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Development and Validation of Dissolution Procedures for Ciprofloxacin.

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Abstract
Dissolution testing has emerged in the pharmaceutical field as a very important tool to characterize drug product performance. Ciprofloxacin HCl as a frequently used antibiotic and has no validated dissolution method in its monograph. *In vitro* dissolution tests of solid oral dosage forms of ciprofloxacin were performed by various methods using different test conditions but always under "sink"conditions. Release profiles of different dosage forms of ciprofloxacin show that release rate in ph 1.2 is complete as compared to ph 6.8, 7.4. the release is much faster in the ph 1.2 and hence absorption of ciprofloxacin from stomach is maximum. The different conditions used were ph 1.2, 6.8, 7.4 and rpm of 100 and 75 respectively. The t80% and t 50% was calculated and compared.

Key Words
Ciprofloxacin, dissolution, validation, % release.

Introduction
To ensure compliance with quality and safety standards, the United States, Europe, Japan, India and other countries have published compendia, or pharmacopeias, that describe official test methods for many marketed drug products. For example, compendia analytical methods found in United States Pharmacopeia 25 (USP 25) are legally recognized analytical procedures under section 501 (b) of the Federal Food, Drug, and Cosmetic Act. For these compendia methods, USP provides regulatory guidance for method validation. In addition, validation of analytical methods is covered by the United States Code of Federal Regulations (CFR)[1-3]. Method validation is defined as the process of proving (through scientific studies) that an analytical method is acceptable for its intended use. Recent guidelines for methods development and validation for new non-compendial test methods are provided by the FDA draft document, "Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation" .This recent document applies to the method development and validation process for products included in investigational new drug (IND), new drug application (NDA) and abbreviated new drug application (ANDA) submissions. Therefore, expectations from regulatory agencies for method development and validation are clear3. Dissolution test is required to study the drug release from the dosage form and its in vivo performance. Dissolution test is used to assess the lot to lot quality of drug product. The development and validation of dissolution procedures is of paramount importance during development of new formulation and in quality control. The dissolution procedure must be properly developed and validated. The objective of this paper is to review the development and validation of dissolution procedure(s) and to provide practical approaches for determining specificity, linearity, range, accuracy, precision, limit of detection, limit of quantitation and robustness of methods[3-5].

Ciprofloxacin (INN) is a synthetic antibiotic of the fluoroquinolone drug class. It is a second-generation fluoroquinolone antibacterial. It kills bacteria by interfering with the enzymes that cause DNA to rewind after being copied, which stops synthesis of DNA and of protein. Ciprofloxacin was first patented in 1983 by Bayer A.G. and subsequently approved by the U.S. Food and Drug Administration (FDA) in 1987. Ciprofloxacin has 12 FDA-approved human uses and other veterinary uses, but it is often used for unapproved uses (off-label). Ciprofloxacin interacts with other drugs, herbal and natural supplements, a characteristic it shares with other widely used antibacterial drugs such as amoxicillin, trimethoprim, azithromycin, cephalexin, and doxycycline. Ciprofloxacin is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria. It functions by

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inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division. The effects of 200–400 mg of ciprofloxacin given intravenously are linear; drug accumulation does not occur when administered at 12 hour intervals. Bioavailability is approximately 70-80%, with no significant first pass effect.[4-7] IV administration produces a similar serum levels as those achieved with administration of 500 mg administered orally. IV administration over 60 minutes given every 8 hours produces similar serum levels of the drug as 750 mg administered orally every 12 hours. Biotransformation is hepatic. The elimination half life is 4 hours[7-11].

Material and Methods

Materials

Ciprofloxacin tablets were procured from the local market. All chemicals were of analytical grade. Double distilled water was used throughout the experiment.

