

Development of the composition and research of the equivalence of suppositories with diclofenac sodium by in vitro method using “Dissolution” test for lipophilic solid dosage forms

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diclofenac sodium, suppositories, dissolution, flow-through cell.

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The aim. Development of the composition and investigation of the equivalence of suppositories with sodium diclofenac by in vitro method on a device with a flow-through cell in accordance with modern requirements of SPhU.

Materials and methods. The development of the suppository composition was carried out with the use of the substance of diclofenac sodium and the excipient of solid fat of various grades. Studies of the active ingredient release in vitro in comparison with the reference listed drug were carried out on a device with a flow-through cell according to the monograph SPhU 2.9.42.

Results. The investigations of the physical-chemical properties of the diclofenac sodium substance (micronisation, solubility) and the basis of the solid fat carrier, which affect the release of the active ingredient from the drug formulation were carried. The «particle size» figure for 2 samples of the active ingredient was from 100 to 400 μm and not more than 15 μm, respectively. The optimal composition of suppositories was developed by the method of 2-factor experiments. The conditions for the «Dissolution» test were determined: the volume of the medium (720 ml), the dissolution temperature (37.0 ± 0.5) °C, the time taken for sampling (15, 30, 45, 60, 90 min), the dissolution medium – buffered solution with a pH of 7.4. The calculated similarity factor f_2 was 67, which indicates the similarity of the release profiles and the equivalence of the researched drug.

Conclusions. The pharmaco-technological properties of sodium diclofenac and the solid fat auxiliary substance were studied. A method for the release of sodium diclofenac with the use of a device with a flow-through cell in accordance with the requirements of the SPhU is developed. The level of release of sodium diclofenac in the dissolution medium from rectal suppositories was determined by the experimental method, as the first step in the bioavailability determination. The equivalence of the tested samples of suppositories with the reference listed drug with the help of the method *in vitro* was established.

Ключові слова:

диклофенак натрію, супозиторії, розчинення, проточна комірка.

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Розроблення складу та дослідження еквівалентності супозиторіїв із диклофенаком натрію методом *in vitro* з використанням тесту «Розчинення» для твердих ліпофільних дозованих форм

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Мета роботи – розроблення складу та дослідження еквівалентності супозиторіїв із диклофенаком натрію методом *in vitro* на приладі з проточною коміркою згідно з сучасними вимогами ДФУ.

Матеріали та методи. Розроблення складу супозиторіїв здійснили з застосуванням субстанції диклофенаку натрію та допоміжної речовини твердий жир різних марок. Дослідження вивільнення діючої речовини *in vitro* порівняно з референтним препаратом виконали на приладі з проточною коміркою відповідно до сучасних вимог ДФУ 2.9.42.

Результати. Провели дослідження фізико-хімічних характеристик субстанції диклофенаку натрію (мікронізація, розчинність) та основи носія твердий жир, що впливають на вивільнення діючої речовини з лікарської форми. Показник «розмір часток» для двох зразків діючої речовини становив від 100 до 400 мкм і не більше ніж 15 мкм відповідно. Методом двофакторного експерименту розроблено оптимальний склад супозиторіїв. Визначили умови тесту «Розчинення»: об'єм середовища (720 мл), температура розчинення (37,0 ± 0,5) °C, час відбору проб (15, 30, 45, 60, 90 хв), середовище розчинення – буферний розчин із рН 7,4. Розрахований коефіцієнт подібності f_2 становив 67, що засвідчує подібність профілів вивільнення та еквівалентності дослідного препарату.

Висновки. Дослідили фармако-технологічні властивості диклофенаку натрію та допоміжної речовини твердий жир. Розроблено методику вивільнення диклофенаку натрію з використанням приладу з проточною коміркою відповідно до вимог ДФУ. Експериментальним шляхом встановили ступінь вивільнення диклофенаку натрію в середовищі розчинення з супозиторіїв ректальних як перший етап визначення біодоступності. Встановили еквівалентність досліджуваних зразків супозиторіїв із референтним препаратом методом *in vitro*.

