# An Assessment of Reasonable Tortuosity Values

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## INTRODUCTION

Tortuosity is a simple concept which is easily understood; however, not all scientific literature shows an appreciation for reasonable tortuosity values. In the context of diffusional matrices, tortuosity ($\tau$) is traditionally defined as the ratio of effective path length which a diffusing molecule takes ($L_e$), to the shortest straight-line and straight-forward distance ($L$), from the "starting point" to the "ending point," as represented by Eq. 1.

$$\tau = \frac{L_e}{L} \tag{1}$$

Tortuosity accounts for the increased effective matrix barrier thickness due to the fact that a molecule cannot diffuse in a straight-forward linear direction. It does not represent the actual path length an individual molecule takes through a medium in which it is mobile; this is inherent in the diffusion coefficient. Tortuosity is intended to be a property of that matrix and not related to diffusant properties.

Porosity is defined as the fractional void volume of a matrix through which a molecule diffuses once penetrated with dissolution medium. The porosity of a system can be inherent, as in the case of a compressed tablet, or created by soluble matrix components (excipients or drugs) after dissolving in the penetrating dissolution medium. Tortuosity values typically range from 2–6 (1–2). Tortuosities in this range are applicable to simple systems which have a reasonable level of pore connectivity, such as high inherent porosity or drug loading. Systems with low porosity and/or drug loading below the critical porosity can have higher tortuosities and in extreme cases may only release drug from the surface due to little to no connectivity of pores.

The intricacies of determining tortuosity and how apparent values can be misleading was demonstrated shortly after the Higuchi "square root of time" equation was introduced (3–5). Tortuosity continues to be used for modeling of drug release from solids; it has also been proposed to be a factor in release from an emulsion, and in the diffusion of drugs through skin.

When modeling release profiles for porous sustained release systems, tortuosity is commonly found by solving for it after determining other parameters in a diffusional mathematical model. Eq. 2 is a simplified form of Fick's law for a system of this type (sink conditions assumed).

$$\frac{dm}{dt} = \frac{D \cdot S \cdot \varepsilon \cdot C}{\tau \cdot h} \tag{2}$$

All parameters can be independently determined, assumed, or not relevant in integrated forms of the equation, except tortuosity. Tortuosity values are substituted in the model until the predicted and actual release profiles best match one another. In this process, observed tortuosity values far greater than the reasonable 2–6 may be arbitrarily accepted, and/or potential "partitioning" of diffusant onto/into the matrix via adsorption or actual solubilization is not considered. If this occurs, a re-examination of the other diffusional parameters and the conceptual model is warranted, or an additional term(s) may be needed to represent the non-inert nature of the matrix to lower the needed tortuosity value. This is particularly true in the case of systems containing low molecular weight drugs with high loading and/or a high level of pore connectivity. Instances can occur where unreasonable values of 1000 or greater can be obtained using the above method (4); however, little information exists in the literature with regard to reasonable values between the typical 2–6 and 1000 in these cases.

More recently, much effort has been put forth in the holistic examination of release of molecules from porous systems including the use of computational chemistry and percolation theory (6–13). Some of this work focuses on macromolecules cast/imbedded in polymeric matrices which typically exhibit retardations of release well beyond what might be expected. Many approaches appropriately avoid the use of a tortuosity value as a single parameter altogether. Despite this, little attention has been given to tortuosity as an independent parameter and there are few assessments of path length contributions to retardations of release alone. In addition, traditional modeling approaches are still used which require the assignment of a tortuosity value. To re-examine the accepted and reasonable tortuosity values of 2–6 for traditional systems with high porosity and connectivity, and to consider larger values that might also be reasonable in these and other specialized cases, a simplistic simulation approach was taken.

## METHODS

A computer program was written to represent the tortuous nature of porous matrices. The model is based on a simple three-dimensional cubic lattice and is generalized to ideally represent various porous structures. The model describes effective barrier path lengths, which tortuosity is meant to represent, and not the actual path length of an individual traveling entity.

