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Investigation of the sustained-release mechanism of hydroxypropyl methyl cellulose skeleton type Acipimox tablets

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Abstract: In this study, we investigate the production of hypolipidemic agents in the form of Acipimox sustained-release tablets, using a wet pelleting process. The purpose of this research is to reduce the total intake time for patients and to lower the initial dose in such that the adverse reactions could be reduced. This study adopts the single-factor method and orthogonal experiments by using hydroxypropyl methyl cellulose (HPMC K15M) as the main sustained-release prescription composition. The final prescription is Acipimox 20%, HPMC K15M 26.67%, sodium carboxymethyl cellulose 30%, polyethylene glycol (PEG 6000) 1%, ethyl cellulose 16.6%, lactose 4.67% and magnesium stearate 1%. The dissolution of tablets reached 85.88% in 8 h. The difference in the weight, hardness and friability of the tables met the requirements in the Chinese Pharmacopoeia; to test the stability, a temperature and illumination accelerated test method was used, the results indicate that the Acipimox sustained-release tablets should be sealed and stored in a dark, cool area. A preliminary study on the tablets' releasing mechanism showed that their release curve fitted the Higuchi model (the formula is $M_t/M_\infty = 31.137\ t^{1/2} - 3.605$ ($R^2 = 0.9903$)). The Acipimox tablets' release principle is dominated by the diffusion mechanism.

Keywords: Acipimox; sustained-release tablet; sodium carboxymethylcellulose; hydroxypropyl methyl cellulose.

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1 Introduction

Hyperlipidemia is a blood lipid metabolic disorder which can lead to atherosclerosis, coronary heart disease, pancreatitis, and other severe complications [1–2]. Acipimox is a derivative of niacin, 4-oxo-5-methylpyrazine-2-carboxylic acid, which is a hypolipidemic drug [3–5]. Acipimox mainly reduces the generations of triglycerides (TG), very low density lipoprotein (VLDL) and low density lipoprotein (LDL) [6–7] by inhibiting the release of free fatty acids from adipose tissue. This drug also has the capacity to increase high density lipoprotein (HDL) generation by inhibiting hepatic lipase and reducing triglycerides (TG) and total cholesterol (TC) levels in plasma. This plays a role in lowering blood lipids. Acipimox is also capable of reducing the incidence of coronary heart disease by decreasing lipoprotein (a) [LP(a)] level [8–9].

Acipimox was developed by Pfizer Inc. in the United States. In Italy, Acipimox capsules first appeared in the market in 1985 [10]. Currently, there are five registered Acipimox-breed drugs in the Chinese market. These are all tablets or capsules, and none of them are sustained-release formulations.

There are two problems that need to be considered when preparing Acipimox release tablets. Firstly, the elimination half-life of Acipimox is 2 hours, so patients need to take it 2–3 times a day [11,12]. As hypolipidemic agent is frequently used as a long-term or lifelong medication, this high frequency of doses is inconvenient for patients. Therefore, our goal is to reduce the number of doses and improve patient compliance. Secondly, sustained-release tablets can reduce the strong impact (causing side effects like facial flushing) of the first dose and improve the initial patient tolerance [13,14].

In this study, we used sustained-release formulation technology. A single dose was administered once a day, and so it was designed to enable a smooth release of the drug in the gastrointestinal tract and maintain a stable blood concentration.

2 Experimental Procedure

This study investigated the effect of different hydroxypropyl methyl cellulose viscosities on the quality and stability of the tablet, while searching for an excellent prescription process. We found that using the matrix hydroxypropyl methyl cellulose (HPMC) enabled us to prepare an Acipimox sustained-release tablet that can be completely released in 8 hours. Moreover, the tablet's *in vitro* level meets FDA (United States Food and Drug Administration) regulations.

Acipimox (Renpu Suzhou Pharmaceutical Co., Ltd.); hydroxypropyl methyl cellulose (HPMC; Weifang Teli Reagent Factory); polyethylene glycol (PEG6000; Jiangsu Province MSC oil chemical plant); carboxymethylcellulose sodium (CMC; Tianjin Fu Chen Chemical Reagent Factory); ethyl cellulose ethoce (EC; Huainan City Cody Chemical Technology Co.); ethanol (Beijing Jijiyuan Chemical Plant); pharmaceutical-grade lactose (Tianjin Fucheng Chemical Reagent Factory); pharmaceutical-grade magnesium stearate (Tianjin Guangfu Fine Chemical Research Institute); distilled water.

