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An intravenous formulation decision tree for discovery compound formulation development

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Abstract

Discovery and pre-clinical animal efficacy assessment formulation development efforts are challenged by limited compound availability and stringent timelines. The implementation and use of a systematic discovery formulation scheme can facilitate this important process. We observed that nearly 85% of Pfizer, Ann Arbor discovery compounds ($n > 300$) submitted for discovery and pre-clinical injectable formulation development in the year 2000 could be formulated by pH adjustment, cosolvent addition, or a combination of the two approaches. Based on the vehicle data generated by this laboratory, a discovery formulation decision tree, that utilizes the solubilization approaches described above, is proposed. The proposed decision tree can be adapted and modified by pharmaceutical scientists to conform to best practices put forth by their institutions for discovery animal studies requiring injectable dosage forms.

Keywords: Solubility; Decision tree; High throughput; Discovery

1. Introduction

In recent years, the progress of combinatorial chemistry and high throughput screening has changed the pace of drug discovery. The use of combinatorial chemistry enables a chemist to synthesize hundreds of interesting, drug-like compounds in a short period of time (Gallop et al., 1994; Gordon et al., 1994). The integration of analytical instruments, robotic systems, and cell line cultures allows discovery scientists to perform hundreds of in vitro screening experiments such as $\log P$, pK_a, solubility, stability, CYPs inhibition, and CACO-2 permeability for further in vivo screening on a weekly basis (Bevan and Lloyd, 2000; Cox et al., 2000; Kariv et al., 2001; Kerns, 2001; Kibbey et al., 2001; Lipinski et al., 1997; Quarterman et al., 1998; Roberts, 2001; Roy et al., 2001; White, 2000). While numerous publications have documented these rapidly emerging technologies, few have addressed the delivery of discovery compounds for high throughput in vivo pharmacokinetics and bioavailability screening particularly in parenteral administration (Zocharski et al., 2001).

Injectable formulation development intended for early phase in vivo animal pharmacokinetic screening is a great challenge. These in vivo screens are necessary to assess the clearance and half-life of discovery compounds in preclinical species e.g. rat. This information is further utilized to help select and optimize new chemical entities prior to lead nomination. Efforts at this early stage of discovery often encounter short timelines, limited compound availability, and

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incomplete physicochemical property characterization as impediments to formulation development. For example, this laboratory typically has a 3-day window and 10 mg per discovery compound with which to formulate and deliver vehicle information in order to stay within discovery timelines. To overcome these limitations and formulate discovery compounds in a more high throughput fashion, the discovery scientist must understand basic solubilization approaches and be able to identify those structural features of a given molecule that would lead to a particular solubilizing approach.

Although the scientific background of formulation/solubilization has been well documented, decision making schemes have rarely been addressed. The objective of this report is to propose a high throughput formulation decision scheme to support early discovery injectable formulation development. To achieve this goal, basic solubilization strategies are discussed. Physical–chemical property information (melting point, measured solubility, log P, and state of ionization at neutral pH) for over 300 discovery compounds formulated by this laboratory are analyzed retrospectively to identify the gaps between high throughput in vitro screening and discovery formulation. Finally, the vehicle compositions for these 300 compounds are compiled and analyzed as a foundation for the formulation decision tree. In vivo evaluations, such as clearance, half-life, and bioavailability of these discovery formulations are not addressed as they are beyond the scope of this report.

2. Solubilization approaches

To dissolve chemicals for parenteral administration, pH adjustment, cosolvent(s), complexation, surfactants, and combinations of these methods, are commonly used. Among these methods, pH adjustment is the most biologically friendly system. On the other hand, the use of cosolvent would be the most powerful tool to solubilize compounds with poor aqueous solubility particularly for compounds without ionizable groups (Rubino, 1990). Complexation agents, such as cyclodextrins, may require significant amounts of time to dissolve compounds and these agents tend to be expensive. Surfactants are problematic in terms of causing allergic reactions in experimental animals (Lorenze et al., 1977). Because of these drawbacks, this laboratory uses pH adjustment, cosolvent(s), and combinations of pH adjustment and cosolvent addition to solubilize discovery compounds. The theoretical basis for our solubilization strategy follows.

