Tropical Journal of Pharmaceutical Research, June 2005; 4 (1): 355-362

Research Article

Limitation observed in the application of the three dimensional solubility parameters to the coating formulation of poly (3-hydroxybutyrate-hydroxyvalerate) systems

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Abstract

Purpose: *Poly (3-hydroxybutyrate-hydroxyvalerate) displayed high dipole-dipole interaction, a high hydrogen bonding but low polar interaction, and was therefore expected to be miscible with solvents/plasticizers that exhibit similar pattern of cohesive interaction. To determine the applicability, or otherwise of the theory of the three dimensional solubility parameters to the formulation of poly (3-hydroxybutyrate-hydroxyvalerate) polymeric coating system, and hence identify any limitation in the application of the theory. This aspect was investigated in the study.*
Method: *The structural group contribution method was employed to compute the partial and total solubility parameters of the compounds – the biopol polymer, a series of organic solvents and plasticizers. The computed partial solubility parameters included: dipole-dipole (δ_d), polar (δ_p) and hydrogen bonding (δ_h). Following a standard procedure in the literatures, the δ_d and δ_p values were combined to form a composite solubility parameter, δ_v: where $\delta_v = \sqrt{\delta_d^2 + \delta_p^2}$. A plot of δ_h versus δ_v gave the energy maps, which depicted the energy levels of the various compounds and from which the miscibility of the compounds were predicted.*
The closer the position of the solvent or plasticizer to the polymer in the map, the greater, the probability of mixing. Cast films of the various polymeric formulations were made and examined for homogeneity by scanning electron microscopy.
Results: *It was possible to select suitable plasticizers that were miscible with the polymer by applying theory of solubility parameters. The prediction for the solvents was, however, erroneous and this may be attributable to the inability of the δ_v parameter to clearly reflect the differences between the δ_d and δ_p interactions of the polymer on the one hand and those of the various solvents in all situations on the other hand. This means that in certain instances, the δ_v values of the polymer and the solvents were similar even though their δ_d and δ_p interactions were dissimilar.*
Conclusion: *The analysis of the data showed that the composite solubility parameter δ_v of compounds could be similar even though the actual energies of δ_d and δ_p interactions are different. This is a limitation in the application of the theory of the three dimensional solubility parameters.*

Key words: *Solubility parameters, cohesive energy, miscibility of compounds, poly (3-hydroxybutyrate-hydroxyvalerate) system.*

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Introduction

The term solubility parameter (δ) is defined as the square root of the cohesive energy density (E/V) of a compound[1], thus:

$$\delta = \sqrt{E/V} \qquad (1)$$

where E is the molar cohesive energy of a compound of molar volume, V. The total solubility parameter (δ_t) is made up of three partial or component cohesive interactions namely: dipole - dipole (δ_d), polar (δ_p), and hydrogen bonding (δ_h) interactions. Thus:

$$\delta_t = \delta_d + \delta_p + \delta_h \qquad (2)$$

The corresponding expression for the total molar cohesive energy is:

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad (3)$$

The theory of solubility parameters has application in the prediction of miscibility of compounds by simulation studies[2, 3, 4, 5]. In such simulations, similarity in the total or partial solubility parameters of the compounds determines their miscibility. The total solubility parameter is applicable to non-polar compounds only where the dipole-dipole interaction is predominant over other forces of interaction[6]. With polar compounds, the two dimensional solubility parameter is applied whereby δ_p is plotted against δ_d to obtain energy maps, which depict the energy levels of the various compounds under test. Rowe applied the energy maps of the two dimensional solubility parameters to predict miscibility between ethyl cellulose and hydroxypropyl cellulose and the miscibility of plasticizers with the polymer blends[7]. However, such two dimensional based maps could not be used to select or predict the solvents and plasticizers that are miscible with the acrylatemethacrylate copolymer where the dipole-dipole interactions are considerable and should therefore be considered with the other forces of interaction in the simulation. With this type of compounds, the three dimensional solubility parameters is applied whereby the δ_d and δ_p interactions are combined to form a composite solubility parameter designated δ_v[8]. Two of the three parameters are combined since it is not possible to represent all three parameters graphically as y-x plots. A plot of δ_h versus δ_v yields the energy maps from which miscibility can be predicted. Closeness of the compounds to each other in the map implies miscibility. By this approach, all three-component interactions (δ_d, δ_p, and δ_h) are considered together in determining the energy level of a compound. From Eqn. 3, the value of δ_v is given by:

$$\delta_v^2 = \delta_d^2 + \delta_p^2 \qquad (4)$$

or

$$\delta_v = \sqrt{\delta_d^2 + \delta_p^2} \qquad (5)$$

The distance between the positions of any two compounds in the map is a measure of the exchange cohesive energy ($\Delta^2\delta$), which must be overcome for the interaction to occur. The lower the $\Delta^2\delta$ value the greater the probability of miscibility. The $\Delta^2\delta$ value is given by the expression[5, 8]:

$$\Delta^2\delta = \Delta^2\delta_h + \Delta^2\delta_v \qquad (6)$$

For a polymer (P) and solvent (S), $\Delta^2\delta_h = [\delta_h(P) - \delta_h(S)]^2$ and $\Delta^2\delta_v = [\delta_v(P) - \delta_v(S)]^2$. The $\Delta^2\delta$ values for the polymer – plasticizer interactions are similarly obtained.

The three dimensional solubility parameters have been used to predict accurately the skin permeability and intestinal absorption of various drugs[5, 9]. Eichie et al also employed these parameters to select plasticizers and solvents, which are miscible with the acrylate methcrylate copolymers[10]. However in this report we present evidence to show that there is an identifiable limitation in the general application of the theory. The formulation of poly (3-hydroxybutyrate-hydroxyvalerate) polymeric coating system is used as a case in point.

Materials and Methods

The test polymer poly (3-hydroxylbutyrate – hydroxylvalerate) was received under the trade name, Biopol®, from Zeneca Bioproducts, Monsanto, Portugal. Its chemical structure is given in Fig. 1. It is water insoluble but swellable in aqueous fluids. It has been investigated as a biodegradable polymer for slow biorelease of drugs[11, 12]. The solvents and plasticizers employed for the miscibility tests were all of reagent grade (BDH) and are listed in Tables 1 and 2.

