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Development of discriminative and biorelevant dissolution test method for atorvastatin /fenofibrate combination with appliance of derivative spectrophotometry.

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ABSTRACT

Now a days, market is flooded with combination of drugs in various dosage forms, but lack of official methods to quantify them. A single dissolution test method for the analysis of combined dosage form is preferred for simplification of quality control testing. If the developed dissolution medium mimics the bio-relevant and discriminating dissolution procedure for drug products with limited drug aqueous solubility is a useful tool for qualitative forecasting of *in-vivo* behavior of formulations. Dissolution profiles are evaluated for atorvastatin and fenofibrate in capsules, using paddle type USP dissolution apparatus in 900 mL of medium at 100 rpm and 37 ± 0.5 °C. The best medium was 900 mL of 0.5% w/v sodium lauryl sulphate. The cumulative % dissolution was more than 85% within 45 min time for marketed tablets. The proposed dissolution test conditions have the discriminative power, dissimilarity factor (f_1) are low (12-16%) and similarity (f_2) factor values were also low (45-48%). Hence the use of 0.5% w/v sodium lauryl sulphate solution is justified. The dissolution method was validated (% RSD < 1). To quantify both drugs simultaneously, a second derivative spectrophotometric method was established (λ_{max} 281 nm and 296 nm, respectively, for atorvastatin and fenofibrate) in acetate buffer, pH 2.8 solution.

Key words: Derivative spectrophotometry/quantification simultaneously, Atorvastatin/Fenofibrate combined dosage form, Bio relevant/discriminative dissolution method.

INTRODUCTION

Dissolution is considered as one of the most routinely performed quality control test on dosage forms to ensure uniformity and reproducibility of production batches. Process parameters and ingredients are optimized during product development¹⁻³, whether changes made in the formulations or their manufacturing processes are likely to affect the performance in the clinic or not are decided using dissolution methods⁴. An immediate release dosage form is designed to deliver the drug rapidly into systemic circulation. Hence, the dissolution may become the rate limiting step for its absorption. The absorption of a drug substance may vary by diverse parameters like its solubility and permeability in the conditions associated with the gastrointestinal (GI) tract after oral administration⁵⁻⁷. Keeping all these points into consideration, there is a need to put more research efforts on developing *in vitro* GI fluids that mimics the *in-vivo* conditions. The discriminative dissolution method has ability to differentiate the dissolution profiles between manufacturer process variations and product composition variations⁸⁻¹¹.

Fenofibrate, chemically known as Isopropyl 2-[1-(4-chlorobenzoyl)2-phenoxy] methyl propanoate, is a fibric acid derivative with lipid regulating properties striving its therapeutic effects through a activation of peroxisome proliferator activated receptor α (PPAR α) (Figure-1A). Atorvastatin Calcium chemically [*R*-(*R*^{*},*R*^{*})]-2-(4-Fluorophenyl)- β , δ -dihydroxy-5-(1-methyl-1H-pyrrol-3-yl)-3-phenyl [(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, is a HMG-Co A reductase inhibitor with hypolipidemic properties¹¹⁻¹²(Figure-1B). The combined dosage form of fenofibrate and atorvastatin is therapeutically used for hyper lipidemic patients. Fixed dose combination of drugs has been a challenge; if possible a single dissolution method is preferred to simplify quality control testing procedures¹³⁻¹⁵. Few analytical methods were reported for simultaneous quantification of atorvastatin calcium and Fenofibrate by HPLC and spectrophotometric method¹⁶⁻¹⁹. The facility of derivative spectroscopy may be used with minimum error for the quantification of one analyte^{20,21}. Overlaid zero-order spectra exhibited similar nature and overlapping for atorvastatin calcium with fenofibrate denotes development of the derivative graphical method. To the best of our knowledge, only one first and second derivative spectrophotometric method

reported for simultaneous quantification of ATV and FEN in methanol as solvent, but methanol is environmental toxic and expensive than aqueous buffers and one wavelength is 245 nm, which is normally originated by the benzenoid ring system. Since several compounds may contain benzene rings, it is always better to avoid 245 nm and select a wavelength away from 245 nm. Literature data signify the need of simple, economic, eco friendly and specific analytical method for simultaneous quantification of ATV and FEN combination in tablets and dissolution samples. The development of a single dissolution method is practically challenging due to the low water solubility for combination of atorvastatin and fenofibrate. Keeping these points into consideration, an attempt is made to develop and validate the simple dissolution test for simultaneous quantification with application of simple derivative spectrophotometric technique.

