Automatic Design Optimisation of Pharmaceutical Tablets using PDEs

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Abstract: Pharmaceutical tablets and capsules are the dominant forms for drug delivery. Both types of dosage forms need to be strong enough to handle different types of stress due to packaging and loading conditions before use. Hence, it is important to produce these pharmaceutical forms with maximum mechanical strength while conserving the properties of their active ingredients during the design process. The present work describes a methodology for parametric design and optimisation of a solid cylindrical tablet and a soft spherical capsule, which is based on the use of Partial Differential Equations (PDEs). The PDE-based formulation is capable of parameterising complex shapes using the information at some boundary curves that describe the shape. It is shown that the optimal designs of both tablet and capsule can be obtained using an automatic design optimisation which is performed by combining the PDE method and a standard method for numerical optimisation.

1 INTRODUCTION

In the past few decades, tablets and capsules have become the important dosage form for drug delivery in pharmaceutical industry. Tablets and capsules have many advantages over other dosage forms. They are convenient to use by patients and have long storage stability. Additionally, they can hide the unpleasant taste of their contents.

These types of dosage forms have been made in many shapes, sizes and consistencies. This helps to distinguish different medicines and is also useful for product branding. The most common shapes for tablets are round, oval and caplet whereas capsules are divided into two types: hard-shelled capsules and soft-shelled ones. The size of these dosage forms varies from a few millimetres to about a centimetre. The quality of both tablets and capsules are described by several parameters such as hardness, content uniformity, and accurate mass and height (Elkhider et al., 2007).

Tablets are produced through three distinct stages. These are die filling, compaction process and ejection. It has been reported in Coube et al. (2005) that the mechanical strength or disintegration of a tablet depends on the behaviour of powder during all stages of the tabletting process. The most important stage of tablet production is the powder compaction stage that involves compression and decompression of the powder bed. During this stage, the compaction properties (compressibility and compactibility) of the pharmaceutical powder bed can be determined. Compressibility, which is usually analysed using the Heckel, Kawakita and Walker models (Ilić et al., 2009), explains the mechanical properties of the bed in terms of elasticity and plasticity (Ilić et al., 2009). Meanwhile, compactibility refers to the ability of powders as small particles to change into the coherent solid dosage form (Sonnergaard, 2006). Compactibility can be estimated by measuring the mechanical strength of the powder compact which is generally characterised by the measurement of tensile strength (Han et al., 2008).

The tensile strength of a solid dosage form measures the ability of the object to resist forces before it breaks. This can generally be determined using the diametrical or axial compression tests (Han et al., 2008). The measured force (F) obtained from the test together with the diameter (D) and thickness (h) of the dosage form are used to calculate the tensile strength

$$\sigma_{\mathrm{T}}^{d} = \frac{2F_{\max}}{\pi D h}, \tag{1}$$

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and

$$\sigma_{\mathrm{T}}^{a} = \frac{4F_y}{\pi D^2}, \tag{2}$$

where $F_{\max}$ is the maximum crushing force and F_y is the force at the yield point. Equations (1) and (2) represent the tensile strength of a dosage form obtained from the diametrical and axial compression test respectively. It has been reported in Elkhider et al. (2007) that the properties of dosage forms such as density and surface area can influence the tensile strength of the form.

Given that the shape and size of dosage forms play an important role in determining their mechanical properties, this work proposes a method to model solid shapes of cylindrical tablet and spherical capsule interactively based on the use of parametric surface representations. Additionally, a methodology for automatic design optimisation within an interactive environment for both dosage forms is also described in this work. The objective is to obtain an optimal shape for a tablet and also predicting the optimal thickness of a spherical capsule's shell. Many authors have reported that the choice of the design variables is important in shape optimisation. Moreover, the number of design variables also needs to be considered because too many variables may increase the computational time (Ugail, 2003).

