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Original Article

Hansen Solubility Parameter Approach in the Screening of Lipid Excipients for the Development of Lipid Nano Carriers

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ABSTRACT

Background: The complex physicochemical properties of the lipids have considerable impact on the solubility and stability of the Lipid Based Nanocarriers (LBN). The major challenge in the successful development of LBN lies on the selection of suitable lipid and its ability to achieve high drug payloads. The wet lab screening of lipids is time consuming and economically not viable. Therefore, the present research aims to apply Hansen solubility parameters to predict the solubility/miscibility of 5-Fluorouracil (5FU) and curcumin in various lipids. **Materials and Methods:** The apparent solubility of 5FU and curcumin in various lipids were determined by shake flask method. Theoretical predictions of Hansen Solubility Parameter (HSP) for lipids and actives were done by group contribution method proposed by van Krevelen. The various molecular descriptors of 5FU, curcumin and the range of lipids are obtained from Qikprop predictions, version 4.4, Schrodinger. **Results:** Lipids exhibit low dispersion force component (δ_D) than 5FU and curcumin indicating that they are poor solvents; rather the polar and hydrogen bonding components might have contributed to the solubility of the actives in lipids. Hence, the actives are more soluble in those lipids with free -OH groups as in case of Maisine CC, Labrafac PG and Compritol 888 ATO which is in good correlation with the experimental values. **Conclusion:** The HSP sphere radius provides an insight to screen the excipients prior to wet lab experiments. Thus, the HSP approach can be utilized as a promising tool in the preliminary screening of lipid excipients in the development of lipid nanoparticles.

Keywords: Solubility parameter, Computational Pharmaceutics, Curcumin, 5-FU, Solubility.

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INTRODUCTION

Most of the chemotherapeutic agents fall under the category of sparingly water-soluble drugs resulting in very low dissolution rates and bioavailability. Lipid drug delivery systems are the excellent platform to deliver these type of drug molecules to the target site i.e., the cancerous cells by passive targeting. Amidst the diverse lipid drug delivery systems, Nanostructured Lipid Carriers (NLCs) spring up as second generation lipid nano carriers with the advantages of high drug payload, greater stability and reduced drug leakage.[1] NLCs are binary mixtures of solid and liquid lipids dispersed in an aqueous phase containing surfactants. Also, lipid nano carriers owe the benefits of biodegradability and compatibility as the lipids employed would belong to the category of generally regard as safe. The major challenge in the development of lipid nano carriers is to attain high drug pay load and stability, which is anticipated as loading capacity and entrapment efficiency of the developed formulation. Thus, it is essential to achieve high loading capacity and thereby to ensure sufficient solubility of the drug in the lipids. Accordingly, the screening of various lipids for their solubilising potential by performing trial and error method is highly tedious, time consuming and expensive. Furthermore, solubilisation of actives in lipids involve various kinetic and thermodynamic factors such as crystal structure, hydrophilicity, surface charge, molecular volume and so forth.[2]

The aforementioned can be surmount with the evolution of computational pharmaceutics approach.[3] Currently, the *in silico* pharmaceutical formulation design have become a part of the drug development research. Computational pharmaceutics involve the application of *in silico* tools as Flory-Huggins, Molecular dynamics and docking, artificial intelligence and machine learning in the prediction of solubility of drugs in lipids as well to some extent the drug loading in lipid based formulations.[4-6] These tools aid to appreciate the influencing physicochemical properties of the drugs with their solubility.

Solubility Parameter (SP) which relates the solvency behaviour of a particular solvent was proposed by Hildebrand and co-workers

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emphasizing the general principle of "like dissolves like". It is defined as the square root of the cohesive energy density of a compound and represented in terms of molar heat of vaporization and molar volume of the substance[7] which is given in equation 1.

$$\delta = \sqrt{C.E.D}\ ;\ \delta = \sqrt{\frac{\Delta Hv - RT}{Vm}} \quad \text{(1)}$$

Hildebrand SP theory is limited to regular solutions and fails to meet the complex systems such as the pharmaceutical substances. Hansen Solubility Parameter (HSP) is the extension of the Hildebrand concept in which the total cohesive energy comprises of three components namely, dispersion forces, dipole-dipole forces and hydrogen bonding forces. It is possible to calculate the partial solubility parameters from the chemical structure of the drug using the group contribution methods proposed by van Krevelen-Hoftzer, Hoy and Fedors.[8] The partial solubility parameters can be estimated from the various attraction constants which include F_{di}, molar attraction constant due to dispersion component, F_{pi}, molar attraction constant due to the polar component, E_{hi}, hydrogen bonding energy and V (molar volume). The total HSP is presented as follows in equation 2.

$$\delta_T = \sqrt{\delta_d^{\,2} + \delta_p^{\,2} + \delta_h^{\,2}} \quad \text{(2)}$$

$$\delta_d = \frac{\sum F_{di}}{V};\ \delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V};\ \delta_h = \sqrt{\frac{\sum E_{hi}}{V}} \quad \text{(3)}$$

The partial solubility parameters can be determined individually by using the equation 3.

$$R_a = \sqrt{4*(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2} \quad \text{(4)}$$

The hypothetical radius of interaction (R_0) or the Hansen solubility parameter space of any drug/solute can be obtained by performing the solubility analysis in about 20 to 30 different solvents and grouping them as good or bad solvents. The solubility analysis might be by simple visual observation or any other suitable method of estimation. It is understood that the solute and solvent are miscible if their Radius of interaction (R_a) calculated using equation 4 lies within the hypothetical Radius of interaction (R_0).