MATERIALS AND METHODS

Materials

Atorvastatin and fenofibrate were obtained as gift samples from Dr.Reddy's, Laboratories limited, Hyderabad, India. Methanol, hydrochloric acid, ortho-phosphoric acid, potassium di hydrogen orthophosphate, sodium hydroxide, sodium chloride and sodium acetate were purchased from Sd Fine-Chem limited, Mumbai; sodium lauryl sulfate (SLS), tween 80, cetrimide, cetium and sodium taurocholate were purchased from Himedia Ltd, Mumbai, India. Double distilled water was used throughout the study. Atorvastatin and fenofibrate combination tablet formulations – Atocor (Dr.Reddy's, Laboratories Pvt. Ltd) and Fibator (Sun Pharma, Sikkim) were obtained from local market.

Instrumentation

Double beam 800 UV-Visible spectrophotometer (Shimadzu, Japan), dissolution apparatus (Electro lab TDT-08L), analytical balance (Shimadzu AUX 220, Japan), tablet compression machine (Lab press- CIP machineries, Ahmedabad, India), hardness tester (Secor, Hyderabad, India) pH meter (Elico, Hyderabad) and ultrasonic cleaner were used for the study (Calibration of instruments were done according to standard procedure)

Analytical method

First-order-derivative overlaid spectra of atorvastatin calcium and fenofibrate denotes that there was no zero crossing point for atorvastatin calcium for quantification of fenofibrate (Figure 2). Hence first derivative spectrum was not suitable for simultaneous estimation and this problem was minimized by second-order-derivative method, which permitted to select the suitable wavelengths that make the quantification possible with zero crossing, where fenofibrate zero absorbance at 281 nm, while atorvastatin calcium gave the significant derivative response likewise atorvastatin gave zero absorbance at 296 nm, while fenofibrate gave the significant derivative response. Therefore, 281 nm and 296 nm were selected for estimation of atorvastatin calcium and fenofibrate, respectively.

Dissolution test conditions

The log P values of atorvastatin calcium and fenofibrate were 6.36 and 5.28, respectively indicating low water solubility so the development of a single dissolution method for this combination is challenge and a single *in vitro* dissolution studies were not reported for this combination along these lines, an attempt is made to develop and validate a single dissolution test for atorvastatin calcium and fenofibrate in combined tablets.

Evaluated the dissolution profiles of atorvastatin calcium (10 mg) and fenofibrate (145 mg) bulk drug-filled capsules in 900 mL of seven buffers of distinct pH (1.2/2.8/ 3.6/ 4.7/ 5.6/ 6.8 and 7.4), bi-relevant media such as [SGF (pH 1.2), SIF (pH 7.5), FaSSIF (pH 6.5), FeSSIF (pH 5.0), modified fasted state (pH 6.5) and fed state (pH 5.0) simulated intestinal fluids] and three different surfactants and at 2 different concentrations at 50 rpm using type 2, USP dissolution apparatus and samples were withdrawn for 30 min, replaced with same volume of fresh medium. Samples withdrawn were evaluated with regression equation of proposed analytical technique for quantification of dissolved-drug followed by plot counter to time. A combination of these media was utilized for identifying the optimized dissolution medium, in which highest drug release, stability and sink conditions were obtained, was chosen as the *in vitro* dissolution medium.

Discriminatory power of the dissolution method

Dissolution method ability to discriminate was ascertained by the tablets punched under distinct conditions, such as; discrete manufacturing process (hardness of 5.0

kg/cm² and 8.0 kg/cm²) and discrete product composition (with/with-out disintegrant). Scrutinizing the dissolution-profiles in test conditions followed by data was estimated with factors of comparison (f_1 and f_2).

Stability determination

Sample solutions withdrawn for the optimized dissolution medium were analyzed at 0 time, consonantly samples were kept for 24 hours and 48 hours and analyzed by proposed method.

Validation of the dissolution method

The validation of dissolution method is required to ensure that a proposed dissolution method is scientifically and experimentally sound, obtaining the results of specificity, linearity, accuracy and precision as per standard guidelines.

The method specificity was assessed by comparing the spectra obtained from the commercial formulations and the synthetic mixture from standard solutions by preparing similar dose ratio of synthetic and tablet dosage form. Then analytical method was applied in order to check if any component of the formulation could generate a response or an absorption wavelength similar to the drugs.

Linearity was determined by standard concentrations of atorvastatin (2-12 µg/mL) and fenofibrate (1-35 µg/mL) were quantified with second derivative spectrophotometric technique then absorbance was recorded and calibration curve was constructed by plotting the analyte response versus the drug concentrations.

Intra-day and inter-day precision studies were evaluated as per ICH guidelines, in which six tablets were subjected to the dissolution test conditions, on the same day (intra-day precision) and for three consecutive days (inter-day precision), then % RSD was calculated.

