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ORIGINAL ARTICLE / ÖZGÜN MAKALE

TABLETING AND EVALUATION OF MULTIPLE-UNIT COMPOSITION OF ISOSORBIDE DINITRATE WITH MODIFIED RELEASE

İZOSORBİD DİNİTRATIN MODİFİYE SALIM YAPAN ÇOK BİRİMLİ BİLEŞİMİNİN TABLET ŞEKLİNDE BASILMASI VE DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: *This study was aimed to create a multiple-unit dosage form of isosorbide dinitrate by pressing spherical matrix granules into tablets, selecting the optimal technology parameters and evaluating the obtained tablets.*
Material and Method: *The tablet cores were prepared from mixtures of active matrix granules and shock-absorbing auxiliary granules in various ratios using diverse tabletting forces. The dissolution profiles of the obtained tablet compositions were evaluated in comparison with the reference preparation.*
Result and Discussion: *An optimal ratio of spheroids with the active component with auxiliary granules along with optimal compression parameters were determined. The resulting as multiple-unit tablets exhibited a release profile similar to that of Cardicket Retard. Used technological approach makes it possible to regulate the dissolution profile of tablets by changing the ratio of active granules with different kinetics of the active substance release.*
Keywords: *Active substance release profile, as multiple-unit tablets, isosorbide dinitrate, spherical matrix granules*

ÖZ

Amaç: *Bu çalışma, küresel matris granüllerinin tabletler şeklinde basılmasıyla izosorbid dinitratın çok birimli dozaj formunu oluşturmayı, optimum teknoloji parametrelerini seçmeyi ve elde edilen tabletleri değerlendirmeyi amaçlamıştır.*
Gereç ve Yöntem: *Tablet çekirdekleri, çeşitli oranlarda ve çeşitli tabletleme kuvvetleri kullanılarak aktif matris granülleri ve yardımcı granüllerin karışımlarından hazırlandı. Elde edilen tablet bileşimlerinin çözünme hızı profilleri, referans ürün ile karşılaştırılarak değerlendirildi.*
Sonuç ve Tartışma: *Used technological approach makes it possible to regulate the dissolution profile of tablets by changing the ratio of active granules with different kinetics of the active substance release. Aktif sferoidler ve yardımcı granüllerin optimum oranı, optimum basınç parametresi ile belirlendi. Elde edilen çok birimli tabletler Cardicket Retard'ınkine benzer etkin madde salım profili göstermişti. Kullanılan teknolojik yaklaşım, etkin maddenin farklı kinetiklerle*

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salımı ile aktif granüllerin oranı kullanılarak tabletlerin çözünme profilini düzenlemeyi mümkün kılmaktadır.
Anahtar Kelimeler: *Aktif maddenin salım profili, izosorbid dinitrat, küresel matris granülleri, multidozlu tabletler*

INTRODUCTION

Isosorbide dinitrate (Figure 1) belongs to the group of organic nitrates. It is a drug for the treatment and prevention of angina pectoris attacks. When taking traditional forms of isosorbide dinitrate (tablets, sprays), the effect comes immediately and the total duration of action does not exceed 6 hours [1,2]. Existing forms contribute to rapid relief of angina attacks, but are not suitable for their prevention, when a gradual release of active ingredient for an extended period (about 10-12 hours) is needed. In turn, prolonged forms of isosorbide dinitrate have a high prophylactic efficacy. Modified release preparations combine high pharmacological activity, a long period of therapeutic action and the absence of serious side effects characteristic of all nitrate group preparations [2,3].