In addition, the actives and lipid (excipients) are said to be miscible when their partial solubility components exhibit similar value.[9-11] Various approaches are put forward to predict the probability of miscibility/ solubility of drugs in solvent/polymer or excipients. Van Krevelen and Hofzter introduced the term$\Delta\delta$ as in equation 5 as one of the approaches and suggested the possibility of higher miscibility at the $\Delta\delta$ values less than 5 $MPa^{1/2}$. Nevertheless, the most widely used and validated method[12-14] of approach was given by Greenhalgh, which emphasizes the difference in total solubility parameter between two components to be less than 7 $MPa^{1/2}$ for their miscibility. Also, the approach has demonstrated that the components would be immiscible provided the $\Delta\ \delta$ greater than 10 $MPa^{1/2}$.

$$\Delta\delta = \sqrt{(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2} \quad \text{(5)}$$

$$\Delta\delta = |\ \delta_{T2} - \delta_{T1}\ | \quad \text{(6)}$$

Previously, HSPs were applied in the prediction of miscibility/ solubility of drug with excipients/polymeric carriers in solid dispersions,[15-17] co-crystal formation.[12] In recent years, many studies have been carried to predict the drug payload in various lipid and polymeric nanocarriers employing HSP approaches.[9,18-20]

The study involves the loading of dual drugs namely 5FU and curcumin into the nanostructured lipid matrix. However, they demonstrate different physicochemical properties, in which the former belong to BCS class III with high solubility and the latter falling under BCS class IV with low solubility. Thus, it is essential to screen a suitable lipid combination for solubilizing both the drugs and to identify the various factors influencing the solubilization. In light of the above considerations, it led to the search for a suitable *in silico* tool to aid in the screening of various lipid excipients. Accordingly, the present research aims to manifest the effectiveness of Hansen solubility parameters as a tool to predict the solubility/miscibility of 5-Fluorouracil (5FU) and Curcumin in various lipids.

MATERIALS AND METHODS

5 Fluorouracil was purchased from Otto Chemie Pvt. Ltd., Mumbai; Curcumin was obtained as gift sample from Zeus Hygia Life Sciences Pvt. Ltd., Hyderabad; Compritol 888ATO, Maisine CC, Precirol ATO 5, Labrasol, Labrafac PG were kindly provided as gift samples by Gattefosse India Pvt. Ltd., Mumbai; Glyceryl monoleate was acquired as sample from Mohini organics, Mumbai.

Screening of Liquid Lipids

The apparent saturation solubility of 5FU, CUR in different liquid lipids (Labrafac PG, Oleic acid, Maisine CC) was determined by placing the tube containing an excess quantity of the actives in a shaking water bath for 72 hr at 25°C. It is then capped and stirred to attain equilibrium. Finally, centrifuged at 4,000 rpm and 4°C for 30 min. The supernatant was quantified appropriately.[21]

Screening of Solid Lipids

First excess of the actives was placed in 10 mL of water in test-tube, to achieve the saturation solubility. The solids remaining were removed by filtration and 100 mg of solid lipid was added to each test-tube. Then, all the test-tubes were subjected to shaking by placing in a water bath at 75°C for 1 hr followed by cooling at room temperature. The congealed solid lipids were removed and dissolved in chloroform separately. The amount of actives entrapped in the solid lipid solution was estimated by UV-visible spectrophotometer.[21]

Hansen solubility parameter calculations and Optimal fitting of HSP

Hansen solubility parameter predictions are done by group contribution method proposed by van Krevelen for the range of lipids, 5FU and curcumin.[7,22] The composition of the lipids as specified in the manufacturer information sheets and their partial and total solubility parameter were calculated and shown in Table 1. Based on the composition of the lipids, the HSP values are calculated and a sample calculation is presented in Table 2. The binary solubility data was obtained using different solvents by classic binary fit method[10] in which the solvents are assigned scores as 0 and 1 to classify them as bad and good solvents respectively (data not shown). The solubility of 5FU and curcumin in the solvents are established by visual inspection for clear solution at the end of 24, 48 and 72 hr and assigned the score 1. Those with turbidity or sediment are given the score of 0. The data are fed into the HSPiP software to obtain HSP sphere with optimal fit value.

RESULTS

Experimental screening of liquid and solid Lipids

The solubility of actives in lipids is essential for maximum entrapment of the drug in the lipid nanocarrier matrix. The apparent solubility's of 5FU and curcumin in the selected lipids were determined and are represented in Figure 1.