Ключевые слова:

диклофенак натрия, супозитории, растворение, проточная ювета.

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Разработка состава и исследования эквивалентности супозиторий с диклофенаком натрия методом *in vitro* с использованием теста «Растворение» для твердых липофильных дозированных форм

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Цель работы – разработка состава и исследования эквивалентности супозиторий с диклофенаком натрия методом *in vitro* на приборе с проточной юветой в соответствии с современными требованиями ГФУ.

Материалы и методы. Разработку состава супозиторий проводили с использованием субстанции диклофенака натрия и вспомогательного вещества твердый жир различных марок. Исследования высвобождения действующего вещества

in vitro в сравнении с референтным препаратом проводили на приборе с проточной кюветой в соответствии с монографией ГФУ 2.9.42.

Результаты. Проведены исследования физико-химических характеристик субстанции диклофенак натрия (микронизация, растворимость) и основы носителя твердый жир, которые влияют на высвобождение действующего вещества из лекарственной формы. Показатель «размер частиц» для двух образцов действующего вещества составил от 100 до 400 мкм и не более чем 15 мкм соответственно. Методом 2-факторного эксперимента разработан оптимальный состав суппозитория. Определены условия проведения теста «Растворение»: объем среды (720 мл), температура растворения ($37,0 \pm 0,5$) °C, время отбор проб (15, 30, 45, 60, 90 мин.), среда растворения – буферный раствор с pH 7,4. Рассчитанный коэффициент подобия f_2 составил 67, что свидетельствует о подобии профилей высвобождения и эквивалентности исследуемого препарата.

Выводы. Исследованы фармако-технологические свойства диклофенака натрия и вспомогательного вещества твердый жир. Разработана методика высвобождения диклофенака натрия с использованием прибора с проточной кюветой в соответствии с требованиями ГФУ. Экспериментальным путем установлена степень высвобождения диклофенака натрия в среде растворения из суппозитория ректальных как первый этап определения биодоступности. Установлена эквивалентность исследуемых образцов суппозитория с референтным препаратом методом *in vitro*.

It is known that in clinical practice, diclofenac has been used since 1971, and nowadays it is recognized as the gold standard in rheumatology [1]. Many researchers and pharmaceutical companies improve dosage forms with diclofenac sodium to improve the quality and compliance with modern requirements for equivalence and to reduce the effects of adverse reactions on the human body.

The advantage of the rectal formulation is in the fact that their application can achieve the required pharmacological effect at the shortest possible intervals. The range of drugs containing diclofenac sodium in the form of rectal suppositories is presented on the Ukrainian market as well as by domestic producers and by foreign firms' drugs. Among domestic manufacturers, the production of suppositories under the trade name Diclofenac is carried out by the following companies: PJSC "Monfarm", Monastyrshche (0.05 g rectal suppositories), LLC "Pharmex Group", Boryspil (100 mg rectal suppositories), PJSC "Lekhim-Kharkiv" (rectal suppositories of 0.1 g). The leading foreign companies that have registered rectal sodium diclofenac suppositories in Ukraine are: "Novartis Pharma Stein" AG, France (Voltaren® 25 mg, 50 mg, 100 mg) and "Berlin-Chemie" AG (Dicloberl 50 mg, 100 mg) [2].

But today approaches, that research the generic medicinal products by *in vitro* method with the use of the dissolution test and which are used to simulate the profile of active substance release in the body when using suppositories and to prove their equivalence with the reference listed drug are still imperfect. At the stage of the development of the optimal composition of suppositories, modern researchers apply individual approaches to the dissolution test and the establishment of a profile for the release of active substances. The method of equilibrium dialysis by Kravchinsky, where the release of the active substance occurs through a cellophane semipermeable membrane-film at a temperature of 37.0 ± 0.5 °C is widely used [3–5]. Also, the dissolution estimation, as the first stage of bioavailability, is carried out using a device with a basket (USP Apparatus 1), where suppositories are dissolved in a volume of 900 ml phosphate buffer at pH 7.4 [6,7]. The literature describes suppository studies where the release of the active ingredient profile was performed using a paddle-plate device (USP Apparatus 2) with a mixing mode of 50 rpm [8].