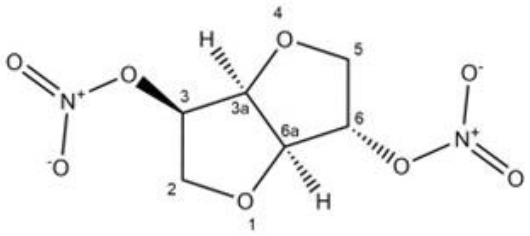

Figure 1. The chemical formula of isosorbide dinitrate

The most common dosage forms with modified release are matrix tablets. Such forms are produced by incorporating active pharmaceutical ingredients into polymer matrices to achieve controlled drug release [4-6]. In turn, today multicomponent dosage forms are increasingly used in comparison with monolithic medicinal forms. They have a number of potential benefits, such as predicted gastrointestinal movement, overdose risk absence, ability to manage the release profile, increased bioavailability, and also less intra-subject and inter-subject variability in pharmacokinetic characteristics [7-9]. The drugs requiring long-term therapeutic effect for the treatment of such cardiovascular diseases, in particular such as arterial hypertension and angina pectoris, are suitable for the development of sustained release multi-dose formulations [10,11].

The key characteristics of pellets to be compressed into tablets are the size, shape and density, type and amount of the polymer coating. The core of the granule must be strong, but with some plasticity [12]. Given that the granules contain a large proportion of a substance with a narrow therapeutic range, maintaining the integrity of the granules and their coating after tableting is a primarily responsible for the dosage form safety.

The extrusion-spheronization technology was chosen to produce isosorbide dinitrate pellets. This approach provided a high concentration of the active substance, high density and smooth surface of the granules [13-17]. The tabletability and tear resistance of the functional coating of the granules are highly dependent on their deformability. Harder particles are less deformed during pressing, which contributes to the preservation of the outer layer. As expected, the strength of pellets depends on the composition chosen for them.

Microcrystalline cellulose was used as the main auxiliary substance for the manufacture of spheroids. It has excellent ductility and cohesiveness when wetted, as well as the ability to absorb, retain and release water. The predominant mechanism of residual deformation of microcrystalline cellulose granules is plastic deformation. In addition to the above properties, microcrystalline cellulose particles are small in size and allow to obtain granules with a smoother surface than when using other fillers [18-24].

To provide complete leaching from the matrix of the active component lactose was included into

the pellets. Due to high solubility the use of lactose as a filler is unacceptable when moistened with water. However, binary mixtures of microcrystalline cellulose and lactose retain the absorption and adsorption properties of microcrystalline cellulose. And they are absent or minimal in the compositions with lactose [14,25].

Polyacrylate copolymer in the form of an aqueous 30% dispersion of Eudragit NE 30D was selected as the polymer, that modifies the release of the active component. In addition, the polymer used is the key in pellets binder to maintain release characteristics. This polymer is insoluble in water, highly ductile and it doesn't require plasticizer. Along with microcrystalline cellulose the polyacrylate dispersion forms a polymer matrix and provides plastic deformation of the pellets during pressing. Film of Eudragit® NE 30 D is very flexible and the drug release from pellets is not affected by compression [26,27].

Another important aspect of maintaining the release from multi-unit tablets is the use of auxiliary cushioning components. Such tablet components may be either primary powder particles or in the form of secondary agglomerates, such as granules. Before tableting process, excipients are mixed with pellets as cushioning agents to prevent the direct contacts between pellets. And thereby to avoid or to reduce the damage to coating films. The protective effect of the excipient depends on the particle size and characteristics of the material. The amounts of excipients in the tablets are also important for the cushioning effect [10].

The general goal of this work was to develop multi-unit tablets of isosorbide dinitrate with a dissolution profile similar to those of the original product "Cardiket Retard". Given the potential risk of uncontrolled release of the active substance, secondary goals were to develop a technology for the manufacture of isosorbide dinitrate and auxiliary shock-absorbing granules, find the optimal ratio of these granules, and adjust the characteristics of the compressing process.

MATERIAL AND METHOD

Reference Drug

Prolonged-release tablets "Cardiket Retard" 40 mg (Aesica Pharmaceuticals GmbH, Germany) were used. That was done to determine the reference release profile of isosorbide dinitrate for multiple-unit compositions.

