THE EFFECT OF TABLET GEOMETRY ON TRAMADOL HYDROCHLORIDE RELEASE FROM MATRIX SYSTEMS

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The objective of this study was to explore the effect of geometry and tablet design on release pattern of tramadol hydrochloride as a model of freely soluble drug from matrix systems. Hydrophilic and hydrophobic matrices were prepared by direct compression method using HPMC with two different molecular weight and Kollidon® SR as a release-retarding agent respectively at drug: polymer ratio (1:5) for each excipient, in distinct strengths and geometries (i.e. shape, size and dimensions) at parallel and differing surface area to volume ratios. It was found that tramadol release from manufactured tablets is similar when the surface area to volume ratio is equal, regardless of the type of matrix former, drug strength, tablet design. Per contra, the tablet with smaller surface area to volume values had the slower release rate among the same shape. Thus, tablet geometry supplies additional versatility for these systems, making formulators to achieve the desired release characteristics for their drug of option.

KEYWORDS: Matrix systems, Tablet geometry, Surface area to volume ratio, Tramadol hydrochloride

INTRODUCTION

Matrix systems consist of a release-retarding polymer (hydrophilic or hydrophobic) through which the drug is homogenously embedded or dispersed¹κ². The market of the matrix devices is broadening readily over the last 40 years and emerging as a major technology platform for the oral controlled delivery of drugs, and there is perception to continue in the future³. The causes among these; simplicity of formulation, and relatively low cost of manufacturing⁴. In the publications, considerable variables have been described to affect drug release profiles from matrix tablets. From which, physicochemical properties of the drug, polymer type and content, inclusion other excipients in the formulation, porosity and dosage form geometry¹⁴. Generally, the importance of tablet design with multiple shapes comes in several aspects, including; swallowability and esophageal transit, so on patients' acceptance and adherence, which are besides the factors mentioned above related to the visual appearance of the dosage form⁵κ⁶. Therefore, more complex shapes (elongated tablets i.e. oval and caplet) are designed to aid in ease of dealing and swallowing⁵κ⁷. The success of the tablets coating and scoring/splitting process also directly depends on geometry and dimensions of the system⁸κ⁹. Moreover, it was noticed that the changing tablet shape related to the mechanical properties too⁵κ¹⁰. In addition, lamination and capping can be minimized by modifying system geometry¹¹. The size of the tablet perhaps orders the polymer content need in the extended release dosage forms. If mini matrix tablets are required, the level of the matrix-forming agent should be raised¹²κ¹³. However, tablets may vary greatly in volume

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and weight relying on the intended dose, and manner of the drug delivery.8

But first of all how drug release has been influenced by the geometric shape and dimensions of the tablet has permanently drawn attention of the formulators.16&17. It seems that the geometry of the matrix has a considerable effect regarding the onset of the action in oral administration of some therapeutic systems. However, references indicate that to produce longer release duration, the best shape of a tablet is spherical. As well, it is valuable to mention that the geometry not only affects in vitro drug release, but also the in vivo gastro-residence time (GRT). Geometric features can be applied to modify the site of drug liberation, for example; pellets, floating systems and “release modules assemblage”. Moreover, abundant devices and inventions have been established in order to attain a broad spectrum of drug release patterns by particular geometries and surface area configurations. Additionally, we should point the butterfly geometry with swellable matrices, which is formed due to contribution of the particle size of HPMC, compression force and solubility of used excipients.