Imagine a molecule sitting at a point in a cubic lattice. The fate of the molecule is to ultimately move in a forward direction. The molecule can move to any adjacent point within its lateral plane (a non-forward movement), or can move to any adjacent forward point in the cubic lattice (Fig. 1). Any of the 17 positions can be moved to at random and with equal probability. After moving to that random position, another move is made at random to the next position, and so on. This process is repeated with a total of 100 moves repre-

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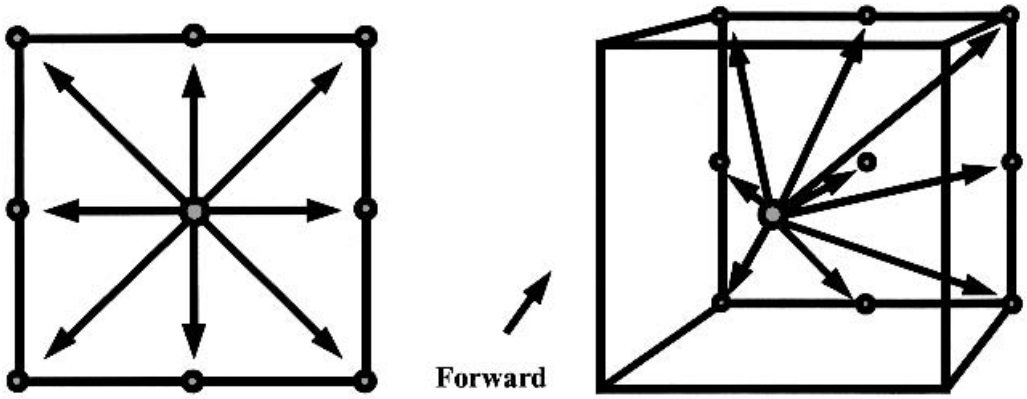


**Fig. 1.** Three dimensional depictions of the 17 various single movements a molecule can make (a) non-forward/lateral movements, and (b) forward movements. Movements start at the center of the face of the cubic network closest to the viewer and move within that plane (as in the case of non-forward/lateral movements) or into the cube and away from the viewer (as in the case of forward movements).

senting a single simulated tortuous path. As this random path is created, the actual path length is summed, and the shortest "straight-line" forward movement is summed. For each random simulated path, the tortuosity is calculated (actual path length divided by the "straight-line" path length).

Other features were added to the program using the concept of "excursion paths." The intent of incorporation of these paths was to try to create contrived extremes in tortuosity where the molecule would periodically deviate from the simple random movement within the cubic lattice. The fraction of excursion paths encountered as well as the length of the excursion path was varied. The fraction of excursion paths represents how often a path of this nature is encountered. For example, 1 excursion in every 10 moves is represented by the fraction 0.1. Conceptually, and in the program, the molecule moves to the next random position, however, the length for that particular move is longer by the addition of the excursion path length. Fraction of excursion paths encountered was varied from 0–1 and the excursion path length was varied from 0–50 (50 times the length of a straight forward movement). Excursion paths can be viewed as empirical exaggerations in path length as a means to examine contrived extremes; however, they also have physical relevance. They can represent: 1) channels/paths of greater length than that of the simple lattice moves, 2) dead end channels/pores which do not connect with other pores or channels, or 3) specialized porous structures which consist of large pores connected by narrow channels. The latter is applicable to macromolecules cast in polymeric matrices (6,8).

## RESULTS

Table I contains average tortuosity values and ranges of individual path tortuosities for each condition of fraction of excursion paths encountered and length of excursion path. For any condition of fraction of excursion paths = 0 or excursion path length = 0, average tortuosity values of 2.60 resulted. Increasing fraction or length of excursion paths increased average tortuosity to as high as 98 over the range these parameters were varied. As expected, the random simulation approach yielded tortuosity values, in the absence of excursion paths, which follow a normal distribution with the 50% frequency occurrence approximating the average value of 2.60.

