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Research Article

MICROSCOPIC STUDIES OF THE SHAPE AND SIZE OF PARTICLES OF SAMPLES OF AMLODIPINE BESYLATE SUBSTANCES FROM SELECTED PHARMACEUTICAL MANUFACTURERS

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ABSTRACT

Here are the results of the microscopic study of the shape and size of particles of 5 samples of amlodipine besylate substance of world manufacturers, registered and used in the pharmaceutical industry of Uzbekistan. Such characteristics as the size and shape of particles, as well as the crystalline state with the simultaneous photos have been evaluated. Factors of the shape of particles of the substance of the studied samples were calculated.

KEYWORDS

Amlodipine besylate substance, optical microscopy of particles, crystal forms, crystal size, shape factor.

INTRODUCTION

Leaders of the country pay special attention to the development of the pharmaceutical industry.

In conformity with the Decree of the President of the Republic of Uzbekistan from January, 28th, 2022 № DP 60 "About strategy of development of New

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Uzbekistan for 2022-2026", for the purpose of determination of priority directions of reforms, on the further improvement of the welfare of people, the transformation of branches of economy and accelerated development of business the State program "Year of interests of the person and development of mahalla" according to which till 2026 provides an increase in the volume of production of the pharmaceutical industry in three times is established. The same program provides for the organization of new production enterprises for the production of medicines used for the treatment of cardiovascular diseases [1, 2].

By the data WHO in the general structure of mortality by non-infectious diseases, cardiovascular diseases occupy the leading place, among which arterial hypertension has the greatest prevalence [3, 4, 5, 6, 7].

Modern medical practice nowadays has a fairly large range of hypotensive drugs used to correct high blood pressure.

One of the widely used is amlodipine besylate (hereinafter amlodipine), which is - (±)-2-[(2-amino-ethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5 - pyridine dicarboxylic acid 3-ethyl 5-methyl ester and by pharmacotherapeutic action belongs to the group - slow calcium channel blockers (SCBs) of II generation.

ATX code: C08CA01 (Amlodipine) [8, 9].

There are only 38 pharmaceutical manufacturers of amlodipine tablets registered in the Republic of Uzbekistan, including 5 domestic firms [9]. Domestic pharmaceutical manufacturers do not cover the required volume of demand for this drug and therefore amlodipine tablets are imported to the country in rather large quantities.

It is necessary to note that the composition and technology of amlodipine tablets approved for medical use significantly differ from each other and each of them is the intellectual property of manufacturing companies. Proceeding from the above stated, the development of improved technology of amlodipine tablets with the purpose of its further implementation on the basis of domestic pharmaceutical enterprises is of certain interest for further increase in production volumes.

Chemical substances are active components of drugs, by their chemical nature belong both to organic and inorganic substances and, accordingly, exhibit a variety of physical, chemical, structural, mechanical, and technological properties.

Therefore, the crystalline shape and size of the particles as well as their surface properties largely depend on the technological synthesis scheme, the raw materials used, individual production factors such as temperature, pressure, peculiarities of technological equipment, etc. Based on the above, the same active substances produced by different companies may differ from each other, and this, in turn, determines the corresponding structural and mechanical, and technological properties of the substance having a predictive value to determine the appropriate method of tableting, as well as the selection of appropriate excipients.

The results of a study of the shape and size of amlodipine particles are presented in this report.

The following manufacturers' samples of amlodipine substance, registered in the Republic of Uzbekistan, were subjected to study:

-Synerzys novaceuticals Pvt. Ltd., India;

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-Cadila Healthcare Ltd., India;

-Mylan Laboratories Ltd., India;

-Changzhou Ruiming Pharmaceutical, China;

-Rakshit Drugs Pvt. Ltd., India [9].

The experiments were carried out by the methods recommended in State Pharmacopoeia of the Republic of Uzbekistan, in particular, by optical microscopy (p.2.9.37) with simultaneous evaluation of such characteristics as particle size and shape, as well as the crystalline state with simultaneous photographing [10].

The microscopic studies of amlodipine substances were performed using a polarizing microscope "Bipolan"-USA and an electron microscope "BS-242E"-Czech Republic.