In fact, matrix geometry term covers the shape and size of the system, i.e. tablet surface area to volume ratio (SA/V). Once the Lapidus and Lordi model arisen (Equation 1), the effect of the initial SA/V ratio has been widely investigated on drug release rate from any matrix tablet subjecting diffusion by many researchers.

\[ M_t/M_0 = 2(\frac{SA}{V})(D_{eff} t/\pi)^{1/2} \quad \text{(Eq. 1)} \]

where \( M_t \) is the amount of drug released at time \( t \), \( M_0 \) is the drug dose in the dry matrix, \( SA \) is the matrix tablet surface area, \( V \) is the matrix tablet volume, and \( D_{eff} \) is the effective drug diffusion coefficient in the matrix. When designing a new generic drug, it should guide pharmaceutical scientists to initiate the drug release profile of brand formulations to increase the probability of bioequivalence between the test and brand formulas. US FDA and numerous formulators indicated that the similar drug release mechanisms can be achieved by the identical SA/V ratio of studied matrix tablets. Where many literatures have indicated that the best parameter in representing tablets geometry is the SA/V ratio as this value is valid regardless of the shape of the used matrix. Thus, the actual advantage of this is to minimize the volume and costs of the work involved in improving a novel extended release dosage form without modifying the type and level utilized materials.

Tramadol HCl is a synthetic 4-phenylpiperidine analog of codeine and a dual-action opioid centrally analgesic. WHO has categorized it as a step 2 in management of mild to moderate chronic pain. The half-lives of the oral conventional dosage forms are about of 5-6 hrs, and it is regarded as a freely water-soluble drug according to USP and EP. Therefore, it was used as a model drug in this research to achieve dominantly diffusion-controlled matrix tablets. Consequently, the purpose of this paper is to in vitro evaluate the effect of different matrix tablet geometries, doses and weights on tramadol HCl release from the prepared tablets using two types of matrix former; hydrophilic (HPMC K4M & HPMC K100M) and plastic (Kollidon® SR) with constant and different SA/V ratios. However, considering that round and caplet shapes are the most common in the pharmaceutical industry, they will be used in this study.

MATERIAL AND METHODS

Materials

Tramadol HCl (99% purity) was supplied from Sigma-Aldrich (Germany), Kollidon® SR was kindly donated from BASF (Germany), Methocel® K4M and K100M premium CR were gifted from City Pharma and Universal pharmaceutical industries respectively, Comprecel® M102 was supplied by MINTAI Chemical Co. LTD. (Taiwan), Aerosil® 200 was provided from Degussa AG (Germany), magnesium stearate and hydrochloric acid (37%) were purchased from Merck Chemicals Co. (Germany). All the other chemicals used were of analytical grade.

Methods

Formulation and Preparation of Matrix Tablets

Table 1 summarizes composition of the matrix tablets of tramadol HCl, that prepared with several geometries and weights. Drug to matrix-forming agent ratio was (1:5) in all formulations (T1-T5) regardless the type of the used polymer for release controlling.
Table 1: characteristics of tramadol hydrochloride matrix tablets at drug: polymer ratio (1:5).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Polymer Type</th>
<th>Geometric Shape</th>
<th>Dimensions (mm)</th>
<th>Weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>HPMC K4M</td>
<td>Caplet</td>
<td>12 X 6</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biconvex Round</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scored-Round</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>HPMC K100M</td>
<td>Caplet</td>
<td>12 X 6</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biconvex Round</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scored-Round</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Kollidon SR</td>
<td>Caplet</td>
<td>12 X 6</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biconvex Round</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scored-Round</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>HPMC K100M+</td>
<td>Large Biconvex Round</td>
<td>13</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>Comprcel® M102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small Biconvex Round</td>
<td>8</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small Biconvex Round</td>
<td>8</td>
<td>200</td>
</tr>
<tr>
<td>T5</td>
<td>Kollidon SR+</td>
<td>Large Biconvex Round</td>
<td>13</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>Comprcel® M102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small Biconvex Round</td>
<td>8</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small Biconvex Round</td>
<td>8</td>
<td>200</td>
</tr>
</tbody>
</table>

Direct compression method was used in the production of the matrices. All components were screened through an appropriate sieve and blended uniformly, then lubricated with Aerosil 200 and magnesium stearate (1%) and again mixed manually for further some minutes before the compression. The blend was compressed using an alternative tablet machine (Tablet Press EP-1, ERWEKA GmbH, Germany) fitted with single punch eccentric to manufacture odd shaped matrices with various dimensions (Table 1). The press speed was adjusted to provide tablets with hardness between 20 and 40 kPa.