Theoretical screening of solid and Liquid Lipids

The chemical structure of the molecules under study are given in Figure 2. The physicochemical properties and the various molecular descriptors of all the lipids, curcumin and 5FU are predicted using QikProp, version 4.4, Schrödinger, LLC, New York, NY, 2015 and presented in Table 3.

All the lipids and actives partial solubility parameters were calculated based on the group contribution method as proposed by van-Krevelen. The values are summarized in Table 4. The partial and total solubility parameter values of all the components are in agreement with the previously reported results.[9,19,23-25] Generally, it was observed that the dispersion force components of all the lipids remains closer which can be related to their corresponding change in molar volume. However, they differ in their polar and

Table 1: Trade name, chemical constituents and their percent composition of various lipid mixtures used in the study.

Lipid (Trade Name)	Chemical Constituents	Percent Composition	δ_D (MPa$^{1/2}$)	δ_P (MPa$^{1/2}$)	δ_H (MPa$^{1/2}$)	δ_T (MPa$^{1/2}$)
Maisine® CC	Glyceryl monolinoleate	34.5% w/w	16.83	3.18	11.59	20.68
	Glyceryl dilinoleate	52.4% w/w	16.49	1.72	7.30	18.11
	Glyceryl trilinoleate	12.6% w/w	16.36	1.59	4.76	17.11
Labrafac™ PG	Propylene glycol dicaprylate	56.3% w/w	18.46	4.25	7.44	20.35
	Propylene glycol dicaprate	42.7% w/w	15.01	3.89	7.12	17.06
Compritol® 888 ATO	Glyceryl monobehenate	17.9% w/w	17.07	2.62	10.52	20.23
	Glyceryl dibehenate	51.5% w/w	16.81	1.40	6.57	18.10
	Glyceryl tribehenate	28.8% w/w	16.71	1.28	4.27	17.30
Precirol® ATO 5	Glyceryl monostearate	18.3 % w/w	17.12	3.09	11.42	20.82
	Glyceryl monopalmitate		17.16	3.39	11.97	21.19
	Glyceryl distearate	52.9% w/w	16.82	1.67	7.18	18.6
	Glyceryl dipalmitate		16.82	1.85	7.56	18.54
	Glyceryl tripalmitate	27.6% w/w	16.70	1.71	4.94	17.49
	Glyceryl tristearate		16.70	1.53	4.68	17.41
Glyceryl monoleate	Glycerol mono ester of oleic acid	55% w/w of monoglyceride content	16.98	3.14	11.87	20.95
Glyceryl mono stearate			17.12	3.09	11.42	20.81

Table 2: **Sample calculations in the determination of partial Hansen solubility parameters for the lipid Maisine® CC.**

Constituents	Functional groups with frequency	F_{di} ($J^{1/2}xcm^{3/2}xmol^{-1}$)	F^2_{pi} ($J^{1/2}xcm^{3/2}xmol^{-1}$)	E_{hi} (J/mol)	V_m (cm^3/mol)
Glyceryl monolinoleate	1 x (-CH_3-)	420	0	0	33.5
	14 x (-CH_2-)	3780	0	0	225.4
	1x (-CH-)	80	0	0	-1
	4 x (=CH-)	800	0	0	54
	1 x (-COO-)	390	240100	7000	18
	2 x (-OH -)	420	1000000	40000	20
		$\delta_d=\Sigma F_{(di)}/V=16.83$	$\delta_p=\sqrt{(\Sigma F^2_{pi})}/V=3.18$	$\delta_h=\sqrt{\Sigma (E_{hi}/V)}=11.59$	Σ=349.9
Glyceryl dilinoleate	2 x (-CH_3-)	840	0	0	67
	26 x (-CH_2-)	7020	0	0	418.6
	1 x (-CH-)	80	0	0	-1
	8 x (=CH-)	1600	0	0	108
	2 x (-COO-)	780	960400	14000	36
	1 x (-OH-)	210	250000	20000	10
		$\delta_d=\Sigma F_{(di)}/V=16.49$	$\delta_p=\sqrt{(\Sigma F^2_{pi})}/V=1.72$	$\delta_h=\sqrt{\Sigma (E_{hi}/V)}=7.29$	Σ=638.6
Glyceryl Trilinoleate	3 x (-CH_3-)	1260	0	0	100.5
	38 x (-CH_2-)	10260	0	0	611.8
	1 x (-CH-)	80	0	0	-1
	12 x (= CH-)	2400	0	0	162
	3 x (-COO-)	1170	2160900	21000	54
		$\delta_d=\Sigma F_{(di)}/V=16.36$	$\delta_p=\sqrt{(\Sigma F^2_{pi})}/V=1.59$	$\delta_h=\sqrt{\Sigma (E_{hi}/V)}=4.76$	Σ=927.3

Table 3: **Various molecular descriptors of 5FU, curcumin and the lipid excipients obtained from the Qikprop of Schrodinger.**