Excipients, which were used: Isosorbide dinitrate (RPF "MICROKHIM", Ukraine);Polyacrylate dispersion Eudragit NE 30D (Evonik, Germany);Microcrystalline Cellulose HEWETEN 101 (JRS Pharma, USA); Lactose monohydrate Pharmatose 200M and Lactochem Super Fine Powder (DFE Pharma, Germany); Hydroxypropylmethylcellulose Mantrocel E-6 (Mantrose-Haeuser, USA); Talc (Imifabi, USA); Maize starch (AVEBE, Germany); Colloidal silicon dioxide Aerosil 200 (Evonik, Germany); Povidone Kollidon 30 (BASF, Germany); Magnesium stearate (FACI, Italy).

Determination of the Required Amount of a Mixture of Matrix Granules in a Given Ratio

The content of the isosorbide dinitrate in the obtained matrix pellets was determined by means of their own validated analytical HPLC technique. The analysis was performed on a Shimadzu LC-20AD XR liquid chromatograph with a diode-array detector under the following conditions: Supelco Discovery C18 chromatographic column (150 mm x 4.6 mm, 5 μm); mobile phase - water R - buffer solution (pH 4.7) - methanol R2 (35:10:55); elution mode - isocratic; mobile phase velocity – 1.0 ml / min; the detection wavelength is 220 nm [28].

To prepare buffer solution (pH 4.7) 15.4 g of ammonium acetate R was poured into a volumetric flask with a capacity of 1000.0 ml. After 300.0 ml of water R and 11.5 ml of glacial acetic acid R were added. Content was mixed and volume of solution was adjusted the with water to the mark. The pH of the solution was adjusted as needed with glacial acetic acid R.

To prepare a comparison solution of 0.120 g (precise portion) CRS isosorbide dinitrate was added to a volumetric flask with a capacity of 500.0 ml. Then 300.0 ml of methanol R2 was added and kept in an ultrasonic bath for 10 minutes. The volume of the solution as adjusted to the mark by methanol R2 and mixed thoroughly.

To prepare the test solution, about 0.24 g (exact portion) powder of ground matrix granules was

placed into a volumetric flask with a capacity of 200.0 ml. Then 100.0 ml of methanol R2 was added and kept on ultrasonic bath for 30 minutes at 40-50°C. The solution volume was adjusted to the mark with methanol R2 and mixed thoroughly. The obtained solution (25.00 ml) was transferred to a volumetric flask with a capacity of 50.0 ml and the volume of the solution was adjusted with the mobile phase to the mark was adjusted. Afterwards mixed thoroughly and filtered through the PES syringe filter (d = 25 mm; 0.45 μm) or similar, discarding the first portions of the filter installment.

The required weight of the mixture's sample of uncoated and coated granules which is needed to match the dosage of the isosorbide dinitrate in the experimental compositions was calculated by means of the formulas:

$$M_0 = \frac{D_{ISDN}}{W_0};$$

$$W_0 = \frac{(W_{uncoat} + k \times W_{coat})}{1 + k},$$

where M_o is the calculated mass of the mixture's sample of matrix granules;

D_{ISDN} is the isosorbide dinitrate dosage (amount) in the experimental composition;

W_o is the isosorbide dinitrate mass fraction in the mixture of matrix granules;

W_{uncoat} is the isosorbide dinitrate mass fraction in uncoated spherical granules;

W_{coat} is the isosorbide dinitrate mass fraction in coated spherical granules;

k is the ratio coefficient between the obtained amounts of coated and uncoated granules, respectively.

Obtaining of the Auxiliary Protective Granules

Auxiliary protective granules were obtained by means of the extrusion-spheronization with an aqueous solution of povidone as a moisturizer and binder liquid.

Weighted amounts of dry components were mixed in a drum mixer HSD5-100 (SaintyCo, China). The obtained dry mixture was moistened with 10% of the mass by an aqueous solution of povidone and was mixed in a planetary granulator-mixer XF DH-5L (Nantong KMM, China). The resulting mass was extruded on a screw radial extruder YC-910 (Pilotech, China) with a sieve diameter of 1,0 mm.

The obtained extrudate was spheronized in a laboratory spheronization installation YC-910 (Pilotech, China), equipped with a corrugated disk with a diameter of 250 mm with a corrugation step of 2 mm (600 rpm).

