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PHARMACEUTICAL TECHNOLOGY

PHARMACOPOIEAL QUALITY OF NON-EXPIRED AND EXPIRED NIFEDIPINE FORMULATIONS FROM ESTONIAN AND RUSSIAN FEDERATION MEDICINAL PRODUCTS MARKET

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Abstract: The pharmacopoeial quality of non-expired and expired nifedipine tablets of the same batches purchased from the Estonian and Russian Federation medicinal product markets was evaluated. The IR spectroscopy, HPLC analysis for quantitative content and purity of the active pharmaceutical ingredient (API), and dissolution test techniques were applied. In the experiments with non-expired nifedipine tablets, in all Estonian (n = 8, label claims 10, 20, and 40 mg) and Russian Federation (n = 4, label claim 10 mg) registered formulations the API was identified and quantified as nifedipine in amounts set by the European Pharmacopoeia and without exceeding the tolerance limits for the impurities. The dissolution rate was variable but all 10 and 20 mg non-expired nifedipine tablets released at least 80% of API in 12 h. The expiration of the nifedipine tablets led to somewhat increased dissolution rate while only traces of the nifedipine degradation products were discovered in the dissolution medium. In conclusion, our present study shows that with minor variations the Estonian and Russian Federation registered nifedipine tablets are comparable, the API preserves well beyond the expiration date but the expired nifedipine tablets may release the API faster than the non-expired tablets.

Keywords: nifedipine, tablets, pharmacopoeial quality, expiration

Nifedipine (ATC code: C08CA05), a calcium channel blocking agent with predominantly vascular effects, is one of the most utilized dihydropyridine derivatives (1, 2). Nifedipine is mainly administered *per os* in a form of the extended release formulations and due to the lack of major metabolic adverse effects it is a relatively safe and well tolerable medication (3). However, nifedipine as an active pharmaceutical ingredient (API) is a light sensitive and well degradable compound (4). Therefore, it is of utmost importance that the appropriate pharmaceutical procedures for the manufacture of the nifedipine formulations and the subsequent optimal storage conditions of the finished pharmaceutical products (FPP) are strictly followed.

The research oriented studies on the stability of market authorized FPP are rare. Recently, Jasinska et al. (5) demonstrated that expiration of the metoprolol and propranolol tablets did not influence the dissolution rate of the API [as confirmed by the dissolution curve similarity factors $f2 > 50$, (5)] neither it was affected the quality of the API (6). Similarly to the latter studies, the first objective of the present study was to evaluate the pharmacopoeial quality of the non-expired and expired nifedipine tablets. However, with respect to the experimental timeline, our study differs from those of Jasinska et al. (5, 6): the tests and assays with the non-expired tablets were performed during the shelf-life of the formulations, then the formulations of the same batches were stored at normal laboratory conditions, and after years the left-over tablets were subjected to dissolution test. The nifedipine FPP used for our study were purchased of distinct sources. Consequently, the second objective of the study was to evaluate the pharmacopoeial quality of nifedipine tablets registered in EU (purchased from Estonia) to those not registered in EU but legally self-imported for personal use from Russian Federation.

The cross border merchandise of medications is an increasing trend in many world regions such as USA and Mexico (7), and EU and CIS (Commonwealth of Independent States). However, Mexico and CIS countries are not the ICH (International Conference on Harmonization) parties and thus they are entitled to set their own quality standards for

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API and FPP (8). Further, since the price tag of medications imported cross border may differ several times, people tend to import maximal amounts of medications allowed by the local legislation and consequently they store these medications over longer time period. Our former research has unveiled that several medications registered and distributed in Russian Federation contained high quality and purity API, however, the performance in dissolution test of some formulations has not always been exactly within the limits set by the pharmacopoeias of the ICH member countries [i.e., the European Pharmacopoeia (EP), US Pharmacopoeia (USP), British Pharmacopoeia(BP)] (9-11). Thus, though in general, the Russian Federation registered medications tested so far have been comparable with the European competitors, the effect of expiration to their quality and performance is not known. Consequently, our study results give some practical advices for the expectancy of the shelf-life stability of the medications imported from CIS countries, particularly for the communities living adjacent to a CIS state.

EXPERIMENTAL

Study timeline

The pharmacopoeial quality of the non-expired nifedipine formulations was evaluated in January-April 2006. Then, the remained nifedipine tablets were stored in their original package at ambient temperature (22 ± 2°C) in a dark storage room. The expired nifedipine formulations were tested for their dissolution performance again in June-September 2010, the number of formulations tested in 2010 was smaller due to shortage of tablets of some formulations. In order to test the possible presence of the nifedipine degradation products in the dissolution medium (12), after completion of the nifedipine dissolution, test the randomly selected dissolution medium samples were assayed for the impurities (2010 only).

