Organic Process Research & Development **2007**, *11*, 133–137

Perspective on Solvent Use in the Pharmaceutical Industry

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Abstract:

Solvent use consistently accounts for between 80 and 90% of mass utilization in a typical pharmaceutical/fine chemicals (non-polymer) batch chemical operation. Moreover, within these operations, solvents play a dominant role in the overall toxicity profile of any given process; i.e. on a mass basis, solvents account for the largest proportion of chemicals of concern used in the process. However, for the typical synthetic organic chemist, solvents are just a medium in which a reaction takes place; the interest is in the reactivity and building of a molecule, not in the means by which this is carried out. So, in a typical retrosynthetic analysis, solvent and solvent-reactant interactions, separability, and particle engineering are generally not included. The best means in which this reaction can take place is also not considered; i.e., the reaction space, configuration, order of addition, heat/mass transfer, etc., is generally not considered. This publication presents a case for greater awareness of solvent issues in batch chemical operations typically found in the pharmaceutical industry.

Introduction

Practicing synthetic chemists in the chemical processing industries devoted to pharmaceutical manufacturing are faced with what is arguably a broad array of competing and, at times, seemingly opposing design criteria. In addition to the principle design objective to produce complex intermediates that lead to an active pharmaceutical ingredient (API), they must develop a robust process to produce these substances at high purity, with known and consistent quality, and high yields. They also need to ensure volume efficiencies, operability, safety, and as few environmental impacts as possible. Given this backdrop of competing demands, it is not surprising that solvent selection has historically been one of the more undervalued and least considered components in modern pharmaceutical synthetic chemistry.

Despite an extensive literature describing solvent issues,[1,2] solventless reactions,[3−5] nontraditional solvents,[6−12] and process considerations for good solvent selection,[13−17] it is fair to say that chemists responsible for the earliest synthesis of compounds used in drug discovery activities do not consider solvent selection. This situation is somewhat perplexing, given the attention that solvents and solvent use have been given at various symposia and conferences over the past 10 years or more. It also begs the question as to why the academic synthetic organic chemistry community has been so slow on the uptake in considering solvent selection as part of a broad consideration of a synthetic route and subsequent isolation. Simply put, solvents matter greatly to the practice of synthetic organic chemistry in the chemical processing industries, but they obviously do not capture the imagination of the typical synthetic chemist.

This paper is not intended to be a review of the latest solvents to be offered as "green" or "greener", of methods to evaluate solvents, or of better approaches to solvent selection, as the authors believe these subjects have been extensively and well treated elsewhere (e.g., ref 18). Nor is the paper intended to be a prospective or anticipatory paper of environmental regulations affecting solvent use; a safe assumption here is that regulatory efforts to increase restrictions on solvent type and use will continue. Rather, this paper is intended to highlight the current state of solvent use as a spur towards the development of more sustainable replacements. We also reiterate the importance of solvents to synthetic organic chemists in the modern chemical processing

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10.1021/op060170h CCC: $37.00
Published on Web 12/14/2006

Table 1. **Comparison of solvent use in GlaxoSmithKline Pharmaceuticals (GSK) prior to 2000 and in pilot plant processes carried out in 2005**

	2005 rank	1990−2000 rank
2-propanol	1	5
ethyl acetate	2	4
methanol	3	6
denatured Ethanol	4	8
n-heptane	5	12
tetrahydrofuran	6	2
toluene	7	1
dichloromethane	8	3
acetic acid	9	11
acetonitrile	10	14

industries. Our hope is that some might be more deliberative and selective in solvent selection and use from the earliest considerations of route and process.

The Challenge

As an example of solvent use within a large pharmaceutical company, Table 1 shows the top 10 most frequently used solvents for highly developed chemical processes from 1990−2000 and again from all pilot-plant processes carried out in 2005. These 10 solvents account for >80% of the frequency of solvent use and are an indication of the solvent mix that will be present in manufacturing in the not too distant future. It is also interesting to note that over these same time periods an average of six different solvents are used in any given process.