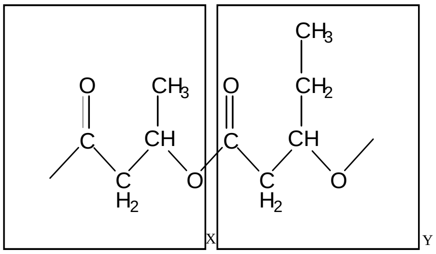


Fig. 1: Chemical structure of biopol. showing the various structural groups

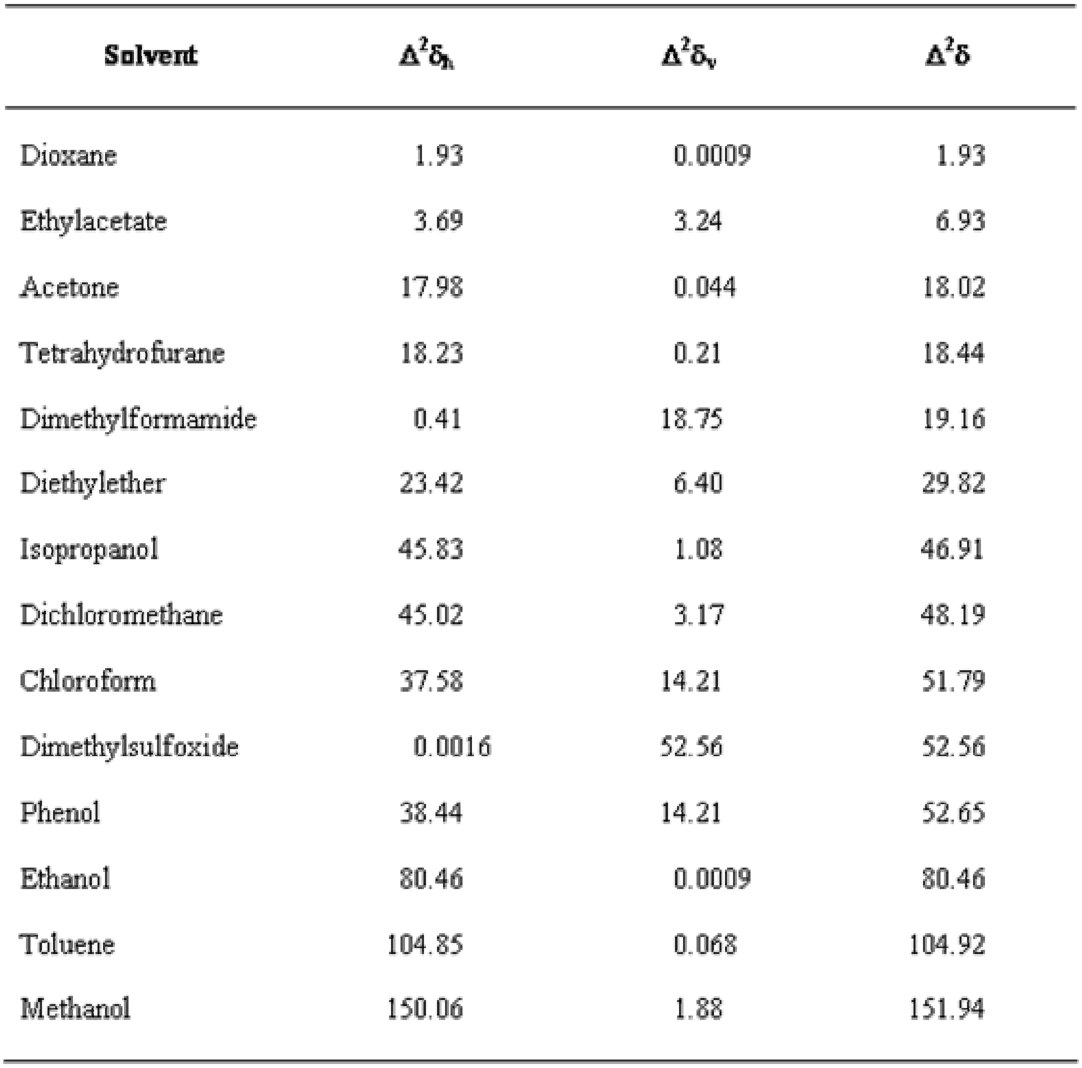
Computation of the partial solubility parameters

The partial solubility parameters, δ_d, δ_p and δ_h, for each compound were calculated using the published values of the partial molar cohesive energy (due to dipole, polar, or hydrogen bonding) of each structural group in the compound[13], designated F_d, F_p or F_h respectively, and the published molar volumes of such structural groups[14]. Details of the procedure have been published earlier [5, 9,10]. Essentially, the known values of the molar cohesive energies for the various structural groups and the corresponding molar volumes (V) of the structural groups are typed into an advanced parameter set, based on a computer programme, SPWin® version 2, developed by Groning and Braun[5]. The partial solubility parameter of each structural group is given by

Table 1: Calculated values of the solubility parameters of the compounds

Compound	Solubility parameters ($J.cm^{-3}.mol^{-1}$)				
	δ_d	δ_h	δ_p	δ_v	δ_t
Polymer	17.41	10.24	0.48	17.41	20.20
Solvents					
Acetone	14.67	6.00	9.72	17.62	18.59
Chloroform	20.14	4.11	6.56	21.18	21.58
Dichloromethane	18.25	3.53	5.92	19.19	19.51
Dioxane	16.89	8.85	4.10	17.38	19.50
Ethanol	15.10	19.21	8.72	17.44	25.94
Isopropanol	14.87	17.01	6.84	16.37	23.61
Tetrahydrofurane	16.27	5.97	4.75	16.95	17.97
Toluene	17.64	0.00	1.05	17.67	17.67
Plasticizers					
Acetyltributylcitrate	16.87	8.77	2.69	17.09	19.20
Acetyltriethylcitrate	16.91	10.23	3.67	17.30	20.10
Dibutylphthalate	17.90	7.45	2.78	18.11	19.59
Diethylphthalate	18.28	8.64	3.74	18.66	20.56
Glycerol	17.81	29.24	11.10	20.98	35.99
Paraffin	16.15	0.00	0.00	16.15	16.15
Sorbitol	19.96	33.61	10.38	22.50	40.45
Triacetin	16.42	10.63	4.57	17.05	20.09
Tributylcitrate	17.03	11.22	2.95	17.28	20.61
Triethylcitrate	17.13	13.39	4.20	17.64	14.48

Table 2: Exchange cohesive energy ($\Delta^2\delta$) for the interaction between biopol and solvents based on three- dimensional analysis.