Sl. No.	Compound Name	mol MW	dipole	Volume	donorHB	accptHB	dip^2/V	ACxDN^.5/SA
1.	Curcumin	368.385	0.633	1215.586	2	7	0.000329	0.014017
2.	Curcumin	368.385	4.228	1204.126	2	4.75	0.014842	0.009569
3.	5-fluorouracil	130.078	5.483	385.644	2	3.5	0.077963	0.018927
4.	Glyceryl monosterate	358.56	5.09	1486.308	2	5.4	0.017433	0.008829
5.	Maisine® CC	879.398	4.756	3663.431	0	6	0.006175	0
6.	Stearic acid	284.481	6.54	1234.214	1	2	0.034656	0.002753
7.	Precirol ®ATO 5	284.481	6.54	1234.214	1	2	0.034656	0.002753
8.	Palmitic acid	256.428	6.863	1119.154	1	2	0.04208	0.002994
9.	Oleic acid	282.465	6.664	1213.563	1	2	0.03659	0.002793
10.	Labrafac™ PG	668.993	3.504	2418.567	2	8	0.005075	0.009033
11.	Glyceryl monoleate	356.545	4.966	1363.042	2	5.4	0.018094	0.01027
12.	Compritol®888ATO	1059.814	5.186	4359.782	0	6	0.00617	0

hydrogen bonding components. Labrafac PG is a mixture of diesters of caprylic and capric acid of propylene glycol. Compared to the free fatty acids such as oleic acid, stearic acid and palmitic acid, Labrafac PG possesses high polar and hydrogen component due to the presence of the short-chain length of Caprylic (C8) and Capric acid (C10). Moreover, computational prediction using the accptHB descriptor has found that Labrafac PG has a higher number of hydrogen bond acceptors compared to the free fatty acids (oleic acid, stearic acid and palmitic acid). The presence of more hydrogen bond acceptors in Labrafac PG suggests that it may have stronger intermolecular interactions and a higher capacity to form hydrogen bonds with the actives.

Table 4: **The calculated values of Hansens partial and total solubility parameters for 5FU, curcumin and the lipids with their Hansen sphere radius of interaction and theoretical screening of the lipid excipients using Greenhalgh and van Krevelen approach.**

Sl. No.	Name	Hansens partial, total solubility parameter and Hansen sphere radius							Greenhalgh Approach			van Krevelen method		
		δ_D	δ_P	δ_H	δ_T	R_a5FU	R_aCUR (diketo form)	R_aCUR (Enol form)	$\Delta\delta=\delta_{T2}-\delta_{T1}$ (5FU)	$\Delta\delta=\delta_{T2}-\delta_{T1}$ (CUR Enol form)	$\Delta\delta=\delta_{T2}-\delta_{T1}$ (CUR Diketo Form)	$\Delta\delta$ 5FU	$\Delta\delta$ CUR (Enol form)	$\Delta\delta$ CUR (Diketo form)
1	5FU	18.8	18.4	13.6	29.61									
2	Curcumin -Diketo form	17.17	5.47	12.33	21.83									
3	Curcumin -Enol form	16.80	5.54	14.16	22.66									
4	Compritol® ATO 888	16.87	1.76	7.12	18.54	18.27	6.42	7.99	11.07	4.12	3.29	17.96	8.0	6.4
5	Precirol ®ATO 5	16.89	2.21	7.96	18.97	17.56	5.48	7.04	10.64	3.69	2.86	17.25	7.0	5.5
6	Stearic acid	16.12	1.28	5.53	17.09	19.67	8.26	9.72	12.52	5.57	4.74	19.11	9.6	8.1
7	Palmitic acid	16.50	1.46	5.91	17.58	19.16	7.69	9.22	12.03	5.08	4.25	18.74	9.2	7.6
8	Maisine®CC	16.56	2.16	7.88	18.64	17.79	5.68	7.15	10.98	4.02	3.19	17.36	7.1	5.6
9	Labrafac™ PG	16.74	4.07	7.28	18.71	16.19	5.31	7.04	10.90	3.95	3.95	15.79	7.0	5.3
10	GMO	16.98	3.14	11.87	20.95	15.78	2.41	3.34	8.66	1.71	0.88	15.46	3.3	2.4
12	Oleic acid	16.06	1.32	5.59	17.06	19.64	8.22	9.67	12.55	5.60	4.77	19.06	9.6	8.0
13	GMS	17.12	3.09	11.42	20.81	15.83	2.55	3.73	8.80	1.85	1.02	15.55	3.7	2.5