After spheronization, granules were dried in an oven at 60°C for 8 hours.

Screening of the Auxiliary Granules

A set of stainless steel laboratory sieves with a mesh size of 0.25 mm; 0.5 mm; 0.8 mm and 1.0 mm was used [29] to determine the particle size composition of the obtained granules and separation them into fractions.

Obtaining of the Tablet Cores of Multiple-Unit Composition

Compression of the tablet mass obtained from an active spheroids'mixture and auxiliary granules was performed on a rotary tablet press U& M-1000 (Shanghai Unique Machinery Technology, China) using biconvex punches with a diameter of 8 mm.

Determination of Tablet Cores' Friability

To test the friability, a sample of whole tablet cores weighing as close as possible to 6.5 g was taken. Before testing, the tablets were thoroughly dedusted, the sample was accurately weighed, and the tablets were placed in a drum. After 100 revolutions of the drum, the tablets were removed, the dust was removed and weighed accurately again [29].

Friability was calculated by the formula:

$$F = \frac{m_1 - m_2}{m_1} \cdot 100,$$

where F is the abrasion,%;
m_1 is the mass of the sample before the test, g;
m_2 is the mass of the sample after the test, g.

Dissolution Test

Dissolution test was carried out using Apparatus 1 (rotating basket; 100 rpm). To test 1 tablet or sample of the mixture of granules (which corresponds to 40 mg of the isosorbide dinitrate) were placed in glasses filled with 500.0 ml of water. After 1 hour of dissolution 10.0 ml of solution was selected from the center of the glass, filtered through a paper filter "blue ribbon", discarding the first portions of the filtrate. The sample was diluted 1:1 with water R. After 2, 4, 6, 8, 10 and 12 hours from the beginning of the dissolution, samples undergo process in a similar manner.

A standard isosorbide dinitrate solution preparation. A sample of the isosorbide dinitrate CRS equivalent to 0.050 g of 100% isosorbide dinitrate was placed into a 50.0 ml volumetric flask. Then 2/3 of flask was filled with methanol R2. It was kept in an ultrasonic bath for 10 minutes. The volume of flask was brought by methanol R2 to the mark and stirred. The resulting solution of 1.0 ml was transferred into a volumetric flask with a capacity of 25.0 ml, bring the volume of the solution with water R to the mark and mix.

Preparation of a buffer solution with a pH of 4.7. 15.4 g of ammonium acetate R was placed in a volumetric flask with a capacity of 1000.0 ml. 300.0 ml of water R, 11.5 ml of glacial acetic acid were added, mixed and brought the volume of the solution by water R to the mark. If necessary, the pH of the solution was adjusted potentiometrically with glacial acetic acid R.

The test solution of 50 µl and the standard isosorbide dinitrate solution of 50 µl were chromatographed on a liquid chromatograph with a UV detector (wavelength 210 nm), using a column of 150 mm x 4.6 mm in size. It was filled with LS-18 sorbent and mobile phase: water R was a buffer solution with pH 4.7 and methanol R2 (350: 100: 550) with a flow rate of 1.0 ml/min.

Comparison of Dissolution Profiles

To compare the dissolution profiles of matrix granules and tableted compositions, the difference factor f1 and the similarity factor f2 were calculated according to the formulas [30]:

$$f_1 = \frac{\sum_{i=1}^{n} |R_i - T_i|}{\sum_{i=1}^{n} R_i} \cdot 100;$$

$$f_2 = 50 \cdot log\left\{\left(1 + \frac{1}{n}\sum_{i=1}^{n} |R_i - T_i|^2\right)^{-0.5} \cdot 100\right\}.$$

where n is the number of time points; R_i is the amount of active substance transferred to the solution from the comparison drug at the i-th time point (on average, %); T_i is the amount of active substance transferred to the solution from the test drug at the i-th time point (on average, %).

The value of $f1$, which is in the range from 0 to 15, reflects the degree of difference between the two curves.

The value of $f2$, which is in the range from 50 to 100, indicates to a similar dissolution kinetics of drugs.