PDE method has been widely used as a surface-modelling technique in many areas (González Castro et al., 2010). This method can generate a smooth surface of complex geometries from a few design parameters. Furthermore, the PDE surface can be manipulated intuitively by changing the boundary curves or design parameters (Ugail, 2003). This method also has been proven to be useful to address optimisation problems including in biological (Ugail and Wilson, 2003) and industrial applications (Ugail, 2003). The PDE-based optimisation is performed within a reasonable computational time by combining engineering design criteria as constraints into the geometric design of PDE surfaces (Ugail, 2003). Therefore, the PDE method is used in this work to perform the automatic design optimisation of pharmaceutical tablets and capsules.

2 THE PDE METHOD

The PDE method produces a parametric surface, $\mathbf{X}(u, v)$ that is generated by solving the fourth order elliptic PDE

$$\left(\frac{\partial^4}{\partial u^4} + 2\frac{\partial^4}{\partial u^2 \partial v^2} + \frac{\partial^4}{\partial v^4}\right)\mathbf{X}(u, v) = 0, \tag{3}$$

where u and v are the independent variables in domain [0, 1] and [0, 2π] respectively. Equation (3) is known as the Biharmonic equation. The analytic solution to Equation (3) is found using separation of variables subject to four periodic boundary conditions.

For the sake of brevity, the present work employed the approximated solution of Equation (3) which has been truncated to N Fourier modes

$$\mathbf{X}(u, v) = \mathbf{A_0} + \sum_{n=1}^{N} [\mathbf{A_n}(u)\cos(nv) + \mathbf{B_n}(u)\sin(nv)] + \mathbf{C}(u, v), \tag{4}$$

where

$$\mathbf{A_0} = \mathbf{a_{00}} + \mathbf{a_{01}}u + \mathbf{a_{02}}u^2 + \mathbf{a_{03}}u^3, \tag{5}$$

$$\mathbf{A_n} = (\mathbf{a_{n1}} + \mathbf{a_{n3}}u)e^{nu} + (\mathbf{a_{n2}} + \mathbf{a_{n4}}u)e^{-nu}, \tag{6}$$

$$\mathbf{B_n} = (\mathbf{b_{n1}} + \mathbf{b_{n3}}u)e^{nu} + (\mathbf{b_{n2}} + \mathbf{b_{n4}}u)e^{-nu}, \tag{7}$$

$$\mathbf{C} = (\mathbf{c_1} + \mathbf{c_3}u)e^{\beta u} + (\mathbf{c_2} + \mathbf{c_4}u)e^{-\beta u}. \tag{8}$$

Given that $\mathbf{a_{00}}, \mathbf{a_{01}}, \cdots, \mathbf{a_{11}}, \mathbf{a_{12}}, \cdots, \mathbf{b_{11}}, \cdots, \mathbf{b_{N4}}$ are vector valued constants. Their value is determined by the boundary conditions at $u = 0$ and $u = 1$. The term $\mathbf{A_0}$ represents the spine of the patch which brings out the symmetry of the patch while the remaining terms in Equation (4) define the position of a point on the surface relative to the spine. The vector $\mathbf{C}$ is known as a remainder function which is responsible for fully satisfying the original boundary conditions. Thus, the vectors $\mathbf{c_1}, \cdots, \mathbf{c_4}$ and β are obtained from the difference between the original boundary conditions and the one satisfied by the first two terms in Equation (4).

As mentioned earlier in this section, four boundary conditions are needed to solve the Biharmonic PDE. Hence in this work, four periodic curves are chosen as the boundary conditions to create a PDE surface. These curves are shown in Figure 1(a) where the positional boundary curves, P_1 and P_2 correspond to the boundary conditions on the edges of the surface at $u = 0$ and $u = 1$ respectively while d_1 and d_2 define the derivative boundary conditions. Figure 1(b) illustrates the resulting shape of a fourth-order PDE surface. Figure 1(d) shows the effect of changing the derivatives boundary conditions (d_1 and d_2) originally shown in Figure 1(a). These boundary conditions have been resized and vertically translated from the corresponding positional boundary curves. From this example, it is shown that the shape of the surface can simply be controlled by the shape of the boundary conditions.

