

Geometry in Pharmaceutical Systems

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Abstract

The aim of the paper is to brief out geometry in pharmaceutical systems, i.e., influence of tablet surface area/volume (SA/Vol) on drug release from controlled-release matrix tablets containing hydroxyl propyl methyl cellulose (HPMC) and describes a situation where the erosion rates of the tablet are different in the radial and axial directions, 3D printing technologies available for the manufacture of modern medicines and so on.

Keywords: 3D-printing, tablets, drug, geometry.

AMS subject Classification (2010):53C60

Kim C [1] proposes simple uncoated compressed tablets with a central hole (donut-shape) to provide a constant drug release over a long period of time (> 20 hrs) and he investigates the effect of hole size and drug solubility on the release kinetics. Here, the donut-shaped polyethylene oxide (PEO, $M_w = 4 \times 10^6$) tablets (600 mg and 12 mm diameter) are bored with a drill bit (3/32", 7/64", 1/8", and 5/32"). The release of theophylline from the donut-shaped tablets is zero order (80-90% release) before rapidly decreasing. As the hole size is increased from 7/64" to 5/32", the release rate increases and the release time is shortened. However, the release of theophylline from the donut-shaped tablet with a hole size of 3/32" follows the same anomalous release profile from a tablet without a hole. As drug solubility increases, the duration of linear drug release is shortened to 65-70% release followed by a severe tailing at the later stage of the release. Finally, he concludes that Donut-shaped PEO tablets with a hole provide zero-order release kinetics because the effect of the releasing surface area on the release kinetics is reduced.

To achieve parabolic and linear drug release profiles, CDST (Coated donut-shaped tablets) were designed. When rapidly erodible polymers (HPMC E3, HPC, PEG8000, PEOs ($M_w=100000$ and 200000)) were used, the release profiles of diltiazem HCl from the tablets becomes parabolic whereas zero-order release was achieved by using slowly erodible polymers (HPMC E5, HPMC E15, PEO ($M_w=300000$)). Drug release from the rapidly erodible polymers was governed by the pure erosion of the polymer while both polymer erosion and drug diffusion controlled drug release from the slowly erodible polymers. As drug loading was increased from 10% to 39% w/w, the drug release rate from CDST based on HPMC E3 became faster and parabolic whereas that from CDST based on HPMC E5 was linear. The slowly erodible polymer (HPMC E5) provided parabolic release profiles when drug loading was greater than 49% w/w. In this case, drug release mechanisms likely shifted from a combination of polymer erosion and drug diffusion to pure polymer erosion due to the enhancement of polymer erosion by faster influx of water. As drug solubility decreased from 61.6% w/v (diltiazem HCl), 1.0% w/v

(theophylline), to 0.5% w/v (nicardipine HCl), the drug release rate from CDST based on HPMC E3 decreased due to polymer erosion mechanism but there was little difference in release rate from CDST based on HPMC E5 due to the greater contribution of drug diffusion to drug release kinetics along with polymer erosion. As expected, the drug release rate of diltiazem HCl from HPMC E3 and E5 was significantly influenced by stirring rate and hole size [2].

In 2000, the authors Karasulu HY, Ertan G, Köse T, in their study reveal statistically how various geometrical shapes such as triangle, cylinder, half-sphere affect the release rate of the active substance called theophylline in erodible hydrogel matrix tablets. They have tried to indicate these changes in the release rate of theophylline by supporting our aim with the mathematical equations developed by Hopfenberg and Katzhendler et al. The model developed by Hopfenberg assumes that drug release occurs from the primary surface area of the device but Katzhendler et al. (I. Katzhendler, A. Hoffman, A. Goldberger, M. Friedman, Modelling of drug release from erodible tablets, *J. Pharm. Sci.* 86 (1997) 110-115), described a situation where the erosion rates of the tablet are different in the radial and axial directions. Hydrogel matrix tablets were prepared with hydroxyl propylmethylcellulose (HPMC E(50)) possessing different geometrical shapes as triangular, cylindrical and half-spherical using experimental design. When the dissolution results have been evaluated, it has been observed theophylline release from different geometrical erodible tablets fitted with that of the Katzhendler et al., equation. The equation which was suggested for cylindrical tablets was also used to interpret half-spherical and triangular tablets. According to the above stated equation, n has been determined as 4 for triangular tablets and 1.5 for half-spherical tablets and they have also suggested that, these n values could be used in the kinetic programs [3].