As is the case with any set of data, there are multiple interpretations, but these data suggest there is a trend towards decreasing tetrahydrofuran (THF), toluene, and dichloromethane use. While these differences in the respective solvent frequency distributions may be a reflection of attempts to change the solvent choice towards "greener" solvents, it may just as easily be explained by solubility, operability, or other drivers facing the synthetic chemist. Clearly, the fact that dichloromethane and THF are still in common use within GlaxoSmithKline (GSK) would be seen by many as not a good thing from a "green" perspective, but replacements for these solvents in early route/process development and on into routine production is still not common. While replacements for dichloromethane are being increasingly discussed and, in some companies, more routinely used, there are still those who would argue that using dichloromethane or other chlorinated solvents is not a problem. Moreover, in some cases, they would argue that a chlorinated solvent such as dichloromethane is a "greener" alternative to many solvent choices so long as the dichloromethane or chlorinated solvent is not released and its use reduces solvent numbers, mass, and other environmental impacts.

From a standpoint of materials of concern, i.e. those materials facing future increasing regulatory constraints because of their environmental, health, and safety impacts, solvents are once again the largest contributor on a mass basis. As seen in Figure 1, dichloromethane is the largest mass contributor to GSK materials of concern. An additional sobering statistic regarding the use of dichloromethane in terms of mass used per stage is that its use has not decreased. For routes prior to 2000, average use of dichloromethane per stage intermediate was 16.4 kg/kg intermediate, whereas for late phase routes evaluated in 2005, dichloromethane use averaged 15.3 kg/kg intermediate. One would hope for a larger reduction in dichloromethane use over this period, but it is clear that, as long as one carries out chemistry in batch processes and uses dichloromethane, the amount is not going to change to a substantial degree. Clearly, this points to the importance of finding a replacement for dichloromethane, or if this is not possible, using different kinds or styles of reactors to reduce the volume dependency of a typical batch reactor should be investigated.

Another major concern is for suitable replacements for dipolar aprotic solvents such as 1-methyl pyrolidin-2-one (NMP), *N*,*N*-dimethylformamide (DMF), and *N*,*N*-dimethylacetamide (DMA). These are extremely useful solvents for their solvation characteristics and promotion of a variety of chemistries given their dipolar characteristics. Suitable replacements for these or alternative synthetic strategies that avoid their use are required, given their designation as reproductive toxins. Their use in places such as the United Kingdom is coming under increasing scrutiny as a part of the Solvent Emissions Directive, and similar legislation is present throughout the European Union. These solvents also pose environmental difficulties given that they are usually involved in aqueous work-ups. Mixed aqueous/organic wastes of this type are difficult to separate and costly in the context of batch chemical processing in terms of energy and capital equipment. Discharge to wastewater treatment incurs a high BOC/COD and nitrogen loading that can be problematic, and high water content usually requires additional fuel to incinerate with the added problem of NO_X emissions. This is an instance where solvent manufacturers have been rather slow in providing alternative solvents that on the one hand avoid the health risks associated with these solvents and on the other hand ensure appropriate separability characteristics in mixed aqueous/organic solvent systems.

A second problem of increasing concern when considering solvent use and replacement has to do with a phenomenon we have observed over the past 5−10 years related to our focus on the material or mass intensity of any given process. If one looks at both early- and late-phase manufacturing processes common to the pharmaceutical industry and collects data related to solvent mass relative to process chemical mass (excluding water), it is very clear that the overriding process mass contribution results from solvent use. Solvents in routine GSK development processes consistently average between 85 and 90% of the mass contribution to the overall process mass leading to an API. Not coincidentally, the life cycle environmental impacts associated with these same processes are overwhelmingly a result of solvent use, despite the process complexity and complex chemical building blocks used to make the API.[17] Furthermore, these same data suggest that within the GSK context, the biggest gains in reducing environmental impacts from our considerable efforts to optimize and "green" processes are directly