Response surface modeling (Design Expert Version 5.0.5, Stat-Ease, Inc.) reveals a simple mathematical function. Tortuosity as a function of length and fraction of excursion paths is seen in Eq. 3.

$$\tau = 2.60 - 0.000305 \cdot l - 0.0150 \cdot f + 1.90 \cdot l \cdot f \qquad (3)$$

This equation is true in the case of excursion path lengths greater than 50. Calculated tortuosities using excursion path lengths as high as 10,000 were in agreement with values generated via actual simulation. Response surface modeling also

**Table I.** Average Tortuosity Values and Ranges of Individual Path Tortuosities as a Function of Fraction of Excursion Paths Encountered and Excursion Path Length

| Excursion path length | Fraction of excursion paths encountered | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 0.2 | 0.4 | 0.6 | 0.8 | 1.0 |
| 0 | 2.60 (2.02–3.32) | 2.60 (2.02–3.32) | 2.60 (2.02–3.32) | 2.60 (2.02–3.32) | 2.60 (2.02–3.32) | 2.60 (2.02–3.32) |
| 10 | 2.60 (2.02–3.32) | 6.41 (4.84–8.19) | 10.2 (7.72–13.1) | 14.0 (10.6–18.0) | 17.8 (13.4–22.8) | 21.6 (16.3–27.7) |
| 20 | 2.60 (2.02–3.32) | 10.2 (7.72–13.1) | 17.8 (13.4–22.8) | 25.5 (19.1–32.6) | 33.1 (24.9–42.3) | 40.7 (30.6–52.1) |
| 30 | 2.60 (2.02–3.32) | 14.0 (10.6–18.0) | 25.5 (19.1–32.6) | 36.7 (27.7–47.2) | 48.3 (36.3–61.9) | 59.7 (44.9–76.5) |
| 40 | 2.60 (2.02–3.32) | 17.8 (13.4–22.8) | 33.1 (24.9–42.3) | 48.3 (36.3–61.9) | 63.5 (47.7–81.4) | 78.8 (59.1–101) |
| 50 | 2.60 (2.02–3.32) | 21.6 (16.3–27.7) | 40.7 (30.6–52.1) | 59.7 (44.9–76.5) | 78.8 (59.1–101) | 97.8 (73.4–125) |

reveals a symmetry in the simulation. This is best reflected in the contour plot seen in Fig. 2 (graphical representation of Eq. 3). Fraction of excursion paths and length contribute equally in the resulting tortuosity over the range they were studied. This is also the reason identical tortuosity values can be found in Table I for different excursion path conditions.

## DISCUSSION

### Systems of High Porosity

The simulation approach yielded a tortuosity of 2.60, in the absence of excursion paths, which is consistent with historically accepted values of 2–6 for typical systems. Even under the most highly contrived conditions (fraction of excursion paths = 1, excursion path length = 50) the average tortuosity was only 98 and the highest individual tortuous path was 125. These extreme conditions are not representative of the effective path a diffusing molecule might travel through porous channels in a system with high porosity. In addition, tortuosity values on the order of 100–1000 were not obtained. Even if these highly contrived tortuous paths were to exist, it is unlikely that large tortuosity values would be of value in helping to describe diffusion. It is easy to imagine that long paths might become "saturated" with the diffusant yielding an effective tortuosity at steady state of 2–6 and would not effectively participate in steady state release. In the early stages of release it is possible that channels of this nature could retard release as they become filled with diffusant.

Limiting the length and fraction of excursion paths enables speculation on what an upper limit of tortuosity might be. Assuming that an excursion path length that would effectively participate in retarding diffusion would be no greater than 10 (10 times that of a straight forward move), and that these paths would be encountered no more than 20% of the time, the maximum possible tortuosity is 6.4. Whereas these assumptions are somewhat arbitrary, they yield an upper limit consistent with observed values considered reasonable.

