug release curves as depicted in Fig. 3. USP Dissolution apparatus 2 is therefore not suitable for determining the *in vitro* release of sustained release resinates.

USP Dissolution Apparatus 4

Since resinate was exposed to continuous flow of medium, slow and complete drug release was observed over the stipulated period. Results indicated 80% release in 8 h in case of verapamil hydrochloride resinates and more than 90% release in 12 h in case of ciprofloxacin hydrochloride, ofloxacin and diltiazem hydrochloride resinate (Fig. 3). Thus, USP Dissolution apparatus 4 was proved to be successful for studying the release of drug from resinates.

$$\text{Drug} + \text{Resin} \underset{\text{Complexation}}{\rightleftharpoons} \text{Drug Resinate} \underset{\textit{In vitro}\ \text{release}}{\rightleftharpoons} \text{Drug} + \text{Resin}$$

The comparison of the release profile by USP Dissolution apparatus 2 and USP Dissolution apparatus 4 was as shown in Fig. 3.

Complexation between drug and resin and the release of the drug from resinate is an equilibrium process. The rate of achievement of equilibrium is dependent on the ionic concentration in the surrounding medium. When *in vitro* release was studied in USP Dissolution apparatus 2, equilibrium was achieved prior to complete release of drug. In case of USP Dissolution apparatus 4, resinate was continuously exposed to fresh medium, thus maintaining sink conditions. This facilitated the continuous release of actives from the resinate obviating equilibrium attainment, thereby simulating *in vivo* conditions. Hence, it could be concluded that USP Dissolution apparatus 4 is the ideal candidate for determining the *in vitro* release of sustained release resinates.

SUMMARY AND CONCLUSION

Verapamil hydrochloride, ciprofloxacin hydrochloride, ofloxacin and diltiazem hydrochloride were complexed with strong acid resin. *In vitro* release study using USP Dissolution apparatus 2 did not give the desired release profile. After 1 to 2 h, the released drug was recomplexed with free resin and this phenomenon continued until equilibrium was attained. USP Dissolution apparatus 4 was successfully used for studying the release of the drug from resinates. Recomplexation and equilibrium never existed in USP Dissolution apparatus 4 as it maintained the sink conditions simulating *in vivo*. Comparison of dissolution profiles with both these methods demonstrated a greater sensitivity and discriminative capacity of USP Dissolution apparatus 4 in detecting differences of the dissolution behaviour of resinates studied. USP Dissolution apparatus 4 provided improved drug dissolution results and potentially improved relevance to *in vivo* drug release characteristics. The present investigation helps in selection of appropriate dissolution apparatus for sustained release resinate of class I drug using ion exchange resins.

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