Formulations

All nifedipine formulations were purchased in mid-2005. The nifedipine formulations registered in Estonia were purchased from a local Pharmacy of the University of Tartu, those registered in Russian Federation were from a community pharmacy of Tomsk, West Siberia, Russian Federation. Full list of formulations tested, batch numbers, and expiration dates are given in Table 1.

Identification of API

Shimadzu IR-spectrometer FTIR-8400S with GoldenGate ATR interface and IP Solution software (analysis settings: Apodization-Happ Genzel; Number of scans – 20; Resolution – 4.0; Min – 600;

Table 1. List of tested nifedipine formulations.

Formulation	Manufacturer/ holder of marketing authorization	Lot	Expiration
Adalat retard, 10 mg	Bayer HealthCare AG, Germany	BXBGGW1	04/2008
Cordipin retard, 20 mg	KRKA, d.d., Slovenia	J30240	10/2008
Cordipin XL, 40 mg	KRKA, d.d., Slovenia	T05982	05/2006
Corinfar retard, 20 mg	AWD pharma GmbH & Co.KG, Germany	4H146A	08/2007
Cornifar, 10 mg #	AWD pharma GmbH & Co.KG, Germany	4H241A	08/2007
Nifedipin retard-ratiopharm, 20 mg	Merckle GmbH, Germany	E36586	10/2007
NifeHEXAL retard, 20 mg	Salutas Pharma GmbH, Member of Hexal Group, Germany	320K44	12/2007
Nycopin, 40 mg	Nycomed SEFA AS, Estonia	55582	01/2008
Vero-nifedipine, 0.01 g *	ZAO "Verofarm", Russian Federation	10604	07/2006
Nifedipine-Shtshelkovsky, 0.01 g *	OAO " Shtshelkovsky vitaminnyi zavod, Russian Federation	10504	06/2006
Nifedipine-Farkos, 0.01 g *	OOO NPF "Farkos", Russian Federation	030504	06/2006
Fenigidin, 0.01 g *	OOO Farmacevticheskaya kompanuya „Zdarov'ye", Ukraine	40104	02/2007

*formulations registered and sold in Russian Federation, # – conventional tablets.

Max – 4000 cm^{-1}) were used for identification of API.

Quality and quantity of API

The quality and quantity of nifedipine and the related substances were studied according to the HPLC method described in Nifedipine monograph of EP (13).

The HPLC system Shimadzu Prominence with a diode-array spectrophotometric detector SPD-M20A was used. The whole process was directed, saved, and analyzed by software LCsolution. The chromatographic procedure was carried out using the stainless steel Luna column by Phenomenex (size: l = 0.15 m; ∅ = 4.6 mm; stationary phase = C_{18}, 5 µm). Twenty µL of the test solution was injected into the column using an attached autosampler. The optical absorbance was measured at the wavelength of 235 nm. The run time of the test was set to 22 min, the flow rate of the mobile phase (acetonitrile, methanol, and water 9 : 36 : 55, v/v/v) was 1.0 mL/min.

The three randomly selected tablets of a nifedipine formulation and two reference solutions (10 mg/25 mL) were tested simultaneously according to the modified EP Nifedipine monograph. In total, 8-10 tablets of each formulation were tested. The nifedipine tablets were carefully crushed and dissolved in 5 mL of methanol (using an ultrasonic bath) and further diluted to 25.0 mL with the mobile phase. The solutions were filtered using the microcellulose filters (∅ = 0.45 µm) and transferred to 2 mL HPLC vials. To prevent photodegradation of nifedipine, all samples were hidden from the direct light and brown glassware was used.

According to the EP Nifedipine monograph, two major impurities of nifedipine are nitrophenylpyridine and nitrosophenylpyridine (referred as impurities A and B, respectively). The EP Nifedipine monograph tolerance limits set for these impurities are (formally applicable for the pure API but not for the finished pharmaceutical product):

- Impurity A: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1%).
- Impurity B: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1%).
- Any other impurity: not more than the area of the peak due to the nifedipine in the chromatogram obtained with reference solution(c) (0.1%).
- Total: not more than 0.3%.
- Disregard limit: 0.1 times the area of the peak due to nifedipine on the chromatogram obtained with reference solution (c) (0.01%).

