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New screening methodology for selection of polymeric matrices for transdermal drug delivery devices

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Transdermal drug delivery systems, such as patches, are viewed as one the best technologies that enhance greater patient compliance thus providing the desired therapeutic results. However, one of the main challenges is to find the right polymeric matrix that will provide the desired active therapeutic concentration. This is usually accomplished empirically and is not always the effective approach. In this study, the authors describe a predictive screening methodology based on material parameters to identify materials that will accomplish therapeutic targets.

List of notations

V_c	Active critical volume, cm^3
$\hat{V}_{pj}$	Critical hole free volume, cm^3/mol
T_c	Critical temperature of the active, K
$\hat{V}_{si}$	Molar volume of the pure solvent at a chosen reference temperature, cm^3/mol
$\hat{V}_s$	Solvent molar volume, cm^3/mol
$\hat{V}_{s(0)}$	Molar volume of the equilibrium liquid solvent at 0 K, cm^3/mol
μ	Solute viscosity
C_{1p}	Polymer WLF parameter
C_{2lp}	Polymer WLF parameter, K
C_{ij}	William, Landel, Ferry viscosity constant
D	Patch-active binary mutual diffusion coefficient, cm^2/h
D_o	Einstein–Stokes liquid diffusion coefficient, cm^2/s
E^*	Energy parameter
k	Boltzmann's constant
K_{1p}	Polymer free volume parameter, cm^3/(g K)
K_{1s}	Solvent free volume parameter, cm^3/(g K)
$M_{(t)}$	Amount of active released from the patch at time t, g/cm^3
M_i	Molecular weight of component i
M_∞	Initial active concentration in the patch, g/cm^3
P_c	Active critical pressure, atm
R	Gas constant
R_0	Solute molecular radius
T	Absolute temperature, K
T_g	Glass transition temperature
T_{gi}	Glass transition temperature of component i, K
V_c	Critical solvent molar volume, cm^3/mol
V_{FH}	Average hole free volume of the mixture, cm^3/g
V_i	specific critical hole free volume of component i, cm^3/g
w_i	Mass fraction of component i in the polymer phase
γ	Overlap factor
δ_i	Solubility parameter of component i, (cal/cm^3)$^{1/2}$
ξ	Ratio of solvent to polymer jumping units
ω	Pitzer's accentric factor
η_s	Solvent viscosity, g/(cm s)

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1. Introduction

The delivery of drugs is the basis for the improvement in patient's health. The usual route is to develop such deliveries to be administered orally for improved patient compliance.

However, use of the oral route can cause issues such as the following:

(*1*) Irritation of the gastrointestinal tract (GIT). GIT is the chemical interaction between the drug active and mucosa membranes of the GIT consisting of the upper esophagus to the duodenum region of the intestine that can create discomfort from potential chemical erosion of the membranes. This in turn can make the patient to either skip or discontinue the use of the treatment thus making the patient to no longer abide by the therapeutic regime set by the physician thus effectively delaying the sought after benefits. This is perhaps one of the major issues encountered by physicians when prescribing orally delivered therapies.

(*2*) First pass metabolism or presystemic metabolism, which is defined as the condition in which the bio-available concentration of the drug is significantly reduced when passing through the liver before it is in contact with the bloodstream.[1,2] Therefore, in order to overcome this, the concentration of the drug must be substantially increased in order to take this into effect thus ensuring that the patient receives the correct amount. However, as seen in Figure 1,[3] this can create situations during which the drug is rarely at the desired therapeutic level (TL). This can be either fully below or above the TL, thus practically rendering the treatment inadequate or dangerous.

(*3*) Low patient compliance: in order for any treatment to be effective, the patient must adhere to the regime prescribed by the physician. Besides, the influence of GIT along with busy schedules, people very often skip doses thus rendering the designed procedure to be therapeutically ineffective.

Therefore, alternate drug delivery technologies are highly sought by pharmaceutical companies and physicians alike, thus increasing efficiency, safety and convenience for the patient.

