Solvent Replacement Strategies for Processing Pharmaceuticals and Bio-Related Compounds—A Review

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Abstract: An overview of solvent replacement strategies shows that there is great progress in green chemistry for replacing hazardous di-polar aprotic solvents, such as N,N-dimethylformamide (DMF), 1-methyl-2-pyrrolidinone (NMP), and 1,4-dioxane (DI), used in processing active industrial ingredients (APIs). In synthetic chemistry, alcohols, carbonates, ethers, eucalyptol, glycols, furans, ketones, cycloalkanones, lactones, pyrrolidinone or solvent mixtures, 2-methyl tetrahydrofuran in methanol, HCl in cyclopentyl methyl ether, or trifluoroacetic acid in propylene carbonate or surfactant water (no organic solvents) are suggested replacement solvents. For the replacement of dichloromethane (DCM) used in chromatography, ethyl acetate ethanol or 2-propanol in heptanes, with or without acetic acid or ammonium hydroxide additives, are suggested, along with methanol acetic acid in ethyl acetate or methyl tert-butyl ether, ethyl acetate in ethanol in cyclohexane, CO₂-ethyl acetate, CO₂-methanol, CO₂-acetone, and CO₂-isopropanol. Supercritical CO₂ (scCO₂) can be used to replace many organic solvents used in processing materials from natural sources. Vegetable, drupe, legume, and seed oils used as co-extractants (mixed with substrate before extraction) can be used to replace the typical organic co-solvents (ethanol, acetone) used in scCO₂ extraction. Mixed solvents consisting of a hydrogen bond donor (HBD) solvent and a hydrogen bond acceptor (HBA) are not addressed in GSK or CHEM21 solvent replacement guides. Published data for 100 water-soluble and water-insoluble APIs in mono-solvents show polarity ranges appropriate for the processing of APIs with mixed solvents. When water is used, possible HBA candidate solvents are acetone, acetic acid, acetonitrile, ethanol, methanol, 2-methyltetrahydrofuran, 2,2,5,5-tetramethyloxolane, dimethylsorobide, Cyrene, Cygnet 0.0, or diformylxylose. When alcohol is used, possible HBA candidates are cyclopentanone, esters, lactone, eucalytol, MeSesamol, or diformylxylose. HBA—HBA mixed solvents, such as Cyrene—Cygnet 0.0, could provide interesting new combinations. Solubility parameters, Reichardt polarity, Kamlet—Taft parameters, and linear solvation energy relationships provide practical ways for identifying mixed solvents applicable to API systems.

Keywords: Reichardt polarity; Kamlet—Taft parameters; green chemistry; solvent substitution; pharmaceuticals

1. Introduction

Solvents are commonly viewed as being polar or nonpolar, depending on whether their molecular structure contains highly electronegative (N, O, S, Cl, Br, I) elements or only (C, H) elements. However, for a molecule to be polar, it must contain a polar bond and have asymmetry in its structure that causes an imbalance in charge separation between two...
Liquids 2024, 4

(+ and −) poles referred to as dipoles. The presence of an asymmetrically arranged polar bond, such as C-Cl in chloromethane (CH$_3$Cl), causes the molecule to be polar, whereas the presence of four symmetrically arranged C-Cl bonds in carbon tetrachloride (CCl$_4$) cause the molecule to be nonpolar. For two solvents to be miscible, similarity in molecular polarity is required, as given by the well-known adage, “like dissolves like”, which in other words means that, for the solvation of polar molecules to occur, dipole—dipole interactions must exist, and conversely, for the solvation of nonpolar molecules to occur, dipole—dipole interactions must be absent. There are many exceptions to this adage, and certainly, system conditions (temperature, pressure) and van der Waals-London forces (dispersion) play important roles in solvation processes. Moreover, for solvent mixtures as discussed in this review, composition and interactions between hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) molecules are important.

Physical properties such as dipole moment ($\mu$), dielectric constant ($\varepsilon$), octanol-water partition coefficient (logK$_{ow}$ or logP), normal boiling point ($T_b$), melting temperature ($T_m$), entropy of fusion ($\Delta_{fus}S$), Hildebrand solubility parameter, and Hansen solubility parameter help to characterize the macroscopic polarity of a molecule. On the other hand, empirical polarity scales based on solvatochromic probes (dyes), such as Reichardt $E_T(30)$ [1] and normalized $E_T^N$ values [2], Kamlet—Taft (KT) acidity (α), basicity (β) and dipolar/polarizability (π*) values [3,4], and Catalán parameters [5], help to characterize the microscopic polarity of a solvent [6]. In solvent selection guides developed by the industry [7,8] and chemical societies [9–12], pure component solvent properties are analyzed in detail for developing solvent replacement strategies; however, as a focus of this review, considerable opportunities exist if mixtures of two kinds of polar solvents are used to create environments of microscopic polarity. For example, mixing an HBD solvent with an HBA solvent causes complex molecules (e.g., HBD—HBA pairs) to form, such that heterogeneity (local composition) is observed for simple alcohol—water mixtures [13,14] or ethylene glycol-water mixtures [15]. In this review, the emphasis is placed on taking advantage of the local composition and microscopic polarity of a solvent mixture as opposed to the bulk properties of a pure solvent, even though temperature and pressure can also be used to vary the properties of a pure solvent.

Solutes, in the context of this review, are active pharmaceutical ingredients (APIs) and bio-related molecules that can have multiple functional groups and can contain both polar (hydrophilic) and nonpolar (hydrophobic) regions in their structure. Functional groups in the solute can interact within the molecule (intramolecular) or between neighboring molecules (intermolecular) to form associated, cyclic, complex, network, or tertiary structures, and thus, the dissolution of an API into a solvent can be the result of many different molecular interactions. The composition of a solvent mixture can be used to fine-tune dipole—dipole interactions that sometimes lead to the solubility enhancement of the API in solution that is higher than that in either of the pure mono-solvents, which is known as synergistic behavior.

2. Substances of Very High Concern (SVHC)

In the synthesis and processing of APIs, polar protic (water, alcohols, carboxylic acids), dipolar aprotic (ketones, lactones, esters, ethers), or nonpolar aprotic (hydrocarbons) solvents are used. Notably, hazardous and unsafe dipolar aprotic chemicals (e.g., N,N-dimethylformamide (DMF), 1-methyl-2-pyrrolidinone (NMP), 1,4-dioxane (DI)) account for over 40% of total solvents used in synthetic, medicine-related, and process chemistry [16], and these solvents and more than 480 others are on the candidate list of substances of very high concern (SVHC), as designated under the European Chemicals Agency (ECHA), as the European Union Registration, Evaluation Authorization and Restriction of Chemicals (REACH) guidelines limit or prohibit the use of chemicals, especially those having reproductive toxicity, carcinogenicity, or explosive decomposition properties (Table 1). Thus, the key motivation of employing mixed solvents instead of mono-solvents, new solvents, or newly developed solvents is based on environmental health and safety (EHS) guidelines.
for compounds with known chemical properties and conformity with the “International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use” (ICH). Namely, EHS and ICH should be primary factors in solvent replacement, rather than apparent greenness or economic or sustainability factors, because few newly developed solvents or solvent systems have had sufficient time for scrutiny in all areas highlighted by governmental agencies and in the solvent guides discussed below. In this review, solvent replacement strategies are analyzed with the aim of highlighting a method for identifying safe solvent mixtures for the research development and chemical processing of organic compounds.

