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Sequential Injection Analysis: A useful Analytical Tool in Drug Dissolution Testing

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Sequential-injection analysis (SI) is considered to be the second generation of flow injection techniques and was initially developed by Ruzicka and Marshall [1,2] as an alternative sample-handling technique to the well-established Flow injection analysis (FI) [3-5]. As can be seen in a typical SI setup in Figure 1, the heart of a SI manifold is a multiposition selection valve. Fluids are manipulated within the manifold by means of a bi-directional pump. A holding coil is placed between the pump and the common port of the multiposition selection valve. The selection ports of the valve are reservoirs, detectors, pumps, reactors, separators, special cells, other manifolds etc. After aspiration of a discrete volume (zone) of sample into the holding coil via the sample line, the sample can be subjected to very complex physical and chemical pre-treatment in different ways within the SI manifold. SI offers great potential for sample handling because it is a bidirectional, stopped-flow sample-handling technique enabling the sample to be serially processed in the different modules connected to the selection valve by means of repetitive aspiration and delivery steps. The advantages of SI over FI are the following: a) SI makes use of a simpler manifold that can be employed for a larger range of analytical methods without (or minimal) alterations in its physical configuration; b) in SI, discrete volumes of sample and reagents are aspirated and their consumption is drastically reduced; c) the bidirectional and stopped-flow operation of SI provides great scope for pre-treatment of the sample. This last attribute of SI makes it ideally suited to clinical and biochemical applications for which sample pre-treatment is usually necessary prior to the actual analytical measurement (Figure 2).

Drug absorption after oral administration of a solid dosage form depends on the release of the active ingredient from the formulation, its dissolution under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to the prediction of *in vivo* performance [6-8]. It is therefore widely accepted that dissolution testing is a very important tool in the pharmaceutical industry for providing valuable information to both formulation teams that design new products and quality control scientists for ensuring lot-to-lot quality and consistency within pre-defined specification criteria [9,10].

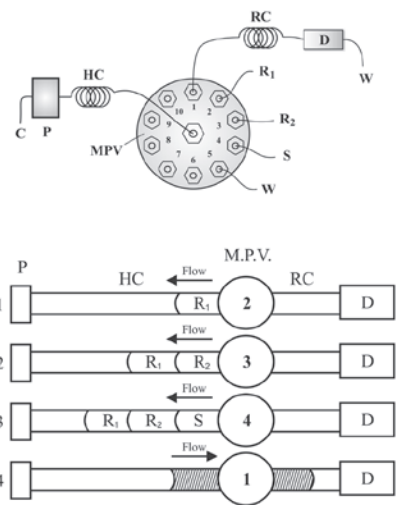

Figure 1: Typical SI setup and SI sequence steps: P = pump; C = carrier solution; HC = holding coil; MPV = multi-position valve; RC = reaction coil; D = detector; W = waste; R_1 & R_2 = reagents; S = sample; S1-S4 = SI steps.

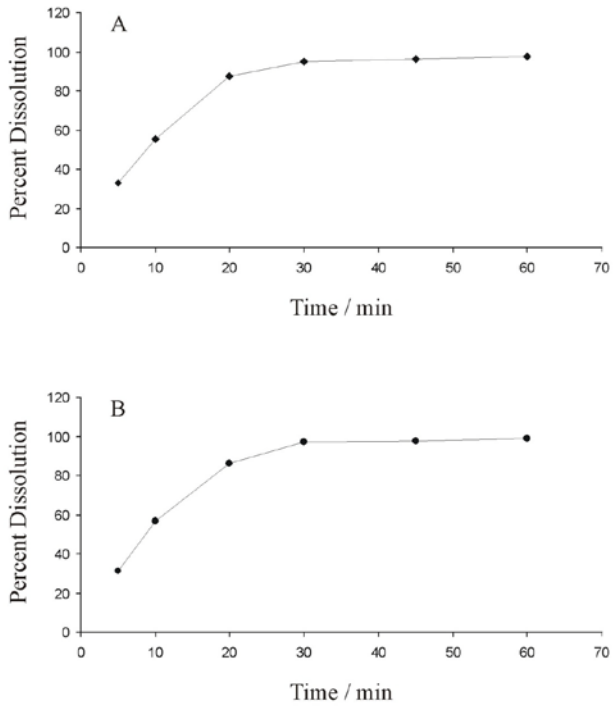

Figure 2: Comparative dissolution profiles of mexiletine formulations using SI (A) and HLPC (B) [14].

SI has proven a useful analytical tool for drug dissolution studies due to the enhanced automation capabilities and increased robustness of the

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Analyte	Principle/Detection	LOD	Range	Sampling	Ref
Indomethacin	Reagent-free method based on photo-induced flurimetric detection (287/378nm)	1.2 μmol L^{-1}	4.1-90 μmol L^{-1}	20	[11]
Captopril	On-line derivatization with methyl and butyl propiolate esters (285nm)	0.2 μmol L^{-1}	10-220 μmol L^{-1}	40	[12]
Gemfibrozil	On-line dilution based on zone-sampling by coupling of SI to fast HPLC	2.3 mg L^{-1}	30-750 mg L^{-1}	60	[13]
Mexiletine	On-line derivatization by o-phthalaldehyde in the presence of sulfite followed by fluorimetric detection (350/446)	3.4 mg L^{-1}	10-300 mg L^{-1}	25	[14]
Propranolol	Native fluorescence of propranol HCl in Krebs-Ringer Buffer (ex: 210nm)	0.02 mg L^{-1}	0.2-80 mg L^{-1}	60	[15]
Aminocaproic acid	On-line derivatization by o-phthalaldehyde in the presence of N-acetylcysteine followed by fluorimetric detection (350/450 nm)	0.25 μmol L^{-1}	0-60 μmol L^{-1}	40-50	[16]
Prazosin HCl	Native fluorescence of prazosin HCl (244/389 nm)	0.007 mg L^{-1}	0.02-2.43 mg L^{-1}	70	[17]
Ascorbic acid	Seperation by SI coupled to solid phase extraction	10-100 mg L^{-1}	1.0 mg L^{-1}	26	[18]
Rutin trihydrate	Detection at 262 nm.	2-20 mg L^{-1}	1.5 mg L^{-1}		
Ergotamine tartrate	Native fluorescence of Ergotamine (236/390 nm)	0.01 mg L^{-1}	0.03-0.61 mg L^{-1}	120	[19]
Acetylsalicylic acid	Potentiometric detection by ion-selective electrode	0.05 mmol L^{-1}	0.05-10 mmol L^{-1}	20	[20]

Table 1: Applications of SI to drug dissolution studies.

technique under continuous operation. An overview of the published SI methods applied to the dissolution studies of pharmaceutical formulations for quality control purposes is presented in Table 1 [11-22]. The active pharmaceutical ingredients are detected either directly by UV-Vis or Fluorescence spectroscopy, after suitable derivatization reactions or following HPLC separation. Automated sample treatment steps include – among others – dilution, filtration and on-line solid phase extraction. From the validation point of view, in contrast to assay methods, it is critical to evaluate the linearity from the LOQ e.g. 120% of the established level in order to obtain a dissolution profile. A common validation pitfall is the study of the specificity. Normally in SI methods applied to the QC of pharmaceuticals the selectivity is examined using either individual excipients or a suitable placebo. When the application of the method involves dissolution tests it is necessary to subject the spiked placebo mixture (synthetic samples) to the dissolution test as well under the exact same operating conditions.

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