Transdermal drug delivery (TDD) is one of these technologies.[4] TDDs are passive drug delivery systems that provide a constant flow of the drug to the patient through the skin. The advantages of leveraging TDD against any other non-oral delivery can be summarized as follows[4,5]:

The FDA approved the first TDD patch (TDDP) in 1981. The active was scopolamine, and it was for the treatment of motion sickness. In the late 1980s, pharmaceutical companies began developing patches for smoking cessation treatments (nicotine patches) that began to appear in the US market. There are several TDDs in the market today.[4]

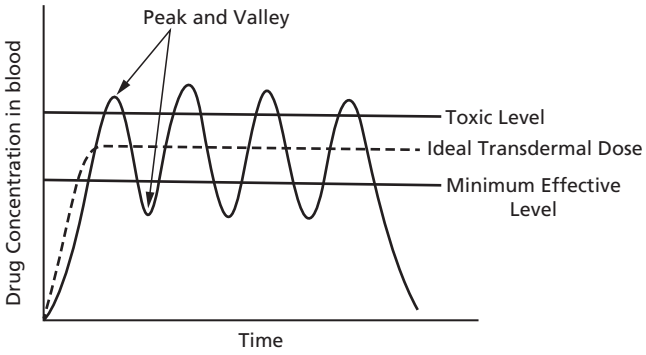

Figure 1. Hypothetical blood-level pattern from a conventional multiple-dose schedule and the idealized pattern from a transdermal controlled release system.[3]

- Complete avoidance of the first pass metabolism through the liver
- Non-GIT incompatibility
- Lower side effects or better plasma–concentration time profiles
- Greater predictability and long period of drug activity
- Increased patient compliance
- Enhanced therapeutic efficacy
- Dose frequency is reduced
- Increased flexibility in ending protocol by simply removing the source
- Noninvasive and ease of implementation/use

The TDD market in 2009, within the USA, was valued at $5·6 billion,[6] and the global market was estimated by Jain Pharma Biotech, to be $12·7 billion in 2005 with expected increases to $21·5 billion and $31·5 billion in 2010 and 2015, respectively.[7] Although, with all the advantages these TDDs can offer, there have been several incidents in which the safety and design have been put to question.[6–8] This has prompted in the redesign of several TDDs. There are 675 patents and patent applications in the USA alone[9]; the majority of these submissions have taken place since the late 1990s. However, from the accomplished work and products seen in the market to date, pharmaceutical companies must continue to develop advanced designs, not because of competition alone, but also from safety concerns raised from citizens and governmental, regulatory agencies alike on the patches sold.

The objective of this article is to propose a new approach on setting a more robust screening methodology for redesigning or designing new TDDP, especially for the ones in which the drug is embedded within the body of the matrix.

2. TDD development

A set of selection rules for materials in TDDP was suggested by Williams.[10] These rules have been well accepted and can be summarized as follows:

(*1*) Selection of a good drug candidate:
  (*a*) Molecular size limited to 300–500 Da
  (*b*) Active release of drug in the range of 1 mg/cm^2/day
  (*c*) $\log P_{octanol/water} = 1 - 3{\cdot}5$, where P is the partition coefficient
  (*d*) Aqueous solubility >100 μg/ml
  (*e*) Daily dose ≤ 10 mg/day
(*2*) Maintain optimum drug saturation, keeping in mind that the thermodynamic activity is the key driving force instead of concentration
(*3*) Drug flux can be optimized by formulation design
(*4*) Use of vehicles/solvents with good partition coefficients can increase dose delivery
(*5*) A drug molecule will continue to move after penetrating the skin

However, the most difficult part is to create a TDDP that will yield the desired dose delivery. Therefore, in addition to Williams' rules, most research work invokes a trial and error process in order to find the polymeric matrix that will release the drug at the desired TLs since drug delivery is determined by the permeation rate in the patch. However, the critical factor in the permeation rate is the diffusion coefficient of the actives through the TDD matrix.

3. Theoretical background

3.1 Diffusion coefficient determination

The diffusion coefficient is derived from Fick's Second Law[11] given by

1. $$\frac{\partial C}{\partial t} = -\frac{\partial J}{\partial x}$$
$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

where, C is the active concentration, *t* is the time, *x* is the traveling distance and D is the diffusion coefficient.

The solution of the equation to a planar surface, a TDDP in this case, when the diffusion coefficient is constant, was shown by Crank[12] to be

2. $$C = \frac{M}{2\sqrt{(\pi Dt)}}\exp\left(-\frac{x^2}{4Dt}\right)$$

In most cases, TDDP systems are designed to deliver under nonsteady state situations in which the following boundary conditions must be in place. Accordingly, Equation 2 can be further simplified as

3. $$\frac{M_t}{M_\infty} = \frac{4}{l}\left(\frac{D}{\pi}\right)^{\frac{1}{2t^2}} \cdots\cdots \text{when } \frac{M_t}{M_\infty} \le 0{\cdot}5$$

where, M_t is the active released from the patch at time *t*, M_∞ is the initial concentration of the active in the patch, D is the diffusion coefficient and *t* is the time of release.