Table 1. Selected chemicals from candidate list of substances of very high concern (SVHC) for authorization by the European Chemicals Agency (ECHA) as of 2023. Chemicals shown in various categories are for educational purposes only. Specific hazards, detailed information, case decisions, or discussion should be accessed from ECHA website [17]. LD₅₀ values from PubChem or online sources based on rat/mouse oral or dermal (d) studies.

<table>
<thead>
<tr>
<th>Chemical (CAS No.)</th>
<th>LD₅₀ (mg/kg)</th>
<th>Chemical (CAS No.)</th>
<th>LD₅₀ (mg/kg)</th>
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<tbody>
<tr>
<td>1,2,3-trichloropropane (96-18-4)</td>
<td>120</td>
<td>cis-cyclohexane-1,2-dicarboxylic anhydride (13149-00-3)</td>
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<td>1,2-dichloroethane (107-06-2)</td>
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<td>Cyclohexane-1,2-dicarboxylic anhydride (85-42-7)</td>
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<td>1,4-dioxane (122-91-1) (DI)</td>
<td>1550</td>
<td>Glutaral (111-30-6)</td>
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<td>2,4-dinitrotoluene (121-14-2)</td>
<td>268</td>
<td>Toxic to Reproduction</td>
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<td>4,4’-Diaminodiphenylmethane (101-77-9)</td>
<td>120</td>
<td>1-Methyl-2-pyrrolidone (NMP) (872-50-4)</td>
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<td>4-aminoazobenzene (60-09-3)</td>
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<td>1-vinylimidazole (1072-63-5)</td>
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<td>Acrylamide (79-06-1)</td>
<td>170</td>
<td>2-ethoxyethyl acetate (110-80-5)</td>
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<td>Biphenyl-4-ylamine oil (92-67-1)</td>
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<td>2-methoxethanol (108-96-4)</td>
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<td>2-methoxyl acetate (110-49-6)</td>
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<td>Furan (110-00-9)</td>
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<td>2-methyldimidaole (693-98-1)</td>
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<td>Propylene oxide (75-56-9)</td>
<td>1245</td>
<td>4,4’- sulphonyldiphenol (80-09-1)</td>
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<td>N-(hydroxymethyl)acrylamide (924-42-5)</td>
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<td>Dibutyl phthalate (84-74-2) (DBP)</td>
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<td>o-aminotoluene (95-53-4)</td>
<td>300 (deg)</td>
<td>Dicyclohexyl phthalate (84-61-7)</td>
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<tr>
<td>Phenoxytoxin (77-09-8)</td>
<td>670</td>
<td>Diethyl phthalate (84-75-3)</td>
<td>29,600</td>
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<td>Potassium dichromate (7778-50-9)</td>
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<td>Diisobutyl phthalate (84-69-5)</td>
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<td>Trichloroethylene (79-01-6)</td>
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<td>Diisopentyl phthalate (605-00-5)</td>
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<td>Endocrine disruptor</td>
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<td>Diocetyl dilaureate (3648-18-8)</td>
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<td>2-(isononylphenoxy)ethanol (85005-55-6)</td>
<td>-</td>
<td>Formamide (75-12-7)</td>
<td>5577</td>
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<td>4-(1-ethyl-1-methylhexyl)phenol (52427-13-1)</td>
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<td>Methoxycetic acid (625-45-6)</td>
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<td>4,4’-(1-methylpropylidene)bisphenol (77-40-7)</td>
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<td>4-tert-butylphenol (98-54-4)</td>
<td>2951</td>
<td>Nitrobenzene (98-95-3)</td>
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<tr>
<td>Isoheptyl-4-hydroxybenzene (4242-02-3)</td>
<td>2600</td>
<td>N-methylacetamide (79-16-3)</td>
<td>5</td>
</tr>
<tr>
<td>Nonylphenol (22515-52-3)</td>
<td>1200</td>
<td>n-pentyl-isopentyl phthalate (77297-69-9)</td>
<td>-</td>
</tr>
<tr>
<td>Nonylphenol, ethoxylated (9016-45-9)</td>
<td>1300</td>
<td>Perfluoroethanic acid (375-85-9)</td>
<td>500</td>
</tr>
<tr>
<td>Human health effects</td>
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<td>Phenol, 4-dodecyl, branched (21055-94-5)</td>
<td>2000</td>
</tr>
<tr>
<td>Melamine (108-78-1)</td>
<td>3161</td>
<td>Phenol, tetrapropylene (57427-55-1)</td>
<td>2000</td>
</tr>
<tr>
<td>Persistent, Bioaccumulative and Toxic (PBT)</td>
<td></td>
<td>Very Persistent, Very Bioaccumulative (vPvB)</td>
<td>-</td>
</tr>
<tr>
<td>Alkanes, C14-16, chloro (1372804-76-6)</td>
<td>23</td>
<td>Phenthantere (85-10-8)</td>
<td>700</td>
</tr>
<tr>
<td>Anthracene (120-12-7)</td>
<td>&gt;17</td>
<td>Terphenyl, hydrogenated (6788-32-7)</td>
<td>17,500</td>
</tr>
<tr>
<td>Dodecamethylcyclohexasiloxane (540-97-6)</td>
<td>&gt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octamethylcyclotetrasiloxane (556-67-2)</td>
<td>1540</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrene (129-00-0)</td>
<td>2700</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Solvent Guides

To address the issue of the overuse of hazardous dipolar aprotic chemicals in API synthesis and processing and to improve the awareness of chemical professionals who perform solvent selection on a day-to-day basis, pharmaceutical industries have developed solvent guides with ranking systems. Chemical agencies have developed lists for solvents evaluated as hazardous that require formal authorization for use in chemical processes.

The GlaxoSmithKline (GSK) solvent guide [7,18,19] contains detailed analyses of a total of 154 small molecules (e.g., alcohols, aromatics, carbonates, chlorinated, dipolar aprotics, esters, ethers, hydrocarbons, ketones, organic acids, water) commonly used in pharmaceutical industries. The GSK solvent guide has the following categories: (i) waste (incineration, recycling, biotreatment, VOC emissions), (ii) environment (aquatic impact, air impact), (iii) human health (health hazard, exposure potential), and (iv) safety (flammability and explosion, reactivity). The GSK solvent guide allows for the quick evaluation and
qualitative comparison of replacement solvents based on four primary categories that include life-cycle assessment (LCA), and it ranks solvents in their categories on a scale from 1 (major issues) to 10 (few known issues).

The European consortium and Innovative Medicines Initiative (IMI) produced CHEM21 [8], which contains guidelines and metrics for solvent usage. Byrne et al. reported environmental, health, and safety (EHS) tools and guidelines for solvents and highlighted key points in available guidelines [11]. The CHEM21 solvent guide ranks solvents in EHS categories on a scale from 1 (recommended) to 10 (hazardous), which is contrary (and opposite in order) to the scale of the GSK solvent guide. Both solvent guides provide extremely useful evaluations of solvent risks and issues and provide solvent replacement recommendations.