RESULT AND DISCUSSION

Dissolution Test Validation

For simplicity and convenience of research, water itself was chosen as the dissolution medium for evaluating the compositions [31]. This approach is acceptable, since the active ingredient and dosage form have a pH-independent solubility and do not have a significant effect on the properties of the aqueous medium themselves.

The method was validated according to ICH Q2 (R2) guidelines [32]. Validation parameters were

shown in the Table 1.

All evaluated validation parameters do not exceed the established acceptance criteria. Method is validated and suitable for analysis.

Table 1. Dissolution test validation parameters

Parameter		Acceptance criterion	Result
1		2	3
Suitability of the chromatographic system	Number of theoretical plates, N	≥ 750	7645
	Peak symmetry factor, A_s	0.8 – 1.5	1.35
	Relative standard deviation, RSD,%	≤ 1.19	0.096
Linearity	Free member of linear dependence, | a |: - statistical insignificance - practical insignificance	 ≤ 0.51 ≤ 1.01	0.2057
	Critical residual standard deviation, S_o	≤ 1.58	0.4150
	Correlation coefficient, R_c	≥ 0.9994	0.99996
Convergence and correctness	Relative confidence interval, Δ, % Systematic error, δ, %	≤ maxΔ_{As} =3.0 Criterion of statistical insignificance: $\delta \leq \Delta/3$ = 0.40	1.19 0.09
Intralab accuracy	Relative confidence interval, Δ_{intra} , %	≤ maxΔ_{As} =3.0	0.18
Limit of detection (LOD),%		≤ 0.04 mg/ml	0.88 % (0.000352 mg/ml)
Limit of quantitation (LOQ),%		≤ 0.04 mg/ml	2.68 % (0.001072 mg/ml)
Specificity	Effect of placebo components	Separation of additional peaks with the peak of isosorbide dinitrate	Additional peaks separated
		No additional peaks in placebo and solvent chromatograms with retention time matching peak of isosorbide dinitrate	No peaks
Specificity	Forced degradation study	Separation of additional peaks with a peak of isosorbide dinitrate in chromatograms of solutions subjected to forced degradation	Additional peaks separated
		On all chromatograms of placebo solutions subjected to forced decomposition, there are no peaks coinciding in retention time with the peak of the main substance	No peaks
Stability of solutions over time	Relative confidence interval, Δ_t , %; - standard solution (CRS); - test solution	≤ max δ = 0.96	 0.12 0.20
Prediction of the total uncertainty of the method, Δ_{As}, %	≤ maxΔ_{As} =3.0	1.37	
Robustness	Method robustness parameters: - change in the composition of the mobile phase; - change in the pH of the aqueous component of the mobile phase; - change in flow rate; - other manufacturer of column	Obtaining a reliable result and fulfilling the requirements of the "Chromatographic system suitability test".	The chromatographic system suitability test is met. The reliability of the results of the analysis with minor changes in the parameters of the method has been proven.

Selection of Excipients and Production of Protective Granules

Among the existing commercially available products [13] that provide the function of protecting

pellets with the active substance from destruction and uncontrolled dissolution, lactose-based compositions are of particular interest. On its basis, they are formed with high density, which are also well soluble in water. Such properties are ensured by obtaining a strong multi-dose tablet with rapid effective disintegration of active pellets.

The composition of the auxiliary granules was based on the existing product StarLac (Meggle, Germany) based on lactose and starch, which accelerates the disintegration of the composition due to its leavening properties additionally [34].

The extrusion-spheronization method was also chosen to obtain auxiliary granules that will have the physical and technological properties closest to the active spheroids. The technology considered the properties of the original lactose as the main component of the auxiliary granules (Table 2).

The degree of the surface active pellets' destruction depends on the the lactose particle size used in the auxiliary granules. Maximum damping functions of the particles are achieved using the smallest lactose crystals, so a special micronized brand Lactochem® Super Fine Powder was used in the composition. Povidone Kollidon 30 in the amount of 5% was used as a binder.

Colloidal silicon dioxide in the amount of 0.5% was included in the composition. That was done to ensure efficient mixing of dry components and to achieve the most uniform distribution of the used excipients' particles.