Constant SA/V ratios were carried out on different shapes, strengths, weights and diameters of the same formulations (T1-T3) as noted from the Table 1 to study the influence of these variables on tramadol release. Meanwhile, to examine the effect of tablet thickness on release rate for particular geometric shape (biconvex round), the formulas (T4 & T5) were manufactured with inconstant SA/V ratios by changing the tablet weight, this was achieved for each polymer. However, Comprcel® M102 has been used to reach a specific weight in the later formulas (i.e. T4 & T5). Later, the tablets were estimated for physical and mechanical properties, including weight uniformity, content uniformity, hardness and friability tests.

Evaluation of Matrix Tablets
Appearance and Dimensions measurement
The uniformity of shape, color, and size of manufactured tablets was verified visually, and were checked for dirty marks, abrasion erosion, cracks and splits, or any other adulteration.

The dimensions of 10 tablets of each formula were measured prior the dissolution studies using Gilbert digital electronic caliper. Surface area (SA), volume (V) and SA/V ratio were calculated based on these dimensions employing SolidWorks™ software 2016 SP 2.0 (Dassault Systems 3DS, France).

In-vitro drug release studies
Erweka DT 600 (Germany) was used to carry out this test according to USP 40. Dissolution test conditions; Apparatus 1 (Basket method), at 75 rpm, $\lambda_{max} = 271$ nm, 37 ± 0.5 °C in medium of 0.1N hydrochloric acid; 900 ml over a period of 16 hrs. Aliquots (10 ml) for the drug were withdrawn with a syringe, filtered through 0.45µ filters, and assayed at predetermined time intervals (2, 4, 8, 10, 16) hr using Jasco V-530 UV/VIS spectrophotometer (Japan), and the resultant
loss in volume was replaced with the same volume of fresh dissolution medium, to maintain the Sink conditions. Six tablets of each formulation were examined, and the results were expressed as the cumulative percentage of the released drug as a function of time.

Statistical analysis
All the numerical results were expressed as mean values ± standard deviation (SD) using Microsoft Excel 2016 software. IBM® SPSS® Statistics 20 software was also used to compare the means of drug release during 16 hrs by applying one-way ANOVA and Independent-samples Student’s t tests. Significance was accepted at p < 0.05.

RESULTS AND DISCUSSION
Appearance and Dimensions Measurements
The results of visual inspection showed that there is identity in the geometry of the prepared tablets, without any breaks, gaps or pinholes on the external surface. However, findings of dimensions of formulated hydrophilic and inert matrices view in the Tables (2-4). Three-dimensional (3D) structures of prepared matrix tablets, that were produced by SolidWorks™ CAD software with different geometries illustrate in Figure 1. The diversity in thickness of the resulting tablets comparatively between the polymers applied can be explained by the compressibility of the matrix forming excipient on one hand, and its physical characteristics such as density on the other hand.

Physical Properties
All manufactured tablets were pharmacopeially accepted in terms of weight and content uniformity tests.

Average values of hardness test ranged between 20 and 40 ± 0.6 kPa approximately. There are no pharmacopoeial parameters for this test results, but hardness sometimes has a noticeable role in extended release dosage forms. Accordingly, the prolonged release tablets should present a definite mechanical strength to prohibit the undesired burst effect resulted from gastrointestinal movement.

Thus, the harder the matrix tablet is, the lower drug release at times is achieved. However, this may not be applied on some systems such as Hypromellose and Kollidon® SR matrices. This could be suggested to interpret the results of Kollidon® SR tablets with high hardness values (45 kPa approximately) which did not achieve a prolongation of tramadol HCl release.