According to the modern requirements, the choice of conditions and the realization of the dissolution test for solid dosage forms in the form of suppositories is regulated by the pharmacological and technological checkouts 2.9.42.

Dissolution test for solid lipophilic dosage forms of the State Pharmacopoeia of Ukraine (SPHU), which provides the use of a device with a flow-through cell [9].

Thus, the development and improvement of the composition of the drug based on diclofenac sodium in the form of suppositories, the introduction of a method for determining the kinetics of the release of active substances from suppositories into the buffered medium, conducting comparative studies of the dissolution profiles of the reference listed drug and the samples of the generic drug samples under current requirements remains an actual direction of pharmaceutical science.

The aim

The aim of the study – the development of the composition and research the equivalence of suppositories with diclofenac sodium by *in vitro* method on a device with a flow-through cell in accordance with the current requirements of the SPhU [9].

Materials and methods

The development of the suppository composition was carried out using the active pharmaceutical ingredient (API) of diclofenac sodium produced by "Amoli Organics Ltd.", India. According to its physical and chemical characteristics, API is a white or almost white, yellowish powder, a little hygroscopic, slightly soluble in water, freely soluble in methanol, soluble in 96 % ethanol.

In developing the composition of the dosage form used excipients, which are related to the solid fats of different lines and certain physical and chemical characteristics. While conducting research, solid fat was chosen which is a mixture of C12–C18 triglycerides and provides better bioavailability, especially for low-soluble substances such as diclofenac sodium. This base is sufficiently investigated and recommended for the development of suppositories, and does not require the addition of excipients (thickeners, surfactants, structurifiers, etc.) [10].

A brand-name drug, Voltaren® 100 mg, "Novartis Pharma Stein" AG, France, was chosen as the reference listed drug during the period of the research, with which comparative studies of the equivalence of the tested samples of suppositories with diclofenac sodium at 100 mg were carried out.

The size of the particles in the API was controlled by laser light diffraction in accordance with the requirements of Article 2.9.31. Determination of Particle Size by Laser Diffraction Method, SPhU using the laser Malvern Mastersizer 2000E particle analyzer [9]. Laser diffraction particle size method was used for the measurements of particles size with Malvern laser diffraction analyzer Mastersizer 2000 (Malvern Instruments Ltd., United Kingdom) equipped with a dry sample-dispersion unit [9].

Compressed air entered the dry sample-dispersion unit at pressure of 2.5–3.5 atm. After the analysis stage with a laser diffraction sensor, the sample was then removed via a vacuum system. 5–10 g of sodium diclofenac substance was placed in the container of dispersion module for samples and the following parameters were included: sample feed rate – 80 g/min, compressed air pressure – 2.0–2.4 atm. Three parallel measurements were performed. The results of particle size distribution were obtained as a volume distribution curve.

The suppositories were prepared by casting method, sodium diclofenac was injected into the base by the type of suspension, homogenized and slopped into a preformed polymer strip.

The development of a method for releasing the active ingredient and determining the kinetics of release was developed in accordance with the requirements of Article 2.9.42. of the SPhU using the device recommended for the determination of the Dissolution test for solid lipophilic drug dosage forms – a device with a SOTAX CE 7 flow-through cell, Switzerland [9].

Comparative researches of the equivalence of the reference listed drug of Voltaren® 100 mg and the investigated samples of the drug were conducted by *in vitro* method using the Dissolution test. The amount of sodium diclofenac released into the buffer solution was carried out by the method of absorption spectrophotometry in the ultraviolet region at a maximum wavelength of 282 nm in accordance with the requirements of the SPhU [9]. The compensation solution was prepared by dissolving the standard sample of sodium diclofenac in the appropriate dissolving medium.