UVmini-1240 spectrophotometer (Shimadzu, Japan); T-214 electronic scale (Sartorius (Shanghai) Trading Co. Ltd); GZX-DH202-4-BS-II electrothermal constant temperature drying oven (Shanghai Wan Rui laboratory equipment factory); DP12 Rotary tablet press machine (Shandong Tianqi pharmacy press factory); RC-14DF intelligent dissolution instrument (Tianjin Chuangxing Electronic); GTSONIC-T3 Ultrasonic clean instrument (Jinan Cole Ultrasonic Equipment Co., Ltd.); YD-2 Hardness instrument (Tianjin Chuangxing electronic); CS-2B tablet friability & hardness tester (Tianjin Chuangxing Electronic); SHH-150SD Drug stability test chamber (Chongqing Yongsheng Experimental Instrument Factory).

2.1 Sustained-release Acipimox tablets preparation method

1. Each component of the prescription was crushed and sieved (through a #80 mesh sieve).
2. Each component of the prescription was weighed proportionately, then mixed.
3. Ethanol (85%) solution was used to moisturize the mix materials, then the wetted material was divided into small particles by a #20 mesh sieve.
4. The wet particles were dried at 50–60°C for 2 hours.
5. The particles were sieved again (#18 mesh sieve).

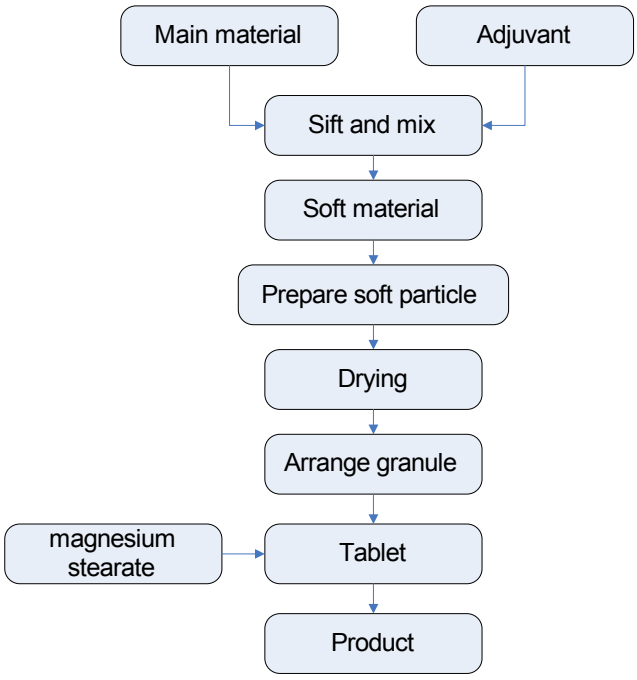

Figure 1: Manufacturing process of Acipimox sustained-release tablets.

6. Magnesium stearate 1% was added to the particles and tableting was done following thorough mixing (Figure 1).

2.2 Analytical method

To determine the content of Acipimox, ultraviolet (UV) analysis was applied. 2.1 mg Acipimox was dissolved in 10 mL water; the mother liquid was diluted 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 mL to 10mL by water, the working calibration curve based on Acipimox standard solutions demonstrated strong linearity over the range of 2.1 μg/mL < C < 12.6 μg/mL. The regression line was represented by $y = 11.657x - 0.58$ ($R^2 = 0.9996$), where y is the concentration of Acipimox (μg/mL) and x is the absorbance at 264 nm.

2.3 Determination of the rate of release

A drug sample was taken in accordance with Chinese Pharmacopoeia for determination of the release rate (Chinese Pharmacopoeia 2010, edition two, appendix XC) [15]. The paddle device of the dissolution test method was used. Nine hundred milliliters of water were released at a speed of 100 r/min. According to the second method,

10 mL of solution were taken and filtered at intervals of 1, 2, 4, 8 and 10 hours; then the same volume of water at the same temperature was added at once. The filtrate was diluted and then the concentration (C) was measured by UV spectrophotometry. According to Acipimox's standard curve, the main ingredients per tablet are 0.03 g with a rate of release of $900\times C\times 10^{-6}/ 0.03$. The release was evaluated at 1, 2, 4, 8 and 10 h. Usually, there are at least three dissolution time intervals. Generally, the first interval of the sampling time was 0.5 to 2 hours; at this time, we examined whether the drug had been released in a burst. The second interval was the cumulative release of about 50%; it is indicative of the drug's characteristics and whether it has been released smoothly. The final interval was the cumulative release of at least 80%.