Friability test results indicate that all formulations were acceptable as being have weight loss < 1% according to EP. So, the formulas have good mechanical attributes.

Different Shape and Constant SA/V Ratio
Figure 2 shows tramadol HCl release profiles vs. time from each tablet geometric shape for HPMC K-4M, HPMC K100M and Kollidon® SR matrices at drug: polymer ratio (1:5). As the drug release rates were regarded identical, pointing that altering matrix tablet geometric shape did not significantly affect the release profile in the case of comparable SA/V ratios (p > 0.05). Thus, the release process is not dependent on the shape of the tablets but only follows the initial SA/V ratio of these tablets. This finding complies with other previous studies, which can be attributed to the similar diffusion pathways in the tablets having similar SA/V ratios, according to Lapidus and Lordi's model.
Fig. 2: Tramadol hydrochloride release from T1-T3 formulations at drug: polymer ratio (1:5) with constant SA/V values and different shapes.

Table 2: physical parameters of matrices at tramadol: polymer ratio (1:5) with similar SA/V values for each matrix former.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Geometric Shape</th>
<th>Thickness (mm)</th>
<th>Surface Area (mm$^2$)</th>
<th>Volume (mm$^3$)</th>
<th>Surface Area to Volume ratio (mm$^2$/mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Caplet</td>
<td>5.24 ± 0.01</td>
<td>245.86 ± 0.08</td>
<td>295.14 ± 0.04</td>
<td>0.833 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>Biconvex Round</td>
<td>5.95 ± 0.05</td>
<td>219.85 ± 0.05</td>
<td>265.41 ± 0.04</td>
<td>0.828 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Scored- Round</td>
<td>4.98 ± 0.05</td>
<td>240.08 ± 0.1</td>
<td>284.19 ± 0.06</td>
<td>0.844 ± 0.03</td>
</tr>
<tr>
<td>T2</td>
<td>Caplet</td>
<td>4.67 ± 0.02</td>
<td>224.26 ± 0.11</td>
<td>250.15 ± 0.10</td>
<td>0.896 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>Biconvex Round</td>
<td>5.81 ± 0.03</td>
<td>217.34 ± 0.01</td>
<td>260.38 ± 0.02</td>
<td>0.834 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>Scored- Round</td>
<td>4.91 ± 0.03</td>
<td>237.1 ± 0.04</td>
<td>277 ± 0.07</td>
<td>0.855 ± 0.02</td>
</tr>
<tr>
<td>T3</td>
<td>Caplet</td>
<td>5.67 ± 0.04</td>
<td>258.2 ± 0.09</td>
<td>320.85 ± 0.06</td>
<td>0.804 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>Biconvex Round</td>
<td>6.26 ± 0.03</td>
<td>229.31 ± 0.04</td>
<td>285.51 ± 0.05</td>
<td>0.805 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Scored- Round</td>
<td>5.35 ± 0.06</td>
<td>249.03 ± 0.05</td>
<td>305.77 ± 0.04</td>
<td>0.812 ± 0.05</td>
</tr>
</tbody>
</table>

However, it should be noted that Kollidon$^\text{®}$ SR matrix tablets at drug: polymer ratio (1:5) had entirely released the drug within the first 2 hr of the test regardless of shape of the tablet, although the literatures indicated that less ratio is sufficient to control drug release$^{33,35}$. This may be due to the high water solubility of tramadol HCl, which affects the porous structure of the matrix system. Dimensions of tablets with the same SA/V ratio, weight and formula are shown in the Table 2.
Different Strength and Constant SA/V Ratio

Dissolution studies analysis emphasize that geometry performs a remarkable part in determine drug release profiles, (Fig. 3). The results showed that the tablets which possess approximate SA/V values and unequal strength, weight and geometry (i.e. the shape and dimensions) have relatively the same drug release patterns too (p > 0.05) for T4 and T5 formulations separately. On the other hand, although of the statistically significant differences between T4 and T5 formulas for the same size (p< 0.05) but not important as the later formulations have inconstant composition. Dimensions of tablets are shown in the Table 3.