The American Chemical Society (ACS) Green Chemistry Institute (CGI) and pharmaceutical roundtable produced a solvent selection website (Figure 1) [10,12] dedicated to solvent usage in pharmaceutical and chemical industries and a solvent guideline [9]. Figure 1 shows a sample screen of a solvent selection tool developed for the ACS GCI Pharmaceutical Roundtable (GCIPR) that uses principle component analysis (PCA) to identify potential solvent replacements. PCA combines many physical properties, characteristics (presence of functional groups), and environmental data to generate correlations and scores according to user constraints. The solvent selection tool (Figure 1) was described by Diorazio et al. [20] and was originally designed by AstraZeneca in Spotfire, and a version was donated to GCIPR. The GCIPR solvent selection tool is useful for identifying replacement solvents based on both quantitative and qualitative characteristics (Figure 1).

Figure 1. ACS Green Chemistry Institute and Pharmaceutical Roundtable (GCIPR) solvent selection tool https://www.acsgcipr.org/tools-for-innovation-in-chemistry/solvent-tool/ (accessed on 1 April 2024) described by Diorazio et al. [20]. Copyright ACS, 2023.
4. Replacement Solvents in Synthetic Chemistry

Syntheses of APIs are commonly performed in multistep batch processes that use hazardous or unsafe dipolar aprotic solvents in some of the key steps. Replacement strategies for non-green dipolar aprotic solvents used in reactions were suggested by Gao et al. [21]. Table 2 summarizes replacement solvents for 15 classes of synthetic reactions identified by Jordan et al. [16]. Possible replacement solvents for dipolar aprotics (Table 2) include novel water-surfactant (PS-750-M) systems that eliminate organic solvents [22], dipolar aprotic solvents with improved safety and sustainability, namely N-butyl-2-pyrrolidinone (NBP), propylene carbonate (PC), dimethylisosorbide (DMI) [23], dihydroevoglucosenone (Cyrene) [24], eucalyptol [25], or dimethylcarbonate (DMC), or the use of mixed solvents, such as 2-methyltetrahydrofuran (2-MeTHF) with methanol (Table 2). Besides THF or DMF in Sonogashira cross-coupling reactions (Table 2), eucalyptol can possibly replace solvents such as anisole, bromobenzene, chlorobenzene, chloroform, diethyl ether (DE), N,N-dimethylacetamide (DMA), dimethyl ether (DME), DI, ethyl acetate, ethyl benzoate, and toluene [25].

Table 2. Possible replacement solvents for dipolar aprotic solvents used in synthetic chemistry transformations. Content was summarized and adapted from Unified solvent selection guide for replacement of common dipolar aprotic solvents in synthetically useful transformations contained in ref. [16]. Copyright ACS, 2022.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Unsafe Dipolar Aprotics</th>
<th>Replacement Solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amide formation</td>
<td>DCM; DMF</td>
<td>Cyrene; surfactant-water</td>
</tr>
<tr>
<td>Boc deprotection</td>
<td>DI</td>
<td>HCl in CPME; TFA in PC</td>
</tr>
<tr>
<td>Borylation chemistry</td>
<td>DI</td>
<td>2-MeTHF:MeOH (1:1); CPME; MTBE; CH</td>
</tr>
<tr>
<td>Buchwald–Hartwig amination</td>
<td>DI</td>
<td>2-MeTHF; tBuOH</td>
</tr>
<tr>
<td>Carbylation</td>
<td>THF; DE</td>
<td>DMC</td>
</tr>
<tr>
<td>Carboxylation</td>
<td>THF; DE</td>
<td>2-MeTHF; DMI; DMC</td>
</tr>
<tr>
<td>C-H activation</td>
<td>THF; DMF; DI</td>
<td>2-MeTHF; CH</td>
</tr>
<tr>
<td>Mizoroki–Heck cross-coupling</td>
<td>DI; THF; DMF</td>
<td>NBP; DMI; PC</td>
</tr>
<tr>
<td>Nucleophilic aromatic substitution</td>
<td>THF; DMF; DI</td>
<td>2-MeTHF; PEG-400</td>
</tr>
<tr>
<td>Organometallic reaction</td>
<td>R-MgX; R-Li; hydrides</td>
<td>2-MeTHF; CPME</td>
</tr>
<tr>
<td>Solid-phase peptide synthesis</td>
<td>DMF; DMAc; NMP</td>
<td>NBP; GVL</td>
</tr>
<tr>
<td>Sonogashira cross-coupling</td>
<td>THF; DMF</td>
<td>Cyrene; NBP; DMI; Eucalyptol</td>
</tr>
<tr>
<td>Steglich Esterification</td>
<td>DMF</td>
<td>DMC</td>
</tr>
<tr>
<td>Suzuki-Miyaura cross-coupling</td>
<td>DI; THF; DMF</td>
<td>Cyrene; NBP; DMI; 2-MeTHF</td>
</tr>
<tr>
<td>Urea synthesis</td>
<td>DMF; THF</td>
<td>Cyrene</td>
</tr>
</tbody>
</table>

In the synthesis of APIs with solvents, the type of process employed is an important point that deserves attention. A less obvious way to lower risks associated with solvent usage in API synthesis is through continuous manufacturing (CM) [26], as opposed to batch processing. In a CM process, systems can be automated, quality can be improved, waste can be reduced, and, most importantly, solvent volumes can be greatly lowered over those quantities used in batch systems by lowering the total system volume and by eliminating the storage of API reaction intermediates, such that overall safety of the synthesis can be improved. The number of papers published on the continuous manufacturing of APIs has roughly tripled in the past 5 years, making it a highly active research area. In CM processes, solvent selection and solvent additives play key roles in flow chemistry, product quality, system operability, economics, and sustainability. Furthermore, there are some recent new approaches for CM processes; amidation by reactive extrusion has been developed as a solventless synthesis method and has been used for the preparation of teriflunomide and moclobemide APIs [27].

5. Solubility Parameters

Solubility parameters (SP) are used to characterize substances in solvent replacement strategies. The Hildebrand SP (δ) has the basis of regular solution theory [28], and its
development in solubility theory relates the cohesive energy density defined by Equation (1) to the activity coefficient [29].

\[ \delta \equiv \left( \frac{\Delta U^{\text{vap}}}{V} \right)^{1/2} \]  

(1)

In Equation (1), \( U \) and \( V \) are the molar internal energy of vaporization and molar volume of the substance in its liquid state, respectively. The definition of the Hildebrand SP is typically simplified by replacing \( U \) with \( (H - PV) \) and assuming ideal gas behavior:

\[ \delta = \left( \frac{(\Delta H^{\text{vap}} - RT)}{V} \right)^{1/2} \]  

(2)

Hansen [30] divided the total cohesive energy given in Equation (1) into three parts: (i) dispersion (van der Waals (London) forces) interactions \( (\delta_d) \), hydrogen bonding interactions \( (\delta_h) \), and polar (or dipole-dipole) interactions \( (\delta_p) \). Hansen solubility parameters (HSPs) are used to determine a solubility parameter distance (Ra) between two substances “1” and “2” as follows:

\[ (Ra)^2 = 4 \cdot (\delta_{d1} - \delta_{d2})^2 + (\delta_{h1} - \delta_{h2})^2 + (\delta_{p1} - \delta_{p2})^2 \]  