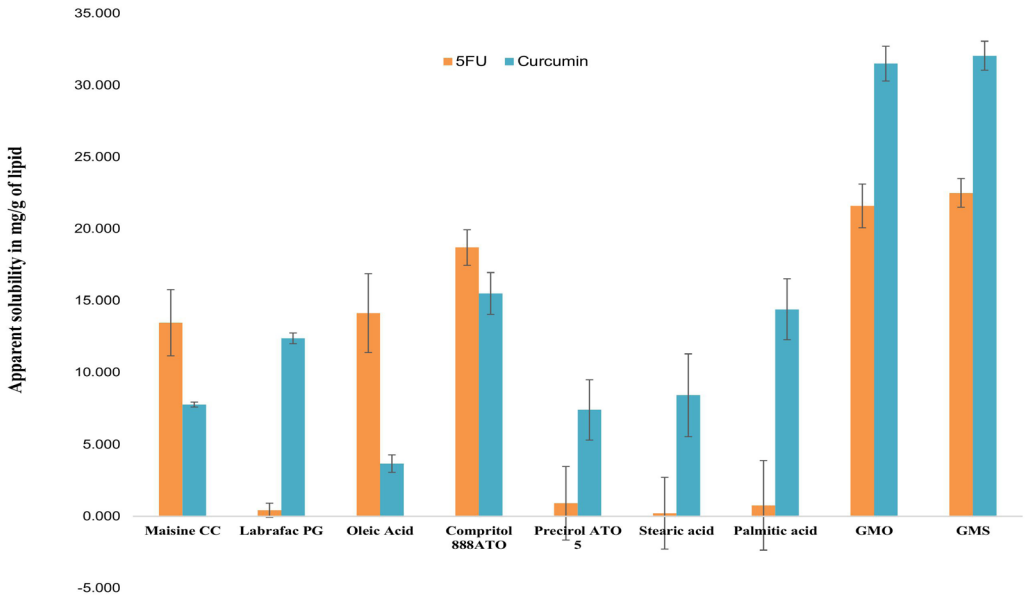


Figure 1: Shows the apparent solubilities of the actives in various lipid excipients determined experimentally. The experiments were carried out in triplicates.

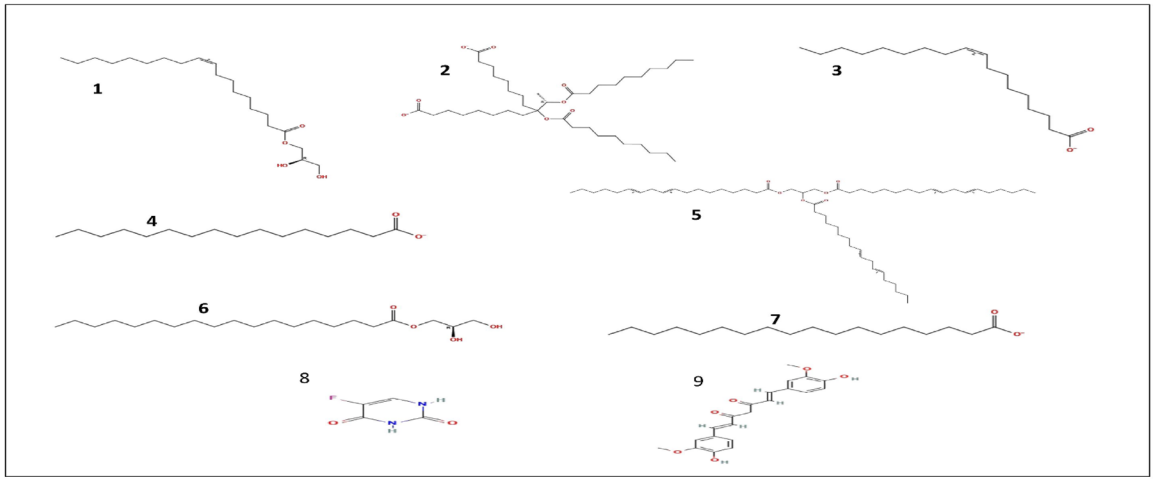


Figure 2: Illustrates the chemical structure of various lipid excipients and the actives: 1- Glyceryl monoleate; 2- Labrafac PG; 3- Oleic acid; 4- Palmitic acid 5- Maisine CC; 6- Glyceryl monostearate; 7- Stearic acid; 8- 5 Fluorouracil and 9 -Curcumin.

Due to the presence of more hydroxyl groups in glycerol, maisineCC, compritol and precirol are expected to exhibit higher δ_h values. When using qikprop predictions to assess the number of accptHB (hydrogen bond acceptors), it was found that precirol has a lower number of hydrogen bond acceptors compared to maisineCC and compritol. Interestingly, the presence of two free hydroxyl groups in glyceryl monoesters such as glycerol mono oleate and mono stearate contributed to their highest hydrogen bonding components and can exhibit relatively high solubilizing potential for both 5FU and curcumin.