However, diffusion phenomena in TDDS (TDD Systems) must be modeled as small molecule mobility in the macromolecular matrix along with the backbone chemistry as perhaps the main influential factor. Yet, in these types of systems, the mobility is considerably influenced by temperature and concentration. These conditions are mostly pronounced near the glass transition temperature (T_g) where it has been shown that an increase in 1% of the solvent weight fraction in the matrix can effectively increase diffusion (D) by three orders of magnitude. Therefore, significant experimentation is the key to obtaining satisfactory approximation as well as optimization of results for this particular situation that is actually governed by molecular transport. However, this implies that several attempts of trial and error are required to determine the appropriate matrix that will provide the release rate of the solute into the skin to achieve the desired therapeutic effect. However, this approach does not take into account the complexity of the matrix and the molecular shape and size of the active; thus, free volume concept must be considered. Free volume can be simply defined as the difference between the specific volume and the calculated molecular volume. In general terms, the free volume of a polymeric system can be stated as the volume difference between the one at a particular temperature of interest and the one of the same system that would exist at absolute zero. Therefore, free volume can be seen as creating holes where solute can diffuse and pass through. Free volume can be seen as the overall contribution of all the entities present in the matrix, solute and polymer in the TDDS case. From this, it could then be assumed that free volume is the key factor that controls the diffusion of solutes through the polymeric matrix.

This assumption was first suggested by Cohen and Turnbull.[13] They originally thought that this approach was only suited for liquids that could be visualized as the uniform aggregation of hard spheres. However, from the point of view of Cohen and Turnbull, the hard-sphere molecules that would compose an ideal liquid would exist in empty spaces that are created by the nearest neighbors. In other words, the total volume can be seen as two volumetric compartments, one occupied and the other free. The sphere does not have the ability to migrate within its space unless a thermal natural fluctuation would create a gap (vacancy) next to its enclosure. This gap has to be sufficiently large enough to enable the displacement of a spherical molecular entity. The diffusion or molecular movement is deemed successful when the empty space, left behind by a molecule, is then filled by the adjacent molecule. This is a mechanical and not translational motion that does not need a set energy level to surmount an activation energy barrier. Instead of creating gaps by physical displacement of the nearest neighbors, as indicated in the activation energy approach (DiBenedetto,[14] Brandt[15]; Arnould and Laurence[16]), molecular migration is solely based on the constant rearrangement of free volume entities inside

the liquid. Therefore, the mathematical description of the free volume entities could be better described as a probability function in which the diffusion coefficient can be assumed to be proportional to the probability of locating a gap of volume V^* or larger and could be written as

4. $$D = \mathrm{A}\exp\left(\frac{\gamma V^*}{V}\right)$$

where, V^* is the least volume that a molecule can migrate, V is the specific volume and is a numerical factor between 0·5 and 1·0 to account for the overlap between free volume entities such as the free space (gap) shared by the neighboring molecule. A is defined as the proportionality constant that is associated with the kinetic energy. This clearly indicates that the molecular self-diffusion coefficient is an exponential function of the ratio of the molecular size of the diffusing solute to the free volume per molecule of the matrix. Therefore, if the self-diffusion of a solute in a binary type matrix is considered, Equation 4 can be rewritten as follows:

5. $$D_1 = \mathrm{D}_{01}\exp\left(-\frac{\gamma V_1^*}{V_{FH}}\right)$$

where, V_1^* is the critical molar free volume needed for any displaced singularity of species to move, V_{FH} is the free volume per mole of all individual moving solute units in the matrix and D_{01} is the temperature-independent constant.

However, while Cohen and Turnbull define the moving solute unit as a single hard-sphere molecule that undergoes diffusion, this is not the case when dealing with polymeric systems in which the matrix consists of a macromolecular mixture. Yet, an individual solute molecule can be made of several diffusing units that are united by covalent bonds. Therefore, free volume gaps that can easily accommodate whole polymeric entities will not readily form. Rather, solute migration is seen as a series of continuous jumps of small parts along the matrix. This could be further convoluted when low-molecular-weight solute having sufficient size and maneuverability are able to move in a disposition similar to what is seen in polymeric systems that consist of several components of the molecular chain.[16,17] Generalizing the Cohen and Turnbull theory in depicting the motion in binary systems, the molecular shape and size of the solute must be included. This is where Vrentas and Duda[17] introduced the following relationship:

6. $$V_{FH} = \frac{V_{FH}}{\dfrac{\text{Moles of diffusing units}}{\text{g}}} = \frac{V_{FH}}{\left(\dfrac{w_1}{M_{1j}} + \dfrac{w_2}{M_{2j}}\right)}$$

where, VFH is the specific gap free volume of a solute with a weight fraction ω_i of species i and M_{ij} is the molecular weight diffusing units (i = 1 or 2).