(3)

where the sphere provides a region of favorable solvation for a solute “1” and solvent “2”, i.e., as values of Ra become closer to zero according to a chosen solvent with given HSP values, affinity becomes higher, and the solubility of the solute in the solvent should increase. The factor of four in Equation (3) is empirical and adds statistical weighting to dispersion interactions as being most important in solvation. By taking a substance such as a polymer or biomolecule and seeing whether it dissolves into solvents with known HSP values, the radius of interaction (Ro) can be determined for that compound. Then, a relative energy difference can be defined as follows:

\[ \text{RED} = \frac{Ra}{Ro} \]  

(4)

and solvents or solvent mixtures that have RED < 1 are candidates that dissolve the compound. It is possible, for example, for two solvents outside of the solvation sphere to be mixed, such that they form a good solvent as mixture for a polymer. HSP theory has been used to estimate the solubilities of anti-inflammatory drugs in pure and mixed solvents [31]. Fractional HSP values, which can be plotted on ternary diagrams to facilitate the assessment of interactions, have been used to identify green extraction solvents for alkaloids [32] and to screen solvent mixtures for pharmaceutical cocrystal formation [33]. HSP is a powerful tool used for solvent screening and is especially useful for large molecules, such as polymers or biomolecules, as highlighted by Abbott [34].

In comparing the Hildebrand solubility parameter theory with that of the Hansen solubility theory, the Hildebrand solubility parameter theory has some notable failures in predicting miscibility between materials [30]. However, in a critical comparison of solvent selection for 75 polymers, both theories gave similar results in predicting polymer—solvent miscibility [35]. Namely, Hildebrand SP had a prediction accuracy of 60% for solvents and 76% for non-solvents, whereas HSP had a prediction accuracy of 67% for solvents and 76% for non-solvents [35]. On the other hand, for polar polymers, the Hildebrand SP theory gave a prediction accuracy of only 57% [35]. Both Hildebrand solubility parameters and Hansen solubility parameters are useful screening tools for solvent replacement. Hildebrand SP theory is simple and provides qualitative estimation of solvent interactions for nonpolar molecules or slightly polar molecules; Hansen SP theory accounts for detailed molecular interactions and is applicable to both nonpolar and polar molecules. HSP can be applied to complex molecules, such as lignin [36] or phytochemicals [37]; however, HSP is qualitative when hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) molecular systems are considered [38].
6. Empirical Polarity Scales

Reichardt $E_T^{30}$ parameters are based on the solvatochromic properties of Betaine 30 dye and provide the sensitive characterization of solvent polarity. Reichardt $E_T^{N}$ values are normalized based on the $E_T^{30}$ values of water and tetramethylsilane. Reichardt parameters are firmly established in the chemical literature and form the basis of a widely used polarity scale for organic chemicals [6].

Kamlet—Taft (KT) parameters are based on the solvatochromism of dyes specific to Lewis acidity ($\alpha$), Lewis basicity ($\beta$), and dipolarity/polarizability ($\pi^*$) and have independent scales that depend on reference solvents [39]. The Kamlet—Taft polarity scales are meant to have values of $\alpha$, $\beta$, and $\pi^*$ that are between zero and one; however, when a solvent has a Lewis acidity, Lewis basicity, or dipolarity/polarizability that is outside of the range of reference compounds, ($\pi^* = 0$ (cyclohexane) and $\pi^* = 1$ (dimethylsulfoxide)) values of KT parameters can be greater than unity or less than zero.

Catalán parameters improved the KT parameter approach by using specific dyes for solvent polarizability (SP), solvent dipolarity (SdP), solvent acidity (SA), and solvent basicity (SB) parameters rather than by average values, as in the KT approach. Catalán parameters separate the polarizability (SP) and dipolarity (SdP) contributions of the KT parameter approach. All three scales have wide use in the chemical literature, although there are issues in data reduction methods and parameter values, as pointed out by Spange et al. [40], who reanalyzed polarity scales considering molar concentrations of the solvent ($N$), and Spange and Weiß [41], who proposed a method to unify the acid—based (pKa) and density effects of hydrogen bond donor solvents.

According to Reichardt and Welton [6], common molecular solvents (Figure 2) can be roughly divided into three groupings: (i) dipolar protic (HBD), $E_T^{N} > 0.5$; (ii) dipolar aprotic (HBA), $0.3 < E_T^{N} < 0.5$; and (iii) apolar (non-HBD or nonpolar), $E_T^{N} < 0.3$. Examination of the KT dipolarity/polarizability parameters (Figure 2) shows that longer chain hydrocarbons have $\pi^*$ values less than zero, and water has a $\pi^*$ greater than unity, which is due to the choice of reference solvents in the KT method. Most solvent replacement strategies consider Reichardt, Kamlet—Taft or Catalán parameters in their analysis. For example, dipolar aprotic solvents generally have high KT basicity and low KT acidity (Figure 3). Direct replacement solvents for dipolar aprotics could be N-butyl-2-pyrrolidinone (NBP), Cyrene$^{\text{TM}}$ (Cyr), $\gamma$-valerolactone (GVL), $\gamma$-butyrolactone (GBL), eucalyptol (Eupt), tetramethyloxolane (TMO), dimethyl isosorbide (DMI), or cyclopentyl methyl ether (CPME). However, many solvents have $E_T^{N}$ polarity values that are much lower than that of dipolar aprotics (Figure 2) and KT acidities that are either too high or KT basicities that are too low (Figure 3) to allow direct replacement of dipolar aprotics. Nevertheless, the range of Kamlet—Taft parameters of dipolar aprotics provide valuable information for considering mixed solvents and mixed solvent composition.

![Figure 2](image-url). Reichardt $E_T^{N}$ parameters plotted against Kamlet—Taft dipolarity/polarizability parameters for selected molecular solvents.
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**Figure 2.** Reichardt ETN parameters plotted against Kamlet—TafT dipolarity/polarizability parameters for selected molecular solvents.

**Figure 3.** Kamlet—TafT basicity parameter plotted against acidity parameter for selected molecular solvents.

### 7. Opportunities with Mixed Solvents

Mixtures of solvents (mixed solvents) allow one to vary the chemical properties of the solution in a unique number of ways. For example, when an HBD solvent is mixed with an HBA solvent, KT parameters vary continuously with composition (Figure 4). KT parameters of mixed solvents can show synergistic behavior, which means that their $\beta$ or $\pi^*$ values can be higher than the KT parameters of the pure solvents (Figure 4), especially when water is the HBD solvent. Duereh et al. [42] showed that there is a clear relationship between microscopic (local) polarity, complex molecule (HBD—HBA solvent pairs) interactions, and synergistic behavior in thermodynamic properties (Figure 5).