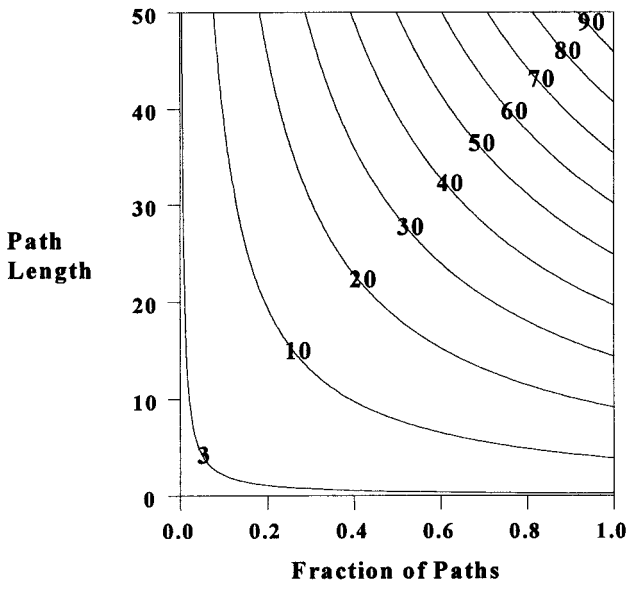


**Fig. 2.** Tortuosity contour plot representing Equation 3. Lines or "contours" represent a given tortuosity value for any combination of length of excursion path and fraction encountered.

### Specialized Porous Systems

It is not unusual for diffusion of macromolecules in porous matrices to exhibit large retardations in release. It has been theorized that multiple mechanisms may be at play and that large tortuosity values may exist in these cases (12). Some systems consist of high molecular weight drugs cast in polymeric matrices possessing little inherent porosity. Depending on drug loading, the resulting porous network can exist as large pores connected by small channels. The nature of the pore network, combined with the fact that these large molecules must travel through relatively narrow channels, are two factors contributing to the large retardations in release. Simulation of single molecule "first passage time" in these pores was shown to be a function of the number of connecting channels and configuration (8). In addition to pore geometry and steric considerations, physical-chemical interaction/partitioning of the diffusant with the matrix walls is another mechanism by which release can be retarded.

Assuming an excursion path represents the effective path length traveled by a molecule in a pore (randomly searching for an exit channel), and that these pores will be encountered on every move (fraction of excursion paths encountered = 1), Eq. 3 can be used to predict the excursion path length in the pore needed to yield a given tortuosity. Eq. 3 reduces to the following:

$$\tau = 2.59 + 1.90 \cdot l \tag{4}$$

If retardation of release due to path length considerations is 10 fold greater than what would be expected in a simple system with high connectivity (tortuosity = 3), the tortuosity would be 30. The excursion path length traveled by the diffusant in the pore would be 14 (14 fold greater than a straight forward move from one pore to another). In these cases, the majority of the total path traveled takes place in the pores. Note that this analysis of path length is independent of the number and configuration of narrow channels connecting to a pore, distance between the pores, and pore size. It simply reflects the relative effective distance traveled in a pore as compared to the distance between pores.

In conclusion, the scientist must be suspicious when tortuosity values greater than 2–3 are needed in the modeling of dissolution/diffusional processes for systems with high porosity. Real systems would include matrices with high inherent porosity (such as a compressed tablet), high drug loading, a high loading of soluble components, and systems containing low molecular weight drugs. It is suggested here that values approaching 10 are suspicious; values greater than 10 and approaching 100 are unreasonable. If large values are needed to best fit data, then the conceptual model is flawed, or the other diffusional parameter estimates are in error. Large tortuosity values should not be used as a parameter to fit experimental data for results that cannot otherwise be explained. The simulation approach considerably narrows the previously wide range between tortuosity values considered to be acceptable and unacceptable in these cases.

In specialized cases, such as macromolecules embedded in a diffusional matrix, meaningful tortuosity values could be as large as 30 (one order of magnitude greater than the typical values). Although this assignment to an upper limit is subjective and has not been proven by the model, it is a reasonable statement when considering factors other than path length

that can also lead to retardations of release and diffusion under steady state conditions. Retardations of release due to a prolonged residence time in a pore may be better represented by something other than tortuosity. In any case, if observed tortuosities are on the order of 100 or greater, they are likely not representative of the true effective path length.

## APPENDIX

$C$ = concentration (at the head of the concentration gradient)
$D$ = diffusivity
$\varepsilon$ = porosity
$f$ = fraction of excursion paths encountered
$h$ = barrier thickness
$l$ = excursion path length
$L$ = shortest straight line path length
$L_e$ = effective path length
$m$ = mass
$S$ = surface area
$t$ = time
$\tau$ = tortuosity

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