However, Vrentas and Duda[17] further simplify this as

7. $$D_\infty = \mathrm{D}_0\exp\left(-\frac{E}{\mathrm{k}T}\right)\exp\left(-\frac{\xi V^*}{V}\right)$$

where, D_∞ is the infinite dilution diffusion coefficient, D_0 is a constant pre-exponential factor, E is the energy which a molecule must possess to overcome attractive forces from the surrounding neighboring entities, V^* is the specific free volume space of polymer needed for molecular jump, V is the space free volume provided by the polymer for solute to diffuse and ξ is the ratio of the solvent critical molar volume jumping unit to the polymer jumping unit.

By combining Equations 5, 6 and 7, the following expression is derived for the diffusion of a solute in a polymeric matrix:

8. $$D_s = \mathrm{D}_0\exp\left(-\frac{E}{\mathrm{k}T}\right)\exp\left(-\frac{\gamma\left[W_s V_s + W_p \xi V_p\right]}{V_{FH}}\right)$$

where, W_s is the weight percent of the solute–drug active present in the matrix, V_s is the volume of the solute or drug active in this case, W_p is the weight percent of the polymer–matrix component, V_p is the volume of the polymer matrix where the active/drug is embedded, ξ is the ratio of the solvent critical molar volume jumping unit to the polymer jumping unit, V_{FH} is the free volume, E is the energy, which a molecule must possess to overcome attractive forces from the surrounding neighboring entities, k is the Boltzmann's constant and T is the temperature at which the diffusion is taking place.

However, if $\overline{V}_{FH}$ is defined as the specific hole free volume in a block copolymer and solute mixture, then the available free volume for molecular diffusion/transport could be written as

9. $$\overline{V}_{FH} = \frac{\widehat{V}_{FH}}{w_1/M_{1j} + w_2\left(W_{2a}/M_{2ja} + W_{2b}/M_{2jb}\right)}$$

where, w_i is the weight fraction of component i (i = 1 or 2), W_{2a} and W_{2b} are the weight fractions of the blocks A and B within the copolymer.

M_{1j}, M_{2ja} and M_{2jb} are the molecular weights of the jumping unit for the solute, copolymers A and B, respectively.

10. $$\xi_{12a} = M_{1j}\,\widehat{V_1^*}\,/\,M_{2ja}\widehat{V_{2a}^*}$$

11. $$\xi_{12b} = M_{1j}\,\widehat{V_1^*}\,/\,M_{2jb}\widehat{V_{2b}^*}$$

Inserting Equations 9, 10 and 11 into Equation 8, the following equation has been obtained:

$$12. \quad D_1 = D_0 \exp\left(-\frac{E}{kT}\right) \exp\left(-\frac{\gamma[W_1\overline{V}_1^* + W_2(W_{2a}\xi_{12a}\overline{V}_{2a}^* + W_{2b}\,\xi_{12b}\overline{V}_{2b}^*)]}{\hat{V}_{FH}}\right)$$

where, V_{2k} (k is for either a or b) is defined as the specific volume of block k in the copolymer at 0 K. In the event that the polymeric system is a homopolymer, then $W_{2a} = 0$ and $W_{2b} = 1$; then Equation 12 is reduced to the original system for solute self-diffusion in a homopolymer as in Equation 8.

4. Experimental details

In this study, nicotine patches were used for this evaluation for two reasons:

(*1*) Nicotine patches have been one of the most predominant (and successful) technologies used to control smoking cessation.
(*2*) These are the most commercially sold TDDP in the market.

The first step was to generate a nicotine UV absorption chart by means of setting a master curve. This master curve was determined from UV readings of various nicotine concentrations in a normal saline solution (0·90% w/v of sodium chloride or about 300 mOsm/l or 9·0 g/l).[18] The reason for using such a system is because the osmolarity of normal saline is a close approximation to the osmolarity of NaCl in blood. Different nicotine concentration solutions were made and UV absorption measurements performed using a Genesys VI UV Spectrophotometer. A UV absorption versus nicotine concentration chart was generated, and the plots were fitted by means of regression. This resulted in a master curve having a linear characteristic with an R^2 = 0·9778, which was deemed acceptable to use as master calibration curve (Figure 2). The nicotine was purchased as 99% active pharmaceutical ingredient from Aceto Chemical.