It is complicated to measure particle sizes, depending on the particle shape, and the number of particles under study should be sufficient to provide an acceptable level of uncertainty of the measured parameters. The most common measurement of particle sizes is the determination of particle length - the greatest distance between the edges of a particle oriented parallel to the ocular scale and particle width - the greatest distance between the edges of a particle oriented perpendicular to the ocular scale, held at right angles to the length [10].

There are more than twenty varieties of drug crystal forms described in various literature sources [11, 12, 13, 14]. GF RUz lists only 6 varieties of the most common crystal forms [10]. Depending on methods of synthesis, purification, crystallization, and subsequent processing, particle forms can be in the form of mono- or polycrystals.

Furthermore, depending on the surface properties, drug particles can form associations of crystals in the form of:

- lamellar - plates arranged on top of each other;

- aggregate - a mass of clumped particles;

- agglomerate - particles fused or bonded together;

- conglomerate - a mixture of two or more types of particles;

- spherolite - radially aggregated particles;

- druzas - particles covered by other tiny particles [10].

Microscopy photos of the particles of the studied amlodipine substance are shown in Figure 1.

Based on the data given, it follows that all the studied substances differ from each other in the shape and size of the particles.

he samples of amlodipine substance from Synerzys novaceuticals Pvt. Ltd., India (Fig.1-1.1) are axis diameter polycrystalline particles, predominantly bacilliform, with partial content of fragments of small lamellar particle shape. They tend to form aggregates, as a mass of cohesive particles.

Substance Cadila Herald, India (Fig.1-1.2) is a single scattered, with relatively similar size bacilliform crystals of anisodiametric shape.

The samples of amlodipine substance by Mylan Laboratories Ltd., India (Fig.1-1.3) consist of small stick-like - lamellar - scale-like polycrystals. They show a tendency to form conglomerates - associations of mixtures of two or more types of particles.

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The amlodipine produced by Changzhou Ruiming Pharmaceu-tical, China (Fig.1-1.4) presents single scattered, relatively small, amorphous, mostly round or torpedo-like particles, isodiametric in shape.

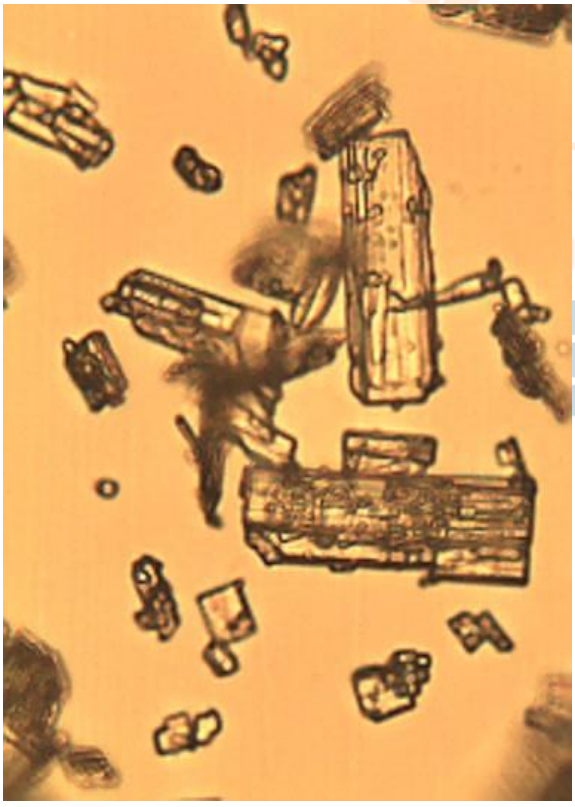
This is a mixture of mostly platelet-shaped polycrystalline forms of Amlodipine produced by Rakshit Drugs Pvt. Ltd, India (Fig.1-1.5) consists of a mixture of predominantly lamellar and stick-shaped forms of polycrystals with different particle sizes. They show a tendency to form lamellar, an association of crowded plates.