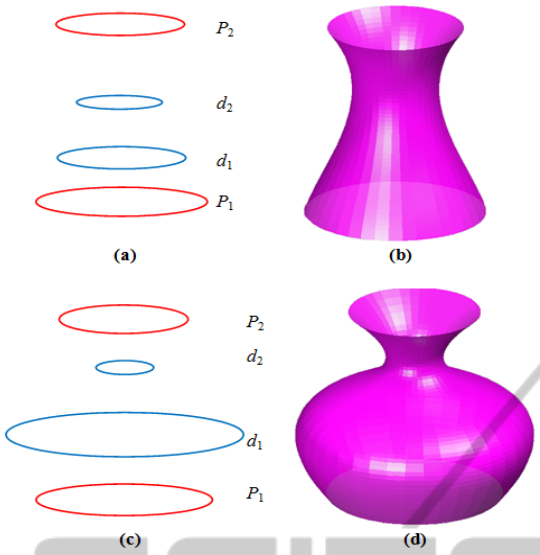

Figure 1: The boundary curves (a) and the corresponding surface shape (b). The effect on the shape of the surface by resizing and translating the derivative curves: the boundary curves (c) and the resulting manipulated surface shape (d).

2.1 Geometry of Tablets and Capsules

This section discusses on how the geometry of a cylindrical tablet and a spherical capsule can be generated based on the analytic solution of the Elliptic PDE. The geometric models representing both objects have been obtained using a number of closed curves. The number of boundary curves depends on how many PDEs are required to produce the tablet shape.

As a simple geometry, a flat-faced cylindrical tablet is fully represented by the solution of one PDE subject to four boundary curves. However, more than one PDE is needed to generate the surface of spherical capsule since the shape of this object is considered as a complex geometry. The graphic representation of such PDE is referred as patch and therefore, complex geometries are represented by several surface patches. Each of the patches is composed of four boundary curves, c_{jk} where c indicates the type of curve, with the letter P denoting the positional curves and d denoting the derivative curves. The index j (j = 1, ..., n) represents the patch; j = 1 for the first patch, j = 2 for the second patch and so forth. The subscript k (k = 1, 2) corresponds to the boundary edges of the surface.

Adjacent patches need to be blended together by sharing one boundary curve with either one or two different PDEs to guarantee the position continuity along the generated surface. In this work, a spherical capsule is generated from a surface composed of two patches representing the outer surface of its hemispheres (upper and lower). As it can be seen in Figure 2(d), the second positional boundary curve of the lower hemisphere corresponds to u = 1 (marked as P_{12}) is used as the first positional curve of the upper hemisphere (P_{21}). Hence, only seven curves are required to generate the outer surface of the capsule. In order to create a hollow spherical capsule, another two patches are needed to represent its inner surface.

Figure 2(a) shows the conditions in terms of the curves to generate a flat-faced cylindrical tablet with radius 4.91 mm and thickness 6 mm. In particular, the four conditions are such that

$$\mathbf{X}(0,v) = P_1, \mathbf{X}\left(\frac{1}{3},v\right) = d_1, \mathbf{X}\left(\frac{2}{3},v\right) = d_2, \mathbf{X}(1,v) = P_2.$$

It can be seen in Figure 2(b) that all curves lie on the resulting surface. In case of generating the axisymmetric spherical capsule, we only consider the upper hemisphere since this object is symmetric. The size (r_i) and position in z-direction (z_i) for each boundary curve representing the upper hemisphere are determined by

$$r_i = R\cos(\psi_i) \text{ and}$$
$$z_i = R\sin(\psi_i) \text{ for } i = 4,5,6,7 \quad (9)$$

where i represents the number of curves, $\psi = \left[0, \frac{\pi}{2}\right]$ and R is the radius of the sphere (a and b denote the outer and inner radius of the capsule respectively). Generally, the coordinate of these boundary curves can be written as

$$(r_i \cos v, r_i \sin v, z_i). \quad (10)$$

Therefore, the coordinate for all boundary curves used to generate the outer surface of an upper hemisphere with a centre (x_0, y_0, z_0) and radius (a) 2.5 mm is such that

$$P_{21}: (x_0 + 2.5\cos v, y_0 + 2.5\sin v, z_0),$$
$$d_{21}: (x_0 + 2.17\cos v, y_0 + 2.17\sin v, z_0 + 1.25),$$
$$d_{22}: (x_0 + 1.25\cos v, y_0 + 1.25\sin v, z_0 + 2.17),$$
$$P_{22}: (x_0, y_0, z_0 + 2.5). \quad (11)$$

