Generalising a Pohlhausen-Type Solution for Dissolution from Multi-Layer Drug Compacts

N. McMahon[1], M. Crane, H. Ruskin, L. Crane[2]
School of Computing, Dublin City University, Dublin 9, Ireland

Abstract

A relatively recent paper outlines a useful semi-analytical technique for approximating the drug dissolution from a simple horizontally layered medicinal tablet (a compact) [1]. Their solution is calculated for the specific cases of three- and five-layer compacts. This technical note generalises their result for p layers and considers the behaviour of the solution as p becomes very large.

1 Introduction

In this technical note, we consider the results presented by Crane et al. in the paper, A Pohlhausen Solution for the Mass Flux From a Multi-layered Compact in the USP Drug Dissolution Apparatus [1], or *the Pohlhausen paper*. This paper is concerned with approximating the mass transfer rate, $\dot{m}$, of *drug* and *excipient* from a simple horizontally layered tablet, or compact, in a USP paddle dissolution apparatus [3]. See Figure 1 and others, below. Excipients are medicinally inert materials used to bind or influence dissolution behaviour, among other things. This rather idealised prototype tablet

[1]Contact: nmcmahon@computing.dcu.ie
[2]INCA: Institute for Numerical Computation and Analysis, Dame Court, Dublin 2, Ireland.

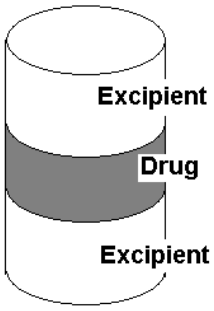

Figure 1: The prototype multi-layer compact, or tablet, considered here: a 3-layer version is shown. The tablet can be imagined as a typical cylindrical over-the-counter *dosage form*, e.g. an (unusual) aspirin tablet.

configuration is a useful starting point for some aspects of the mathematical analysis of dissolution[3].

Two questions come to mind: (1) can the results be generalised to deal with any number of layers and (2) what happens when the number of layers is very large? Do the drug release rates predicted by Crane et al. tend to a limiting value?

2 Generalising the Pohlhausen Solution to Any Number of Drug Layers

From a consideration of the results of the Pohlhausen paper [1], it becomes evident that, for the case of a compact consisting of three equally spaced layers (one drug layer sandwiched between two layers of excipient), we can write the solution for the given mass transfer rate of excipient from the compact in a different, but equivalent way, as,

[3]For the interested reader, this was discussed in a little more detail in an earlier paper [2].

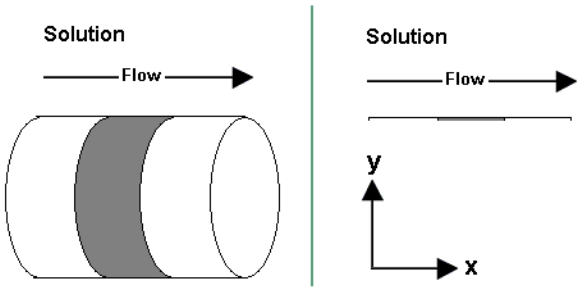

Figure 2: The multi-layer compact can be idealised as a one-dimensional object if the radius of the compact is sufficiently large compared to its length, i.e. for a stumpy cylinder. A 3-layer compact with one layer of drug is again shown; a compact with a larger number of layers can be readily imagined.

$$\frac{\dot{m}_{\text{excipient, 3 layers}}}{\dot{m}_{\text{excipient, 1 layer}}} = \left[\sum_{n=0}^{2}\left(\frac{3-n}{3}\right)^{\frac{3}{4}}(-1)^n\right]^{\frac{2}{3}} \tag{1}$$

Likewise, and for the same condition of three equally spaced and alternating layers, we can write the solution for the given mass transfer rate of drug from the compact in a different, but equivalent way, as,

$$\frac{\dot{m}_{\text{drug, 3 layers}}}{\dot{m}_{\text{drug, 1 layer}}} = \left[1-\sum_{n=0}^{2}\left(\frac{3-n}{3}\right)^{\frac{3}{4}}(-1)^n\right]^{\frac{2}{3}} \tag{2}$$

Similarly, considering the solution for five equally spaced and alternating layers of drug and excipient,

$$\frac{\dot{m}_{\text{excipient, 5 layers}}}{\dot{m}_{\text{excipient, 1 layer}}} = \left[\sum_{n=0}^{4}\left(\frac{5-n}{5}\right)^{\frac{3}{4}}(-1)^n\right]^{\frac{2}{3}} \tag{3}$$

$$\frac{\dot{m}_{\text{drug, 5 layers}}}{\dot{m}_{\text{drug, 1 layer}}} = \left[1-\sum_{n=0}^{4}\left(\frac{5-n}{5}\right)^{\frac{3}{4}}(-1)^n\right]^{\frac{2}{3}} \tag{4}$$

We can at this point easily generalise these observations to p evenly spaced, alternating, layers of drug and excipient by writing,

$$\frac{\dot{m}_{\text{excipient, } p \text{ layers}}}{\dot{m}|_{\text{excipient, single layer}}} = \Big[\sum_{n=0}^{p-1} \Big(\frac{p-n}{p}\Big)^{\frac{3}{4}} (-1)^n\Big]^{\frac{2}{3}} \tag{5}$$

and

$$\frac{\dot{m}_{\text{drug, } p \text{ layers}}}{\dot{m}|_{\text{drug, single layer}}} = \Big[1 - \sum_{n=0}^{p-1} \Big(\frac{p-n}{p}\Big)^{i} (-1)^n\Big]^{\frac{2}{3}} \tag{6}$$

These equations represent only a minor modification of the results presented in the Pohlhausen paper: we explicitly state the general case that these earlier results imply.