2.4 Process research

Process research included repeatability tests, Acipimox sustained-release tablet weight variation detection, the hardness test and the friability test.

2.5 Friability test

According to the Chinese Pharmacopoeia, if the weight of each tablet is 0.65 g or less, samples should take several tables to reach the total weight of approximately 6.5 g. We used a hair dryer to blow off the powder, weighted the tablets, and placed them in the friability tester. The samples were rotated 100 times at a speed of 25 r/min. The tablets were then taken out. Remaining powder were removed using the same method. After weighting again, the weight loss should not exceed 1%. Broken, cracked and/or crushed tablets should not be detected [15].

2.6 Stability study

The stability study included illumination experiments, heat-resistance test and air tests.

2.7 Data analysis

Data are mean values from three independent experiments. Statistical analysis was done using SPSS version 17.0 (SPSS Inc., USA).

Ethical approval: The conducted research is not related to either human or animals use.

Table 1: Factors and levels of orthogonal experimental design.

Level	HPMC(K15) (g)	EC (g)	PEG(6000) (g)	CMC (g)
1	0.30	0.16	0.015	0.23
2	0.40	0.25	0.045	0.34
3	0.50	0.34	0.075	0.45

3 Results

3.1 Formulation optimization of sustained release Acipimox tablets using orthogonal experiment

In the Acipimox sustained-release tablet formulation, hydroxypropyl methyl cellulose (HPMC K15M) is used as the sustained release matrix; EC, PEG 6000 and CMC are used as the binders. In order to meet the release requirements for sustained-release tablets, the amount of each ingredient in the prescription needs to be studied further. An orthogonal experimental offers a way to qualitatively analyze the correlations between relevant variables at different levels; we can achieve this by designing an orthogonal table and performing statistical analysis. As shown in Table 1, we designed the orthogonal table according to four factors and three levels. The four factors were HPMC K15, EC, PEG 6000 and CMC. We then processed the data of the release rates at 1 h, 2 h, 4 h, 8 h and 10 h (Table 2). Finally, K is calculated, which is the average of one certain level with a certain factor; R is the extremum, which is the largest K minus the smallest K (Table 3).

On the basis of univariate analysis, orthogonal experiment design was performed to further optimize the formulation, the results showed that, up to 4 h, B (EC) and C (PEG 6000) had the maximum effect on the release; after 4 hours, the effect of A (HPMC K15) and D (CMC) on the release rate began to grow. In general, for the commercial formulation of Acipimox, the peak of plasma concentration occurs within 2 hours, and the half-life is about 2 hours as well. On the basis of release rate result analysis, the sequence of effects on composite grade to evaluate the release process was: A > D > B > C. The optimum composition was A1D3B2C1, which means HPMC 0.3g, CMC 0.45g, EC 0.25g, PEG 0.015g.

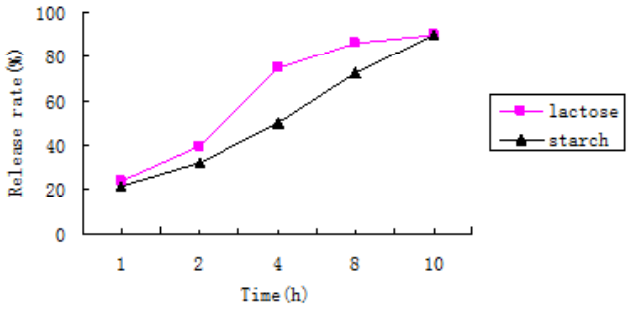

Figure 2: Effect of different fillers on the releasing rate.

Table 2: Results and calculations of $L_9(3)^4$.