The conditions in Equation (11) can be reflected to obtain the conditions corresponding to the lower hemisphere. The inner surface of the capsule with radius (b) 2.0 mm is also created from boundary curves generated using Equations (9) and (10). Figure 2(d) illustrates the geometry of the upper hemisphere of a spherical capsule generated using the analytic solution of the Biharmonic PDE.

Given that the analytic solution of the Elliptic PDE only generates the surface of any given object, a new parameter (w) has been introduced into Equation (4) in order to generate a solid representation of the particular object

$$\mathbf{X}(u,v,w) = \mathbf{A_0} + \mathbf{C}(u,v) + w\sum_{n=1}^{N}[\mathbf{A_n}(u)\cos(nv) + \mathbf{B_n}(u)\sin(nv)] \quad (12)$$

where $0 \le w \le 1$. This parameter describes the volume inside the generated object. The solid cylindrical tablet and spherical capsule are shown in Figures 3(a) and 3(b) respectively. The parametric region of parameter v is set to be from $\frac{\pi}{2}$ to 2π in order to show the interior part of the PDE-based representation of a spherical capsule.

3 DESIGN OPTIMISATION

This section shows how automatic design optimisation of a solid tablet and capsule can be carried out using the parametric model discussed in Section 2. It is assumed that both dosage forms are finite, homogeneous and isotropic. The design optimisation of these objects is performed by solving a constrained optimisation problem formulated based on the objective function together with the boundary conditions (positional and derivatives curves) associated with the geometry of the dosage form and the required constraints.

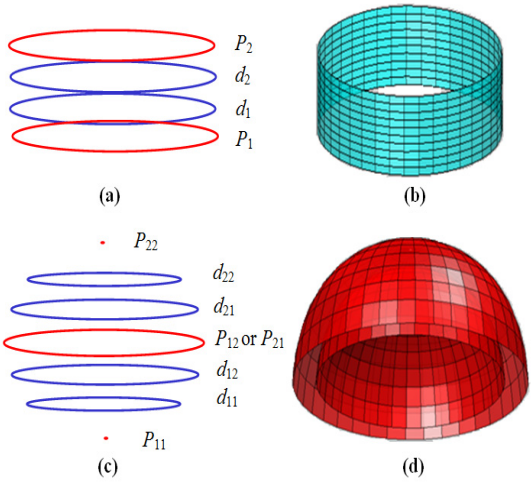

Figure 2: Generating curves in three-dimensional space for tablet (a) and capsule (c). The resulting surface shape of both objects in (b) and (d) respectively.

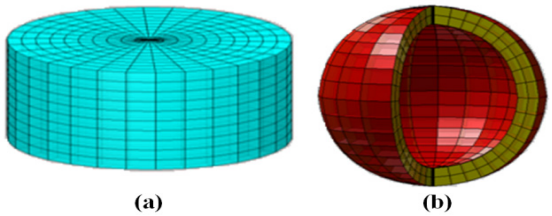

Figure 3: Solid PDE-based representation of cylindrical tablet (a) and spherical capsule (b).

The most important aspect of design optimisation is the definition of a suitable objective function, which has to be minimised or maximised. The general mathematical formulation of an optimisation problem to minimise a given objective function under nonlinear equality and inequality constraints can be written as

$$\begin{aligned} &\text{minimise} && f(\mathbf{x}) \\ &\text{subject to} && g_i(\mathbf{x}) \le 0,\ i = 1,\dots,p \\ &&& h_j(\mathbf{x}) = 0,\ j = 1,\dots,q \\ &&& \mathbf{x_l} \le \mathbf{x} \le \mathbf{x_u};\ \ \mathbf{x} \in \mathbb{R}^n \end{aligned} \quad (13)$$

where $f(\mathbf{x})$ is the nonlinear objective function, $\mathbf{x}$ is a vector of n design variables with sets of lower ($\mathbf{x_l}$) and upper ($\mathbf{x_u}$) bounds, while $g_i(\mathbf{x})$ and $h_j(\mathbf{x})$ represent inequality and equality constraints respectively.