There are various approaches to maintenance matrix SA/V ratio steady to achieve a parallel release rate using tooling shapes or diverse doses\textsuperscript{18,23&24}. This concept was first elucidated by researcher Reynolds (2002)\textsuperscript{25}, and they could be extremely helpful to developers wanting to manufacture further size and strength tablets of a present product or for modification tablet shape to identity multiple tablet strengths.

![Fig. 3: Tramadol hydrochloride release from T4 and T5 formulations at drug: polymer ratio (1:5) with constant SA/V value and shape and different strength and size.](image)

![Table 3: comparison of physical parameters of formulations (T4 & T5) at tramadol: polymer ratio (1:5) with similar SA/V values and different strength and geometry](table)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Geometric Shape</th>
<th>Thickness (mm)</th>
<th>Weight (mg)</th>
<th>Drug strength (mg)</th>
<th>Surface area (mm(^2))</th>
<th>Surface area to volume ratio (mm(^2)/mm(^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>Large Biconvex Round</td>
<td>4.47 ± 0.02</td>
<td>600 ± 0.07</td>
<td>50 ± 0.01</td>
<td>359.48 ± 0.04</td>
<td>0.803 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Small Biconvex Round</td>
<td>5.86 ± 0.02</td>
<td>300 ± 0.04</td>
<td>25 ± 0.02</td>
<td>217.34 ± 0.02</td>
<td>0.834 ± 0.07</td>
</tr>
<tr>
<td>T5</td>
<td>Large Biconvex Round</td>
<td>4.51 ± 0.01</td>
<td>600 ± 0.08</td>
<td>50 ± 0.04</td>
<td>363.32 ± 0.1</td>
<td>0.808 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>Small Biconvex Round</td>
<td>6.18 ± 0.03</td>
<td>300 ± 0.05</td>
<td>25 ± 0.02</td>
<td>227.61 ± 0.04</td>
<td>0.810 ± 0.08</td>
</tr>
</tbody>
</table>
Constant Shape and Different SA/V Ratio

There are two geometric parameters that can be altered for the design of round matrix tablets, the primary diameter and thickness of the system\textsuperscript{17}. Hydrophilic or plastic prepared matrices with the same diameter (biconvex round, 8 mm) and drug: polymer ratio. However, the tablet weight was raised by increasing the height from 4.06 to 5.86 mm and from 4.57 to 6.18 mm, for HPMC K100M and Kollidon\textsuperscript{®} SR matrix tablets respectively. These resulted in decreasing SA/V ratios, Table 4.

As seen in Figure 4, the release rates of drug significantly declined with reducing SA/V ratios of the tablets (p < 0.05). According to Lapidus and Lordi’s equation, it was found that longer diffusion ways could be noticed in larger tablets, as more relative surface area is available for release, taking into consideration that tramadol HCl is a highly water soluble drug\textsuperscript{15}. As mentioned previously, given that the formulas T4 and T5 have a different composition, there will be statistical differences between them for the same weight and shape (p< 0.05).

On the other hand, complete tramadol release (i.e. more than 90\%) during 8 hrs of the experiment was observed in tablets with weight 200 mg. Whilst in the case of larger weight for each studied polymer, drug release forwarded till 16 hrs of examination.