Accuracy studies were conducted using standard addition method where the known amount of drugs at 80, 100 and 120% of the formal assay of atorvastatin and fenofibrate to the placebo sample in the dissolution medium, further subjected to contemplated method; then percentage recovery and relative standard deviation (% RSD) were computed for each concentration.

RESULTS AND DISCUSSION

Development of dissolution method

The selection of a dissolution test method was based on dissolution profiles of atorvastatin (10 mg) and fenofibrate (145 mg) bulk drug filled capsules using a USP type 2 apparatus at a paddle speed of 50 rpm and selection of a dissolution medium to adequate solubility and stability of both atorvastatin calcium and fenofibrate was demand for this dissolution method. The log P values of atorvastatin calcium and fenofibrate respectively were 6.36 and 5.28, denoting low water solubility. Several compendia dissolution media were screened; these include various buffer media (pH 1.2 to 7.4), surfactant media and several bio-relevant media. However, the results showed that the dissolution rate of atorvastatin was found to be maximum in weak acidic buffers because of the specific interaction but fenofibrate dissolution rate was less than 2% in all buffers, indicating that fenofibrate dissolution was independent of pH due to absence of ionizable groups (Table I). Both drugs were showed higher dissolution in 0.5% w/v sodium lauryl sulphate medium than other dissolution media. Dissolution medium with low concentration of sodium lauryl sulphate may resemble gastric environment of our body, and hence this medium is useful for correlating *in-vitro* dissolution behavior of atorvastatin and fenofibrate combined dosage form with their *in-vivo* performance. This medium can also be a useful quality control tool and the selected dissolution test conditions are: USP apparatus 2 at paddle speed 50 rpm in a medium of 0.5% w/v sodium lauryl sulphate. Therefore, dissolution studies were performed for commercial tablets (Atocor and Fibator) in optimised dissolution test conditions.

In-vitro dissolution profiles of commercial tablets

Dissolution studies on Atocor and Fibator tablets were enforced under the optimised dissolution test medium of 0.5% w/v sodium lauryl sulphate, by using USP type 2 apparatus at paddle speed of 50 rpm at temperature 37 ± 0.5 °C and these results are obtained in Figure 3 and 4, indicated that about 85% of both atorvastatin and fenofibrate were released in 45 min from the two brands. In fact, fenofibrate exhibited only 50% dissolution in 60 min (Table I). On the other hand, tablets exhibited 85% dissolution in 45 min; it means that the in active ingredients in the tablets also supported the dissolution. Such a factor should also be kept in mind, while optimising the dissolution conditions. Atorvastatin components of the tablet formulation exhibited 88% dissolution in 45 min, whereas the pure drug exhibited 92% dissolution in 45 min in same medium. Thus the proposed dissolution medium

satisfactorily reproduced the dissolution characteristics of atorvastatin and fenofibrate with initial lag time of 5 min for drug dissolution but lag time is more pronounced in case of fenofibrate. This trend was familiar from the chemical structure of fenofibrate (no functional groups responsible for ionization). Further both drugs are hydrophobic as indicated by the log P values, 6.36 and 5.28, respectively for atorvastatin and fenofibrate. From 5 min to 60 min periods, the dissolution behavior is gradual and linear, which again reflected the hydrophobic nature of the drugs.

Discriminatory power of the dissolution method

Discriminatory power of the dissolution method was determined by manufacturing the tablets under different conditions and studying the behavior of these products in the proposed dissolution method. The effect of tablet hardness (7 kg/cm² vs 8 kg/cm²) and disintegrant (with vs without) were shown in Figure 5 followed by data of dissolution was compute with the factors of comparison using 6 points among these, one point was found to specify the drug release more than 85% (Table II). These results confirmed that the dissolution test procedure has ability to discriminate for distinct composition and process, based on these results, 0.5% w/v sodium lauryl sulphate medium has discriminating power.

Stability determination of atorvastatin and fenofibrate in dissolution medium

The stability of drugs in dissolution medium at different time periods was calculated in order to demonstrate the integrity of the drugs and obtained in Table III, notified that both drugs were stable under dissolution test conditions. The change in drug content was not assessed and likewise no evidence of degradation denotes that the solutions were stable for more than 48 h.

Dissolution method validation

Linearity

The linearity was assessed by the regression equation of calibration curve method. The responses for atorvastatin at 281 nm were found to be linear in the concentration range of 2-12 µg/mL, with a correlation co-efficient (R²) value of 0.9971 likewise the responses for fenofibrate at 296 nm were linear in the concentration range of 1-35 µg/mL, with a correlation coefficient (R²) value of 0.998. The results indicate a good linear relationship between derivative response and concentrations at 281 nm and 296 nm. (Figure 6)

Specificity

Derivative spectrum attained from the commercial formulation solution was correlated with the spectrum of synthetic mixture of standard solutions (atorvastatin and fenofibrate). The spectra of commercial formulation and synthetic mixture were superimposed; denotes no interference from excipients with derivative response of either of drugs (atorvastatin and fenofibrate) at their respective analytical wavelengths 281 nm and 296 nm (Figure 7), hence the method was found to be specific.