**Figure 4.** Kamlet—TafT acidity ($\alpha$) and basicity ($\beta$) versus dipolar/polarizability ($\pi^*$) for aqueous and non-aqueous mixed solvents and pure solvents. Dashed lines show approximate behavior of mixed solvent KT parameters with composition.
Thus, solvent composition of mixed solvents allows one to vary microscopic polarity (local composition) and the concentration of HBD—HBA complex molecules that can be used advantageously in solvent replacement schemes.

In this section, strategies for using mixed solvents to replace hazardous chemicals are highlighted for chromatography solvents, CO2 expanded liquids, supercritical fluids, low-transition temperature mixtures, switchable solvents, and HBD—HBA mixtures of molecular solvents.

7.1. Chromatography Solvents

In chromatographic methods, great progress has been made with the introduction of mixed solvents, such as ethyl acetate (EtAc)-ethanol (EtOH) in heptanes being demonstrated as a superior replacement for dichloromethane (DCM) [43]. Mixed solvent stock solutions are marketed by leading chemical suppliers for HPLC, TLC, and flash chromatography (FC) methods [44], confirming the success of the EtAc—ethanol mixtures.

The reason why EtAc—EtOH in a heptane mixed solvent system can replace DCM can be understood by examining the variation in KT parameters of the mixture compared with the KT parameters of the DCM—MeOH system. In this case, EtOH is the HBD solvent, EtAc is the HBA solvent, and the heptanes have low overall KT acidity for the mobile phase. Composition variation of EtAc—EtOH mixtures allows for the fine control of the basicity and dipolarity/polarizability that transverse methanol KT parameters (Figure 4).

To replace hexane, CO2—EtAc has been suggested to be applicable to thin-layer chromatography (Table 3), and CO2—MeOH has been demonstrated to be applicable to flash chromatography [45]. The entire corporate chemistry division of Syngenta (Table 3) reduced the overall volume of seven hazardous dipolar aprotic solvents (DCM, CHCl3, DCE, DI, DME, DMF, DE) by 75% over a period of two years by using solvent replacement (e.g., EtAc—EtOH mixtures for DCM) and by emphasizing reverse phase chromatography for the separation of polar compounds [46] (Table 3); however, DMF usage increased during that period. Solvent pairs, such as cyclohexanone—MeOH, cyclohexanone—EtOH,

Figure 5. Dynamic viscosity (\(\eta\)) of water (HBD) – hydrogen bond acceptor (HBA) mixed solvent systems as a function of mole fraction of HBA solvent \((x_A)\) at 25 °C. HBA solvents are ordered in terms of Hunter basicity \(\beta^{H^+}\) values (low to high): acetonitrile (● ACN), γ-valerolactone (■ GVL), γ-butylolactone (▲ GBL), tetrahydrofuran (○ THF), 1,4-dioxane (□ DI), acetone (▼ Ace), pyridine (★ PYR), N-methyl-2-pyrrolidone (▲ NMP), N,N-dimethylformamide (● DMF), N,N-dimethylacetamide (○ DMA), and dimethyl sulfoxide (■ DMSO). Reprinted with permission from [42]. Copyright American Chemical Society, 2017.
cyclopentanone–MeOH, cyclopentanone–EtOH, GBL–MeOH, GBL–EtOH, GBL–water, GVL–MeOH, GVL–EtOH, and GVL–water, have been demonstrated as replacements for NMP or DMF in polyamide synthesis and, thus, have possibilities as solvent replacements in analytical method development [47].

Improvements in high-pressure liquid chromatography (HPLC) have been made with the introduction of ultra-high-pressure liquid chromatography (UHPLC), supercritical fluid chromatography (SFC), and ultra-high-pressure supercritical fluid chromatography (UHPSFC), which reduce the amount of solvents necessary in analyses while improving resolution [48]. When UHPSFC—tandem mass spectroscopy is employed, the determination of plant hormones (cytokinins) can be analyzed in 9 min at detection limits close to 0.03 fmol [49]. ACS has introduced the analytical method greenness score (AMGS) calculator developed by Hicks et al. [48] that ranks chromatography methods according to instrument energy, solvent energy, and solvent EHS scores [10].

Table 3. Replacement solvents for dichloromethane (DCM) in high-performance liquid (HPLC), thin-layer chromatography (TLC) and flash chromatography (FC) methods. Analytes consist of neutral, basic, acidic, and polar API.

<table>
<thead>
<tr>
<th>Mixed Solvent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Analyte&lt;sup&gt;b&lt;/sup&gt;</th>
<th>System</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtAc:EtOH (3:1) in heptanes</td>
<td>Neutral</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>EtAc:EtOH in heptanes</td>
<td>Neutral</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>iPrOH in heptanes</td>
<td>Neutral</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>EtAc:EtOH (3:1) in MTBE</td>
<td>Neutral</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>MeOH in MTBE</td>
<td>Neutral</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>EtAc:EtOH (3:1) (2% NH&lt;sub&gt;4&lt;/sub&gt;OH) in heptanes</td>
<td>Basic</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>MeOH: NH&lt;sub&gt;4&lt;/sub&gt;OH (10:1) in EtAc</td>
<td>Basic</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>MeOH: NH&lt;sub&gt;4&lt;/sub&gt;OH (10:1) in MTBE</td>
<td>Basic</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>EtAc:EtOH (3:1) (2% AcOH) in heptanes</td>
<td>Acidic</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>MeOH:AcOH (10:1) in EtAc</td>
<td>Acidic</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>MeOH:AcOH (10:1) in MTBE</td>
<td>Acidic</td>
<td>LC</td>
<td>[43]</td>
</tr>
<tr>
<td>EtAc:EtOH (3:1) in cyclohexane</td>
<td>n.s.</td>
<td>LC</td>
<td>[46]</td>
</tr>
<tr>
<td>acetonitrile:water</td>
<td>Polar</td>
<td>LC</td>
<td>[46]</td>
</tr>
<tr>
<td>tert-butyl acetate</td>
<td>All</td>
<td>LC</td>
<td>[50]</td>
</tr>
<tr>
<td>sec-butyl acetate</td>
<td>All</td>
<td>LC</td>
<td>[50]</td>
</tr>
<tr>
<td>ethyl isobutyrate</td>
<td>All</td>
<td>LC</td>
<td>[50]</td>
</tr>
<tr>
<td>methyl pivalate</td>
<td>All</td>
<td>LC</td>
<td>[50]</td>
</tr>
<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;:EtAc</td>
<td>n.s.</td>
<td>TLC</td>
<td>[51]</td>
</tr>
<tr>
<td>EtAc in heptanes</td>
<td>n.s.</td>
<td>TLC</td>
<td>[51]</td>
</tr>
<tr>
<td>iPrOH in heptanes</td>
<td>n.s.</td>
<td>TLC</td>
<td>[51]</td>
</tr>
<tr>
<td>Ace in heptanes</td>
<td>n.s.</td>
<td>TLC</td>
<td>[51]</td>
</tr>
<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;:MeOH</td>
<td>Neutral</td>
<td>FC</td>
<td>[45]</td>
</tr>
<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;:EtAc</td>
<td>n.s.</td>
<td>FC</td>
<td>[51]</td>
</tr>
<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;:Ace</td>
<td>n.s.</td>
<td>FC</td>
<td>[51]</td>
</tr>
<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;:iPrOH</td>
<td>n.s.</td>
<td>FC</td>
<td>[51]</td>
</tr>
</tbody>
</table>

<sup>a</sup> AcOH: acetic acid; EtAc: ethyl acetate; MTBE: methyl tert-butyl ether; <sup>b</sup> n.s. not specified.