Dissolution test conditions and analysis procedure

Dissolution studies on one commercially available product (film coated tablets) of ciprofloxacin HCl were conducted using USP Apparatus (paddle method, Erweka DT80, Germany). The dissolution medium was 900 mL of either pH 1.2 hydrochloric acid aqueous solution, or pH 7.4 phosphate buffer or pH 6.8 at 37 ± 0.5 ˚C and stirred at 75 and 100 rpm. In all experiments, 5 ml sample aliquots were withdrawn at 5, 10, 20, 30 and 45 minutes and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were assayed by the UV spectrophotometric method. Cumulative percentages of the drug dissolved from the products were calculated and plotted vs. time[10,11].

Results and Discussions

The dissolution method development and validation was performed and it was found that % drug release in case of ciprofloxacin was found out to be more and faster in case of ph 1.2 as compared to ph 6.8 and 7.4. The release studies show that the mechanism of release was anomalous and the best fit model was a mixture of hixon crowell and first order release. The t50% was found to be in the following order ph 1.2>6.8>7.4 and similarly t 80% ph1.2>6.8>7.4. The t50% in case of ph 1.2 was found to be 10 mins and t80% of 27 mins.

Conclusion

Dissolution testing plays a very important role as an in-vitro test for evaluating drug products. Developing and validating dissolution test procedures can be a challenging process, on multiple fronts. Methods must be developed and validated not just for the dissolution test procedure itself, but also for any assay used to evaluate the test results. However, like any task, a systematic and methodical approach taking into account all the components that make up the dissolution test procedure, including the dissolution medium, the choice of apparatus, the test design (including the acceptance criteria), and determining the assay mode will pay great dividends in the end. There are only a few principle differences concerning validation of dissolution methods in the fields of pharmacokinetic studies and in quality control.

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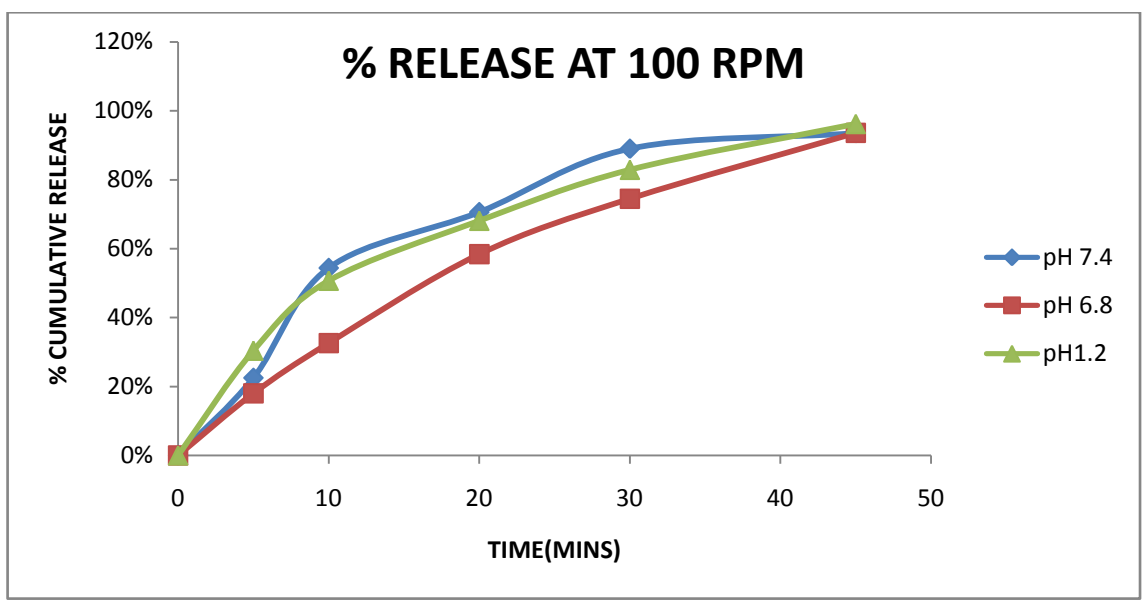

Fig. 1: % release at 100 rpm.