There is a wide variety of methods for numerical optimisation such as Interior-point and Active set methods (Eitrich and Lang, 2006). It has been reported in Leyffer (2005) that the Active set method is more robust than the Interior-point method. The Active set method solves constrained nonlinear optimisation problems by minimising the objective function in each iteration over the active set until the optimal solution is obtained. In this method, the optimisation problem is split into one active and one inactive parts where the active part refers to a subset of the constraints that are locally active (Eitrich and Lang, 2006).

This work carries out the optimisation using the Active set method, which is run in Matlab. A MEX file has been created as an interface between Matlab and Visual C++. A subroutine has been developed in C++ to read the boundary curves that define the shape of the tablet and produce the solution for each set of curves. When the Matlab file is compiled, the MEX file is dynamically loaded and allows calling

the pertaining C++ subroutine within Matlab as if it was a built-in function. Moreover, Matlab was used to display the resulting shapes after the optimisation process is finished.

3.1 Optimisation Process for Cylindrical Tablet

The automatic optimisation of the cylindrical tablet shown in Figure 3(a) is considered. The tablet discussed in this work is composed of 300 mg of α-lactose monohydrate with the value of E = 2460 N/mm^2, γ = 0.21 and true density (ρ_{true}) 1.3 mg/mm^3. The initial diameter and thickness of this tablet are 9.82 mm and 6 mm respectively. Assuming that the tablet is located in the bottom of a bottle filled with tablets, such the tablet experiences a stress. This is due to the weight of the rest of the tablets in the bottle and hence, this tablet becomes either slightly deformed or damage. Therefore, the required strength of the tablet needs to be measured by calculating the maximum tensile strength within the tablet. This is done by means of axisymmetric boundary value analysis where the force is applied on the top plane of the tablet caused by the weight of the other tablets in the bottle. It is also assumed that the bottom plane of the tablet is fixed at $z = 0$.

The objective here is to determine the optimal shape of a cylindrical tablet with a maximum tensile strength subject to a given volume. Therefore, Equation (2) is employed to measure the strength of the cylindrical tablet occurring in the whole structure. The yield force (F_y) in Equation (2) is replaced by the yield pressure (P_y), which can be obtained from the Heckel model

$$\ln\left(\frac{1}{1-\rho_{rel}}\right) = PK + A, \tag{14}$$

where ρ_{rel} is a relative density, P is a pressure, and K and A are constants. The constant K gives the value of the plasticity of a compressed powder bed while A is associated with the particle rearrangement before deformation (Ilić et al., 2009). The yield pressure is measured from the reciprocal of K (Ilić et al., 2009) and hence, Equation (2) is transformed to

$$\sigma_{\text{T}}^{a} = \frac{P}{\ln\left(\frac{\pi hc^2\rho_{\text{true}}}{\pi hc^2\rho_{\text{true}} - m}\right) - A}, \tag{15}$$

where h, c and m represent the thickness, radius and mass of the tablet respectively.

The design space is further restricted by choosing a constraint to represent the volume of the tablet. In this case, the volume is fixed to 235 mm^3, which can be calculated using the expression given by

$$\frac{1}{3}\sum_{i=1}^{M}(\mathbf{X}_i \cdot \mathbf{n}_i)\mathcal{A}_i = 235, \tag{16}$$

where $\mathbf{n}_i$ and $\mathcal{A}_i$ are the unit vector normal and area of the i^{th} defining surface. Here, M represents the number of rectangular surfaces since the PDE-based representation of the tablet in question is generated from cuboid mesh. It is worth mentioning that Equation (16) represents a means for the numerical computation of the volume enclosed within a closed surface. With the above formulation, the boundary curves and their initial size and position for the optimisation process of this tablet are shown in Table 1. Emphasis is made on the fact that we only considered the translation in z direction and dilations in the xy plane for all boundary curves within the defined limits. The radius of each curve is set from 4.5 mm to 5.15 mm while the position in the z-direction for every curve is chosen between 0 to 3.5 mm.