The results of the researchers were expressed as a percentage of the declared content of sodium diclofenac in the unit of the medicinal product.

The similarity factor (f_2) of dissolution kinetics of research objects was calculated mathematically for demonstration and discussion of similarity profiles of medicinal products [11].

Discussion

While the developing of the composition of the drug, it was considered that the active ingredient, diclofenac sodium, belongs to the 2nd class according to the Biopharmaceutical Classification System and has the next properties: low solubility and high permeability [12]. Sodium diclofenac is also not soluble in a suppository basis made from solid fat, so the size of the active ingredient particles has a significant effect on its release and solubility in the buffer medium. For the studied suppositories, 2 samples of API with known particle size, established by the manufacturer, were selected: an average fraction of 100–400 μm in size and micronized powder with a particle size of not more than 15 μm . As a result of the control of micronized substance on a laser analyzer in mode of block for small probes, air as a dispersion medium, the following results are presented, shown in Fig. 1.

It has been established that the fractional composition of micronized sodium diclofenac contains particles in the size from 0.269 to 11.601 μm , and is appropriate to the declared requirements – 100 % of the particles does not exceed 15 μm .

While selecting the type of the basis for developed suppositories, researches of three types of solid fat: Suppocire AIM, Suppocire AS2X and Suppocire AR, produced by “Gattefosse”, France were carried out. According to the handouts, the represented marks are a mixture of triglycerides C12-C18, which differ in terms of decomposition, time of complete deformation and melting point, but the properties correspond to solid fat rectal suppositories Voltaren®.

Selecting of the composition was carried out with the help of the 2-factor experiment in accordance with Table 1 [13].

The received suppositories were evaluated by the “Disintegration” and “Time of complete deformation” of lipophilic suppositories. The analysis of the effect of the “particle size” factor has established that a_2 (no more than 15 μm) > a_1 (100–400 μm), because the use of a non-micronized substance greatly increases the hardness

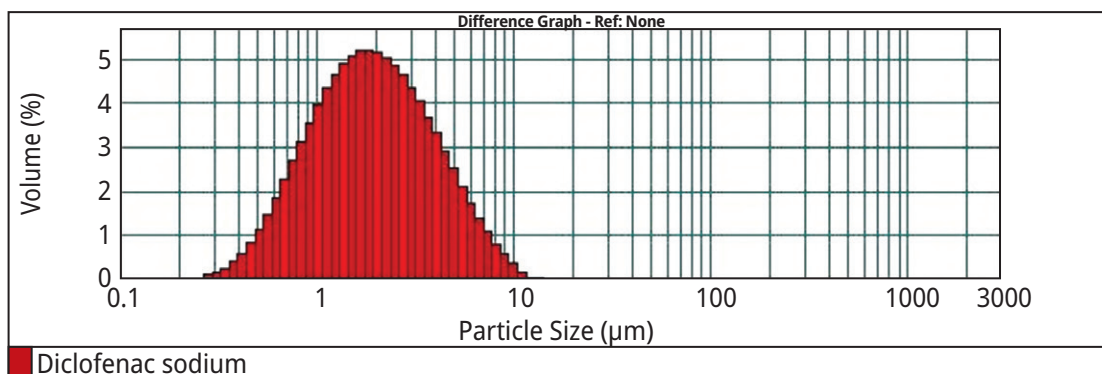


Fig. 1. Particle size distribution of diclofenac sodium produced by “Amoli Organics Ltd.”, India.