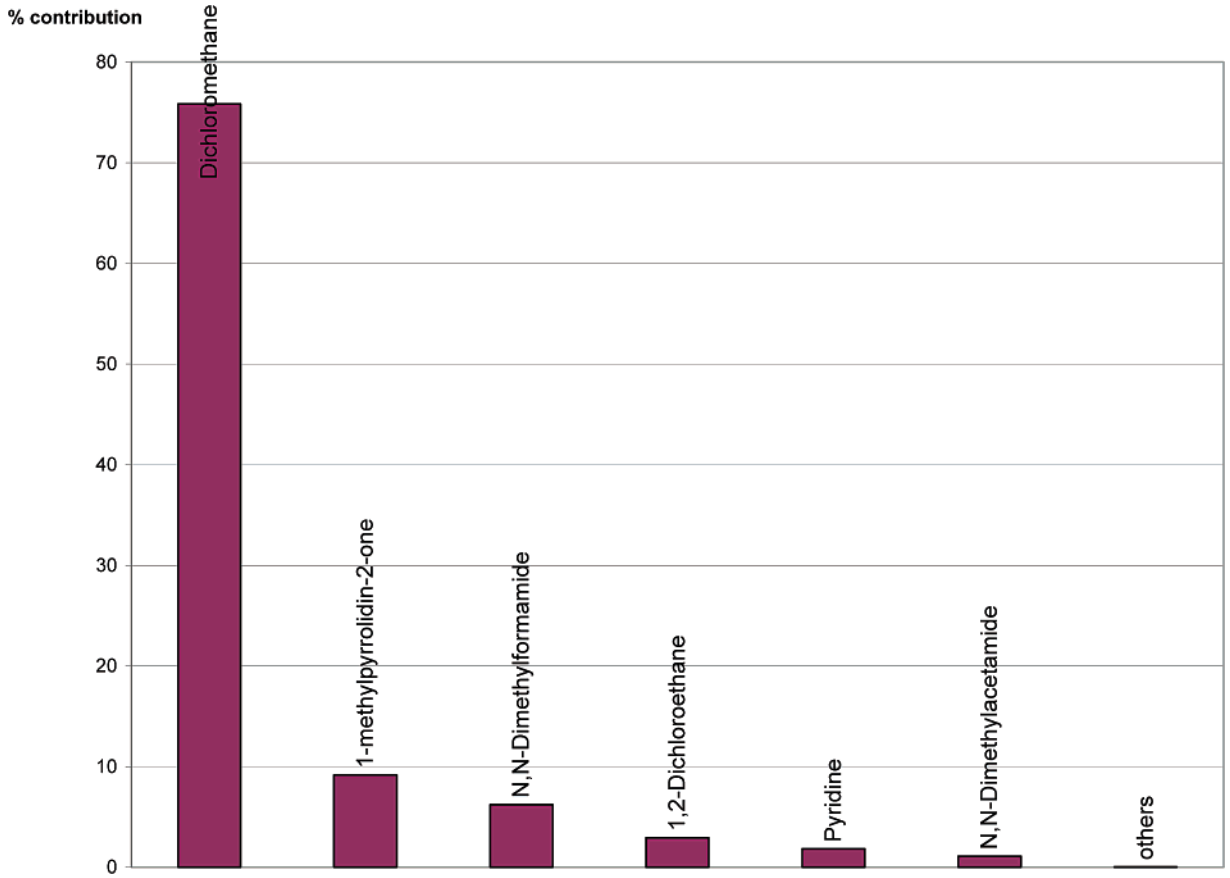

Figure 1. **Mass percentage contribution to materials of concern in GSK processes.**

related to decreases in solvent use and process optimization, not changes to chemistry or the extra mass associated with promoting the chemistry; i.e., the reagents used to support or catalyze the reactants. For example, based on the data discussed above, average solvent use was reduced from 94 kg solvent/kg API prior to 2000 to 75 kg solvent/kg API during 2005, about a 20% reduction in average consumption. This average solvent use is based on a remarkably consistent average of seven stages for API synthesis for both 2000 and 2005 data.