Solvent	$\Delta^2\delta_h$	$\Delta^2\delta_v$	$\Delta^2\delta$
Dioxane	1.93	0.0009	1.93
Ethylacetate	3.69	3.24	6.93
Acetone	17.98	0.044	18.02
Tetrahydrofurane	18.23	0.21	18.44
Dimethylformamide	0.41	18.75	19.16
Diethylether	23.42	6.40	29.82
Isopropanol	45.83	1.08	46.91
Dichloromethane	45.02	3.17	48.19
Chloroform	37.58	14.21	51.79
Dimethylsulfoxide	0.0016	52.56	52.56
Phenol	38.44	14.21	52.65
Ethanol	80.46	0.0009	80.46
Toluene	104.85	0.068	104.92
Methanol	150.06	1.88	151.94

$\sqrt{F/V}$ and the total contribution by all the structural groups in the compound is given by: $\sum(\sqrt{F/V})$. The δ_p interactions of the compound will, for instance be given by:

$$\delta_p = \sum(\sqrt{F_p/V}) \qquad (7)$$

Construction of energy maps and calculation of the exchange cohesive energies ($\Delta^2\delta$).

To obtain the energy maps for the compounds, the computed values of the partial solubility parameters due to hydrogen bonding (δ_h) were plotted against the combined values for polar and dispersion interactions (δ_v Eqn 5) for the polymer, solvents, and the plasticizers. The δ_h

versus δ_v plots showed the specific energy locations of the compounds. The energy difference between any two compounds in the energy map is the exchange cohesive energy ($\Delta^2\delta$) needed for the interaction. The values for the polymer-solvent or polymer-plasticizer interactions were calculated from Eqn 6.

Test for polymer – solvent and polymer – plasticizer miscibility

Free films of thickness, 11±1.47µm were formed by casting a solution of the polymer (3ml, 10%w/v) on a glass plate, allowing 24h drying time at room temperature 20°C. The films were peeled off from the substrate with a knife. Samples of the free film surface were mounted on the specimen stub and vacuum coated with a thin gold shadow using the Balzer Union evaporator (Model: SCD 040). The coated specimens were examined at various magnifications using electron microscopy (model: Stereoscan S4 TL 10701 –OM- 96118, Cambridge, England). A homogenous film surface indicated compatibility while an inhomogenous surface indicated incompatibility of the solvent or plasticizer with the polymer.

Results

Calculated values of the solubility parameters.

These are presented in Table 1 (for the polymer, the solvents and plasticizers), the parameters include the δ_d, δ_h, δ_p,δ_v and d_t values. The first observation is that the polar interaction of the polymer was considerably lower than those of the solvents and the plasticizers. The solvents in turn were more polar than the plasticizers. Some of the solvents displayed similar δ_v values as the polymer even though their δ_p interactions (component of δ_v) were markedly different from those of the polymer. These solvents include: acetone, dioxane, ethanol, tetrahydrofurane, and toluene. This means that the δ_v parameter did not clearly reflect the difference in the δ_p interactions of the solvents compared with the polymer in these instances. Of these four solvents, dioxane also had similar values of δ_h as the polymer. Some of the plasticizers also had similar δ_v values as the polymer (Table 1). These include acetyltributylcitrate, acetyltriethylcitrate, triacetin, tributylcitrate, and triethylcitrate. However, in this case, their δ_p values were closer to that of the polymer than was the case with the solvents. Thus in these situations, δ_v more accurately reflected the pattern of the δ_d and δ_p interactions in both the polymer and the plasticizers.

The energy maps and the exchange cohesive energies ($\Delta^2\delta$) for prediction of compound miscibility.