2.1. pH adjustment

The total solubility (S_{tot}) of a weakly acidic solute, for example, is equal to the sum of the solubility of both the unionized form (S_{HA}) and ionized form (S_{A^-}):

$$S_{tot} = S_{HA} + S_{A^-} \quad (1)$$

The relationship between the solubility of the ionized and unionized forms of a weakly acidic solute and pH can be described by the Henderson–Hasselbalch equation as

$$S_{tot} = S_{HA}(1 + 10^{(pH - pK_a)}) \quad (2)$$

It is apparent that the total solubility of a weakly acidic solute is governed by its intrinsic solubility, pK_a and the pH of its environment. To illustrate the impact of these relationships, several example calculations are tabulated in Table 1. As can be seen from this table, while both barbital and amobarbital have the same pK_a values, amobarbital cannot be formulated to the target concentration because of its lower intrinsic solubility. Naproxen and Phenytoin are virtually insoluble in water. However, Naproxen can be formulated to reach the target concentration via pH adjustment as a result of its favorably low pK_a. Although the discussion has focused on monoprotic acids, the same principle can be applied to polyprotic acids, mono or polybasic compounds, and zwitterions. While the use of pH adjustment is simple, the final formulation may cause irritation due to pH extremes i.e. phenytoin formulation. Thus, a pH range of 4.0–9.0 is regarded as acceptable in our laboratory for routine discovery pharmacokinetic studies (Kaus, 1998). However, acceptable ranges may be modified based on institutional best practices. For reference, a list of commonly used pharmaceutical buffers is provided in Table 2.

2.2. Cosolvency

It is known that the use of cosolvents can enhance the solubility of non-polar solutes by several

Table 1
Examples of the relationship between intrinsic solubility, pH, and pK_a

	Compound			
	Barbital[a]	Amobarbital[a]	Naproxen[b]	Phenytoin[c]
Intrinsic solubility (mg/ml)	7	1.2	0.016	0.02
pK_a	7.9	7.92	4.57	8.3
Target solubility (mg/ml)	50	50	50	50
Target pH	9	9	9	9
Total solubility at target pH (mg/ml)	95	15	430	0.12
pH to reach the target solubility	8.68	9.53	8.06	11.7
Formulatability at target pH	Yes	No	Yes	No

[a] Pinal and Yalkowsky (1987).
[b] Fini et al. (1995).
[c] Alvarez Nunez and Yalkowsky (1999).

Table 2
Examples of commonly used pharmaceutical buffers

Buffering agents	p$K_{a(s)}$	pH range	Commercial products
Maleic acid	1.9, 6.2	2–3	Teniposide
Tartaric acid	2.9, 4.2	2.5–4	Tolazoline HCl
Lactic acid	3.8	3–4.5	Ciprofloxacin
Citric acid	3.1, 4.8, 6.4	3–7	Labetalol HCl, nicardipine HCl
Acetic acid	4.75	4–6	Mitoxantrone HCl, ritodrine HCl
Sodium bicarbonate	6.3, 10.3	4–9	Cefotetan, cyclophosphamide
Sodium phosphate	2.2, 7.2, 12.4	6–8	Warfarin, vecuronium Br

orders of magnitude. This enhancement is due to the ability of cosolvents to interrupt the hydrogen bonding structure of water and to lower the dielectric constant of the resulting binary solvent system. Cosolvents commonly contain both hydrogen bonding and non-hydrogen bonding groups. The hydrogen bonding group interacts strongly with water. This interaction incorporates the non-polar, non-hydrogen bonding groups of the cosolvents into the aqueous media. Incorporation of non-polar moieties into water significantly reduces the polarity of the vehicle and further enhances the total solubility of non-polar solutes. Table 3 lists commonly used injectable cosolvents, their critical physicochemical properties as well as their acceptable proportions for injectable formulations. Combined use of the cosolvent(s) listed in Table 3 should be sufficient to dissolve a wide variety of drug-like substances (Powell et al., 1998; Wang and Kowal, 1980; Nema et al., 1997; Strickley, 1999).