	Test				Release rate (%)				
	HPMC (K15) (g)	EC (g)	PEG-6000 (g)	CMC (g)	1 h	2 h	4 h	8 h	10 h
1	0.30	0.16	0.015	0.23	27.93	46.55	83.10	87.23	88.05
2	0.30	0.25	0.045	0.34	24.95	43.41	81.71	88.13	90.15
3	0.30	0.34	0.075	0.45	22.53	37.62	71.25	92.14	95.22
4	0.40	0.16	0.045	0.45	28.19	49.01	78.61	87.10	90.05
5	0.40	0.25	0.075	0.23	23.50	44.50	80.12	86.82	87.12
6	0.40	0.34	0.015	0.34	23.48	39.89	72.82	84.74	85.62
7	0.50	0.16	0.075	0.34	23.68	43.99	85.14	89.13	90.05
8	0.50	0.25	0.045	0.45	23.78	48.14	85.61	88.44	91.08
9	0.50	0.34	0.015	0.23	21.66	42.06	75.43	88.17	88.74

3.2 Effect of different fillers on the rate of release

Based on the results from the orthogonal experimental design, the final optimum formulation when lactose or starch fillers are used can be summarized as follow: Acipimox 20%, HPMC 26.67%, CMC 30%, EC 16.6%, PEG (6000) 1%, fillers 4.67% and magnesium stearate 1%. The test results presented in Figure 2 show that the type of filler used has a significant effect on the release rate of Acipimox. For instance, the release rate is higher with lactose than with starch. However, considering smooth finish, fluidity and hardness, lactose appears to be superior to starch. Nonetheless, at this point of our experiment, the lactose release has not yet reached the requirements for sustained release.

Table 3: Results from orthogonal design for the release rate.

Release time (h)	Level of factor	HPMC(K15) A	EC B	PEG6000 C	CMC D
1	*K*1	25.14	26.60	24.36	24.36
	*K*2	25.06	24.08	25.64	24.04
	*K*3	23.04	22.56	23.24	24.83
	R	2.096	4.043	2.403	0.7966
2	*K*1	42.53	46.52	42.83	44.37
	*K*2	44.47	45.35	46.85	42.43
	*K*3	44.73	39.86	42.04	44.92
	R	2.203	6.660	4.816	2.493
4	*K*1	78.69	82.28	77.12	79.55
	*K*2	77.18	82.48	81.98	79.89
	*K*3	82.06	73.17	78.84	78.49
	R	4.876	9.313	4.860	1.400
8	*K*1	89.17	87.82	86.71	87.41
	*K*2	86.22	87.80	87.89	87.33
	*K*3	88.58	88.35	89.36	89.23
	R	2.946	0.5533	2.650	1.893
10	*K*1	91.14	89.38	87.47	87.97
	*K*2	87.60	89.45	90.43	88.61
	*K*3	89.96	89.86	90.80	92.12
	R	3.543	0.4766	3.326	4.147

3.3 Analysis and inspection of sustained-release Acipimox tablets

3.3.1 Repeatability detection

In the preparation of 1000 sustained-release Acipimox tablets, the prescription composition was as follows: Acipimox, 30g; CMC, 45g; HPMC K15, 40g; PEG 6000, 1.5 g; EC, 24.9 g; magnesium stearate, 1.5 g; lactose, 7.0 g.

Following the above formulation, we prepared three small batches of sustained-release Acipimox tablets and measured the release rates respectively (Figure 3). The release curve clearly tended to be consistent. Therefore, the release effect could meet the design requirements, indicating that the quality of the sustained-release tablets was stable and the process was reproducible.

3.3.2 Weight variation detection of Acipimox sustained-release tablets

Twenty Acipimox tablets were accurately weighed and these measurements were used to calculate the tablets' average weight. According to the Pharmacopoeia, when

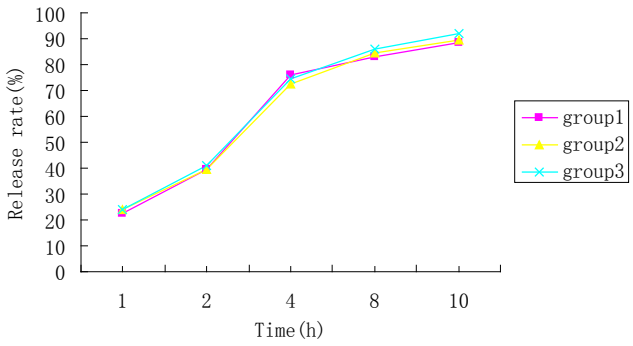

Figure 3: The release rate curve of three batches of Acipimox sustained-release tablets.