Karasulu HY, Ertan G. in their study “Different geometric shaped hydrogel theophylline tablets: statistical approach for estimating drug release [4] discusses how to develop a mathematical equation for the calculation of drug release from different shaped matrix tablets and by this way how to predict release rate related to the geometric shape with the help of the developed mathematical equation and explains how to estimate drug release before the dissolution. For this purpose, they used Hydroxy propyl methyl cellulose (HPMC) E50 as polymer and theophylline as active substance in the matrix tablets prepared for this purpose. Matrix tablets in three different geometrical shapes, namely in triangular, cylindrical and half-spherical forms were prepared by using two different drug-polymer ratio (1:0.5, 1:1) and diluent's in three different percentages (0, 20, 40%). Using rotating paddle and basket methods reported in USP XXIII carried out the release rate studies of these tablets. The Higuchi square-root time model best described the dissolution data. Differential scanning calorimetry (DSC) analysis was performed to identify any solid-state inactivation of the drug. The practical benefit of this work is to improve mathematical equation that can be used to predict accurately the required composition and in order to achieve the desired release profiles of different geometric shaped tablets and by using this equation new pharmaceutical products can be easily improved.

Reynolds TD, Mitchell S, Balwinski KM [5] investigate the influence of tablet surface area/volume (SA/Vol) on drug release from controlled-release matrix tablets containing hydroxyl propyl methyl cellulose (HPMC). They utilized Soluble drugs (promethazine HCl, diphenhydramine HCl, and propranolol HCl) in their study to give predominantly diffusion-controlled release. Drug release from HPMC matrix tablets with similar values of SA/Vol was comparable within the same tablet shape (i.e., flat-faced round tablets) and among different shapes (i.e., oval, round concave, flat-faced beveled-edge, and flat-faced round tablets). Tablets having the same surface area but different SA/Vol values did not result in similar drug release; tablets with larger SA/Vol values had faster release profiles. Utility of SA/Vol to affect drug release was demonstrated by changing drug doses, and altering tablet shape to adjust SA/Vol. When SA/Vol was held constant, similar release profiles were obtained with f_2 metric values greater than 70. Thus, surface area/volume is one of the key variables in controlling drug release from HPMC matrix tablets [5].

Krzysztof Tytkowski[6] presents the presence of Geometry in medicine in various aspects for many years. He says information on geometrical form of particular anatomic structures should not be underestimated since it is both basic and key information in many clinical cases, beginning from fractures to radiotherapy. Technical apparatuses and devices used in doctors' practice also require comprehension of technical documentation in necessary range. The knowledge of some geometrical issues can help in doctors' work although it is necessary to a certain group of doctors.

The nature of surface irregularity affects many phenomena including adsorption/desorption, catalysis, crystal growth, drug dissolution and chromatography. Many excellent models have been developed with the oversimplified assumption that all particles are smooth spheres; fractal geometry allows these models to be expanded to irregular surfaces by providing a quantitative means of assessing surface roughness. An overview of fractal analysis is presented in the following, and the state of the art, as far as pharmaceutical systems are concerned are outlined. Erroneous approaches, as well as the directions pharmaceutical research and technology might take in the area of fractal analysis are suggested. From a historical perspective, micromeritics (the science of particle size, shape and surface area) were first developed with the assumptions that all particles were smooth spheres. Much excellent work has been developed with such an oversimplified model. For example, numerous workers have shown that particle flow through an orifice is a function of "particle diameter", and experiments have most often been carried out on particles as close to spherical as possible, and as monodisperse as possible. The science of micromeritics, the science of small particles, is the making of Dalla Valle (1943) who coined the term in a book of the same name which describes methods of particle size measurement, mostly used by soil scientists [7].

Kovanya Moodley, Viness Pillay, Yahya E Choonara, Lisa C du Toit, Valence M K Ndesendo, Pradeep Kumar, Shivaan Cooppan, Priya Bawa[8] have focused on controlled drug delivery having an advantage over conventional methods. Adequate controlled plasma drug levels, reduced side effects as well as improved patient compliance are some of the benefits that these systems may offer. Controlled delivery systems that can provide zero-order drug delivery have the potential for maximizing efficacy while minimizing dose frequency and toxicity. Thus, zero-order drug release is ideal in a large area of drug delivery which has therefore led to the development of various technologies with such drug release patterns. To perform this function, they have created systems such as multilayered tablets and other geometrically altered devices. One of the principles of multilayered tablets involves creating a constant surface area for release. Polymeric materials play an important role in the functioning of these systems.

Goyanes A, Martinez PR, Buanz A, Basit A, Gaisford S. [9] explore the feasibility of combining hot melt extrusion (HME) with 3D printing (3DP) technology, with a view to producing different shaped tablets which would be otherwise difficult to produce using traditional methods. A filament extruder was used to obtain approx. 4% paracetamol loaded filaments of polyvinyl alcohol with characteristics suitable for use in fused-deposition modelling 3DP. Five different tablet geometries were successfully 3D-printed—cube, pyramid, cylinder, sphere and torus. The printing process did not affect the stability of the drug. Drug release from the tablets was not dependent on the surface area but instead on surface area to volume ratio, indicating the influence that geometrical shape has on drug release. An erosion-mediated process controlled drug release. Their work demonstrated the potential of 3DP to manufacture tablet shapes of different geometries, many of which would be challenging to manufacture by powder compaction.