Table 3
Properties of commonly used water-miscible solvents

	Surface tension[a] (dyn/cm)	Solubility parameter[a] $(cal/cm^3)^{0.5}$	Dielectric constant[a]	% used in the commercial products[b]
Water	72	23.4	81	
Dimethylacetamide	35.7	10.8	37.8	<3
Ethanol	22.2	12.7	24.3	<10
Propylene glycol	37.1	12.6	37.7	≈40
PEG 400	46.0	11.3	13.6	≈50

[a] Yalkowsky (1999).
[b] Strickley (1999).

The influence of cosolvents on solubilization of a non-ionizable solute can be described as

$$S_{tot} = S_{aq}\sum_{i=1}^{n}(10^{\sigma_i f_i}) \quad (3)$$

where the S_{aq} is the intrinsic aqueous solubility of the solute, σ_i the solubilizing power of cosolvent i, and f_i the volume fraction of the cosolvent i. The value of σ_i is the slope of solute solubility in varying percentages of solvent which is highly correlated with compound lipophilicity. σ_i may have positive or negative values. If a chemical has a positive σ value in cosolvent(s) it would likely be dissolved in a cosolvent(s) containing system. Conversely, if a compound has a negative σ value in cosolvent(s), the addition of solvent may result in a reduction of the potential solute solubility in a given system. In other words, the chemical would be much more soluble in the aqueous phase (Millard et al., 2002). It would be a great advantage to have measured σ values for every discovery compound in the commonly used injectable solvents listed in Table 3. However, it is not possible due to the nature of the discovery research. Thus, for simplification purposes, the authors assume a positive σ value for all solvent systems used in this laboratory to formulate Pfizer, Ann Arbor discovery compounds.

2.3. pH adjustment and cosolvent combination

In some cases, discovery compounds cannot be formulated to target concentrations solely by pH adjustment. Hence, a combination of pH adjustment and cosolvent addition is used to overcome this difficulty. For a weakly acidic solute (HA), the solubility of both unionized (S_{HA}) and ionized (S_{A^-}) forms in the cosolvent buffer mixture can be described as

$$S_{HA}^{cosol} = S_{HA} \times 10^{\sigma_{HA} f_{cosol}} \quad (4)$$

and

$$S_{A^-}^{cosol} = S_{A^-} \times 10^{\sigma_{A^-} f_{cosol}} \quad (5)$$

where σ_{HA} and σ_{A^-} are the solubility powers of cosolvent for the unionized and ionized forms, respectively. It is generally believed that σ_{HA} is significantly larger than σ_{A^-}. The combination of Eqs. (4) and (5) with the Henderson–Hasselbalch equation, yields the total solubility (S_{tot}) of a weak acid in cosolvent/buffer system as

$$S_{tot} = S_{HA}(10^{\sigma_{HA} f_{cosol}} + 10^{(pH-pK_a)} \times 10^{\sigma_{A^-} f_{cosol}}) \quad (6)$$

While the σ_{A^-} value is significantly smaller than σ_{HA}, optimization of the pH adjustment ($10^{(pH-pK_a)}$) term can nevertheless generate a high solubility for the ionized form in the cosolvent mixture. Some of the basic solubilization approaches are discussed in this section and details for these topics and their pharmaceutical application are available in the following publications: Yalkowsky (1999); Jain et al. (2001); Simamora et al. (2001); Li et al. (1999); Alvarez Nunez and Yalkowsky (1998); Myrdal and Yalkowsky (2000).