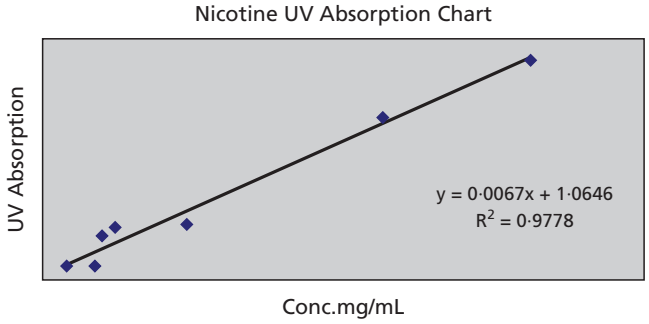

Figure 2. Nicotine UV absorption chart.

The next step was to determine the release from nicotine patches. Samples were purchased from commercially available nicotine patches sold over the counter in the USA. These patches consist of three layers, backing (this is to provide mechanical support as well as protection to the release layer from environmental conditions), nicotine reservoir containing layer that includes the adhesive and the Polyethylene terephthalate disposable piece that is removed when the patch is ready for positioning into the selected area (Figure 3).

The patch used in these experiments was Nicoderm CQ, 7-mg daily dosage patches. Their physical dimensions are 1-inch square with a thickness of 0·229 cm, where the actual thickness of the diffusion layer was estimated to be approximately 0·0113 cm. These patches were assembled into vertical static Franz Cells (Figure 4). Patches from the same lot were used and were placed on top of the Franz cell in direct contact with the saline solution. These patches were secured in place by clamping the top onto the cell body as shown in Figure 5.

The nicotine patch was placed between the top of the cell and the cell body (Figures 4 and 5) in contact with a normal saline solution kept at a constant temperature of 37°C. Samples were taken at 1-h intervals for the first 8 h and then the last one after 24 h. Then, the amount released was estimated as the concentration measured by UV spectrophotometry and the volume present in the vertical static Franz cell reservoir. This was performed in accordance with the FDA SUPAC Guidelines[19] along with those utilized by Thakker

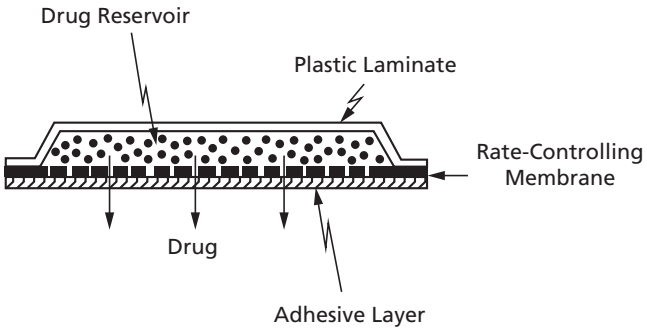

Figure 3. Schematic of a typical commercial nicotine patch.[53]

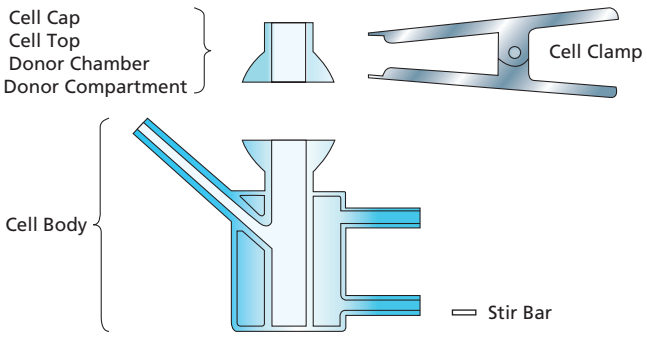

Figure 4. Franz static cell components.[54]

Figure 5. Fully assembled typical Franz static cell.[54]

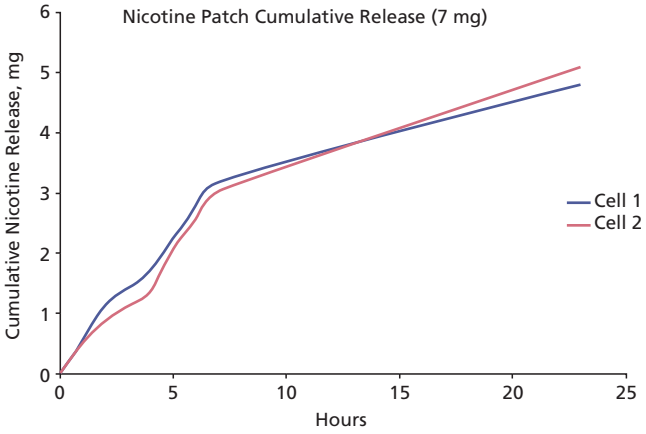

Figure 6. Cumulative nicotine release.

and Chern[20]; Siewert, Dressman, Brown and Shah[21]; Raney, Lehman and Franz[22]; Marangon, Bock and Haltner[23]; Lionberger,[24] Flynn,[25] Hauck, Shah, Shah and Ueda[26] and Addicks, Flynn, Weiner and Chiang.[27] Figure 6 shows the cumulative amount of nicotine released versus time.