To meet the quantity tolerance limit of the EP, the content of the nifedipine should not be less than 85% or more than 115% of the label claim of the formulation.

Dissolution of the API

Dissolution tests were performed using the Sotax AT-7 multi-bath dissolution test system coupled to the Ultrospec III (Pharmacia LKB) spectrophotometer that was fed by the peristaltic pump (Watson-Marlow 202 U/AA). The system was driven by the custom-adapted software.

The USP Nifedipine Extended-Release Tablets monograph (14) implies three different dissolution test designs, while the choice of the particular test has to be done on the bases of the formulation compliance with the test. In the present study, the test 2 (with paddles) was used with UV spectrometric detection instead of HPLC assay and it was applied also for the conventional Corinfar tablets. This method, for comparison only, was applied for the 40 mg strength nifedipine tablets, though according to the USP it is an inappropriate test.

The rotation speed was set at 50 rpm and the temperature was kept at 37 ± 0.5°C) throughout the tests. The test medium (pH = 6.8, 900 mL) contained 11.25 mL of phosphate buffer concentrate, 90 mL of 10% sodium lauryl sulfate solution and water (ad 900 mL). To prepare 1000 mL of buffer concentrate, 330.9 g of dibasic sodium phosphate, 38 g of citric acid, and 10 mL of concentrated phosphoric acid were mixed with water and diluted ad 1000 mL. Exactly 0.45 g of nifedipine was dissolved in 100.0 mL of methanol for the reference stock solution and it was kept in cold at 4°C and in darkness.

Five tablets from each lot were tested at the time. The total number of tablets per formulation tested in 2006 was 10 but in the dissolution experiments of 2010 the number of tested tablets was lower due to the shortage of tablets left over from the 2006 experiments. The nifedipine reference solution (corresponding to 10-40 mg of nifedipine depending on the strength of the tablets tested, per 900 mL dissolution medium) was always analyzed in parallel to verify the system validity. The dissolution test lasted for 12 h, the samples were taken every 15 min and measured by UV spectrophotometer at 238 nm wavelength. During the dissolution test and sample collection the whole test system was completely covered with dark, nontransparent cover to prevent nifedipine photodegaradation.

The USP Nifedipine Extended-Release Tablets monograph sets for each dissolution test their own tolerance limits, in the present study the “Not less

Table 2. Quantitative API content and tablet mass uniformity.

Formulation	Label claim (mg)	Nifedipine content (mg)	Nifedipine content (%)	EP tolerance limits	Tablet average weight (g)	Tablet weight SEM (g)	Relative SEM (%)
Adalat retard	10	9.57	95.7	+	0.0839	0.0002	0.30
Cordipin retard	20	19.4	97.0	+	0.0956	0.0003	0.3
Cordipin XL	40	38.04	95.1	+	0.1585	0.0010	0.6
Corinfar retard	20	17.82	89.1	+	0.1287	0.0005	0.4
Cornifar	10	8.73	87.3	+	0.0648	0.0002	0.4
Nifedipin retard-ratiopharm	20	18.72	93.6	+	0.0937	0.0006	0.6
NifeHEXAL retard	20	18.62	93.1	+	0.0823	0.0004	0.5
Nycopin	40	36.4	91.0	+	0.1556	0.0005	0.3
Vero-nifedipine	10	9.28	92.8	+	0.1053	0.0005	0.4
Nifedipine-Shtshelkovsky	10	9.39	93.9	+	0.0974	0.0012	1.3
Nifedipin-Farkos	10	9.58	95.8	+	0.1008	0.0010	0.9
Fenigidin	10	9.38	93.8	+	0.0986	0.0017	1.7

+, EP tolerance limit met, n = 8-10 for quantitative API content, n = 7-11 for tablet mass uniformity.

than 80% of the labeled amount of nifedipine must dissolve in 12 h" was applied. In addition, for comparative purposes, the percentages of API dissolved at time points 3 h and 6 h are reported.

Estimation of nifedipine degradation products in dissolution medium by HPLC analysis

In order to exclude any interference of the nifedipine degradation products with the dissolution test results, the randomly selected dissolution medium samples, withdrawn immediately after the completion of the 12 h dissolution test were analyzed using the HPLC assay described above for API quantification and impurity estimation (2010 experiments only).

RESULTS

Identification (2006 experiments)

All formulations tested contained nifedipine as the API (the representative examples of six formulations and the Sigma reference compound are given in Figure 1).