The energy maps for the polymer – solvent, and the polymer – plasticizer interaction are presented in Figs 2 and 3, respectively. The exchange cohesive energy values are in Tables 3 and 4. Dioxane with $\Delta^2\delta$ value 1.93 $J.cm^{-3}.mol^{-1}$ was closest to the polymer in the map (Fig.2). Theoretically, this solvent should be miscible with the polymer. In practice, the polymer was not miscible with dioxane, rather it was only

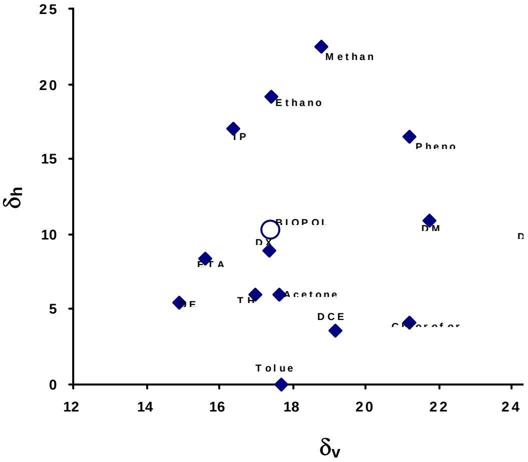


Figure. 2: Energy map showing the energy levels of the various plasticizers and the polymer (three dimensional analysis): DCM = dichloromethane, DEE = diethylether, DMF = dimethylformamide, DMS = dimethylsulfoxide, DX = dioxane, ETA = ethylacetate, IPP = isopropanol, THF = tetrahydrofurane

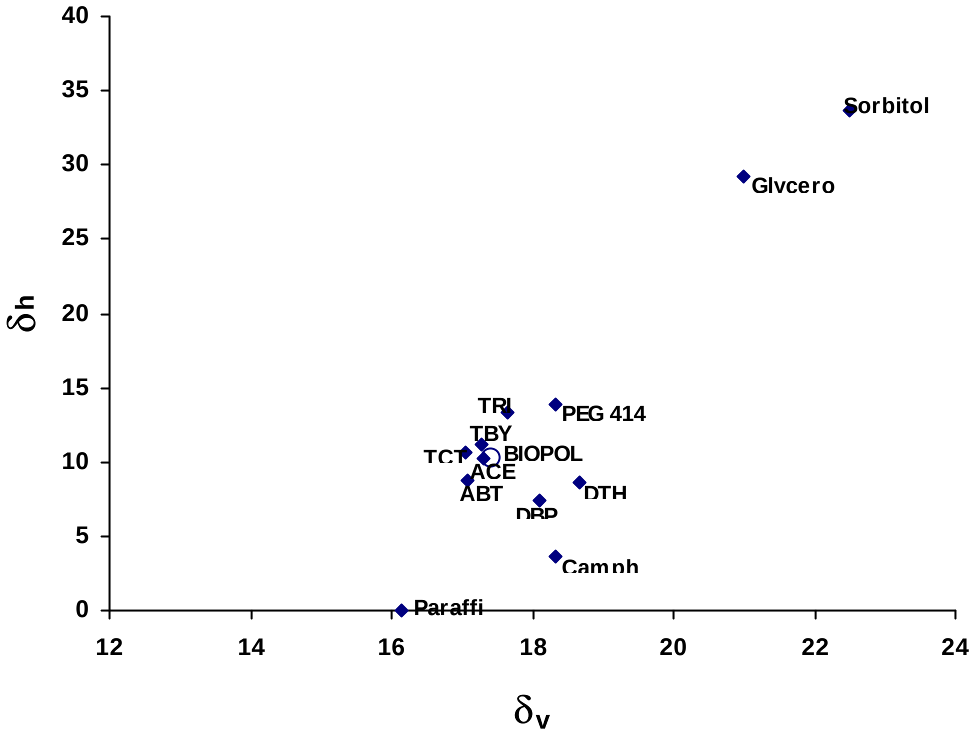


Figure. 3: Energy map showing the energy levels of the various plasticizers and the polymer (three dimensional analysis): ABT = acetyltributylcitrate, ACE = acetyltriethylcitrate, DBP = dibutylphthalate, DTH = diethylphthalate, TCT = triacetin, TBY = tributylcitrate, TRI = triethylcitrate

partially miscible with dichloromethane ($\Delta^2\delta$ = 48.19 Jcm^{-3}mol^{-1}) forming a homogenous colloidal solution. The scanning electron micrographs (SEM) of films cast from these two solvents are shown in Fig 4. The film cast from dichloromethane revealed a homogenous surface while the dioxane cast films were inhomogeneous. Solvents with lower $\Delta^2\delta$ values including dioxane were not miscible with the polymer as theoretically expected, meaning that the prediction was erroneous.