the tablets' average weight is 0.30 g or less, the weight difference limit is ± 7.5% and the tablet weight variation range is between 0.1396 and 0.1622 g. In our experiment, the range of weight variation was 0.1396–0.1622 g, which is 0.1509 (1–7.5%)≤tablet≤0.1509 (1+7.5%). Only one sustained-release tablet had a weight of 0.1368 g, which is not within the range; the other 19 tablets had weight within the allowed range. Since the overweight tablet did not go beyond the weight of 0.1281–0.1735g, which is 0.1509 (1–2×7.5%)≤tablet≤0.1509 (1+2×7.5%), the weight difference was considered to comply with the pharmacopoeia.

3.3.3 Hardness test

Twenty Acipimox sustained-release tablets were fixed in the hardness instrument, and the clamping pressure was gradually increased until the sustained-release tablets were broken. The results showed that the hardness values of all 20 tablets met the requirement in the Chinese Pharmacopoeia. The average hardness is 4.57±0.29 kg.

3.3.4 Friability test

According to the Pharmacopeia [15], the friability test is generally done only once, but if the weight loss exceeds more than 1%, the test should be performed again. The average weight loss determined by three different tests should not exceed 1%, and there should not be any fractured, cracked or crushed tablets.

After blowing off any powder, we placed 44 Acipimox sustained-release tablets (weighing 6.5936 g) in the friability tester. They were turned 100 times and any powder was removed off the surface of the tablets with a hair dryer. At this point, the tablets weighed 6.5372 g. The weight loss, therefore, did not exceed 1%; moreover, there were no broken, cracked or crushed tablets.

3.4 Stability tests

3.4.1 Light-resistance test

We placed the Acipimox sustained-release tablets on a plate under 4500 Lx illumination for 10 days. We took samples on the first, third, fifth and tenth day, and tested their release rates within 10 hours. Our results showed that under 4500 Lx light intensity, the quality of the sample did not change essentially, but the release rate of Acipimox was slightly accelerated; the dissolution of Acipimox sustained-release tablets reached 87.09-87.63% in 8 h during 1-10 days. This indicates that the drug should be stored away from light.

3.4.2 Heat-resistance test

The sustained-release tablets were placed on a plate at 60°C and 80°C for 10 days. The release rate of sample tabletes on the first, third, fifth and tenth day was tested within 10 hours. Our results showed that although there was some increase in the release rate at 60°C, the dissolution of Acipimox sustained-release tablets reached 87.93-89.13% in 8 h during 1-10 days, there was no degradation of tablets, indicating that the tablet is still in compliance. At 80°C, however, the tablet surface turned yellow. Some of the tablets became loose and started breaking down. Thus, this drug should be stored in a relatively cool place.

3.4.3 Air tests

By analogy, we placed the sustained-release tablets on a plate at room temperature for 10 days, and took samples on the first, third, fifth and tenth day. When the release rate was evaluated within 10 hours, the results showed that it was slightly altered under these room temperature conditions. Nevertheless, the tablets still met the quality requirements and showed no degradation products; no significant change was observed in the properties of the sustained-release tablets. The drug should therefore be kept sealed.

Table 4: Release kinetics of Acipimox sustained-release tablets.

Time	1 h	2 h	3 h	7 h	8 h	9 h	10 h
Release rate (%)	24.17	40.85	53.89	80.99	85.88	88.61	91.79

Table 5: The release data are fitted using the zero level, primary level.

Model categories	Regression equation	R^2
Zero-level model	$C = 2.4047t + 8.4577$	0.9563
Primary level model	$\ln C = 0.1299t + 2.2641$	0.8716

3.5 Release mechanism of Acipimox sustained-release tablets

First, we fitted the release data of Acipimox sustained-release tablets (Table 4) using the zero-level model, primary-level model (Table 5) and Higuchi model (Figure 4). The tablets' release curve in the zero-level and primary-level models did not fit very well, indicating that it does not follow these models.