Precision

The precision evaluation data for the dissolution studies was obtained in Table IV, denoted that percent relative standard deviation values for intra-day and inter-day precision studies were found to be less than 2 and there was no significant differences, which indicates the proposed method was reproducible and precise.

Accuracy

The accuracy assessment data for the dissolution studies was obtained in Table V, denoted that percent recovery was from 95 - 100% and percent relative standard values were less than 2, showed that an agreement between the standard values and ascertained values signifies dissolution method was accurate.

CONCLUSION

The present investigation was undertaken with the objective to develop and validate of single test method for the dissolution evaluation of atorvastatin calcium and fenofibrate simultaneously. The best conditions were optimised for dissolution testing for atorvastatin and fenofibrate are: 900 mL of 0.5% w/v sodium lauryl sulphate, using paddle type USP dissolution apparatus, stirring speed of 50 rpm, a temperature of 37 ± 0.5 °C and collection time of 60 min. The proposed dissolution test conditions have the discriminative power, substantiated the usefulness of this biorelevant medium for the two drugs and the dissolution method was validated (% RSD<2). The developed dissolution method can be fruitfully employed as quality control tool as well as research tool.

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REFERENCES

1. Dressman J, Kramer J. Pharmaceutical dissolution testing. 1. ed. London: Taylor and Francies: 2007. 92-8 p.
2. Subrahmanyam CVS. Physical pharmaceutics. 2. ed. Delhi, India: Varadh Prakashan: 2005. 85-96 p.
3. Wang J, Flanagan DR. Fundamentals of dissolution. 1. ed. New York: Academic Press: 2009. 309-18 p.
4. Anumolu PD, Sunitha G, Hima Bindu S, Sathesh Babu PR, Subrahmanyam CVS. Development and validation of discriminating and bio-relevant dissolution test for lornoxicam tablets. *Indian J Pharm Sci.* 2015; 77(3): 312-20.
5. Soni T, Nagda E, Gandhi T, Choudhary NP. Development of discriminating method for dissolution of aceclofenac marketed formulations. *Dissolution Technologies.* 2008; 15(2): 31-4.
6. Dressman JB, Amidon GL, Hennas C, Shah VP. Dissolution testing as prognostic tool for oral drug absorption: immediate release dosage forms. *Pharm. Res.* 1998; 15(1): 11-22.
7. Oliveira E, Medvedo R, Boneilio R, Oliveira DB, Rebeiro GP, Aravjo MB. Dissolution test optimization for meloxicam in the tablet pharmaceutical form. *Braz.J. Pharm. Sci.* 2009; 45(1), 67-73.
8. He Z, Zhang D, Chen X, Liu X, Tang X, Zhao L. Development of a dissolution medium for nimodipine tablets based on bioavailability evaluation. *Eur.J.Pharm.Sci.* 2004; 21: 487-91.
9. Anumolu PD, Sunitha G, Venkat Raju Y, Sathesh Babu PR, Subrahmanyam CVS. Development of biorelevant and discriminating method for dissolution of efavirenz and its formulations. *Asian J Pharm Clin Res.* 2012; 5(3):.220-23.
10. Menegola J, Steppe M, Schapoval EE. Dissolution test for citalopram in tablets and comparison of in vitro dissolution profiles. *Eur. J. Pharm. Biopharm.* 2007; 67(2): 524-30.

