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Dissolution Apparatus for Enteric -Coated Asprin Tablet

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Abstract: *Dissolution method transfer is a complicated yet common process in the pharmaceutical industry. With increased pharmaceutical product manufacturing and dissolution acceptance requirements, dissolution testing has become one of the most labor-intensive quality control testing methods. There is an increased trend for automation in dissolution testing, particularly for large pharmaceutical companies to reduce variability and increase personnel efficiency. There is no official guideline for dissolution testing method transfer from a manual, semi-automated, to automated dissolution tester. Enteric-coated aspirin tablets are designed to resist dissolution in the stomach's acidic environment and release the drug in the more alkaline environment of the small intestine. This delay in dissolution is achieved through a protective coating that prevents the tablet from breaking down in the stomach.*

Keywords: Dissolution method

I. INTRODUCTION

Dissolution behavior was studied for four commercial batches of enteric-coated aspirin tablets from two companies. The USP XIX dissolution procedure was modified by including pretreatment in simulated gastric juice. The effects of five pretreatment times were

studied. Pretreated tablets yielded higher dissolution profiles and fewer undissolved fractions than no pretreated tablets. Among pretreatments, 15 min was adequate and 60 min produced the highest dissolution profiles. None of the pretreatments differed significantly from each other. An F test and conducted on the data indicated that Product X was significantly better than Product Y at the p=0.05 level. Batch C was ranked as the best batch irrespective of pretreatment time, followed by Batch D. Batches A and B were equal, although Batch A appeared to be better than B for the 60-min pretreatment, as indicated by the lower t80% value.

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Historically, the assessment of drug release from oral solid dosage forms was based on tablet disintegration time. It was not until the 1960s that dissolution testing was introduced to assess drug release from dosage forms as a function of time. Dissolution testing is one of the most labor-intensive and time-consuming quality testing procedures involving a number of unit operations. In addition to the duration of the dissolution testing, there are numerous additional steps such as sample withdrawal, sample analysis, temperature
measurements, media filling, media change, pH change, and vessel cleaning,1,2 often consuming twice the time of the testing procedure. As a result, pharmaceutical companies are now investing in more automated laboratory procedures, and a number of automated dissolution devices have been developed to increase the capacity while improving accuracy and reducing variability.

USP apparatus are of 7 types they are as follows

Type 1 USP apparatus: (Basket apparatus)

- Dosage form contained within basket.
- Dissolution should occur within Basket.
- pH change by media exchange.
- Useful for: Tablets, Capsules, Beads, and Floaters

Type 2 USP apparatus: (Paddle apparatus):

- Dosage form should remain at the bottom centre of the vessel
- Sinkers used for floaters
- pH change by media addition Useful for: Tablets, Capsules

Type 3 USP apparatus: (Reciprocating Cylinder):

- Rotations 6-35 rpm
- Useful for: Tablets, Beads, controlled release Formulations

Type 4 USP apparatus: (Flow through cell apparatus):

Useful for: Low solubility drugs , Rapid degradation , Media PH change

Type 5 USP apparatus: (paddle over disk)

- Rotations 25-50rpm
- Useful for: Transdermal patches, Ointments, Floaters, Emulsions, Bolus

Type 6 USP apparatus: (Cylinder Apparatus):

- Useful for: Transdermal patches

Type 7 USP apparatus: (Reciprocating Holder):

- Rotations 30rpm

Useful for: Transdermal patches, Solid dosage forms, pH profile, Small volumes.

USP apparatus 4 and apparatus7 and modifications of the official apparatuses have shown great potential and alue for in vitro release for novel dosage forms.

Materials and Methods

Materials

Enteric-coated 100-mg aspirin tablets were purchased from Bayer (Leverkusen, Germany). Aspirin, USP standard, was Purchased from the United States Pharmacopeial Convention (USP, Rockville, MD). Potassium triphosphate was purchased from VWR (Leicestershire, UK). Hydrochloric acid was purchased from Merck (Darmstadt, Germany). Poroplast 10-µm filters were purchased from ERWEKA (Heusenstamm, Germany).

Preparation of Dissolution Media

In total, 0.1 M HCl was prepared by the dilution of hydrochloric acid 25% (w/w). Preparation of 0.20 M phosphate Buffer (pH 12) was according to the USP.4 Degassing of the media was conducted on a MediPrep 820 (ERWEKA) by

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heating the media to 38 °C, followed by vacuum degassing prior to dissolution testing for both the manual and automated
dissolution testers. Dissolution media prepared according to the USP recommended manual method was compared with dissolution media prepared using a MediPrep 820 for verification of proper degassing procedure as a function of time. Dissolved oxygen in the prepared dissolution media was quantified using a GMH 3630 digital oxymeter (Greisinger Electronic, Regenstauf, Germany).