3 Solution When the Number of Layers Becomes Very Large

In order to answer this question, we need to examine the behaviour of these equations as the number of layers, p , becomes very large. To this end, we tested the series contained in the square brackets, i.e. the quantities subsequently raised to the power of $\frac{2}{3}$, numerically with a simple Python script. For indices, i, greater than 0, the sum of the series appears to converge towards 0.5 as p becomes large. This seems to be true for all $p > 1$, both odd and even. A simple version of the script is given as an appendix. A sample of the numerical results is reproduced in the table below.

On the basis of the results of these numerical experiments, and without recourse to a rigorous mathematical treatment, it seems *likely* that the series converges to 0.5 for all indices $i > 0$ as p becomes very large; that is:

$$\sum_{n=0}^{p-1} \Big(\frac{p-n}{p}\Big)^{i} (-1)^n \to \frac{1}{2} \tag{7}$$

for all $i > 0$ as p becomes large.

i :	0.25	0.75	1.00	2.00	3.00	4.00
$p = 3$	0.8562	0.7009	0.6667	0.6667	0.7407	0.8148
$p = 5$	0.8078	0.6319	0.6000	0.6000	0.6480	0.6960
$p = 101$	0.6400	0.5118	0.5050	0.5050	0.5074	0.5099
$p = 1{,}001$	0.5786	0.5020	0.5005	0.5005	0.5007	0.5010
$p = 10{,}001$	0.5442	0.5003	0.5000	0.5000	0.5001	0.5001
$p = 100{,}001$	0.5248	0.5001	0.5000	0.5000	0.5000	0.5000
$p = 1{,}000{,}001$	0.5140	0.5000	0.5000	0.5000	0.5000	0.5000
$p = 10{,}000{,}001$	0.5079	0.5000	0.5000	0.5000	0.5000	0.5000
$p = 100{,}000{,}001$	0.5044	0.5000	0.5000	0.5000	0.5000	0.5000
$p = 1{,}000{,}000{,}001$	0.5025	0.5000	0.5000	0.5000	0.5000	0.5000

Table 1: Script output: as p becomes large, the sum of the series clearly tends to $\frac{1}{2}$.

So, as p becomes large, and with the results from earlier in this note, we can write that,

$$\frac{\dot{m}_{\text{excipient, } p \text{ layers}}}{\dot{m}_{\text{excipient, 1 layer}}} \approx \left[\frac{1}{2}\right]^{\frac{2}{3}} = 0.63 \tag{8}$$

$$\frac{\dot{m}_{\text{drug, } p \text{ layers}}}{\dot{m}_{\text{drug, 1 layer}}} \approx \left[\frac{1}{2}\right]^{\frac{2}{3}} = 0.63 \tag{9}$$

4 Conclusion

We can generalise the results of Crane et al. [1] to p evenly spaced layers. Exploring this generalised Pohlhausen solution, a tablet consisting of a very large number of alternating layers of drug and excipient will have an initial mass transfer rate of drug equivalent to 63% of the initial mass transfer rate of drug from a tablet that consists entirely of drug.

References

[1] M. Crane, L. Crane, A.-M. Healy, O. Corrigan, K. Gallagher, and L. McCarthy, *A Pohlhausen Solution for the Mass Flux From a Multi-layered Compact in the USP Drug Dissolution Apparatus*, Simul. Model. Pract. Th., 12 (2004), pp. 397–411.

[2] N. McMahon, M. Crane, H. J. Ruskin, and L. Crane, *The importance of boundary conditions in the simulation of dissolution in the usp dissolution apparatus*, Simul. Model. Pract. Th., 15 (2007), pp. 247–255.

[3] United States Pharmacopeial Convention, *USP-NF 24*, Rockville, MD, 19 ed., 2000, ch. Dissolution <711>, p. 1941.

Appendix

```
#This Python script (http://www.python.org/) sums the general series
#described in this technical note.

#Date: 11/2012.
#Copyright (C) 2012 Niall McMahon (nmcmahon@computing.dcu.ie)
#See: http://niallmcmahon.com/legals.html

print
print "Copyright (C) 2012 Niall McMahon. This code comes with ABSOLUTELY NO WARRANTY."
print

#m is the upper limit and i is the index.

m = 5
i = 0.25

sum = 0.0
n = 0.0

while n < m:
    x1 = pow((m-n)/m,i)
    x2 = pow(-1,n)
    nextterm = x1*x2
    sum = sum + nextterm
    n = n + 1
```

```
#Prints the sum
print "Sum for m =",m,", i = ",i,":",sum
print
```

Acknowledgements

The authors would like to thank Professor Martin Clynes and the Irish National Institute for Cellular Biotechnology (NICB) for its support. Additional support from the Institute for Numerical Computation and Analysis (INCA) was invaluable. Professor Michael Ryan, emeritus of the School of Computing at Dublin City University, provided useful assistance. Deirdre D'Arcy of the School of Pharmacy and Pharmaceutical Sciences at Trinity College Dublin provided useful experimental observations, as always.