The obtained granules were dried, then the combined number of spheroids from 10 operations was scattered on laboratory sieves. The scattering results are shown in the table 3.

Table 2. Weights of the components for one extrusion-spheronization operation

Component	**g**	**%**
Lactose monohydrate	238.5	79.5
Corn starch	45.0	15.0
Colloidal silicon dioxide	1.5	0.5
Povidone	15.0	5.0
Purified water	135.0	
Together:	***335.0***	***100.0***

Table 3. Fractional composition of the obtained auxiliary granules

Fraction of granules, mm	**g**	**%**
< 0.25	10.65 ± 2.15	3.55 ± 0.73
0.25- 0.5	53.37± 5.04	17.79 ± 1.71
0.5 – 0.8	103.35 ± 7.49	34.45 ± 2.54
0.8 – 1.0	114.36 ± 7.28	38.12 ± 2.47
> 1.0	13.11 ± 2.39	4.37 ± 0.81
Together:	***294.84 ± 3.63***	***98.28 ± 1.23***

Mass Fraction Influence on Auxiliary Granules on Release Profile

In order to select the most acceptable parameters for as multiple-unit tablets 'compression of the isosorbide dinitrate with modified release, preparation of experimental compositions were investigated. A mixture of uncoated matrix granules were used for that, namely fraction 0.8-1.0 mm and coated matrix granules fraction 0.5-0.8 mm (isosorbide dinitrate content 36.3% of mass.), in a mass ratio of 1 : 2.5 [17].

The required calculated amount of the matrix granules, which provided the required amount of active pharmaceutical ingredient in the mixture to obtain tablets at a dosage of 40 mg, was mixed with the appropriate number of auxiliary granules in a drum mixer. Magnesium stearate (0.5%) was added to the tablet mass as a glidant.

Tablet cores of the compositions 1-6 were obtained by means of compression (force 6 kN) and

the release profiles of the active substance with a mixture of unpressed pellets were compared. The content of the compositions and the obtained results are shown in the table 4.

The results of the "Dissolution" test of the obtained compositions with different ratios of active and auxiliary granules are presented in the table 5 and figure 2.

Table 4. The content of the experimental tablet compositions

Comp. №	The ratio of the isosorbide dinitrate granules to auxiliary granules	Uncoated matrix granules, mg / tab.	Coated matrix granules, mg / tab.	Auxiliary granules, mg / tab.	Magnesium stearate, mg / tab.	Tablet core weight, mg
1	40:60	30.66	76.66	159.34	1.34	268 ± 5.7
2	45:55			129.49	1.19	238 ± 5.2
3	50:50			106.60	1.08	215 ± 4.5
4	55:45			86.70	0.98	195 ± 4.4
5	60:40			70.78	0.90	179 ± 3.8
6	65:35			56.85	0.83	165 ± 3.6

Table 5. Comparative results of the dissolution of the tablet cores' compositions and unpressed pellets

Dissolution time, h	% released isosorbide dinitrate						
	Unpressed mixture of matrix granules	Tablet compositions					
		№1 (40:60)	№2 (45:55)	№3 (50:50)	№4 (55:45)	№5 (60:40)	№6 (65:35)
0	0	0	0	0	0	0	0
1	19.6 ± 2.2	20.2 ± 3.1	20.8 ± 2.9	21.5 ± 3.4	22.1 ± 3.8	26.1 ± 3.5	30.1 ± 3.2
2	30.0 ± 2.2	31.2 ± 3.6	32.3 ± 4.1	33.5 ± 3.9	34.7 ± 4.0	41.4 ± 3.9	48.2 ± 4.0
4	49.4 ± 2.5	50.8 ± 4.4	52.2 ± 4.6	53.6 ± 5.2	55.0 ± 4.8	60.9 ± 5.1	66.9 ± 5.5
6	62.1 ± 3.5	63.2 ± 4.7	64.3 ± 4.3	65.4 ± 4.8	66.5 ± 4.9	72.6 ± 4.6	78.6 ± 5.4
8	72.8 ± 4.1	73.4 ± 5.1	74.1 ± 5.1	74.7 ± 5.4	75.4 ± 5.2	79.8 ± 5.3	84.3 ± 6.1
10	81.7 ± 4.6	82.0 ± 6.1	82.2 ± 6.3	82.5 ± 6.2	82.8 ± 5.8	85.8 ± 6.2	88.9 ± 6.4
12	89.8 ± 4.3	89.5 ± 5.4	89.3 ± 5.9	89.0 ± 5.4	88.8 ± 5.3	90.0 ± 5.3	91.3 ± 5.4
f_1	-	0.91	1.28	2.39	3.67	7.71	**15.17**
f_2	-	95.04	94.28	86.84	79.55	63.93	**49.88**