11. Anthony CM, David MO, Brian W. Clarke's analysis of drugs and poisons. 3. ed. London: Pharmaceutical Press: 2004. 654 p.
12. Indian pharmacopoeia. 7. ed. Ghaziabad: The Indian Pharmacopoeia Commission: 2014. 1099, 1744 p.
13. Vignaduzzo SE, Castellano P, Kaufman, TS. Development and validation of a dissolution test for meloxicam and pridinol mesylate from combined tablet formulation. *India J Pharm Sci.* 2010; 72 (2): 197-203.
14. Anumolu PD, Sirisha N, Haripriya A, Sathesh Babu PR, Subrahmanyam CVS. Development of dissolution test method for a telmisartan/amlodipine besylate combination using synchronous derivative spectrofluorimetry. *Indaz. J. Pharm. Sci.* 2014; 50(2): 330-36.
15. Zongyun H, Ruben L, Robert F, Anne-Francoise A, Alyso S, Denis S. Development of a single in-vitro dissolution method for a combination trilayer tablet formulation of clopidogrel and pravastatin. *Dissolution technologies.* 2011; 18(2):12-19.
16. Bhokare PS, Kane RN, Desai D. Simultaneous spectrophotometric estimation of atorvastatin and fenofibrate in bulk drug and dosage form by using dual wavelength method. *IJRPS.* 2012; 3 (4): 1448-1453.
17. Deepan T, Paul Ambekar K, Vijaya Laksjmi G, Dhanaraaju MD. Analytical method development and validation of RP-HPLC for estimation of atorvastatin calcium and fenofibrate in bulk drug and tablet dosage forms. *Eur J App Sci.* 2011; 3 (2): 35-39.
18. Dhabalkar PN, Gharge DS. Simultaneous spectrophotometric estimation of atorvastatin and fenofibrate in bulk drug and dosage form by using simultaneous equation method. *International Journal of Chem Tech Research.* 2010; 2 (1): 325-328.
19. Rupali H, Ravindra B, Manish K. RP-HPLC method for simultaneous estimation of atorvastatin calcium and fenofibrate in tablet dosage forms. *J Pharm Res.* 2010; 3 (10): 2400-2402.
20. Anumolu PD, Sunitha G, Venkat Raju Y, Sathesh Babu PR, Subrahmanyam CVS. Development of dissolution test method for drotaverine

hydrochloride/mefenamic acid combination using derivative spectrophotometry. *Trop J Pharm Res.* 2013; 12(2): 227-32.

21. Mark H, Work Man JR. Derivative in spectroscopy. *Spectroscopy* 2003; 18(4): 32-3.

22. Raymond CR, Paul JS, Sian CO. Hand book of pharmaceutical excipients. 2. ed. Chicago, London: Pharmaceutical Press: American Pharmacists Association: 2007. 132, 385, 725 p.

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TABLE 1. Screening study results for ATV (10 mg) and FEN (145 mg) bulk drug using a USP type II apparatus at 50 rpm, temperature 37°C ± 0.5 for 60 min

Dissolution media	% Drug released	
	Mean ± SD (n = 12)	
	ATV	FEN
0.1 N Hydrochloric acid	18.40 ± 0.09	1.16 ± 0.07
Acetate buffer, pH 2.8	29.56 ± 0.04	1.47 ± 0.07
Acetate buffer, pH 3.6	41.40 ± 1.66	1.14 ± 0.08
Acetate buffer pH 4.7	48.43 ± 2.16	1.12 ± 0.10
Phosphate buffer, pH 5.6	92.45 ± 2.96	0.93 ± 0.04
Phosphate buffer, pH 6.8	95.45 ± 4.18	1.02 ± 0.02
Phosphate buffer, pH 7.4	86.59 ± 1.40	1.04 ± 0.05
SGF (simulated gastric fluid without enzyme)	50.28 ± 3.71	1.04 ± 0.06
SIF (simulated intestinal fluid)	87.59 ± 2.40	1.94 ± 0.05
BFaSSIF (Blank fasted state simulated intestinal fluid)	95.88 ± 1.76	1.20 ± 0.06
BFeSSIF (Blank fed state simulated intestinal fluid)	92.46 ± 2.45	1.33 ± 0.08
MFaSSIF (Modified fasted state simulated intestinal fluid)	98.00 ± 1.19	5.33 ± 0.75
MFeSSIF (Modified fed state simulated intestinal fluid)	92.45 ± 0.60	4.15 ± 0.21
Cetrimide, 0.25% w/v	98.33 ± 5.41	7.08 ± 0.07
SLS 0.25%w/v	94.00 ± 5.27	30.54 ± 0.54
Tween 80 0.25%v/v	40.87 ± 0.02	2.36 ± 0.17
SLS 0.5%w/v	95.42 ± 2.56	50.54 ± 0.53

Table 2. Dissimilarity factor (f_1) and similarity factor (f_2) for dissolution profiles of tablets.

Name of the drug	Tablets with hardness of 5 kg/cm ² Vs 8 kg/cm ²		Tablets with disintegrant Vs no disintegrant	
	f_1 value	f_2 value	f_1 value	f_2 value
Atorvastatin	16	45.44	12	46.70
Fenofibrate	17	48.30	11	47.81

Table 3. Data for stability of atorvastatin and fenofibrate dissolution samples

Analyte	% Amount of drug found (AM \pm SD) (n=3)		
	Initial time	After 24 h	After 48 h
Atorvastatin	98.24 \pm 0.45	99.47 \pm 1.24	99.05 \pm 0.5
Fenofibrate	99.54 \pm 0.34	100 \pm 0.32	98.74 \pm 0.98

Table 4. Precision data of atorvastatin and fenofibrate for the proposed dissolution method