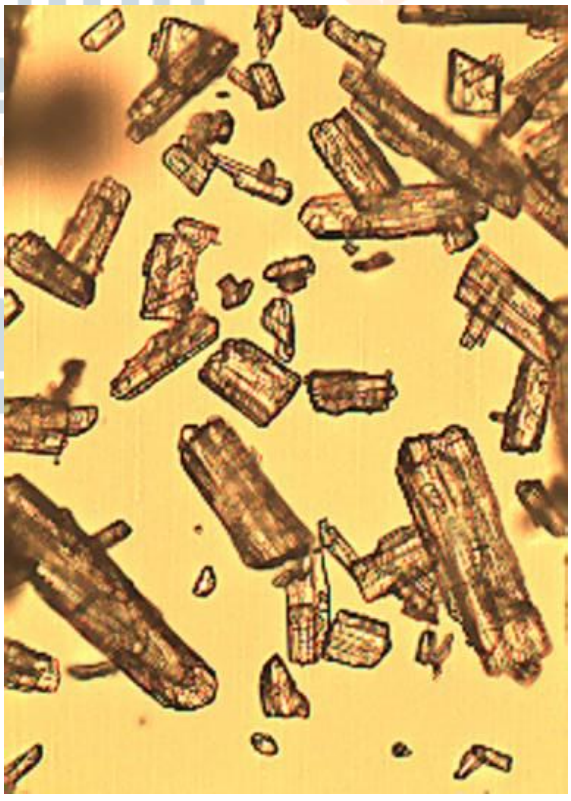
The results of the microscopic study of the shape and particle size of the studied samples of amlodipine substance from different manufacturers are presented in Table 1. It follows from the data given in table 1 that samples of amlodipine from Synerzys novaceuticals Pvt. Ltd., India, are represented by the largest values of particle size with an average crystal length of 276.17 ± 23.31 µm and width of 78.86 ± 6.18 µm. Approximately the same results are found in the study of amlodipine samples from Cadila Healthcare Ltd, India, where the average particle size is 227.46±21.48 µm and the average width is 54.05±6.11 µm.

The average particle size of amlodipine produced by Mylan Laboratories Ltd. in India is more than half the size of the above companies' samples.

Optical microscopy of particles of the substances under study

I.1. **I.2.**





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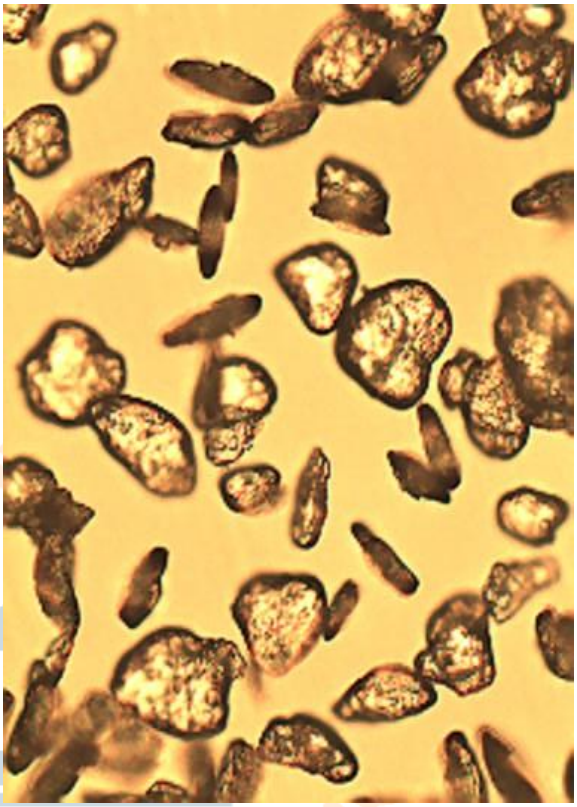
I.3.

I.4.



I.5.

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Figure 1 – Optical microscopy of

particles of amlodipine besylate substances produced by the company:

I.1. – Synerzys novaceuticals Pvt.Ltd., India.

I.2. – Cadila Healthcare Ltd., India.

I.3. – Mylan Laboratories Ltd., India.

I.4. – Changzhou Ruiming Pharmaceutical., China.

I.5. – Rakshit Drugs Pvt.Ltd., India.

At the same time, an average particle length of 115.47±12.23 µm and a width of 25.36±3.19 µm were noted. The crystal size of amlodipine substitution by Rakshit Drugs Pvt. Ltd., India has much smaller sizes with a mean length of 38.56±4.21 µm and a mean width of 15.52±1.28 µm.