Dissolution Testing Parameters

A basket apparatus was used at a rotational speed of 100 rpm and maintained at 37 °C as described under USP chapter 711. The dissolution medium was 0.1 M HCl with a vessel fill volume of 750 mL (pH value of 1.2) for the initial 2 h. From 120 to 210 min, the dissolution medium was phosphate buffer (pH 6.8) by the addition of 250 mL 0.20 M tribasic sodium phosphate (total vessel fill of 1000 mL at a pH value of 6.80). Sampling was conducted at a single time point from the acidic dissolution media at 120 min, fol-lowed by sampling every 15 min after media pH change. All standards were prepared in acidic and basic dissolution media. Standards were prepared prior to dissolution testing due to the sensitivity of aspirin in extreme pH media. Absorbance was measured on an Agilent 8453 Diode Array UV/VIS (Agilent, Santa Clara, CA), where the UV absorbance was determined at the isosbestic point of aspirin and Salicylic acid, 278 nm and 267 nm for the acidic and basic media, respectively. The standard calibration curve was evaluated prior to every dissolution run; during all testing, The regression square exceeded 0.999. control standards were measured after each cycle time point, and the relative standard deviation was less than 1%.RoboDis II Vessel Fill an integrated piston pump sequentially dispenses the dissolution media from the MediPrep 820 into the dissolution vessels. To validate the reproducibility of the fill volume for the acidic and the basic media at zero and 120 min, respectively, we conducted a volume fill verification study. The vessel fill was automatically conducted on a RoboDis II (ERWEKA) over 10 runs for the seven vessels, and the actual fill volume was compared with the programmed fill volume at the zero and 120-min time points.

System Performance Verification

For RoboDis II, since sampling is fully automated, the sampling lines are flushed between each time point. There are several volume options for the sample line flush to contamination from the previous time point sample.5 Since each vessel is equipped with an independent sampling line, cross-contamination between vessels is not possible. A 30- mL flush volume was selected based on a calculated fill volume of the sampling lines.

Since the sampling lines are flushed prior to each sample time point, this may dilute the subsequent samples; therefore, a system performance verification test was conducted. In this study, dissolution testing was performed using an enteric-coated aspirin tablet in the RoboDis II following the same dissolution testing procedure described under Dissolution Testing Parameters. At each time point, samples were withdrawn automatically using the RoboDis II sampling port and with a manual sampling device from each vessel according to USP recommended protocol.

Run-to-Run Carryover in RoboDis II was programmed to wash the dissolution vessels following each dissolution run and to withdraw samples from each vessel prior to sample introduction to guarantee the absence of detectable drug levels. The current study was to determine the carryover effect from previous runs and the number of wash cycles required to completely remove drug residue. The automated system was set up for six runs; each dissolution run was followed by an indicated number of wash cycles, and the same dissolution testing protocol was repeated for subsequent runs (each test included a total of six tablets). The number of wash cycles was increased from one to three cycles for the evaluation of the suitable vessel cleaning protocol. equivalency Study between the Manual .

Automated Tester

The study was conducted on three separate lots of enteric-coated aspirin over 3 consecutive days (n = 18 for each lot, six samples per day). The dissolution testing was conducted using manual dissolution tester ERWEKA DT 726 (ERWEKA), following the same protocol described earlier. The same lot was tested in parallel using an automated dissolution device, the RoboDis II.6 The RoboDis II was programmed to withdraw samples simultaneously from all

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vessels, therefore reducing lag time between one vessel sample to the next. It was further programmed to electronically document each vessel temperature and pH prior to sample introduction, after media pH change, and at each sample time point, since most of the automated dissolution runs were conducted under minimal supervision; such documentation was crucial to assess validity of the data. At the termination of the dissolution run, the RoboDis II was programmed to measure the pH of each vessel to ensure that pH was accurate during the dissolution run. equivalency study between automated testers following the method transfer from the manual dissolution tester to the automated tester, the method transfer among automated dissolution testers was evaluated. In an automated tester, the absence of individual variability should result in a more reproducible inter laboratory method transfer. Three lots of enteric-coated aspirin tablets were tested over 3 consecutive days, with 10 runs per day and six samples per run on two separate RoboDis II systems in isolated laboratories. The RoboDis II systems were programmed and samples were placed in the sample door by different personnel.

Statistical Analysis

The mean and standard deviation (SD) of the results were presented. Data were analyzed using two-tailed Student t tests for the comparison of two groups and analysis of variance (ANOVA) for multiple groups where appropriate. linear regression analyses were used to evaluate correlations and determine correlation coefficients. dissolution data were evaluated using the statistical formulas presented by the Food and Drug Administration.

In-vitro Dissolution Studies:

In-vitro drug release study for the prepared coated tablets was conducted for a period of 90 min using a six- station USP type II (paddle) apparatus at 37 ºC and 75 rpm speed. Tablets were kept in 0.1 N HCl for 2 h and later dissolution media replaced with phosphate buffer pH 6.8.