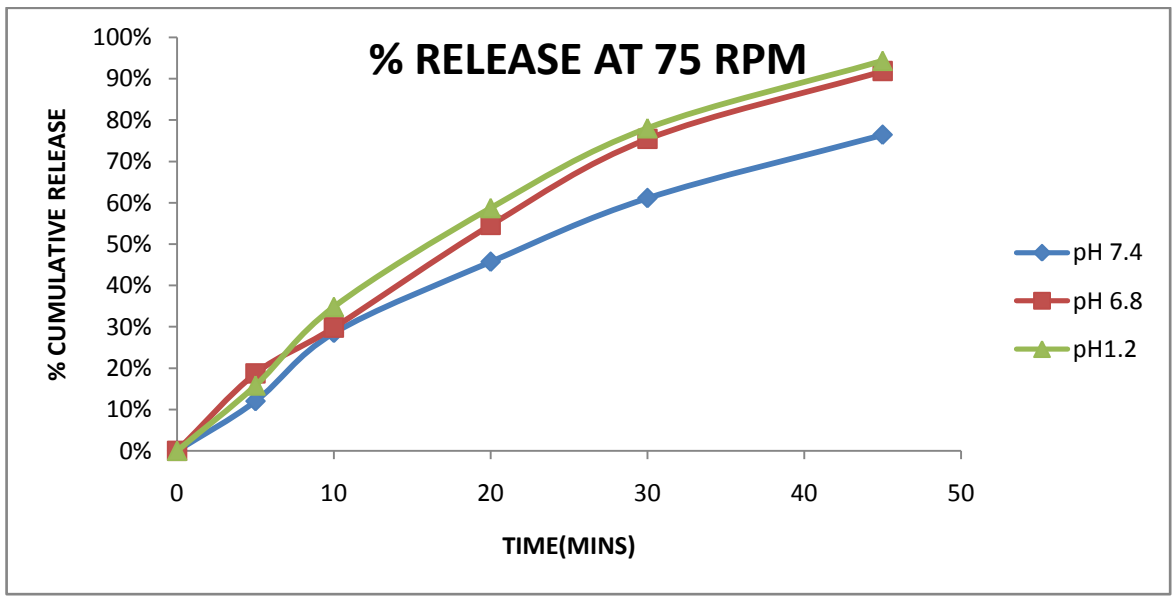

Fig. 2: % release at 75 rpm.

Table 1: % release at 100 rpm.

S.No.	Time	% Release at 100 RPM		
		pH 7.4	**pH 6.8**	**pH1.2**
1	0	0%	0%	0%
2	5	22.50%	18%	30.40%
3	10	54.40%	32.60%	50.70%
4	20	70.60%	58.40%	68.10%
5	30	89%	74.50%	82.90%
6	45	93.50%	93.60%	96.20%

Table 2: % release at 75 rpm.

S.No.	Time	% Release at75 RPM		
		pH 7.4	**pH 6.8**	**pH1.2**
1	0	0%	0%	0%
2	5	12%	18.70%	15.80%
3	10	28.50%	29.80%	34.80%
4	20	45.70%	54.60%	58.70%
5	30	61.10%	75.40%	78%
6	45	76.40%	91.80%	94.3%

Table 3: Mechanism of release at 100 rpm.

MODEL	R^2 VALUE 100RPM		
	pH 7.4	**pH 6.8**	**pH1.2**
ZERO ORDER	0.8403	0.9631	0.8801
FIRST ORDER	0.9783	0.9643	0.9775
HIXON CROWELL	0.9507	0.9960	0.9908
BEST FIT	**FIRST ORDER**	**HIXON CROWELL**	**HIXON CROWELL**

Table no. 4: Mechanism of release at 75 rpm.

MODEL	R^2 VALUE 75RPM		
	pH 7.4	**pH 6.8**	**pH1.2**
ZERO ORDER	0.9628	0.9673	0.9557
FIRST ORDER	0.9968	0.9783	0.9732
HIXON CROWELL	0.9956	0.9946	0.9989
BEST FIT	**FIRST ORDER**	**HIXON CROWELL**	**HIXON CROWELL**

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