Product	Percent amount of atorvastatin				Percent amount of fenofibrate			
	Intra-day		Inter-day		Intra-day		Inter-day	
	Mean±SD*	% RSD	Mean±SD*	% RSD	Mean±SD*	% RSD	Mean±SD*	% RSD
Atocor	98.86±1.751	1.77	99.45±1.82	1.83	99.17±2.203	2.22	98.24±2.02	1.05
Fibator	98.49±1.604	1.62	98.49±1.54	1.56	95.89±0.479	0.49	96.84±0.54	0.55

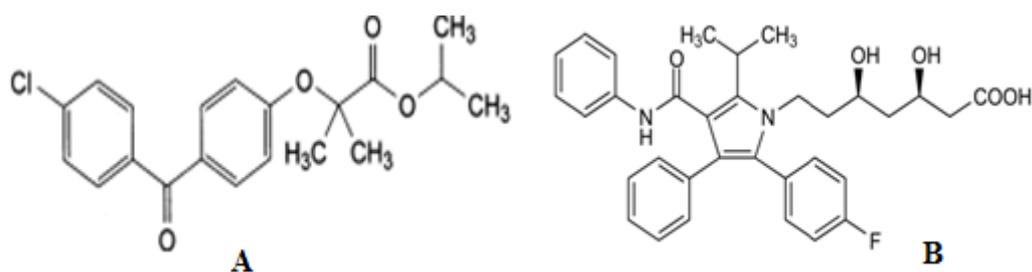


Figure 1. Chemical structure of fenofibrate (A) and atorvastatin (B).

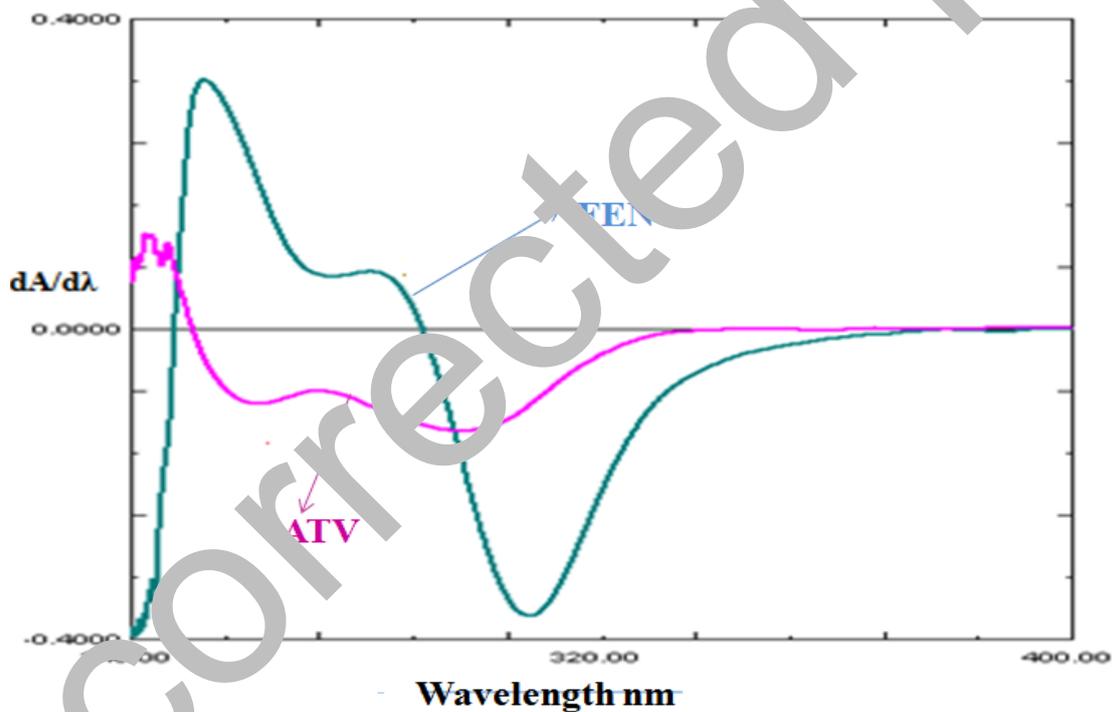


Figure 2. First-order UV overlay spectra of atorvastatin (10 µg/mL) and fenofibrate (10 µg/mL) in acetate buffer, pH 2.8