Selective laser sintering (SLS) 3-dimensional printing is currently used for industrial manufacturing of plastic, metallic and ceramic objects. To date there have been no reports on the use of SLS to fabricate oral drug loaded products; therefore, the aim of this work was to explore the suitability of SLS printing for manufacturing medicines. Two thermoplastic pharmaceutical grade polymers, Kollicoat IR (75% polyvinyl alcohol and 25% polyethylene glycol copolymer) and Eudragit L100-55 (50% methacrylic acid and 50% ethyl acrylate copolymer), with immediate and modified release characteristics respectively, were selected to investigate the versatility of a SLS printer. Each polymer was investigated with three different drug loadings of paracetamol (acetaminophen) (5, 20 and 35%). To aid the sintering process, 3% Candurin® gold sheen was

added to each of the powdered formulations. In total, six solid formulations were successfully printed; the printlets (3D printed tablets) were robust, and no evidence of drug degradation was observed. In biorelevant bicarbonate dissolution media, the Kollicoat formulations showed pH-independent release characteristics, with the release rate dependent on the drug content. In the case of the Eudragit formulations, these showed pH-dependent, modified-release profiles independent of drug loading, with complete release being achieved over 12 h. In conclusion, this work has demonstrated that SLS is a versatile and practical 3D printing technology which can be applied to the pharmaceutical field, thus widening the armamentarium of 3D printing technologies available for the manufacture of modern medicines [10].

Patient-centric medicine is a derivative term for personalised medicine, whereby the pharmaceutical product provides the best overall benefit by meeting the comprehensive needs of the individual; considering the end-user from the beginning of the formulation design process right through development to an end product is a must. One way in which to obtain personalised medicines, on-site and on-demand is by three-dimensional printing (3DP). The aim of this study was to investigate the influence of the shape, size and colour of different placebo 3D printed tablets (Printlets™) manufactured by fused deposition modelling (FDM) 3DP on end-user acceptability regarding picking and swallowing. Ten different printlet shapes were prepared by 3DP for an open-label, randomised, exploratory pilot study with 50 participants. Participant-reported outcome (PRO) and researcher reported outcome (RRO) were collected after picking and swallowing of selected printlet geometries including sphere, torus, disc, capsule and tilted diamond shapes. The torus printlet received the highest PRO scores for ease of swallowing and ease of picking. Printlets with a similar appearance to conventional formulations (capsule and disc shape) were also found to be easy to swallow and pick which demonstrates that familiarity is a critical acceptability attribute for end-users. RRO scores were in agreement with the PRO scores. The sphere was not perceived to be an appropriate way of administering an oral solid medicine. Smaller printlet sizes were found to be preferable; however it was found that the perception of size was driven by the type of shape. Printlet colour was also found to affect the perception of the end-user. Our study is the first to guide the pharmaceutical industry towards developing patient-centric medicine in different geometries via 3DP. Overall, the highest acceptability scores for torus printlets indicates that FDM 3DP is a promising fabrication technology towards increasing patient acceptability of solid oral medicines [11].

Additive manufacturing (3D printing) permits the fabrication of tablets in shapes unattainable by powder compaction, and so the effects of geometry on drug release behavior is easily assessed. Here, tablets (printlets) comprising of paracetamol dispersed in polyethylene glycol were printed using stereolithographic 3D printing. A number of geometric shapes were produced (cube, disc, pyramid, sphere and torus) with either constant surface area (SA) or constant surface area/volume ratio (SA/V). Dissolution testing showed that printlets with constant SA/V ratio released drug at the same rate, while those with constant SA released drug at different rates. A series of tori with increasing SA/V ratio (from 0.5 to 2.4) were printed, and it was found that dissolution rate increased as the SA/V ratio increased. The data show that printlets can be fabricated in multiple shapes and that dissolution performance can be maintained if the SA/V ratio is constant or that dissolution performance of printlets can be fine-tuned by varying SA/V ratio. The results suggest that 3D printing is therefore a suitable manufacturing method for personalized dosage forms [12].