The diffusion constant was estimated according to the methodology described by Crank[28] and Miller, Oehler and Kunz[29] as $D = 1{\cdot}467 \times 10^{-9}$ cm^2/s

5. Theoretical approach/calculation of diffusion coefficient D

The next part of this section is the theoretical calculation of the diffusion coefficient by using the Duda and Zielinski Equation 13:

Property	Value	Reference
$\rho_{nicotine}$	1·014 g/cm^3	39,50
M_w	162 g/mole	39,50
$\mu_{nicotine}$	2·9037 centipoises or 0·021 g/cm × s	39,50

Table 1. Summary of properties of nicotine.

$$13.\quad D_1 = D_0 \exp\left(-\frac{E}{kT}\right) \exp\left(-\frac{\gamma[W_1\overline{V}_1^* + W_2(W_{2a}\xi_{12a}\overline{V}_{2a}^* + W_{2b}\xi_{12b}\overline{V}_{2b}^*)]}{\hat{V}_{FH}}\right)$$

5.1 Estimation of properties of nicotine

D_0 is obtained from the Einstein–Stokes equation:

$$14.\quad D_0 = \frac{kT}{6\pi\mu R_0}$$

where, k is the Boltzmann's constant, μ is the solute viscosity and R_0 is the solute molecular radius.

R_0 can be estimated from the volume V that is defined as $(4/3)\pi R_0^3$.

$$15.\quad (4/3)\pi R_0^3 = m/\rho$$

Where, $m = (M_w/N_A)$, M_w is the molecular weight of nicotine, N_A is the Avogadro Number and ρ is the density of nicotine at 37°C. The following properties, summarized in Table 1, are obtained from the literature.

Rewriting Equation 15, we obtain

$$16.\quad \frac{4}{3}\pi R_0^3 = \frac{M_w}{\rho N_A}$$

Then, R_0 can be defined as

$$17.\quad R_0 = \left(\frac{3M_w}{4\pi N_A \rho}\right)^{1/3}$$

Then, $R_0 = 4{\cdot}062 \times 10^{-8}$ cm. Inserting the values for R_0, $\mu_{nicotine}$ into Equation 17, the authors find that $D_0 = 2{\cdot}67 \times 10^{-5}$ cm^{-2} s^{-1}. The Yamada and Gunn[30] (YG) equation was used to calculate V_s

$$18.\quad V_s = V_c\,(0{\cdot}29056 - 0{\cdot}08775\omega)^{\left(1-\frac{T}{T_c}\right)^{2/7}}$$

The YG equation was chosen because it provides the closest value of V_s for molecules such as nicotine. However, in order to estimate the value of *Vs*, the critical volume (V_c), accentric factor (ω), the temperature (T) and critical temperature (T_c) are needed. Since these values are not available from experimental data, they have to be estimated. The acentric factor is estimated from the Pitzer thermodynamic approximations.[31–37] The T_c, P_c and V_c values for nicotine had to be calculated using the group contribution method described by Joback.[38] The reason for choosing this equation was because of the close approximation found in the estimation of pyridine cyclical structures such as nicotine as seen in Figure 7.

19. $$T_c = T_b\,[0\cdot584 - 0\cdot965\,\Sigma G_i - (\Sigma G_i)^2]^{-1}$$

20. $$P_c = [0\cdot113 + 0\cdot0032 \times N_A - \Sigma G_1]^2$$

21. $$V_c = 17\cdot5 + \Sigma G_1$$

In order to obtain the value of T_c for nicotine, the boiling temperature was required and its experimental value was found to be ~247°C or 520·15 K (Figure 8).[39] Table 2 presents a summary of the critical properties of nicotine that have been determined using Equations 20, 21 and 22.[40]

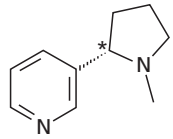

Figure 7. Molecular structure of nicotine.[51]

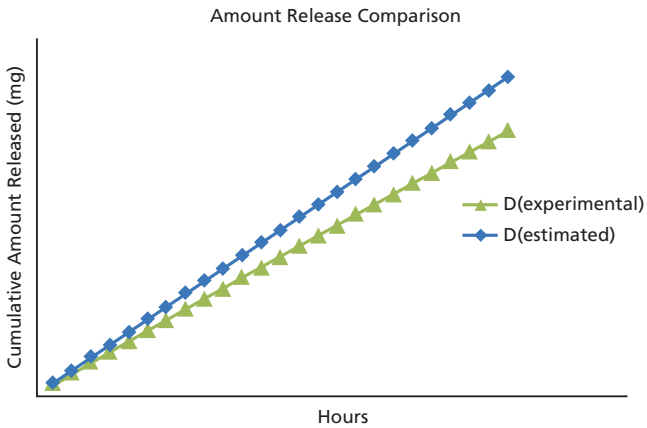

Figure 8. Cumulative release comparison between D_{exp} and D_{calc}.