One Dimensional Evaluation

The evaluation was carried out based on both Greenhalgh and van-Krevelen method in which the correlation is considered between the difference in total and partial solubility parameters of 5 FU, curcumin and the lipids respectively. The data are tabulated in Table 4. The chosen lipids exhibit low δ_d than 5FU and curcumin indicating that they could behave as poor solvents. With respect to curcumin, $\Delta\delta_T$ values were less than 7 $MPa^{1/2}$ which reveals that it is miscible with all the lipids. Experimentally, it was highly soluble in the monoesters such as glyceryl mono

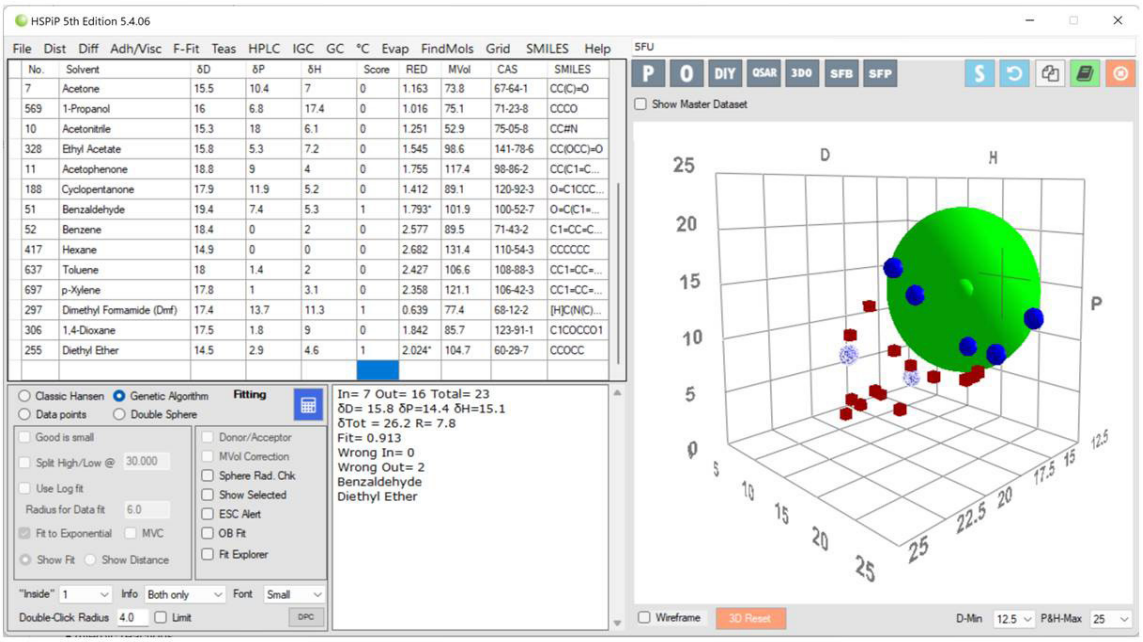


Figure 3: HSP 3D diagram of 5FU with HSP values of solvents used in the optimal fitting study. Blue balls indicate good solvents and red cubes indicate bad solvents.

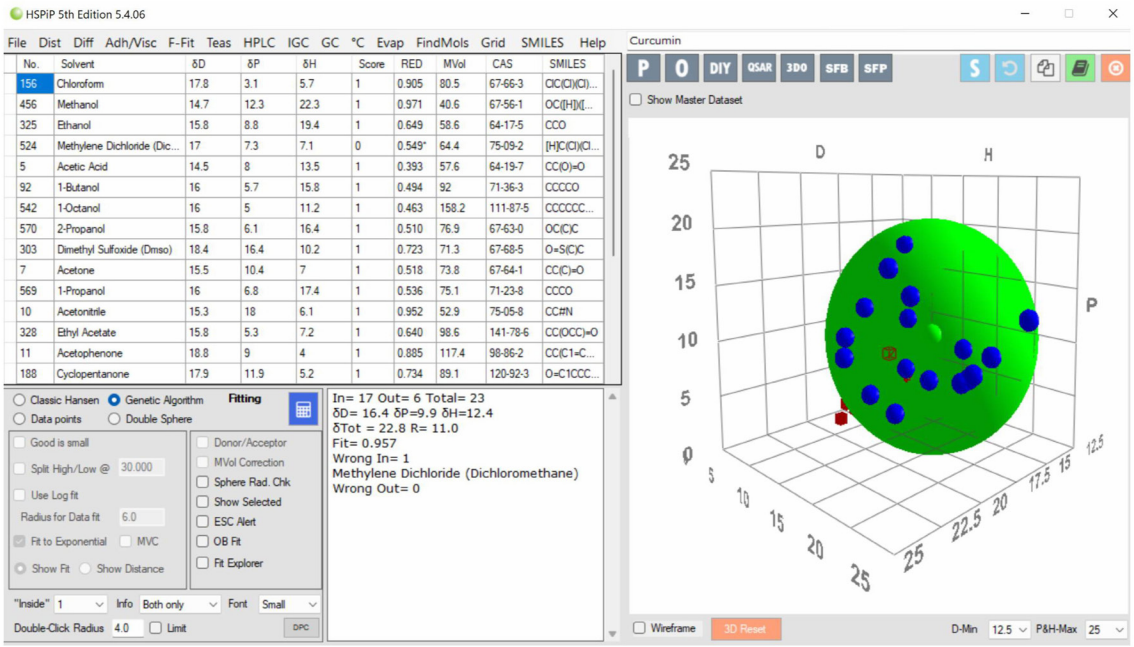
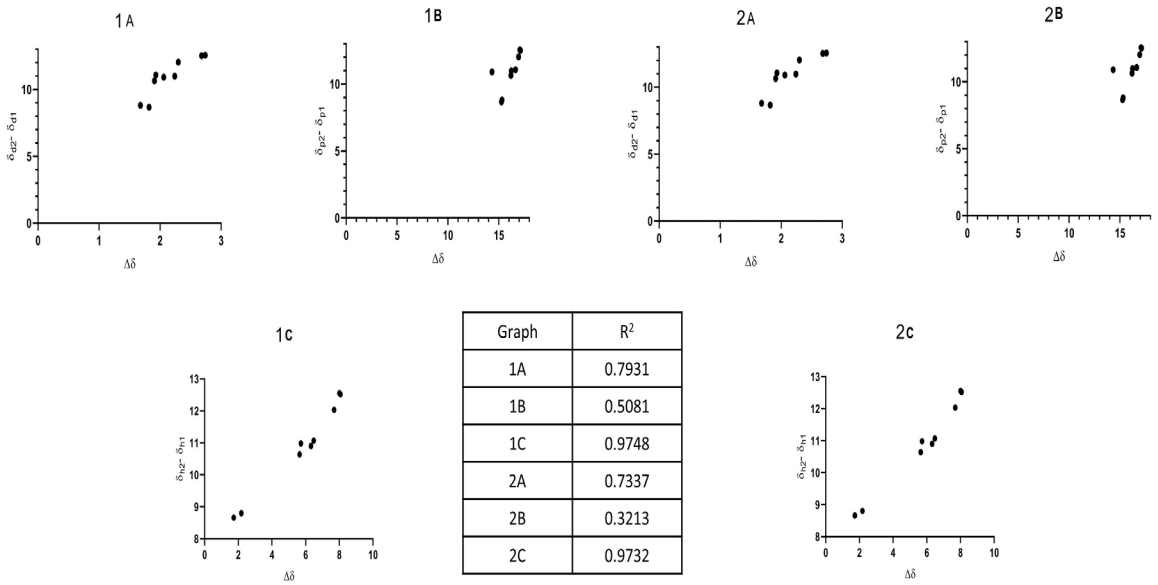