Tablet mass uniformity and quantitative content of API (2006 experiments)

The tablet mass uniformity of formulations tested was good, though the Russian Federation registered tablets tended to deviate more. In all tested formulations, the nifedipine content was in the tolerance limits of EP (Table 2).

Impurities (2006 experiments)

All nifedipine formulations tested contained high purity nifedipine, the impurity A could be observed only as traces, the impurity B levels were close but below the 0.1% EP tolerance limit, neither exceeded the total levels of impurities the 0.3% EP tolerance limit (the representative examples of chromatograms of the 10 mg nifedipine formulations and the reference compounds for nifedipine, impurity A, and impurity B are given in Figure 2).

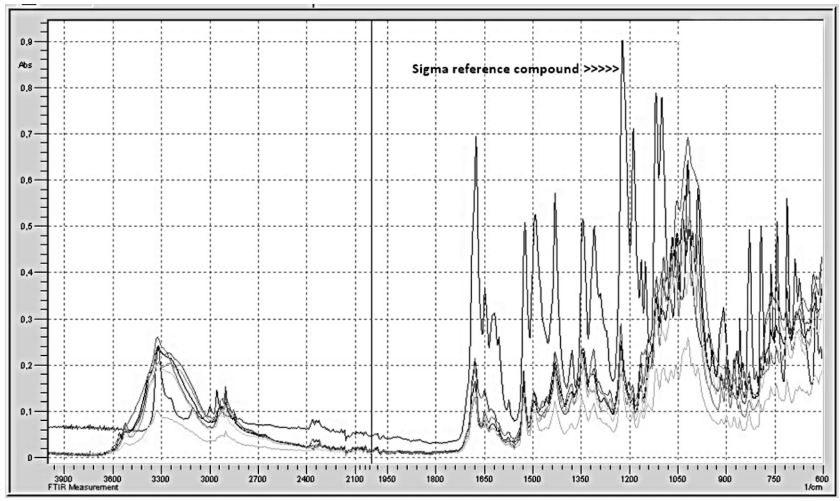

Figure 1. Identification of nifedipine, IR spectra of six nifedipine formulations and a Sigma reference compound tested at 600–4000 cm^{-1}. All tested formulations showed identical IR spectra of the nifedipine fingerprint region (1100–1700 cm^{-1})

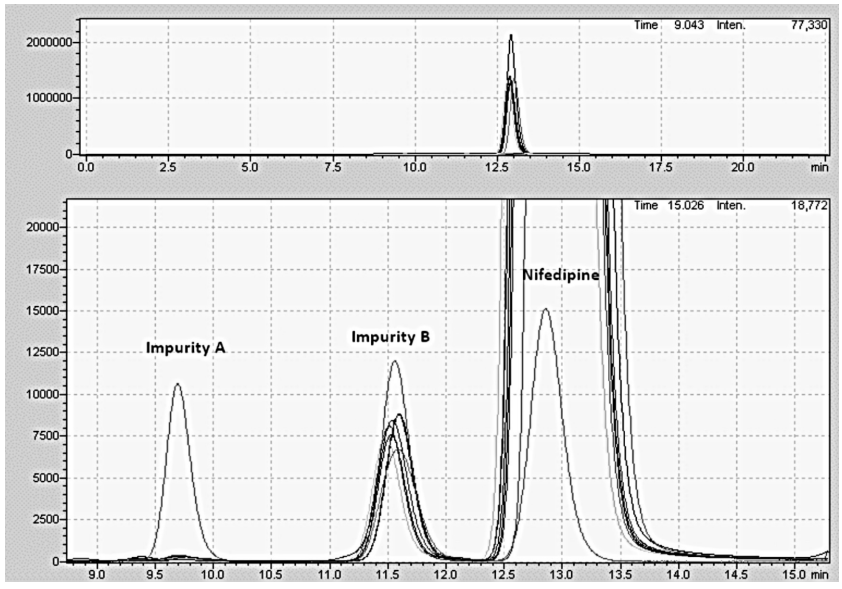

Figure 2. Impurities of the 10 mg nifedipine formulations. Upper panel: compiled original chromatograms (retention time for nifedipine – 12.9 min). Lower panel: magnification of the original chromatograms, the highest peaks for impurity A (retention time 9.75 min) and impurity B (retention time 11.6 min) refer to the tolerance limits of respective impurities for 10 mg nifedipine formulations

Dissolution test (2006 experiments)

All 10 mg and 20 mg nifedipine formulations, irrespective of their country of registration, released during 12 h at least 80% of API. Both 40 mg formulations tested released the same amount (69% of label claim) of nifedipine during 12 h. Expectedly, the conventional Corinfar tablets released most of the API during the first 3 h, however, as a general trend, all extended release tablets released during 3 or 6 h more API than the respective USP tolerance limits foresee (Table 3).