7.2. Expanded Liquids and Supercritical Fluids

Chemists and chemical engineers have introduced many new types of solvents through major research initiatives. CO<sub>2</sub>-expanded bio-based liquids (CXL) have been demonstrated to be favorable for enantioselective biocatalysis [52], and supercritical fluids have been shown to be able to replace the hazardous solvents used in processing APIs [53]. Supercritical carbon dioxide (scCO<sub>2</sub>) has been shown to have a wide application in processing bioactive lipids [54] and bioactive-related food ingredients [55]. A comprehensive review is available on the supercritical extraction of bioactive molecules from plant matrices [56]. A less-studied methodology in the supercritical extraction of bioactive molecules from natural sources is to eliminate organic co-solvents, such as ethanol or acetone, by replacing them with co-extractants that are typically oils from plant materials (Table 4).
In co-extractant methodology (Table 4), natural source substrates (petals, pericarp, etc.) are mixed with a natural oil (co-extractant) from a vegetable, drupe, legume, or seed (or fruit) before extraction with pure scCO$_2$. The co-extractant serves to increase the mass transfer of active components from the natural source to the supercritical phase by solubilization and polarity matching, and the co-extractant properties are enhanced due to scCO$_2$ dissolution into the co-extractant phase that causes the reduction of both surface tension and viscosity while enhancing heat transfer and related properties. Thus, with co-extractant methodology (Table 4), organic co-solvents are completely eliminated in scCO$_2$ extraction such that the contamination of extracts with organic compounds is not an issue. Furthermore, with co-extractant methodology, a final product is realized directly, the cultural processing of many types of food is possible, and food safety is strictly enhanced [70].

Related to developments in supercritical fluid theory, entropy based solubility parameters have been proposed that allow the extension of traditional solubility parameter theory to chemical systems containing supercritical fluids and ethanol [71] or systems at high temperatures or high pressures [72]. Experimental systems for measuring the KT parameters of methanol, ethanol, 2-propanol, and 1,1,1,2-tetrafluoroethane (HFC134a) co-solvents in CO$_2$ have been developed for assessing the HBD alcohol interactions with the HBA Lewis acidity of CO$_2$ in the supercritical state for quantifying polarity enhancements [73].

### 7.3. Low Transition Temperature Mixtures

Low transition temperature mixtures (LTTMs) are special combinations of mixed solvents made up of a hydrogen bond donor (HBD) molecule and a hydrogen bond acceptor (HBA) molecule for the purpose of liquefying the mixture [74]. Ionic liquids (ILs) are combinations of discrete organic moiety containing cations and anions that are in the liquid state at room temperature. Deep eutectic solvents (DESs) are mixtures of Lewis or Brønsted acids and bases that are in the liquid state at room temperature.

The possibility of using either ILs or DESs as solvent replacements or for processing APIs allows them to have many potential innovative applications due to their solvation and tailorable properties [75]. Issues with ILs are their cost, recyclability, and relatively higher viscosity compared to molecular solvents. While DESs are inexpensive, they share some of the same issues as ILs, and in addition, their separation from chemical products may be problematic due to the formation of strong HBD—HBA complexes with the API. One innovative approach that addresses some of these issues is to incorporate the IL chemical structure into the API to improve the bioavailability in drug delivery systems [76,77]. Reviews in the area of combining HBD- or HBA-containing APIs into the structure of ILs for drug delivery systems and other purposes show that there is much activity in this research area [78,79].

### Table 4. Co-extractant methodology for obtaining bio-products from supercritical CO$_2$ extraction of natural sources. Co-extractants: vegetable, drupe, legume, or seed oils or triacylglycerols (TAGs, triglycerides). Bio-product yields shown are maximum values normalized to 100%.

<table>
<thead>
<tr>
<th>Natural Source</th>
<th>Co-Extractant</th>
<th>Bio-Product</th>
<th>T (°C)</th>
<th>P (MPa)</th>
<th>%Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algae</td>
<td>Soybean oil</td>
<td>astaxanthin</td>
<td>70</td>
<td>40</td>
<td>36</td>
<td>[57]</td>
</tr>
<tr>
<td>Brown seaweed</td>
<td>Sunflower oil</td>
<td>carotenoids</td>
<td>50</td>
<td>30</td>
<td>99</td>
<td>[58]</td>
</tr>
<tr>
<td>Carrots</td>
<td>Canola oil</td>
<td>carotenoids</td>
<td>70</td>
<td>35</td>
<td>92</td>
<td>[59]</td>
</tr>
<tr>
<td>Mangosteen</td>
<td>Virgin coconut oil</td>
<td>xanthohinoids</td>
<td>70</td>
<td>35</td>
<td>31</td>
<td>[60]</td>
</tr>
<tr>
<td>Mangosteen</td>
<td>Virgin coconut oil</td>
<td>α-mangostin</td>
<td>60</td>
<td>35</td>
<td>76</td>
<td>[61]</td>
</tr>
<tr>
<td>Marigold</td>
<td>Medium-chain TAGs</td>
<td>lutein esters</td>
<td>65</td>
<td>43</td>
<td>98</td>
<td>[62]</td>
</tr>
<tr>
<td>Marigold</td>
<td>Soybean oil</td>
<td>lutein esters</td>
<td>53</td>
<td>30</td>
<td>93</td>
<td>[63]</td>
</tr>
<tr>
<td>Propolis</td>
<td>Virgin coconut oil</td>
<td>flavonoids</td>
<td>50</td>
<td>15</td>
<td>25</td>
<td>[64]</td>
</tr>
<tr>
<td>Pumpkin</td>
<td>Olive oil</td>
<td>carotenoid</td>
<td>50</td>
<td>25</td>
<td>41</td>
<td>[65]</td>
</tr>
<tr>
<td>Red sage</td>
<td>Peanut oil</td>
<td>diterpenoids</td>
<td>50</td>
<td>38</td>
<td>90</td>
<td>[66]</td>
</tr>
<tr>
<td>Tomato</td>
<td>Canela oil</td>
<td>lycopene</td>
<td>40</td>
<td>40</td>
<td>86</td>
<td>[67]</td>
</tr>
<tr>
<td>Tomato skin</td>
<td>Hazelnut oil</td>
<td>lycopene</td>
<td>66</td>
<td>45</td>
<td>40</td>
<td>[68]</td>
</tr>
<tr>
<td>Tomato skin</td>
<td>Olive oil</td>
<td>lycopene</td>
<td>75</td>
<td>35</td>
<td>58</td>
<td>[69]</td>
</tr>
</tbody>
</table>

In co-extractant methodology (Table 4), natural source substrates (petals, pericarp, etc.) are mixed with a natural oil (co-extractant) from a vegetable, drupe, legume, or seed (or fruit) before extraction with pure scCO$_2$. The co-extractant serves to increase the mass transfer of active components from the natural source to the supercritical phase by solubilization and polarity matching, and the co-extractant properties are enhanced due to scCO$_2$ dissolution into the co-extractant phase that causes the reduction of both surface tension and viscosity while enhancing heat transfer and related properties. Thus, with co-extractant methodology (Table 4), organic co-solvents are completely eliminated in scCO$_2$ extraction such that the contamination of extracts with organic compounds is not an issue. Furthermore, with co-extractant methodology, a final product is realized directly, the cultural processing of many types of food is possible, and food safety is strictly enhanced [70].