Figure 4: HSP 3D diagram of Curcumin with HSP values of solvents used in the optimal fitting study. Blue balls indicate good solvents and red cubes indicate bad solvents.

oleate and glyceryl mono stearate which was found to be in accordance with the theoretical prediction of $\Delta\delta_T$ values less than 2 $MPa^{1/2}$.[23] Whereas in case of 5FU, $\Delta\delta_T$ values for all the lipids were found to be greater than 10 $MPa^{1/2}$ anticipating immiscibility. The above mentioned holds good with lipids such as precirol ATO5, stearic acid, palmitic acid demonstrating their poor solubilizing potential during analysis.

Three dimensional evaluation

The three-dimensional space (R_0) was determined using HSPiP software by utilizing the binary solubility data obtained with different solvents. It is represented in Figures 3 and 4. The radius of interaction for curcumin and 5FU were found to be 11 and 7.8; with the fit value of 0.957 and 0.913 respectively. The low R_0 value of 5FU revealed that it possesses limited solubility. The



Graph	R^2
1A	0.7931
1B	0.5081
1C	0.9748
2A	0.7337
2B	0.3213
2C	0.9732

Figure 5: The graph illustrates the correlation between the difference in partial solubility parameters of actives and lipids to their difference in total solubility parameter with their R^2 values. The graph 1A and 2A gives the correlation between the difference in dispersion force component of 5FU and curcumin with all the lipid excipients to their difference in total solubility parameter (Greenhalgh approach) respectively. 1B and 2B gives the correlation between the difference in polar force component of 5FU and curcumin with all the lipid excipients to their difference in total solubility parameter (Greenhalgh approach) respectively. 1C and 2C gives the correlation between the difference in hydrogen bonding force component of 5FU and curcumin with all the lipid excipients to their difference in total solubility parameter (Greenhalgh approach) respectively.

three-dimensional solubility parameter space (R_a) for all the lipids were estimated using the equation 4 and are given in Table 4. The findings showed that R_a value of all the lipids with curcumin were found to be less than 11 demonstrating that curcumin is soluble in all the lipids. In that instance, the R_a value of all the lipids with 5FU were estimated to be more than 7.8, indicating its poor solubility.

DISCUSSION

The successful development of the lipid drug delivery system relies on its drug pay load which in turn depend on the ability of the lipid to solubilize the drug. A graph was plotted between the difference in partial solubility parameters of actives and lipids to their difference in total solubility parameter to elucidate the possible mechanism of interaction between the lipid excipients and 5FU, curcumin. Based on the correlation co-efficient (R^2) value as given in Figure 5, it is evident that the actives, 5FU and curcumin might interact with the lipids and undergo solubilization by means of hydrogen bonding[26] and weak dispersion forces.