The Higuchi model expression is: $M_t/M_\infty = kt^{1/2}$

Where M_t is the amount of drug released at time t; M_∞ is the maximum amount of drug released; t is the time and k is the release rate constant.

With the regression equation: $M_t/M_\infty = 31.137\ t^{1/2} - 3.605$ ($R^2 = 0.9903$), the release profile of the Acipimox tablets showed a better fit to the Higuchi model, which is based mainly on a diffusion mechanism [16]. The data still needs to be fitted in order to determine if there are any corrosion mechanisms involved.

The Ritger–Peppas model expression is: $M_t/M_\infty = kt^n$

With the regression equation: $\log(M_t/M_\infty) = 0.568\log(t) + 1.4182$ ($R^2 = 0.9863$), the results did not fit the Ritger–Peppas model (Figure 5) as well as the Higuchi model.

The release principles of sustained-release tablets are basically diffusion mechanism, dissolution mechanism, and corroding mechanism. The releasing process data can fit the curves of different equations such as the zero-level model, primary-level model, and Higuchi model. The ingredients of the Acipimox sustained-release tablets are released at a non-constant speed over time, during which the amount of initial release is large and the amount released later is less. The "peak/valley" fluctuations are smaller; a relatively stable plasma concentration, which provides the best treatment, can be achieved. With the

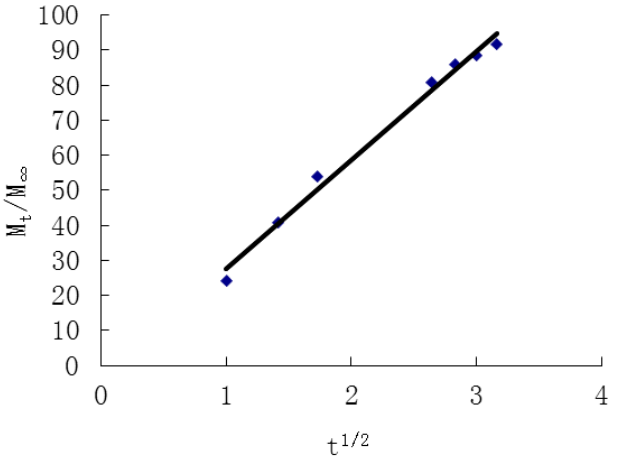

Figure 4: Release data Higuchi model fitting diagram.

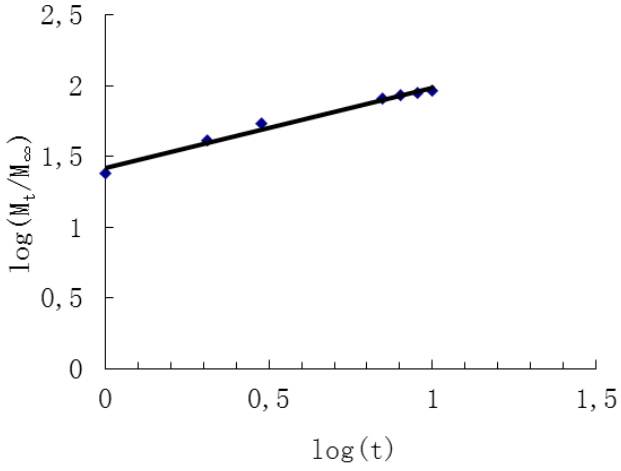

Figure 5: Release data Ritger-Peppas model fitting diagram.

Higuchi model regression equation: Mt/M∞ = 31.137 t1/2–3.605 (R2=0.9903), the release profile of the Acipimox tablets has shown to fit better with the Higuchi model. We conclude that the release process of the Acipimox tablets is mainly dominated by the diffusion mechanism.

4 Conclusions

Using HPMC K15M as the sustained release matrix and EC, PEG 6000 and CMC as the binders, we are able to prepare Acipimox in the form of sustained-release

tablets; its releasing process takes less than 10 hours. The tablet release curve has shown to fit better with the Higuchi model, which is based mainly on the diffusion mechanism. The tablet release behavior meets the design requirements; the drug delivery systems are theoretically and practically valuable. In this study, we have showed that producing Acipimox tablets via wet granulation is feasible, cost-effective and reproducible, and that the tablets meet the FDA standard.

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Disclosure statement: The authors declare no conflict of interest.