Related to developments in supercritical fluid theory, entropy based solubility parameters have been proposed that allow the extension of traditional solubility parameter theory to chemical systems containing supercritical fluids and ethanol [71] or systems at high temperatures or high pressures [72]. Experimental systems for measuring the KT parameters of methanol, ethanol, 2-propanol, and 1,1,1,2-tetrafluoroethane (HFC134a) co-solvents in CO$_2$ have been developed for assessing the HBD alcohol interactions with the HBA Lewis acidity of CO$_2$ in the supercritical state for quantifying polarity enhancements [73].
7.4. Switchable Solvents

Switchable polarity solvents (SPS) \[80\], switchable hydrophilicity solvents (SHS) \[81\], switchable water (SW) \[82\], solvent-assisted switchable water (SASW) \[83\], and high-pressure switchable water (HPSW) \[84\] are new types of mixed solvents that can change their polarity, hydrophilicity, or characteristics through the introduction or removal of CO\(_2\). Switchable solvent systems would seem to have many applications in processing API, and furthermore, it could be highly advantageous if APIs with an existing or added amidine group could have modified hydrophilicity with CO\(_2\) \[85\] for the purposes of separation, purification, or analysis.

7.5. HBD—HBA Mixtures of Molecular Solvents

The attractiveness of using molecular solvents to form HBD—HBA mixtures is that their EHS data are available, making it possible to assess their safety. With the EHS safety of the solvents assessed, it becomes possible to focus on the technical issue of solubilizing the API in the mixed solvent for processing operations.

Duereh et al. \[86\] developed a methodology for replacing dipolar aprotic solvents with safe HBD—HBA solvent pairs based on solubility and Kamlet—Taft windows (Figure 6). In the methodology \[86\], solvent pairs are evaluated from a database with user-defined solubility parameter and KT parameter windows of an API to determine working compositions and a prioritized list of mixed solvents according to a composite GSK score. The open-access software given in ref. \[86\] can be extended with activity coefficient models or quantum chemistry methods to broaden the scope of the methodology.

![Figure 6. Concept of solubility parameter and Kamlet—Taft windows for identifying replacement solvents of an API (paracetamol): (a) window for solubility parameter, (b) window for API acidity,](image-url)
(c) window for API basicity, (d) window for API dipolarity/polarizability. (left): Range of solubility and Kamlet—Taft parameters for dissolution of API in known solvents, including hazardous ones. (right): Range of solubility and Kamlet—Taft parameters superimposed onto theoretical calculations and available literature data to determine working composition ranges for a given mixed solvent pair (acetone—water). Reprinted with permission from ref. [86]. Copyright American Chemical Society, 2016.

In developing solvent replacement methodologies, physical properties can be important attributes for solvent selection. Jouyban and Acree [87] developed a single functional form for the correlation of viscosity, density, dielectric constant, surface tension, speed of sound, Reichardt $E_{T}^N$, molar volume, and isentropic compressibility of binary mixed solvents. Nazemieh et al. [88] reported data for a new set of mixed solvents, namely p-cymene with α-pinene, limonene, and citral correlated with the Jouyban—Acree model for physico-chemical properties (PCPs). Lee et al. [89] developed a local composition regular solution theory model for the correlation and prediction of API solubility in mixed solvents that had a single functional form for all compounds studied. The advantage of similar functional forms in correlative and predictive schemes for PCPs and activity coefficients is that machine learning techniques can be applied as the size of the database increases.

8. Kamlet—Taft Parameter Windows for APIs

APIs are commonly designated as being water soluble or non-water soluble. When the Reichardt $E_{T}^N$ and KT parameters are plotted for mono-solvents that solvate 45 water-soluble APIs (Figure 7) and 47 water-insoluble APIs (Figure 8), the range of $E_{T}^N$ and KT parameter values becomes visible, which characterizes the apparent polarity of the API. Although many water-soluble APIs are solvated by dipolar protic solvents ($E_{T}^N > 0.5$) and dipolar aprotic solvents ($0.3 < E_{T}^N < 0.5$) over a wide range of KT acidities ($\alpha$), there are minimum values of $\pi^*$ and $\beta$ required for solvation (Figure 7). On the other hand, water-insoluble APIs are solvated by a relatively narrow range of solvent polarities ($0.2 < E_{T}^N < 0.75$) and KT acidities ($\alpha$), in which there are maximum values of $\pi^*$ and minimum values of $\beta$ required for solvation (Figure 8).

When an API is dipolar protic, it interacts with basic dipolar aprotic solvents by forming hydrogen bonds with the solvent that must be stronger than those in the solid phase for solvation to occur. If the dipolar aprotic solvent is not basic or if it has insufficient basicity, then the dipolar protic API will have low solubility in the solvent, because dipole-dipole interactions generally do not have sufficient strength to break hydrogen bonds in the solid phase. On the other hand, when an API is dipolar aprotic, it interacts with dipolar aprotic solvents through dipole—dipole interactions that must be stronger than those in the solid phase for solvation to occur.

Conversely, if a solvent is dipolar protic, then the API must have sufficient basicity to accept hydrogen bonds that must be stronger than those in the solvent phase. Thus, scales for molecular basicity are extremely important in identifying potential new solvents and solvent systems. However, note that all KT $\alpha$, $\beta$, and $\pi^*$ parameters influence API solubility in a mixed solvent and that they depend on the mixed solvent local composition, frequently in a non-linear or synergistic way [90,91].
Figure 7. Reichardt $E_r^N$ and Kamlet—Taft parameters of mono-solvents that solvate water-soluble APIs at ca. 25 °C. Data from refs. [1,92–302]. Water (Blue). Less-hazardous solvents (Green). Hazardous solvents (Red). Detailed information in Supplementary Materials.
Figure 8. Reichardt $E_T^N$ and Kamlet—Taft parameters of mono-solvents that solvate water-insoluble APIs at ca. 25 °C. Data from refs. [1,92–302]. Less-hazardous solvents (Green). Hazardous solvents (Red). Detailed information in Supplementary Materials.
Consider the HBD—HBA mixed-solvent systems shown in Figure 9. When water is used as the HBD solvent (Figure 9a–c), the HBA solvent addition (increasing $x_2$) lowers the KT $\alpha$ and generally lowers $\pi^*$ values depending on the HBA polarity and causes KT $\beta$ values to initially sharply increase, during which the microscopic polarity changes greatly due to the formation of complex molecules [91]. For example, water—lactone mixed solvents have been shown to exhibit synergy in KT basicity [91]. For an alcohol as the HBD solvent, the addition of an HBA solvent lowers the KT $\alpha$, and it causes the KT $\pi^*$ and KT $\beta$ values to linearly increase or decrease with bulk composition depending on whether the pure alcohol KT $\pi^*$ or KT $\beta$ values are less than, equal to, or greater than those of the HBA solvent alcohol KT $\pi^*$ or KT $\beta$ values (Figure 9d–i). Duereh et al. showed examples of the case of ethanol (HBD)–cyclopentanone (HBA), in which mixed solvent composition can be used to favorably solvate an API (paracetamol), and they also showed a case of methanol (HBD)–cyclopentanone (HBA), in which mixed solvent composition failed to provide any solvation benefit, along with examples of 12 APIs [90].