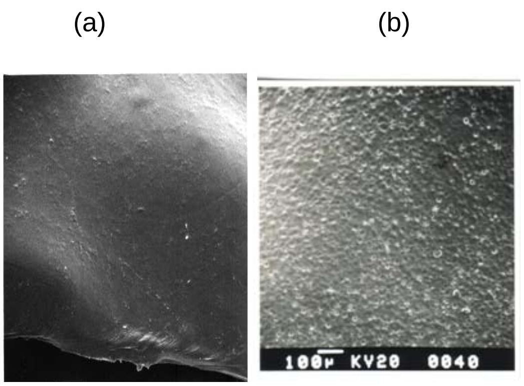


Fig.4: SEM of free films showing: (a) homogenous surface of polymer cast from dichloromethane (indicating miscibility), (b) inhomogenous surface of film cast from dioxane (indicating incompatibility)

In the case of the polymer/plasticizer systems, the following palsticizers were close to the polymer in the energy map (Fig.3): acetyltriethylcitrate, triacetin tributylcitrate, acetyltributylcitrate, and dibutylphthalate. Their $\Delta^2\delta$ values were also low ≤ 4.12 Jcm^{-3}mol^{-1} (Table 3). In practice, these plasticizers were miscible with the polymer, as evidenced by the SEM of resulting films. Thus the plasticizers which clustered around the polymer in the energy maps were actually miscible with the polymer.

Discussion

In the application of the three dimensional solubility parameters, the δ_d and δ_p interactions are usually combined to form a composite solubility parameter δ_v, to allow the plotting of the energy data in a y-x form[5, 8, 10]. The intention is that by plotting δ_h versus δ_v, compounds of similar δ_d, δ_p and δ_h interactions will be close to each other in the resulting energy maps, indicating miscibility. This implies that where two compounds have similar δ_v values, their δ_d and δ_p values should also be similar for miscibility to occur. In the case of the polymer – solvent systems studied, it was identified that some of the solvents (e.g. dioxane), which the theory predicted as miscible with the polymer actually had similar δ_v values as the polymer, whereas their δ_d, and δ_p interactions were in fact different from those of the polymer (Table 1). Of particular notice is that these solvents were considerably more polar than the polymer. The inability of δ_v to clearly reflect difference in the pattern of the δ_d, and δ_p interactions in the polymer and in the solvents in all situations thus accounted for the erroneous prediction.

Table 3: Exchange cohesive energy ($J.cm^{-3}.mol^{-1}$) for the interaction between biopol and the plasticizers based on three dimensional consideration.

Plasticizer	$\Delta^2\delta_h$	$\Delta^2\delta_v$	$\Delta^2\delta$
Acetyltriethylcitrate	0.0001	0.01	0.01
Triacetin	0.15	0.13	0.28
Tributylcitrate	0.96	0.17	0.98
Acetyltributylcitrate	2.16	0.10	2.26
Diethylphthalate	2.56	1.56	4.12
Dibutylphthalate	7.78	0.49	8.27
Triethylcitrate	9.92	0.05	9.97
PEG 414	13.40	0.85	14.25
Camphor	43.80	0.83	44.65
Paraffin	104.86	1.59	106.45
Glycerol	361.00	12.75	373.75
Sorbitol	546.16	25.91	572.07

In the case of the polymer/plascitizer systems, it was identified that the plasticizers (e.g. acetyltrietylcitrate), which the theory predicted as miscible with the polymer, had similar δ_v values as the polymer. Their δ_d and δ_p interactions were also similar to those of the polymer, which explains why in this case the prediction was accurate. The plasticizers were also more polar than the polymer, but the difference was not as exaggerated as was with the solvents.

Conclusion

The study has shown that the composite solubility parameter δ_v does not clearly reflect the difference in pattern of δ_d and δ_p interactions in all situations, which is a limitation in the application of the theory of the three dimensional solubility parameters. Thus, the theory will only be applicable to systems where similarity in the δ_v parameters of the compounds also implies that the δ_d and/or δ_p interactions are also similar.

Acknowledgement

The authors wish to thank Deutscher Akadedmischer Austausdienst (DAAD) Germany for sponsoring this collaborative research.

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