The Active set method finds the design with the lowest possible value of the chosen merit function from the design space. The optimisation took less than an hour to obtain the maximum strength after four iterations starting from a randomly chosen solution point. The optimal shape which had a relative reduction in height of 50 % is found with maximum tensile strength as shown in Figure 4(a). The values of the design curves obtained for the optimal design are given in Table 1.

Table 1: Parameter values for the cylindrical tablet.

Boundary curve	Initial		Optimal	
	Position z (mm)	Radius (mm)	Position z (mm)	Radius (mm)
P_1	0.0	4.91	0.0	4.83
d_1	1.88	4.91	0.9	5.15
d_2	4.12	4.91	2.0	5.15
P_2	6.0	4.91	2.93	4.83
$\boldsymbol{\sigma_{\text{T}}^{a}}$			103.333 N/mm^2	

3.2 Shape Optimisation of a Spherical Capsule

The aim for this example is to identify the optimal thickness of the capsule shell whilst possessing a predefined level of strength. Again, the translation in z direction and dilations in the xy plane of all boundary curves are considered.

Here, the elastic gelatin spherical capsule is subjected to an external pressure (P_{ext}) at its outer surface $r = a$ and an internal pressure (P_{int}) at its internal surface $r = b$. Equation (1) is used in the optimisation routine as the objective function. The thickness of the capsule shell is measured by considering the radial displacement of the pressurised sphere. The displacement is determined by making use of the Love's stress function subjected to particular boundary conditions (González and Fitt, 2002)

$$\mu_r = -\frac{(P_{\text{ext}}a^3 - P_{\text{int}}b^3)r}{(3\lambda + 2\mu)(a^3 - b^3)} - \frac{(P_{\text{ext}} - P_{\text{int}})a^3b^3}{4\mu r^2(a^3 - b^3)}, \quad (17)$$

where λ and μ are the Lame modulus and shear modulus respectively.

A pressure of 153 μN/mm^2 is applied on the outer surface of the capsule while the pressure on its inner surface is 39 μN/mm^2. As far as the material properties are concerned, the Young modulus and Poisson's ratio of the gelatin are 0.11 N/mm^2 and 0.4 respectively (Markidou et al., 2005). For this particular example, the volume of the spherical capsule is fixed to 14.14 mm^3.

With the above formulation, the automatic optimisation was performed about 72 minutes on a Matlab R2008a with 2.20 GHz Intel Core 2 Duo T7500 processor. The resulting optimal thickness of capsule's shell is shown in Figure 4(b). This shape has a relative reduction in thickness and size of 46 % and 40 % respectively. The maximum tensile strength for the capsule was found to be 10.89 N/mm^2.

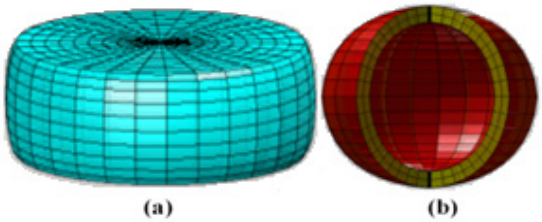

Figure 4: Optimal shape of a tablet (a) and optimal thickness of capsule shell with maximum tensile strength (b).

4 CONCLUSIONS

This work outlines a methodology for shape optimisation of pharmaceutical dosage forms based on the PDE method enabling efficient shape definition and parameterisation of complex geometries. The shape of a tablet and capsule is generated from a small set of design parameters and can be controlled by the chosen boundary curves. Thus, the optimised shape is obtained after carrying out an optimisation analysis and relating the pertaining results to the solution of the corresponding PDE as given in Equation (4). It is worth mentioning that the concise parameterisation characteristics of the PDE method can be used to carry out automatic design optimisation in a practical setting where the time taken for tablet testing can be significantly reduced and encourages future development of pharmaceutical technologies.

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