Even a relatively modest reduction of solvent use results in improvements to the associated environmental life cycle impacts. For example, reducing THF use in a process from 1.00 to 0.75 kg avoids about 4 kg CO_2-equivalent green house gas emissions, when accounting for manufacturing of THF only. Even more CO_2-equivalent green house gas emissions are avoided if one accounts for avoided disposal (i.e., incineration) or recovery (i.e., distillation) emissions. While solvent recovery and reuse is often seen by those outside the Pharmaceutical Industry as a viable option and often practiced, it should be noted that on average within GSK, less than 50% of solvent used is recycled and reused.

While some have focused on chemical reaction efficiency through Trost's introduction of the concept of atom economy,[19,20] the experience at GSK tends to suggest that there does not appear to be much movement towards routine use of different reactions that are effectively reducing the mass intensity (kg input/kg API) of processes. This may be unique to GSK, and there are several possible explanations that come readily to mind. It may represent fundamental thermodynamic or kinetic limits to further improvements in chemical reaction efficiency. Alternatively, it may be a reflection of not being able to pay sufficient attention to discovering and optimizing replacement reactions for currently used reactions. Another explanation may lie in the inherent complexity of pharmaceutical molecules precluding significant gains in sequential atom-efficient reactions. Or equally likely, it is merely a matter of having to work with too many compounds in early-phase development that never make it to commercialization.

The apparent GSK situation stands in stark contrast to such efforts as novel routes to APIs as demonstrated by recent winners of the U.S. Presidents Green Chemistry Awards, e.g., Merck's work with Januvia (common name is sitagliptin), Merck's new drug for treating type-2 diabetes, where novel chemistry profoundly altered the solvent consumption of the process. In the initial route, a total of about 270 kg of waste/kg of sitagliptin was produced where, in the final route, slightly less than 50 kg waste/kg of sitagliptin was produced, about an 80% decrease in total waste. If one assumes that what is true of GSK is true of Merck, most of this waste (85−90%) is solvent, and that represents a significant reduction in overall solvent consumption.

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So, until a set of truly atom-efficient reactions is discovered and routinely used or chemists become better able to direct reactions through nanotechnology or biotechnological means or some other means, it is safe to assume that solvents will continue to be an important component of modern synthetic chemistry. It should therefore be incumbent upon synthetic and process chemists to become increasingly proficient in designing synthetic organic processes where solvents are included as an integral part of the reaction and separation system.

Another way of looking at the effect of large volumes of solvent, or dilute reactions, is to consider the size of the manufacturing plant required to accommodate solvents and solvent recovery operations. Typically, plant throughput is constrained by the size and number of the vessels required to run any given process, with more complicated processes obviously requiring more vessels and operator management. Doubling the concentration at which a reaction is carried out may only decrease the material cost/kg of API by perhaps 10−15%, but it can make a major difference in the amount of capital and operations time required to manage and treat large solvent volumes. There is obviously limited desire at the plant level to use reactor capacity for solvent treatment or recovery operations. There is also not any great desire to manage multiple-mixed solvent reaction wastes, especially the aqueous/organic solvent mixtures commonly encountered in many processes found in the pharmaceutical industry. Consequently, much of the industry relies heavily on incineration—we pay for the solvent, we pay for the capital to manage it, and we pay to burn it.

There are several competing issues in solvent use that continue to cause difficulty for the practicing synthetic chemist that directly impact the use of solvents. This includes both traditional solvents and many of the newer proposed replacement solvents. The first is the general perceived need to run reactions homogeneously. Given the frequently encountered poor solubility of complex intermediates, and/or the API and, in some cases, the additional reactants or auxiliary reagents or catalysts, reactions are carried out, in general, as relatively dilute solutions; i.e., the concentrations of the reactants in solution are generally low. A greater consideration of solvent choice focused on solubility and separability of reactants combined with better use of technology (different types of reactions and reactors) should address many issues associated with using large solvent volumes.