Table 4: comparison of physical parameters of formulations (T4 & T5) at tramadol: polymer ratio (1:5) with different SA/V values and similar geometric shape.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Geometric shape</th>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Surface area (mm\textsuperscript{2})</th>
<th>Surface area to volume ratio (mm\textsuperscript{2}/mm\textsuperscript{3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>Biconvex-round</td>
<td>300 ± 0.02</td>
<td>5.86 ± 0.02</td>
<td>217.34 ± 0.02</td>
<td>0.834 ± 0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 ± 0.01</td>
<td>4.06 ± 0.06</td>
<td>176.54 ± 0.01</td>
<td>0.997 ± 0.05</td>
</tr>
<tr>
<td>T5</td>
<td>Biconvex-round</td>
<td>300 ± 0.01</td>
<td>6.18 ± 0.03</td>
<td>227.61 ± 0.04</td>
<td>0.810 ± 0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 ± 0.04</td>
<td>4.57 ± 0.05</td>
<td>184.67 ± 0.08</td>
<td>0.946 ± 0.02</td>
</tr>
</tbody>
</table>

Fig. 4: Tramadol hydrochloride release from T4 and T5 formulations at drug: polymer ratio (1:5) with varying SA/V values and constant geometric shape.
CONCLUSION

Matrix geometry has an important role to be taken into account regarding pharmaceutical industry, neglected type of matrix former used to extend drug release. Thus, Optimal drug release pattern can be accomplished wanting extra adjustment of a formulation through selecting proper SA/V ratio for a matrix tablets, where this value perhaps utilized to layout tablets in various sizes, shapes, doses, and identical release profiles at the same time. So that, it may guide at times to answer our question regarding the unlike release rates of sustained release tablets having size and composition oneself, and prepared under the same manufacturing circumstances.

Acknowledgments

The authors wish to thank the Faculty of Pharmacy at ASPU University, and Aleppo University for their remarkable assistance. Thanks so much to the Universal (Damascus, Syria) and City Pharma (Aleppo, Syria) for Pharmaceutical Industries for gifting us some excipients.

REFERENCES

5- U. S. Department of Health and Human Services, FDA, CDER, Size, shape, and other physical attributes of generic tablets and capsules guidance for industry, Fed Regist, 80, (2015).
15- S. Missaghi, P. Patel, S. B. Tiwari, T. B. Farrell and A. R. R. Shiahboomi, "Investigation of the influence of tablet shape, geometry and film coating on drug release from hypromellose extended-
تأثير هندسية المضغوططة على تحرر الترامادول هيدروكلوريد من أنظمة القالب

هادي شموت 1 - وسام عبد الواحد 2 - وهاد ابراهيم 3

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2 قسم الصيدلانيات و التكنولوجيا الصيدلية، كلية الصيدلية، جامعة حلب، حلب، سوريا

كان الهدف من هذا البحث هو دراسة تأثير هندسية وتصميم المضغوطات على تلقيح الترامادول هيدروكلوريد كنموذج دواء من خلال تشكيله في الماء من نظام القالب. تم تحضير المضغوطات قابلة للصدأ فارغة وكارهة للإكسسوارات باستخدام هيدروكلوريت ميتيسل سيليولوز كعامل مؤخر للتحرير على الترتيب بنسبة دواء: بوليمر Kollidon® SR بوزنين جزيئيين مختلفين و W زن ور بوزنين جزيئيين مختلفين ومتوسط ونسبة مساواة ونسبة مساواة 1:5 من أجل كل سياق، وبعيرات وتنسقية (شكل، حجم وأبعاد) متنوعة ونسبة مساواة ضحلة إلى حجم متناوب ومتباينة.

لقد وجد بأن تحرر الترامادول هيدروكلوريد من المضغوطات المحضرة يكون مختلفاً عندما تكون نسبة مساواة السطح إلى الحجم متساوية. عرض النظر على نوع العامل المشكل للقالب، عيار المادة الدواوية، تصميم المضغوط وعصابتها. بالمقارنة، أدت المضغوطات التي تمت نسبة مساواة سطح إلى حجم صغيرة معدلات تحرر أبطأ من أجل نفس الشكل الهندسي. بالنتيجة توجد هندسية المضغوطات تتنوعاً إضافياً لأنظمة القالب، مما يمكن علماء الصياح من تحقيق خصائص التحرر المرغوبة لمستخدمهم.

الفعالة المختارة.