![Figure 9. Kamlet—Taft acidity, basicity, and polarity for selected mixed solvents versus HBA solvent mole fraction: (a,d,g) water—HBA; (b,e,h) methanol—HBA; (c,f,i) ethanol—HBA. Trends shown are based on estimations (dashed lines) and actual data (solid lines) [51,86,90,91].](image)

There are a number of HBD—HBA solvent combinations that could be replacements for hazardous solvents (Figure 9). For possible HBD solvents, water, methanol, and ethanol are good candidates. When water is the HBD solvent, possible candidate HBA solvents are
acetone, acetic acid, acetonitrile, EtOH, MeOH, 2-MeTHF, water-2,2,5,5-tetramethyloxolane (TMO), DMI, Cyrene, Cygnet 0.0, or possibly diformylxylose. Safety and conditions must be considered carefully. For example, 2-MeTHF forms peroxides more rapidly than IPE, THF, or CPME when inhibitors are not present; ethereal solvents form peroxides [7]. Cygnet 0.0 is solid at room temperature [303], and 2-MeTHF in water has inverse temperature behavior up until temperatures of 340 K [304], meaning that its solubility in water decreases with increasing temperature.

When alcohols are used as the HBD solvent, cyclohexanone (CHN), cyclopentanone (CPN), many kinds of esters, GBL, GVL, eucalytol (water insoluble), or possibly MeSesamol (water insoluble) [305] or diformylxylose [306] are candidates. Furthermore, interesting HBA—HBA combinations, such as Cyrene—Cygnet 0.0, are being suggested for polymer syntheses [303] to replace hazardous dipolar aprotic solvents, and these types of HBA—HBA mixed solvents could have advantages in processing APIs.

9. Linear Solvation Energy Relationships (LSER)

Polarity parameters originally reported by Kamlet, Abboud, Abraham, and Taft were intended for use in linear solvation energy relationships (LSER) [307], expressed as follows:

\[ \text{XYZ} = \text{XYZ}_0 + s(\pi^* + d\delta) + a\alpha + b\beta + h\delta_H + e\xi \]  

where \( \text{XYZ} \) is a chemical phenomenon, \( \text{XYZ}_0 \) is a reference phenomenon, and \( s, a, b, h, \text{ and } e \) are descriptors that are used to correlate polarity parameters to \( \text{XYZ} \). Many adaptations have been made of Equation (5), and a well-known one is due to Abraham [508], which expressed water—octanol partition coefficients (\( \log P \)) and gas—solvent partition coefficient (\( \log K \)) as follows [309]:

\[ \log (P) = c + eE + sS + aA + bB + vV \]  

\[ \log (K) = c + eE + sS + aA + bB + vL \]  

Where the bold symbols are properties of the solute related to excess molar refraction (E), dipolarity/polarizability (S), hydrogen bond acidity (A), Lewis basicity (B), McGowan’s molecular volume (V), and gas-to-hexadecane partition coefficient (L). LSER models are directly applicable to predict the solubility of APIs in solvents [309]. LSER models are widely used in the field of chromatography for characterizing columns and estimating retention times [310,311] or in the analysis of petroleum distillate conditions with group contribution activity coefficient models such as UNIFAC [312], but they do not appear to have been used more broadly (in reverse) in mixed solvent replacement schemes, although environmentally related partition coefficients are incorporated into life-cycle assessment tools, such as EPA’s CompTox chemical dashboard system [313] or machine learning studies for solvent characterization factors [314].

10. Conclusions

In this work, several strategies were highlighted for the replacement of hazardous dipolar aprotic solvents related to pharmaceutical and bio-related compounds. Solvent guides form the basis of solvent replacement and consider categories of safety, human health, environment, waste, and sustainability. Linking online solvent selection sites with GSK, CHEM21, ECHA, and other guidelines would allow for the efficient dissemination of solvent replacements.

An example of drop-in replacement solvents and several mixed solvent combinations for synthesizing APIs is one strategy that shows it is possible for academia and the industry to replace hazardous dipolar aprotic solvents by adopting new chemical systems that are both efficient and safe. The universal guide for the replacement of hazardous dipolar aprotic solvents in synthetic chemistry is one of the key strategies.
Mixed solvents can be used in many ways to replace hazardous solvents, often with a performance benefit. Dichloromethane can be replaced by ethanol (HBD) and ethyl acetate (HBA) mixed solvents, as is evident from marketed stock solutions by chemical companies. The use of CO₂ with esters or alcohols instead of hexane or chlorinated hydrocarbons is seen to be effective for thin-layer, flash, and supercritical chromatography, and with the introduction of marketed industrial analytical equipment, it is clear that the new technology will become established.

Expanded liquids, supercritical fluids, low-transition temperature (HBD—HBA) mixtures, and switchable solvents all offer safer chemical systems that have low energy, performance, and sustainability benefits. Chemical systems based on HBD—HBA mixtures of molecular solvents for processing APIs offer a simple way to replace hazardous solvents by considering the range of solubility parameters, Reichardt polarity, and Kamlet—Taft parameters of the pure components. Reichardt polarity and Kamlet—Taft parameters of pure components are necessary physical properties for the development of solvent replacement strategies. By using the available solubility data of APIs in mono-solvents, new mixed solvent combinations can be seen.

11. Future Outlook

Presently, there are many measurements of Reichardt polarity and Kamlet—Taft parameters of pure compounds, but far fewer measurements have been made for mixed solvent systems that can potentially replace hazardous dipolar aprotic solvents. Many new measurements are needed of Reichardt polarity and Kamlet—Taft parameters of HBD—HBA and HBA—HBA mixed solvents, especially those systems such as ethanol—ethyl acetate, to understand fundamental interactions of complex molecules with APIs.

Theoretical methods applied to HBD—HBA systems could greatly accelerate the identification of new chemical systems for processing APIs. COSMO-RS is able to quantitatively predict Kamlet—Taft parameters for both molecular solvents and deep eutectic solvents [315]. COSMO-RS gives qualitative predictions of Hansen solubility parameters [316], which is encouraging because the values of APIs could lead to a great reduction in experimental effort.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/liquids4020018/s1, Table S1. Water-soluble APIs solvated by monosolvents and their solvent polarity (ETN), Kamlet-Taft acidity (α), basicity (β) window, dipolarity/polarizability (π*) and corresponding literature. Solvents listed as hazardous in GSK solvent guide are highlighted in red. Table S2. Water-insoluble APIs solvated by monosolvents and their solvent polarity (ETN), Kamlet-Taft acidity (α), basicity (β) window, dipolarity/polarizability (π*) and corresponding literature. Solvents listed as hazardous in GSK solvent guide are highlighted in red.

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