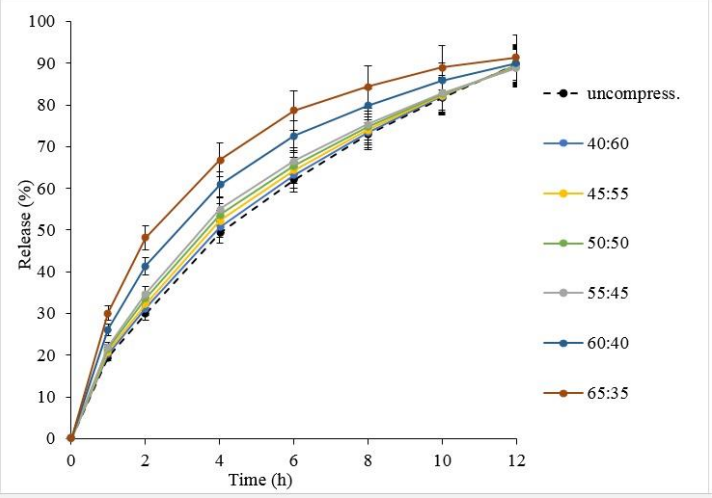

Figure 2. Dissolution profiles of tablet compositions and unpressed pellets

The ratio of active and auxiliary granules 55:45 (composition №4) is optimal because it does not lead to significant destruction of the matrix spheroids'surface and has virtually no effect on the dissolution profile of the multi-dose tablet. More reliable ratios (50:50, etc.) provide a similar result, but lead to a larger weight and size of the tablet. That is less rational from a technological and economic point of view.

Influence of Compression Force During Tabletting on the Release Profile

Composition №4 was used to study the effect of the compression force on the release profile of the isosorbide dinitrate from tablets. The tablet mass was compressed with forces from 2 to 15 kN. In addition to the dissolution kinetics, the abrasion strength of the obtained as multiple-unit tablets was investigated.

The test results and comparative data on the dissolution of the obtained tablet cores with the drug Cardiket Retard 40 mg are presented in the table 6 and on the figure 3.

Table 6. Comparative results of the dissolution of the tablet cores' composition №4 with different compression forces and the tablets Cardiket Retard 40 mg

Dissolution time, h	% released isosorbide dinitrate					
	Cardiket Retard 40 mg	Pressing force, kN				
		2	5	8	12	15
0	0	0	0	0	0	0
1	22.3 ± 2.0	22.1 ± 3.1	24.2 ± 3.8	26.3 ± 3.7	30.1 ± 3.2	32.9 ± 3.6
2	34.1 ± 2.7	34.7 ± 3.1	37.3 ± 3.4	40.0 ± 3.6	48.2 ± 3.3	54.2 ± 3.9
4	53.2 ± 2.6	55.0 ± 4.3	57.0 ± 4.4	59.1 ± 4.6	66.9 ± 4.2	69.0 ± 5.0
6	66.6 ± 3.2	66.5 ± 5.3	67.7 ± 5.3	68.8 ± 5.4	78.6 ± 5.5	77.9 ± 6.3
8	75.9 ± 3.6	75.4 ± 6.1	76.1 ± 5.9	76.9 ± 6.5	84.3 ± 6.2	82.4 ± 6.7
10	83.3 ± 4.1	82.8 ± 6.7	83.7 ± 6.6	84.6 ± 6.3	88.9 ± 6.8	86.2 ± 6.6
12	88.6 ± 4.7	88.8 ± 5.3	89.4 ± 6.1	90.0 ± 5.8	91.3 ± 5.4	87.9 ± 5.5
f_1	-	0.91	2.69	5.12	**15.17**	**16.01**
f_2	-	95.04	81.77	70.89	**49.88**	**46.66**
Abrasion, %		**>10**	**1.84**	0.59	0.15	0.12