Dissolution study was carried out for 90 min in phosphate buffer pH 6.8. Sampling was done after 10, 20, 30, 45, 60 and 90 min interval; samples of 10 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. The sample solution was analyzed at 265 nm for Aspirin by a UV-spectrophotometer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve.

Result

Table 1. RoboDis II System Performance Verification Study for Enteric-Coated Aspirin Tablets.

Sample Time, min	Automated Sampling[a]	Manual Sampling[a]
120	0.5 ± 0.3	ND[b]
165	98.0 ± 0.9	95.0 ± 2.0
210	100.2 ± 1.2	97.0 ± 2.0

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Table 2. Run-to-Run Carryover Study.

	No. of Wash Cycles			
Placebo Dissolution Sampling[a]	Initial Run[b]	1	2	3
Blank sample[c]	0.3 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.3
0.1 M HCl at 120 min	0.2 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.3
Phosphate buffer (pH 6.8) at 210 min	99.3 ± 3.6	100.3 ± 1.4	101.3 ± 1.3	100.2 ± 1.2

[a]Data presented as mean ± SD ($n = 6$) percent weight per weight (w/w) of tablet label claim.
[b]Represents data from the initial run on a validated clean RoboDis II system.
[c]Aspirin concentration was in some cases below the limit of quantitation of the analytical method, and therefore the data presented are estimated.

Table 3. Method Transfer from Manual to Automated Dissolution Testing Equivalency Assessment.

	Day 1		Day 2		Day 3	
Sample[a]	Manual	Automated	Manual	Automated	Manual	Automated
Lot 1						
120 min	0.2 ± 0.2	0.13 ± 0.02	0.26 ± 0.07	0.0 ± 0.0	0.0 ± 0.0	0.4 ± 0.2
165 min	82.5 ± 11.5	95.5 ± 2.0	82.5 ± 11.5	94.8 ± 2.0	99.0 ± 2.6	99.0 ± 2.6
210 min	100.0 ± 1.7	97.6 ± 1.3	100.0 ± 1.7	97.0 ± 1.5	99.9 ± 1.7	101.3 ± 1.3
F2	51.1		55.3		60.8	
Lot 2						
120 min	0.5 ± 0.2	0.20 ± 0.01	0.2 ± 0.1	0.4 ± 0.2	0.25 ± 0.02	0.15 ± 0.02
165 min	86.0 ± 6.4	94.0 ± 3.3	82.5 ± 11.5	97.7 ± 3.5	94.3 ± 2.2	99.3 ± 0.9
210 min	101.4 ± 2.0	97.5 ± 2.2	100.5 ± 1.3	100.3 ± 1.4	97.6 ± 2.1	99.4 ± 0.9
F2	51.9		50.1		53.2	
Lot 3						
120 min	0.2 ± 0.2	0.5 ± 0.3	0.14 ± 0.04	0.5 ± 0.3	0.3 ± 0.2	0.11 ± 0.02
165 min	81.3 ± 21.3	98.0 ± 1.0	98.5 ± 1.3	98.6 ± 1.3	94.5 ± 1.8	98.4 ± 1.4
210 min	100.9 ± 1.2	100.2 ± 1.2	100.2 ± 1.0	97.1 ± 1.1	97.1 ± 1.9	99.8 ± 1.1
F2	52.1		50.9		61.6	

II. CONCLUSION

pared under vacuum for 1, 2, 5, and 10 min using a MediPrep

There are a few automated dissolution testers on the market, and method transfer to a fully automated Dissolution tester requires the assessment of the critical dissolution parameter attributes. Ideally, an automated tester should be fully USP compliant, showing the least deviation with regard to critical factors such as time gap between specimen introduction into vessels, position of sampling within dissolution vessel, and site of filtration, which should be conducted within the dissolution vessel to avoid removal of undissolved tablet fragments. RoboDis II used in this Study is fully USP compliant; nonetheless, a full method Transfer validation is essential. A number of criteria were Evaluated for the proper dissolution method transfer from a Manual to fully automated dissolution system. Transferring Current methods from manual or semi-automated devices fully automated devices requires planning and a number of Systematic tests to validate the transfer and determine the Suitable process parameters to eliminate sample carryover And sampling line contamination. The effective transfer is Dependent on the product and validation of the dissolution Method, and software setup requires knowledge and statistical equivalency verification. Once the method has been Effectively transferred to an automated dissolution system, Software programming facilitates method transfer among automated systems with minimal variation among units. The use of automated dissolution testing devices is an added advantage to pharmaceutical companies, particularly With the increased number of required dissolution tests and the added requirements to narrow quality control

specifications. Automated systems achieve high productivity and Perform test runs continuously and automatically.

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