Table 3. Dissolution performance of non-expired and expired nifedipine tablets.

Formulation	Label claim (mg)	Percentage of nifedipine released from tablets					
		2006: 3 h	2006: 6 h	2006: 12 h	2010: 3 h	2010: 6 h	2010: 12 h
Adalat retard	10	60 ± 4	78 ± 4	93 ± 3	80 ± 2	85 ± 3	95 ± 1
Cordipin retard	20	53 ± 2	78 ± 2	92 ± 2	66 ± 3	82 ± 4	89 ± 2
Cordipin XL	40	32 ± 3	41 ± 4	69 ± 4	40 ± 4	52 ± 3	81 ± 2
Corinfar retard	20	40 ± 2	49 ± 2	80 ± 2	75 ± 2	81 ± 3	81 ± 3
Cornifar	10	80 ± 5	85 ± 4	87 ± 2	60 ± 5	78 ± 4	87 ± 3
Nifedipin retard – ratiopharm	20	63 ± 4	75 ± 4	83 ± 4	80 ± 2	93 ± 1	93 ± 1
NifeHEXAL retard	20	51 ± 2	67 ± 3	80 ± 2	67 ± 4	86 ± 2	93 ± 3
Nycopin	40	28 ± 2	38 ± 2	69 ± 2	33 ± 4	59 ± 4	90 ± 3
Vero-nifedipine	10	70 ± 2	76 ± 2	81 ± 2	n.t.	n.t.	n.t.
Nifedipine – Shtshelkovsky	10	71 ± 2	78 ± 2	83 ± 2	91 ± 4	93 ± 3	93 ± 4
Nifedipin-Farkos	10	77 ± 4	83 ± 4	87 ± 4	92 ± 3	93 ± 3	93 ± 3
Fenigidin	10	74 ± 3	81 ± 2	84 ± 2	82 ± 3	84 ± 4	91 ± 3

n.t. – not tested due to shortage of tablets.