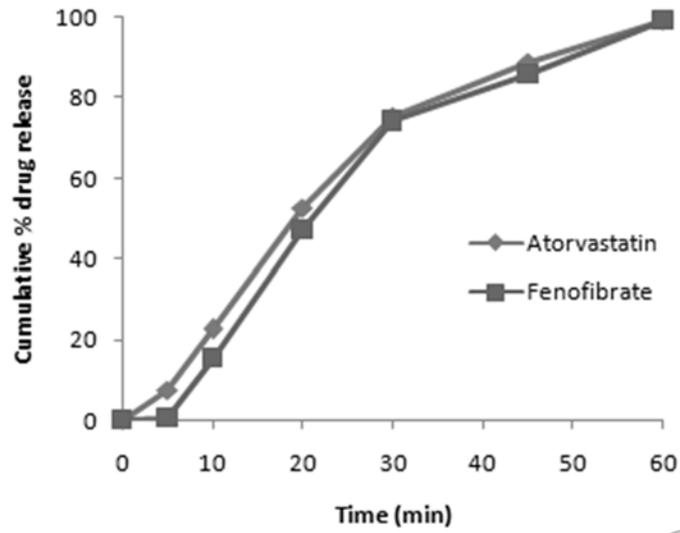


Figure 3. In-vitro dissolution profiles of Atocor tablets in 0.5% W / V SLS medium.

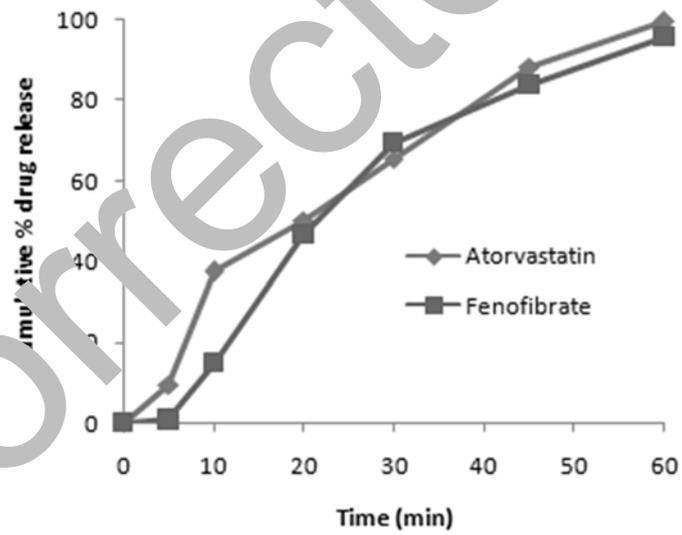


Figure 4. In-vitro dissolution profiles of Fibator tablets in 0.5% W/V SLS medium.

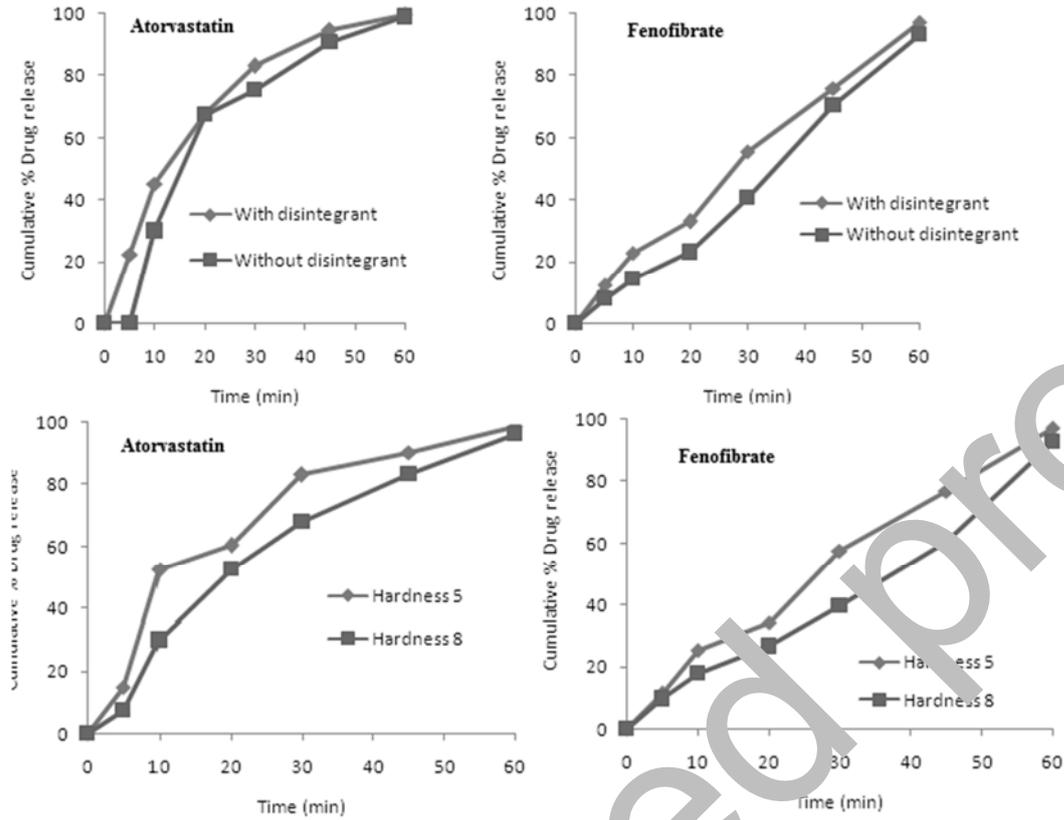


Figure 5. Dissolution profiles of atorvastatin/fenofibrate self punched tablets in 0.5% w/v sodium lauryl sulphate medium