Property	Value
T_c	749·016 K
P_c	22·6365 atm
V_c	463·5 cm³/mole

Table 2. Summary of critical properties of nicotine.

The accentric factor for nicotine was found to be $\omega_{pr\ (nicotine)} = 0\cdot1432$

Using YG, the values of V_s for nicotine at 37°C (310·15 K) and 0 K (–273·15ºC) were calculated and the results are summarized in Table 3.

5.2 Estimation of the values of Matrix components

As shown by Fierro *et al*.[41]

22. $$\frac{\hat{V}_{FH}}{\gamma} = w_1\left(\frac{K_{11}}{\gamma_1}\right)\left(K_{21} - T_{g1} + T\right) + w_{2a}\left(\frac{K_{12a}}{\gamma_{2a}}\right)\left(K_{22a} - T_{g2a} + T\right) + w_{2a}\left(\frac{K_{2b}}{\gamma_{2b}}\right)\left(K_{22b} - T_{g2b} + T\right)$$

Temperature	V_s (cm³/mole)	V_s (cm³/g)
310·15 K (37°C)	154·606	0·954
0 K	94·002	0·580

Table 3. Summary of volumes of nicotine at 310 and 0 K.

Block element	C_1	C_2	T_g	W_a
Ethylene	17·4[d]	51·6[d]	237[b]	0·5989[c]
Vinyl acetate	15·6[a]	104·4[a]	305[b]	0·399[c]

[a]Ref. 51.
[b]Ref. 40.
[c]Refs. 41,42.
[d]Ref. 52.

Table 4. Physical properties of ethylene and vinyl acetate units/blocks.

Block element	V^*_{2j} (cm³/mole)	V_2 (g/cm³)	K_{1i}/γ	K_{1i}-T_{gi}
Polyethylene	91·392	1·005	$4\cdot825 \times 10^{-4}$	–219·56
Polyvinyl acetate	102·882	0·728[a]	$4\cdot33 \times 10^{-4}$	–258·2

[a]Ref. 51.

Table 5. Summary of results.

where, w_1, w_{2a} and w_{2b} are the weight fractions for nicotine, ethylene and vinyl acetate, respectively.

The free volume parameters used in this study, particularly for polymers, are related to the Williams–Landel–Ferry (WLF)[42] equation constants, C_{1p} and C_{2p}, by the following relationships:

23. $$K_{2p} = C_{2p}$$

24. $$\frac{\gamma V_p}{K_{1p}} = 2 \cdot 303\,(C_{1p})\,(C_{2p})$$

Hong[43] showed how $\hat{V}^*_{2j}$ can be estimated as follows:

25. $$\hat{V}^*_{2j}\,(\mathrm{cm}^3/\mathrm{mol}) = 0 \cdot 0925\,T_{g2}\,(\mathrm{K}) + 69 \cdot 47, \text{ if } T_g < 295\ \mathrm{K}$$

26. $$\hat{V}^*_{2j}(\mathrm{cm}^3/\mathrm{mol}) = 0 \cdot 6334\,T_{g2}\,(\mathrm{K}) + 86 \cdot 95, \text{ if } T_g > 295\ \mathrm{K}$$

Then, taking the values from Table 4 and inserting them into Equations 23, 24 and 26, the values for $\frac{\gamma V_p}{K_{1p}} = 2 \cdot 303\,(C_{1p})(C_{2p})$, $\hat{V}^*_{2j}\ (\mathrm{cm}^3/\mathrm{mol})$ and $K_{li} - T_{gi}$ are obtained and they are summarized in Table 5.

5.3 Values for nicotine

Now, the values for nicotine must be estimated. By leveraging Vrentas' modified version of the Doolittle equation for viscosity,[44]

27. $$\ln \eta_2 = \ln A_2 + \frac{(\gamma V_2^*/K_{12})}{K_{22} + T + T_{g2}}$$

Property	Value
$\frac{(\gamma V_2^*/K_{12})}{K_{22}+T+T_{g2}}$	57·32
K_{11}/γ	3·41 × 10^{-2}
K_{21}-T_{g1}	–121·495
Ξ (nicotine/ethylene)	0·797
Ξ (nicotine/vinyl acetate)	0·577

Table 6. Summary of properties of nicotine.