From among those studied only, the samples of amlodipine substance of Changzhou Ruiming Pharmaceutical are presented as an amorphous powder and in this regard, they have close average particle length and width values of 131.12±11.59 µm and 116.31±10.92 µm, respectively.

According to the ratio of their length to width, the particles of substances are divided into isodiametric and anisodiametric forms. The indices of the shape factor have a determining value in attributing the belonging of medicinal substances to the above classifications, i.e., the closer the indices of the shape factor to one, the particles belong to isodiametric ones and vice versa, the higher the indices of the shape factor, the more they are characterized as anisodiametric.

Table 1

The results of microscopic study of the shape and size of the particles of the studied samples of amlodipine drug substances from different manufacturers

№ п/п	Name of manufacturer	Particle shape	Particle size, µm		Shape factor
			length	width	
I.1	Synerzys novaceuticals Pvt. Ltd., India	Anisodiametric polycrystals are predominantly rod-shaped with some fine lamellar particle fragments. They tend to form aggregates as a mass of cohesive particles.	276,17±23, 31	78,86±6,1 8	3,50

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I.2	**Cadila Healthcare Ltd., India**	Single scattered, relatively closely spaced bacilliform crystals of anisodiametric shape.	227,46±21,48	54,05±6,11	4,21
I.3	**Mylan Laboratories Ltd., India**	Small rod-shaped, lamellar-scalloped polycrystals. Tends to form conglomerates - mixtures of two or more types of particles	115,47±12,23	25,36±3,19	4,55
I.4	**Changzhou Ruiming Pharmaceutical, China**	Single scattered, relatively small, amorphous, predominantly round or torpedo-shaped particles, isodiametric in shape.	131,12±11,59	116,31±10,92	1,13
I.5	**Rakshit Drugs Pvt. Ltd., India ***	A mixture of predominantly lamellar and rod-shaped polycrystalline forms with varying particle sizes. Exhibits a tendency to form lamellars - an association of crowded plates	38,56±4,21	15,52±1,28	2,48

Note to Table 1: marked * appears for comparison from previously published work by the authors [15, 16].

The shape factor values, within certain ranges of total particle sizes, have predictive value for the evaluation of the technological properties of powders. With the same values of the average particle sizes, powders with isodiametric particle shapes have better indices of such technological properties as flowability, natural slope angle, bulk density, compatibility, and compatibility, while powders with high values of the shape factor have relatively negative indices of flowability, natural slope angle, bulk density, compatibility, and compatibility.

During the determination of particle size, the shape factor was calculated in parallel for each sample of amlodipine substance under study, which is the ratio of crystal length to width.

The following shape factors were established for the substance of Synerzys novaceuticals Pvt. Ltd., India - 3.50; Cadila Healthcare Ltd., India - 4.21; Mylan Laboratories Ltd., India - 4.55; Changzhou Ruiming Pharmaceutical, China - 1.13; Rakshit Drugs Pvt. Ltd., India - 2.48.

The above results of the microscopic examination of amlodipine substance samples will be the basis for predicting the use of appropriate complex excipients and carrying out special technological operations to obtain pressed masses with satisfactory technological properties allowing the proper act of tableting.

CONCLUSIONS

1. Studies on the study of crystalline characteristics with simultaneous photographing as well as the determination of the size and shape of particles of amlodipine besylate substance registered and used by domestic companies in the production of finished drugs in the Republic of Uzbekistan were carried out.

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2. The results of the study by optical microscopy showed that the samples of substance from Synerzys novaceuticals Pvt, Mylan Laboratories Ltd., and Rakshit Drugs Pvt. Ltd., are represented by anisodiametric polycrystals consisting mainly of bacilliform and lamellar forms of crystals prone to the formation of aggregates, conglomerates and lamellar.

3. Microscopic studies have shown that the amlodipine substances of Cadila Heavy Care Ltd, India, consist of single scattered, identical, stick-like crystals of anisodiametric shape with different sizes, which do not exhibit a tendency to aggregation.

4. A sample of Changzhou Ruiming Pharmaceutical amlodipine substance was found to consist of amorphous, with close average values of particle length and width of 131.12±11.59 μm and 116.31±10.92 μm respectively, with a shape factor of 1.13.

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