Table 1. Planning matrix and results of researches of disintegration ((min), n = 3) and time of complete deformation ((min), n = 3) for suppositories with diclofenac sodium

Factor A	Factor B					
	b ₁		b ₂		b ₃	
a ₁	Disintegration	14.1	Disintegration	15.5	Disintegration	13.5
		13.7		14.7		13.3
		14.5		14.9		12.8
		42.3		45.1		39.6
	Time of complete deformation	15.0	Time of complete deformation	17.7	Time of complete deformation	13.1
		14.7		16.6		12.6
15.6			17.0		13.3	
	45.3		51.3		39.0	
a ₂	Disintegration	12.0	Disintegration	13.1	Disintegration	10.8
		11.7		13.5		10.6
		12.3		13.6		11.3
		36.0		40.2		32.7
	Time of complete deformation	14.4	Time of complete deformation	15.1	Time of complete deformation	12.2
		14.2		14.6		12.9
13.7			15.3		12.4	
	42.3		45.0		37.5	
Comparative drug Voltaren®			Disintegration	12.1	Time of complete deformation	14.2
				11.8		13.8
				12.1		14.3
				36.0		42.3

Designations of researched factors:

A: the size of the particles of substance diclofenac sodium: a₁: 100–400 µm; a₂: no more than 15 µm. **B:** solid fat, grade: b₁: Suppocire AIM; b₂: Suppocire AS2X; b₃: Suppocire AP.**Table 2.** The level of release (%) of sodium diclofenac in a pH of 7.4 dissolution medium for the researched drug and reference drug

№	Diclofenac Sodium Suppository 100 mg						Voltaren® suppositories of 100 mg					
	10 min	15 min	30 min	45 min	60 min	90 min	10 min	15 min	30 min	45 min	60 min	90 min
1	9.72	13.30	21.77	28.65	35.68	37.09	7.80	12.63	23.94	35.46	42.49	43.75
2	9.66	12.94	22.24	27.98	33.44	34.53	7.80	12.34	24.68	34.12	39.57	40.76
3	11.97	13.95	23.69	30.49	37.84	39.31	7.73	13.22	25.83	36.54	43.89	45.10
4	9.78	12.30	21.52	28.88	34.51	35.63	7.71	12.26	23.67	35.16	40.79	42.02
5	10.58	13.38	22.59	29.48	36.51	37.92	7.74	12.38	23.79	35.76	42.79	44.00
6	9.95	13.50	22.32	29.30	35.38	36.60	7.73	12.95	25.04	33.96	40.04	41.24
7	10.41	13.74	23.56	29.37	34.88	35.99	8.80	13.62	25.56	36.17	41.69	42.94
8	11.99	14.82	23.38	30.78	36.40	37.52	8.79	13.37	25.76	36.38	41.99	43.21
9	10.33	12.33	21.12	28.34	35.57	37.01	7.69	12.20	24.26	33.57	40.80	41.99
10	9.74	13.10	22.64	30.05	35.98	37.16	8.37	13.11	25.35	36.00	41.93	43.00
11	11.93	13.93	23.25	30.46	36.11	37.24	8.16	13.42	25.65	36.31	41.96	43.04
12	10.50	13.77	23.04	28.82	34.41	35.53	7.90	12.92	24.71	35.09	40.68	41.91
Average	10.55	13.42	22.59	29.38	35.56	36.79	8.02	12.87	24.85	35.38	41.55	42.75
RSD%	8.65	5.06	3.52	2.94	3.11	3.27	4.96	3.69	3.06	2.75	2.82	2.74

of the suppository in relation to the experimental suppositories with the micronized substance and in relation to the comparison drug. The processing of the results of the influence of the factor B allows to set the following sequence: b₁ (Suppocire AIM) > b₃ (Suppocire AP) > b₂ (Suppocire AS2X). Thus, the composition a₂b₁ for the next stage of research was selected.

The development of a method for the release of sodium diclofenac in the buffer medium, the quantitative determination of the API, the design of the research, the conditions and parameters were established in accordance with the guidelines of the current legislation [11]. As clear recommendations for the media of dissolution

are not presented in leading pharmacopoeia, SPH and manuals, the choice of dissolution media was carried out on the basis of literature studies [14–16]. An optimal buffer solution with a pH of 7.4, which corresponds to the value of the drug use medium, was chosen. The dissolution test was carried out in 3 replicates in a dissolution medium with a pH of 7.4.