Property	Ethylene	Vinyl acetate
E_{COH} (J/mol)	9500	25 300
$V_{copolymer}$ (cm³/mole)	32	72

Table 7. Hildebrand coefficients for ethylene and vinyl acetate.

where, $(\gamma V_2^*/K_{12})$ / K_{22} + T+T_{g2} and K_{22} + T are determined from a nonlinear regression using viscosity–temperature data.[44] Results are summarized in Table 6.

We can then obtain the value for $\frac{\hat{V}_{FH}}{\gamma}$ as 0·1465.

5.4 Energy calculations (*E**)

The energy component is calculated from the Tonge and Gilbert[45] equation:

28. $$\log_{10}(E^*) = 0 \cdot 8988 \ln(\log[(\delta_1 - \delta_2)^2\,\hat{V}_s]) + 2 \cdot 8377$$

29. $$\delta = \frac{\sqrt{H - RT}}{\sqrt{V}}$$

30. $$\delta_{(\text{coploymer})} = \sqrt{\frac{E_{COH\ (\text{copolymer})}}{V_{(\text{copolymer})}}}$$

Property	Value
E_{COH} (J/mol)	56 520
V (cm³/mol)	139·7
δ_{NIC} (cal/cm³)	10·02 697

Table 8. Hildebrand coefficients for nicotine.

Parameter	Nicotine	Vinyl acetate	Ethylene
W_s	0·018	0·399	0·5989
$K_{11/\gamma}$	3·41 × 10^{-2}	4·33 × 10^{-4}	4·825 × 10^{-4}
K_{21}-T_{g1}	–121·495	–258·2	–219·56
Ξ (nicotine/ethylene)			0·577
Ξ (nicotine/vinyl acetate)		0·797	
V_i	0·954	0·728	1·005
E^*		8·0722	

Table 9. Parameters used to estimate the theoretical diffusion coefficient.

Property	Value (cm²/s)
D (experimental)	1·467 × 10^{-9}
D (calculated)	1·781 × 10^{-9}

Table 10. Comparison between experimental and calculated values for the diffusion coefficient.

where,

31. $$E_{COH} = m_1 \times E_{COH}(\text{homopolymer of repeat unit1}) + m_2 \times E_{COH}(\text{homopolymer of repeat unit 2})$$

32. $$V_{copolymer} = m_1 \times V(\text{homopolymer of repeat unit 1}) + m_2 \times V(\text{homopolymer of repeat unit 2})$$

33. $$m_i = \frac{\left(\frac{\omega_i}{M_i}\right)}{\sum_{j=1}^{n}\left(\frac{\omega_j}{M_j}\right)}$$

The energy values for ethylene and vinyl acetate were estimated by Van Krevelen[46,47] as shown in Table 7.

Then, using the results from Table 7 and Equations 31, 32 and 33, the energy value for the EVA copolymer is found to be 55·66 $(cal/cm^3)^{0.5}$.

Because no values were found in the literature for nicotine, they had to be estimated by using the Fedor's equation/model.[48] This model uses the structure to calculate the approximate values of E_{COH} and volume and this in turn yields the Hildebrand coefficient. The results are summarized in Table 8.

Then inserting the values for δ_{NIC} and δ_{pol} into Equation 28, E^* was found to be 8·0722 cal/mol.

6. Results and discussion

Then, inserting all the values listed in Table 9 into Equation 14, the value of the diffusion coefficient was estimated to be $1{\cdot}781 \times 10^{-9}$ cm^2/s.

In Table 10, a comparison between the experimental and calculated values of the diffusion coefficient is presented.

Wong *et al.*[49] in US patent 5603947, have reported typical diffusion coefficient values, that were experimentally determined, in nicotine patches to be between 10^{-8} and 10^{-9} cm^2/s. This is in accord with the experimental and theoretical values obtained in this research. Therefore, this study shows that the Duda Zelinsky equation[55] can be used to obtain a good approximation of the diffusion coefficient of polymeric matrices.

7. Conclusions

The authors have successfully demonstrated that the Duda Zelinsky equation can be used as a good screening tool to determine the best polymeric matrices that will deliver the therapeutically required amount of the active. The authors also showed that careful consideration is required when selecting the right model to determine the physical parameters that are not experimentally available. This methodology can help to minimize the amount of experimental work required thus helping to expedite the selection of the best TDDP material.

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