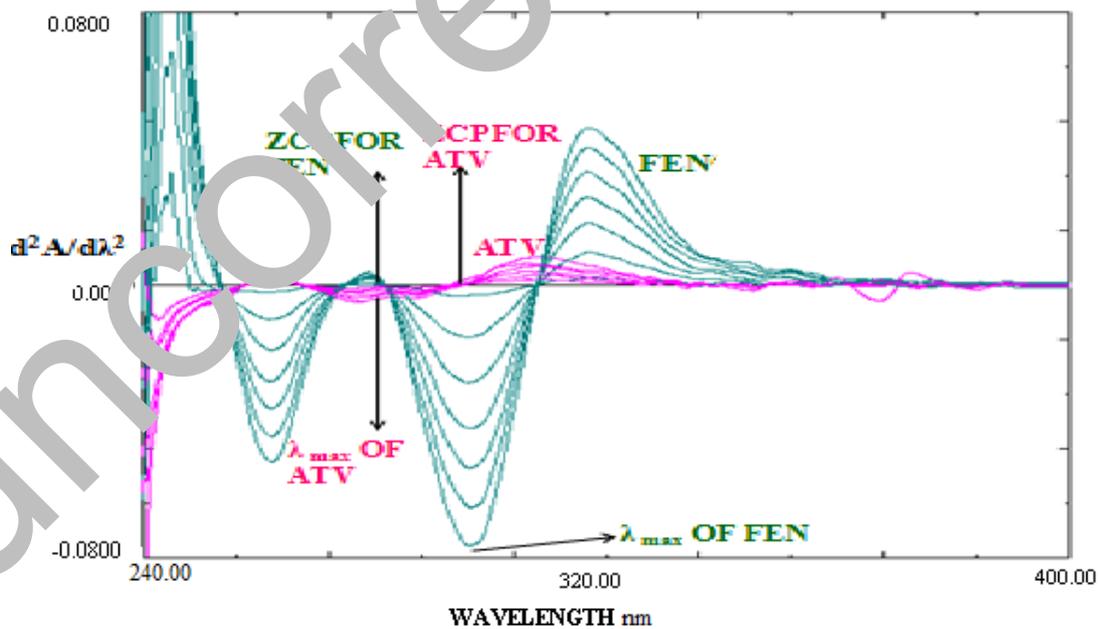


Figure 6. Second derivative linearity spectra of atorvastatin (ATV) and fenofibrate (FEN).

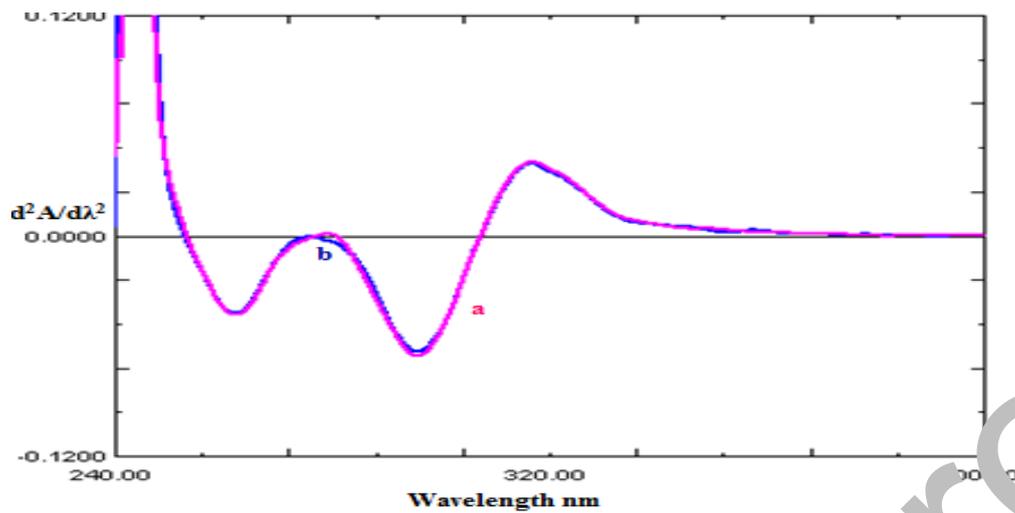


Figure 7. Second order derivative overlay spectra of commercial formulation (a), standard mixture (b)