References

[1] Eaton, Charles B., Hyperlipidemia, Primary Care, 2005, 32(4),1027–1055.
[2] Hsu J. H., Chien I. C., Lin C. H., Increased risk of hyperlipidemia in patients with bipolar disorder: a population-based study, General Hospital Psychiatry, 2015, 37(4), 294–298.
[3] Yan F. F., Tian L., Xiao Z., Li, S.Y., Fu, M.D., Tian H.M., Comparison of the efficacy of fenofibrate and acipimox on plasma lipoprotein subclasses distribution in the Chinese population with Type 2 diabetes mellitus and hypertriglyceridemia, Clinical Lipidology, 2014, 9(2), 171–177.
[4] Xing J. N., Zhang Y. P., Han S. J., Li, B., Synthesis, crystal structures, and characterization of two new complexes constructed from Acipimox ligands: two three-dimensional networks formed via hydrogen bonding, Inorganic Metals - Synthesis and Reactions in Organic and Nano-Metals Chemistry, 2016, 46(3), 409–413.
[5] Nellemann B., Søndergaard E., Jensen J., Pedersen S. B., Jessen N., Nielsen S., Kinetics and utilization of lipid sources during acute exercise and acipimox, American Journal of Physiology Endocrinology & Metabolism, 2014, 307(2), E199–208.
[6] Seed M., O' Connorb B., Perombelonc N., O'Donnell M., Reaveley D., Knight BL., The effect of nicotinic acid and acipimox on lipoprotein(a) concentration and turnover, Atherosclerosis, 1993, 101, 61–68.
[7] Franceschini G., Bernini E., Michelagnoli S., Stefano B., Viola V., Remo F., Cesare R.S., Lipoprotein changes and increased affinity of LDL for their receptors after acipimox treatment in hypertriglyceridemia, Atherosclerosis, 1990, 81(1), 41-49.
[8] Ball M.J., Vella M., Rechlass J.P.D., Acipimox in the treatment of patients with hyperlipidaemia: A double blind trial, European Journal of Clinical Pharmacology, 1986, 31, 201-204.
[9] Gianantonio S., Aldo G., Alfredo A., Gemfibrozil and mediterranean diet for patients with high plasma levels of lipoprotein [Lp(a)] and cholesterol—Pilot study, Cardiovascular Drugs and Therapy, 1995, 9,347–350.
[10] Jin L.R., Chen W.C., Hu W.G., Bao Y.Q., The lipid-lowering effect of acyclovir, Chinese Journal of New Drugs and Clinical Remedies, 1999, 12(5), 297–298.
[11] Efthymiopoulos C., Strolin B. M., Poggesi I., Ruff F., Basileo G., Musatti L., Pharmacokinetics of acipimox and of its N-deoxy metabolite following single and repeated oral administration of a sustained release formulation to healthy volunteers, Therapie, 1993, 48 (1) , 23-26.
[12] Yang X.G., Nie S.F., Bai H.J., Zhang G.J., Pan, W.S., The pharmacokinetics and bioequivalence of acipimox sustained-release tablets after a single and multiple oral administration in healthy dogs, Acta pharmaceutica Sinica, 2005, 40(5), 457–461.
[13] Efthymiopoulos C., Strolin B.M., Ruff F., Advenier C., Musatti L., Bioavailability of a sustained release formulation of acipimox, following a single dose in healthy volunteers in fasting and fed conditions, European Journal of Pharmacology, 1990, 183(2), 391–391.
[14] Pontiroli A.E., Fattort B., Pozza G., Pianezzola E., Benedetti M. S., Musatti L., Acipimox-induced facial skin flush: Frequency, thermographic evaluation and relationship to plasma acipimox level, European Journal of Clinical Pharmacology, 1992, 43,145–148.
[15] The Pharmacopeia Committee of China. Chinese Pharmacopoeia (2010 version appendix 201). Beijing (BJ): Chinese Medical Science and Technology Press; 2010.
[16] Zhang J.W., Zhong D.F., BI D.Z., The release-division method: a novel in vitro pharmacokinetic evaluation method for the sustained release dosage forms with a release profile characterized by the Higuchi equation, Journal of Shenyang Pharmaceutical University, 2001, 18(5), 324–326.