The conditions of the dissolution test were determined: volume of medium (720 ml), dissolution temperature (37.0 ± 0.5) °C, sampling time (15, 30, 45, 60, 90 min), the flow rate of the buffer medium is 480 ml/h. These parameters are included in the "For suppositories" device program. Also, the automatic sampling (in time, volume)

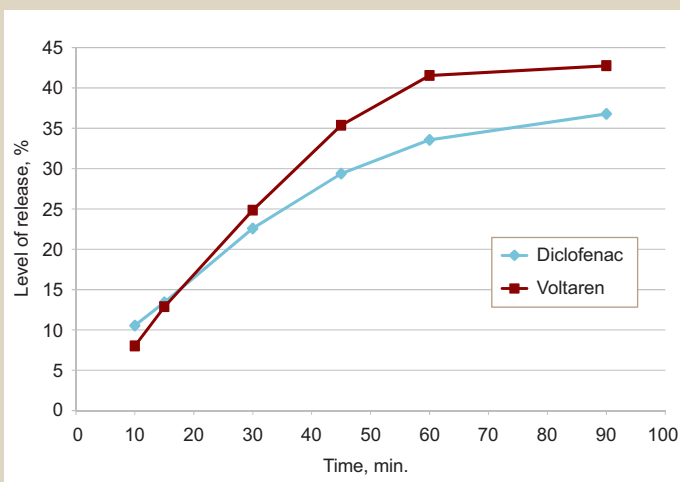


Fig. 2. Release kinetics of Diclofenac sodium suppositories, 100 mg, medium pH 7.4.

is set, the filtration mode of the selected samples through the membrane filter (fiberglass, area 25 mm \varnothing) is additionally set. In a flow-through cell for research one suppository containing diclofenac sodium was placed.

The results of comparative studies of diclofenac sodium release confirmed the theoretical position of the particle size influence on the speed and completeness of API release from suppository and the impact of basis-excipient on the time of softening of drug (Table 2).

The level of release of sodium diclofenac in a pH of 7.4 dissolution medium for the researched drug and reference drug shows the level of release of diclofenac sodium in the dissolution medium with pH 7.4 for 12 suppositories of investigational product and 12 suppositories of reference medicinal drug. The graph of the dependance of release level of diclofenac sodium from time for researched drug and reference drug dissolution are presented in Fig. 2.

With the help of the formula [11] the similarity factor f_2 was calculated, which was 67, and is in accordance with the specified criteria such as an f_2 value between 50 and 100 suggests that the dissolution profiles of reference drug and the researched samples are similar [11].

Thus, as a result of the research, a drug based on diclofenac sodium was developed in the form of suppositories, the equivalence of which with the reference drug was proved by the *in vitro* method using the dissolution test according to the requirements of the SPhU.

Conclusions

1. The biopharmaceutical properties of sodium diclofenac API and the excipient solid fats are investigated, which have a significant effect on the release of sodium diclofenac from the medicinal form.

2. Based on the conducted research of two factor experiment, optimal composition of rectal suppositories with diclofenac sodium was developed, which is similar to the reference drug by qualitative and quantitative composition and pharmaco-technological characteristics of disintegration and time of complete deformation.

3. The method of the release and determination of kinetics of dissolution of sodium diclofenac using a device with a flow-through cell was developed in accordance with the pharmaco-technological test 2.9.42. "Dissolution test" for solid lipophilic dosage forms" SPhU [9].

4. The level of release of sodium diclofenac in the dissolution medium from rectal suppositories was determined by the experimental method, as the first step in the determination of bioavailability.

5. The equivalence of the tested samples of suppositories based on diclofenac sodium with the reference drug by *in vitro* method with the use of the dissolution test on a device with a flow-through cell was established.

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