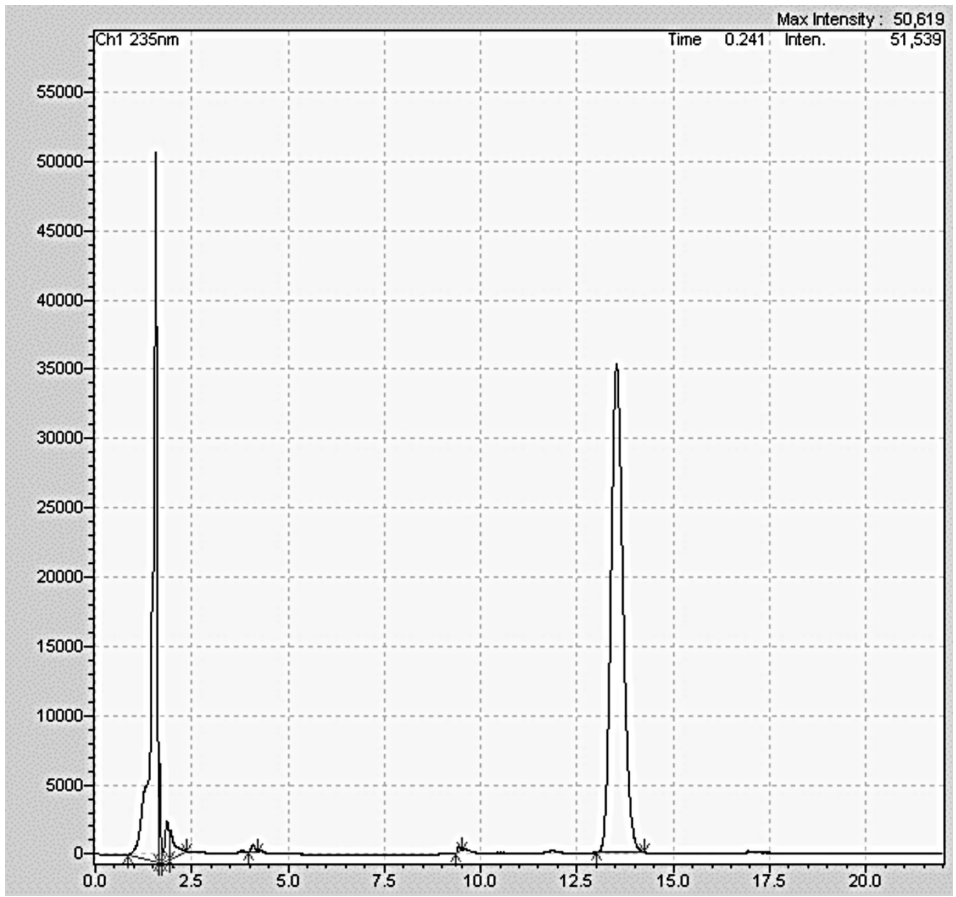

Figure 3. Estimation of nifedipine degradation products in dissolution medium after 12 h dissolution test: the 10 mg Nifedipine-Shtshelkovsky example. Only traces of nifedipine (retention time – 13.4 min) degradation products were detected at 4.1 and 9.45 min

Dissolution test (2010 experiments)

All formulations tested, including the 40 mg tablets, released at least 80% of API after 12 h. It is notable that in all expired Russian Federation registered formulations and the expired extended release tablets of formulations registered in Estonia, the release of API was accelerated during the first 6 h as compared with the non-expired tablets while in the single conventional release formulation, Corinfar, exactly the opposite phenomenon could be found (Table 3).

Estimation of nifedipine degradation products in dissolution medium (2010 experiments)

Only traces of nifedipine degradation products could be discovered from the dissolution medium (a randomly selected example is given in Figure 3).

DISCUSSION AND CONCLUSION

The present study showed that the Russian Federation registered nifedipine formulations are comparable with the European competitors. All tested formulations contained high quality nifedipine as the API. While it was an expected finding for the EU registered formulations, we herewith confirm that the Russian Federation registered formulations comply with the norms set by the ICH parties. It is noteworthy that the all four Russian Federation registered formulations contained almost equal amounts of API very close to the label claim. However, the tablet mass uniformities were not perfect, i.e., the tablet mass uniformity deviations were somewhat higher as compared with the European competitors. Though the quality of the API was within tolerance limits, one has to keep in mind that from a clinical point of view it does not ultimately mean that the formulations are interchangeable (15).

In the present study, it was not known whether the Russian Federation nifedipine formulations are in the conventional or extended release tablet form whereas of the European registered tablets only the 10 mg Corinfar tablets were of conventional type. According to the attached patient information leaflets (PIL), the recommended administration frequency for the EU registered extended release tablets was once or twice daily while for the Russian Federation formulations it was 2 to 3 times daily. The excipients list of Nifedipine-Shtshelkovsky, Nifedipine-Farkos, and Fenigidin reported in PIL resembles that of the conventional tablets (with minor variations, all tablets contained lactose and/or sucrose, starch, Ca-stearate, cellulose derivatives, and some more usual excipients). The Vero-nifedipine tablets contained more advanced excipients and the excipients list resembled that of the European registered extended release tablets (including novel polymers). Nevertheless, all Russian Federation registered nifedipine tablets released the API in almost identical pattern: at least 2/3 of the API was released within 3 h. However, though in the non-expired Russian Federation registered nifedipine tablets the initial release of API was fast, it was still constantly sustained during the first 3 h. In the expired Russian Federation marketed tablets the API was abruptly released and the dissolution curve resembled that of the conventional tablets. Accelerated release of API could be observed also in expired European registered tablets but the release was not as rapid as in Russian Federation registered formulations. As a limitation, one has to keep in mind that the nifedipine release from the extended release formulations is very method-sensitive (16), thus our dissolution test results have to be considered only in the frame of the present test conditions. Further, it is obvious that the dissolution test protocol used is not suitable for the 40 mg tablets and thereby confirms the recommendation of the USP to use alternative test protocols if the label claim exceeds 30 mg (14). Though nifedipine is a photosensitive compound (4) it is notable that the nifedipine degradation products in the dissolution medium did not exceed the trace level. Therefore, apart of the fact that the dissolution tests were performed appropriately, this finding also confirms that in the expired tablets any significant nifedipine degradation did not occur. Consequently, one can say that though the API is well preserved in the expired tablets, the API release may be quick and thus there exists a risk of accelerated nifedipine absorption. The latter should be considered as a medical threat and therefore the use of the expired nifedipine tablets is discouraged.

In conclusion, our present study unveiled that the nifedipine of the extended release tablets as the API preserves well beyond the expiration date regardless of the country of origin of the formulations, however, the expired nifedipine tablets tend to release the API faster than the non-expired tablets.

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