A second issue is the need to set up for subsequent reactions of sometimes very different types of chemistry that are incompatible with the solvent used in a preceding step or steps. This invariably leads to increased process complexity because of the solvent-switching steps that must take place to ensure that the correct solvent is in place for the next step in the reaction. A third issue is related to processing aspects such as ease of mixing or ensuring adequate mass or heat transfer, especially for exothermic reactions. Engaging chemical engineers early in process design in addition to the use of alternate reactors, mixers, etc. could address these sorts of issues.

A fourth issue is the need to isolate materials as often as possible as crystalline substances, either for the purpose of impurity removal, to isolate a particular isomer, or to ease shipment of the material to another location to carry out the next steps of the synthesis. Impurity formation is also a driver, in some cases, for running reactions in slightly more dilute solutions. Better synthetic design, new chemistries, and better engineering may address the first two parts, but isolation for shipment will remain an issue as long as many fine chemical and pharmaceutical processes remain as batch chemical operations. A better understanding of reaction mechanisms and kinetics coupled with alternative reaction configurations (different reactors, order of addition, better mixing geometries, etc.) may provide for process intensification. A final issue of major importance and continuing challenge for the pharmaceutical industry is the need to reproducibly isolate APIs in a known and stable crystalline form. This is clearly beyond the scope of this paper, but it is an area requiring considerable effort to resolve.

Some Concluding Thoughts on What Is Needed

It is encouraging to note that several groups, predominantly in the field of Chemical Engineering, are beginning to take a more deliberative approach to solvent selection and optimization as demonstrated by Elgue, et al.,[13,14] Kolá,[15] and Gani, et al.[16−18] However, these sorts of approaches are still in their infancy, and they are not in common use. Moreover, they support the often expressed, although not as easily practiced, notion that there needs to be greater collaboration between synthetic organic chemists and the chemical engineering communities to move towards more sustainable solvent use.

Some of the things we think are important areas to work on to reduce overall use of solvents include the following:

- Validated and comprehensive but easy to use literature and data bases that catalogue solvent selection with respect to specific chemistries, reactions, and the effects of solvent variation on those chemistries. The work of Carlson[21] and Reichardt[22] represent attempts at doing this, but these works need to be updated, simplified, and automated, with more recent examples of chemistries run with solvents that are generally identified as being "greener."
- Inclusion of solvent selection as an important design consideration in route selection.
- Synthesis strategies to key intermediates or synthetically useful building blocks that optimize solvent use, reuse, and end-of-life considerations.
- Development of solvent options that provide the desired function (solubility and separability) without the undesirable chemical properties that cause environmental, health and safety issues. While so-called "neoteric" solvents such as ionic liquids, fluorous-phase solvent systems, and supercritical-fluid systems (water and CO_2) have synthetically intriguing and potentially very useful properties, there are a great many unresolved environmental, health, and safety issues

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across their life cycle. This includes issues related not only to their manufacture and use but also to their ultimate disposal. There has been insufficient attention paid to these issues in the excitement to prove their synthetic utility.

- technology options that facilitate process intensification; e.g., new reactors, mixers, solventless reactions, etc.
- alternative solvent use at meaningful scale
- increased use of biotechnology to produce desired synthons and APIs in media where the desired product is easily recoverable in the required form

Movement towards more sustainable chemical synthesis will require a considerable amount of creativity on the part of many to bring it about. A key component in becoming more sustainable is the use of solvents. It is well worth greater attention on the part of the synthetic chemistry community.

Acknowledgment

We gratefully acknowledge the many helpful comments and strong support for green chemistry of John Hayler and Tom Roper in particular, and more generally, the Sustainable Processing Team at GlaxoSmithKline.

Received for review August 15, 2006.

OP060170H