Danae Karalia, Angeliki Siamidi, Vangelis Karalis and Marilena Vlachou [13] present the factors influencing the mechanical properties of 3D-printed oral dosage forms. Their study also explores how it is possible to use specific excipients and printing parameters to maintain the structural integrity of printed drug products while meeting the needs of patients. Three-dimensional (3D) printing is an emerging manufacturing technology that is gaining acceptance in the pharmaceutical industry to overcome traditional mass production and move toward personalized pharmacotherapy. After continuous research over the last thirty years, 3D printing now offers numerous opportunities to personalize oral dosage forms in terms of size, shape, release profile, or dose modification. However, there is still a long way to go before 3D printing is integrated into clinical practice. 3D

printing techniques follow a different process than traditional oral dosage from manufacturing methods. Currently, there are no specific guidelines for the hardness and friability of 3D printed solid oral dosage forms. Therefore, new regulatory frameworks for 3D-printed oral dosage forms should be established to ensure that they meet all appropriate quality standards. The evaluation of mechanical properties of solid dosage forms is an integral part of quality control, as tablets must withstand mechanical stresses during manufacturing processes, transportation, and drug distribution as well as rough handling by the end user. Until now, this has been achieved through extensive pre- and post-processing testing, which is often time-consuming. However, computational methods combined with 3D printing technology can open up a new avenue for the design and construction of 3D tablets, enabling the fabrication of structures with complex microstructures and desired mechanical properties. In this context, they highlighted the emerging role of computational methods and artificial intelligence. They conclude although the integration of 3D printed oral medicines into clinical practice is still premature, progress is being made every day and additive manufacturing will soon reach the peak of its enormous potential in the pharmaceutical field.

Venâncio, N.; Pereira, G.G.; Pinto, J.F.; Fernandes, A.I. [14] discusses the importance of Patient-centric therapy in pediatrics. Filaments containing 30% w/w of theophylline were produced by hot-melt extrusion and printed using fused deposition modelling to produce tablets. Here, preliminary results evaluating the effect of infill geometry (cross, star, grid) on drug content and release are reported.

References

- [1] Kim C, Compressed donut-shaped tablets with zero-order release kinetic, *Pharm Res.* 1995 Jul;12(7):1045-8.
- [2] Kim C, Release kinetics of coated, donut-shaped tablets for water soluble drugs, *Eur J Pharm Sci.* 1999;7 (3):237-42.
- [3] Karasulu H Y, Ertan G, Köse T, Modeling of theophylline release from different geometrical erodible tablets, *Eur J Pharm Biopharm.* 2000;49(2):177-82.
- [4] Karasulu H Y, Ertan G, Different geometric shaped hydrogel theophylline tablets: statistical approach for estimating drug release, *Farmaco.* 2002;57(11):939-45.
- [5] Reynolds T D, Mitchell S, Balwinski K M, Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. *Drug Dev Ind Pharm.*, 2002;28(4):457-466.
- [6] Krzysztof Tytkowski, Some remarks about geometry in medicine, *The Annual SIGRAD Conference; Special Theme: Computer Graphics in Healthcare; November 28-29; 2007; Uppsala; Sweden, Linköping Electronic Conference Proceedings* 28:8, 35-38.
- [7] J. T. Carstensen, The Use of Fractal Geometry in Pharmaceutical Systems, *Drug Development and Industrial Pharmacy*, 19(1-2):85-100.
- [8] Kovanya Moodley, Viness Pillay, Yahya E Choonara, Lisa C du Toit, Valence M K Ndesendo, Pradeep Kumar, Shivaan Cooppan, Priya Bawa, Oral drug delivery systems comprising altered geometric configurations for controlled drug delivery, *Int J Mol Sci.*, 2012;13(1):18-43.
- [9] Goyanes A, Martinez PR, Buanz A, Basit A, Gaisford S, Effect of geometry on drug release from 3D printed tablets, *Int J Pharm.*, 2015;494 (2):657-663.
- [10] Fina F, Goyanes A, Gaisford S, Basit AW, Selective laser sintering (SLS) 3D printing of medicines, *Int. J Pharm.*, 2017;529:285-293.
- [11] Goyanes A, Scarpa M, Kamlow M, Gaisford S, Basit AW, Orlu M, Patient acceptability of 3D printed medicines, *Int. J Pharm.*, 2017;530:71-78.
- [12] Pamela Robles Martinez, Alvaro Goyanes, Abdul W. Basit & Simon Gaisford, Influence of Geometry on the Drug Release Profiles of Stereolithographic (SLA) 3D-Printed Tablets, *AAPS PharmSci. Tech.*, Volume 19, 3355-3361 (2018).
- [13] Danae Karalia, Angeliki Siamidi, Vangelis Karalis and Marilena Vlachou, 3D-Printed Oral Dosage Forms: Mechanical Properties, Computational Approaches and Applications, *Pharmaceutics*, 2021, 13(9), 1401.

[14] Venâncio, N.; Pereira, G.G.; Pinto, J.F.; Fernandes, A.I., Influence of the Infill Geometry of 3D-Printed Tablets on Drug Dissolution, Med. Sci. Forum, 2021, 5, 15,1-3.