According to Greenhalgh and van-Krevelen, the Δδ less than 5.6 $MPa^{1/2}$ and 7 $MPa^{1/2}$ respectively indicate the miscibility of drug in polymer or excipients. Many studies have suggested that the Δδ more than 10 $MPa^{1/2}$ would result in immiscibility.[27,28] The partial solubility parameter values for 5FU revealed that the molecule is bound by high polar and hydrogen bonding forces with the total solubility parameter value of 29.4. The difference in solubility parameter from Greenhalgh and Van Krevelen methods for 5FU and all the lipids were found to be greater than 10 $MPa^{1/2}$ revealing that the 5FU would be immiscible in lipids. However, experimentally 5FU exhibited considerable solubility in liquid lipids such as Maisine CC, oleic acid and labrafac PG. Among the solid lipids, the saturated fatty acids such as stearic and palmitic acid exhibited poor solubilizing potential experimentally for 5FU. This behavior perhaps associated to the increase in the number of carbon atoms and alkyl chain length of the fatty acids resulting in decreased polar and hydrogen bonding forces to interact. On the other hand, comparatively, the mono glycerides, glyceryl mono stearate and glyceryl mono oleate have shown highest solubilizing potential for 5FU. Subsequently, Compritol 888 ATO, a triglyceride of long chain fatty acid (behenic acid) ranked next to monoglycerides in solubilizing 5FU could be attributed to the presence of free hydroxyl groups. Further, the inability of Precirol ATO 5 to solubilize 5FU might likely be due to its mixed ester composition comprising triglycerides of long chain fatty acids (stearic and palmitic acid). In addition, the polarity and the molecular structure of 5FU might have contributed to its limited solubility.[29,30] Similar results were obtained in another study, where Imatinib mesylate, a hydrophilic drug has been predicted for its solubility in various solid lipids with the difference in total solubility parameter found to be above 10$MPa^{1/2}$.[31]

In general, both the approaches have shown that the diketo form of curcumin would possess high solubility than the enol form. The Greenhalgh approach in the prediction of solubility of curcumin in various liquid and solid lipids indicated that it would be miscible in all the lipids as the difference in solubility parameter is less than 5.6 $MPa^{1/2}$. But then, with van Krevelen method, the difference in solubility parameter was found to be around 10 $MPa^{1/2}$ with fatty acids demonstrating their low solubilizing potential for curcumin. This prediction is in accordance with the experimental values and with other similar studies.[23]

CONCLUSION

Drug loading into the lipid matrix is the backbone for the rational development of the lipid nanocarriers. Therefore, it is essential to quantify the amount of soluble drug in the lipid, which is basically a challenging process. Also, it is reliant on the physicochemical properties of the drugs. Irrespective of the nature of the drug, most of the experimental solubility values for 5FU and curcumin are in accordance with the theoretical prediction by Hansen solubility parameter. The HSP sphere radius of 5FU demonstrated its limited solubility in lipids. The HSP sphere radius provides an insight to screen the excipients prior to wet lab experiments. From the findings it is understood that in the screening of lipids, if the difference in solubility parameter is greater than 10 $MPa^{1/2}$ the HSP predictions must be integrated with experimental and thermal analysis to confirm the best lipid with high solubilizing potential. Hence, the HSP approach can be utilized as a promising tool in the preliminary screening of lipids for the development of lipid-based drug delivery system. The study can be further corroborated by using large set of lipids to develop prediction equation to solve for the apparent solubility of 5FU and curcumin in lipid excipients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HSP: Hansen Solubility Parameter; $\mathbf{F_{di}}$**:** Molar attraction constant due to dispersion component; $\mathbf{F_{pi}}$**:** Molar attraction constant due to the polar component; $\mathbf{E_{hi}}$**:** Hydrogen bonding energy.

SUMMARY

It is essential to achieve high loading capacity for the successful development of lipid nanocarriers and thereby to ensure sufficient solubility of the drug in the lipids. Accordingly, the screening of various lipids for their solubilising potential by performing trial and error method is highly tedious, time consuming and expensive. Furthermore, solubilisation of actives in lipids involve various kinetic and thermodynamic factors such as crystal structure, hydrophilicity, surface charge, molecular volume and so forth. Hence, the study explores the computational pharmaceutics approach in the prediction of solubility/miscibility of the actives in various lipid excipients. In this context, the Hansen solubility parameter for 5-FU, curcumin and lipid excipients were calculated using group contribution method proposed by vanKrevelen. The possible interaction forces involved in solubilization of 5-FU and curcumin in various lipids were predicted by one- and three-dimensional evaluations and was found to be hydrogen bonding and weak dipsersion forces. Further, it was correlated with the various descriptors predicted from QikProp. Finally, the HSP approach in the theoretical screening of lipid excipients was validated by comparing with the experimental solubility study findings. Therefore, our findings suggest that HSP approach can be an alternative in the preliminary screening of excipients for the development of nanostructured lipid carriers.

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