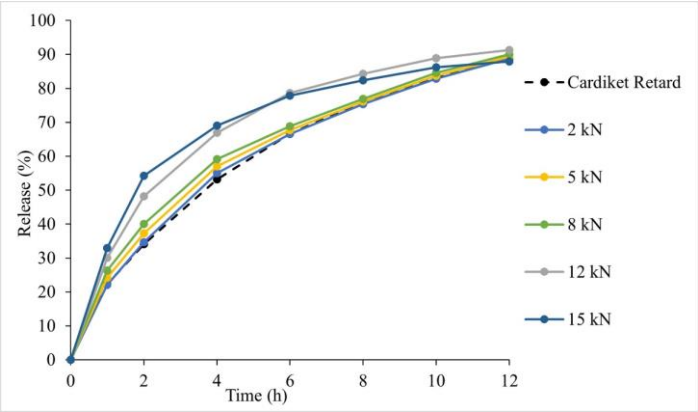

Figure 3. Comparison of the dissolution profiles' tablet cores and Cardiket Retard 40 mg

High-pressure tablet cores have satisfactory abrasion strength. But high pressure during tableting leads to partial destruction of the matrix granules' surface with the active pharmaceutical ingredient. The tablet cores' pressing with less effort prevents the destruction of the film coating, but the tablet cores have an unsatisfactory abrasion index. At a pressing force about 2 kN, the obtained tablets in the abrasion test were partially disintegrated into individual granules.

The selected composition of the protective granules under the found tableting conditions makes it possible to achieve the minimum effect of pressing on the dissolution profile of the pellets with the active component. This is ensured, on the one hand, by the acceptable cushioning properties of the auxiliary particles, and, on the other hand, by their disintegration characteristics. Rapid disintegration of the tablet into individual subunits results in dissolution similar to non-compressed pellets.

Of course, all the difficulties associated with compressing pellets could be circumvented by filling hard gelatin capsules. However, tablets are the preferred oral form because they are less expensive and less difficult to manufacture and are more acceptable to patients. A multi-dose tablet can be divided without compromising the release profile of the drug from the individual units. Such formulation features provide fewer side effects, improved bioavailability, and less variability in drug absorption.

The original prolonged preparation of isosorbide dinitrate Cardiket retard is a matrix tablet and, therefore, has all the usual disadvantages of monolithic dosage forms. Tablet release modification is achieved by hot melting of isosorbide dinitrate with a polymer and other functional excipients, which is a very specific and time-consuming technology.

Based on this, obtaining a multi-dose form of prolonged action is an urgent and promising task. The use of a combination of granules with different release kinetics provides a dissolution profile similar to the matrix tablet. At the same time, the multi-dose tablet technology provides a predictable release of the active ingredient and a consistent safety and efficacy profile of the antianginal drug.

The tablet composition obtained at a compression force about 8 kN has a satisfactory abrasion strength, and also provides the most similar release profile of the isosorbide dinitrate to the reference drug.

Summing up, a laboratory technology of the multi-dose isosorbide dinitrate tablet cores production has been developed. The optimal mass ratio of active pellets and auxiliary granules for tableting was established. The influence of the compression force of the tablet cores on the release profile of the active substance has been studied.

Invented technological conditions and parameters allow to obtain the required nature of the isosorbide dinitrate tablets dissolution, similar to the reference drug.

Generally, the approach of combining uncoated and coated spherical matrix granules makes it possible to ensure the controlled release of the active ingredient from the dosage form and to achieve its compliance with any target prototype.

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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