3. Data analysis

3.1. Physicochemical properties information

A list of over 300 Pfizer, Ann Arbor compounds formulated in the year 2000 by our laboratory was generated from a request-tracking database. Measured aqueous solubility (S), log P, melting point (MP), and ionization form at pH 7.4 for these discovery compounds were retrieved from a Pfizer corporate database. The experimental methods to generate log P and aqueous solubility values have been discussed by Kibbey et al. (2001). Ionization constants (K_a) were calculated using WebPK software (developed by Pfizer Co.) and the ionization forms were assigned based on the calculated values. For ease of use, this data was divided into arbitrarily defined ranges within each property. Table 4 presents the binning strategy for each physicochemical property.

3.2. Discovery formulations composition information

Vehicle data for each compound evaluated was retrieved from our discovery formulation database according to the Pfizer identification number. Target concentrations for these formulations ranged from 0.35 to 3 mg/ml and each formulation contained 1–5 compounds. Formulations were also binned according to the amount of organic cosolvent comprising the

Table 4
Physicochemical binning strategy and distribution of formulated compounds in binned categories ($n = 317$)

Measured aqueous solubility (μg/ml)	Distribution	<3.0	3.0–30.0	30.0–60.0	>60.0	N/A
	No. of compounds (%)	49 (16)	71 (22)	19 (6)	83 (26)	95 (30)
Log *P*	Distribution	<1.0	1.0–3.0	3.0–5.0	>5.0	N/A
	No. of compounds (%)	1 (0.3)	76 (24)	117 (37)	12 (3.7)	111 (35)
Melting point (°C)	Distribution	<50	50–125	125–200	>200	N/A
	No. of compounds (%)	0	21 (7)	94 (30)	70 (22)	132 (41)
Ionic form at pH 7.4	Distribution	Ionic			Non-ionic	N/A
	No. of compounds (%)	167 (53)			104 (33)	46 (14)

Table 5
Discovery compound decision tree vehicle zone classifications

	% of organic	% of aqueous	No. of compounds ($n = 317$)	% of compounds
Zone 1	0–5	95–100	89	28
Zone 2	25–30	70–75	50	15
Zone 3	45–55	45–55	45	14
Zone 4	60–80	20–40	81	26
Zone 5	100	0	18	6
Not formulatable[a]	–	–	34	11

[a] Vehicle falls outside the described binning strategy.

total vehicle (by volume). Table 5 depicts the vehicle binning strategy.

4. Results and discussions

Table 4 lists the physicochemical properties for over 300 discovery compounds which were formulated by this laboratory in year 2000. As can be seen from the table, values for log *P*, calculated pK_a, measured solubility and melting point spread over a wide range. There are 38% of compounds with measured solubilities values lower than 30 μg/ml and 30% of compounds with no measured solubility. Over 40% of compounds have log *P* values ≥3.0 indicating that most are highly lipophilic; 35% of compounds did not have a measured log *P* value. Twenty-two percent of the discovery compounds have melting points higher than 200 °C and 41% are missing this value. The ionization of these discovery compounds is distributed as 53% ionized and 33% non-ionized. For 14% of the compounds, an assessment of pK_a was not possible using WebPK due to structural omissions in the compound database and unusual structural motifs present in select structures.

Although the data shown in Table 4 indicate that over 30% of discovery compounds are missing at least one measured physicochemical parameter, they also suggest a trend of low aqueous solubility and high lipophilicity within these 317 compounds. At first glance, incomplete solubility and log *P* data would be expected to prohibit the discovery formulator from estimating suitable vehicles for formulation development. However, the scientist also knows that at least 50% of compounds are ionized at neutral pH. This information is important for the selection of initial solubilization strategies.

Acknowledging the gap between in vitro screening and discovery formulation development, this laboratory was implemented to formulate compounds with minimal formulation information such as structure and target concentration. The formulation distribution of these 317 discovery compounds is categorized and presented in Table 5. As can be seen from the table, vehicles in zone 1 (aqueous zone) contain up to 5% organic solvent. The addition of this small portion of cosolvent is intended to overcome the initial dissolution step for solution preparation and to shorten the overall formulation time. The percentage of cosolvents increases as one moves from formulation zone 1 to 5.

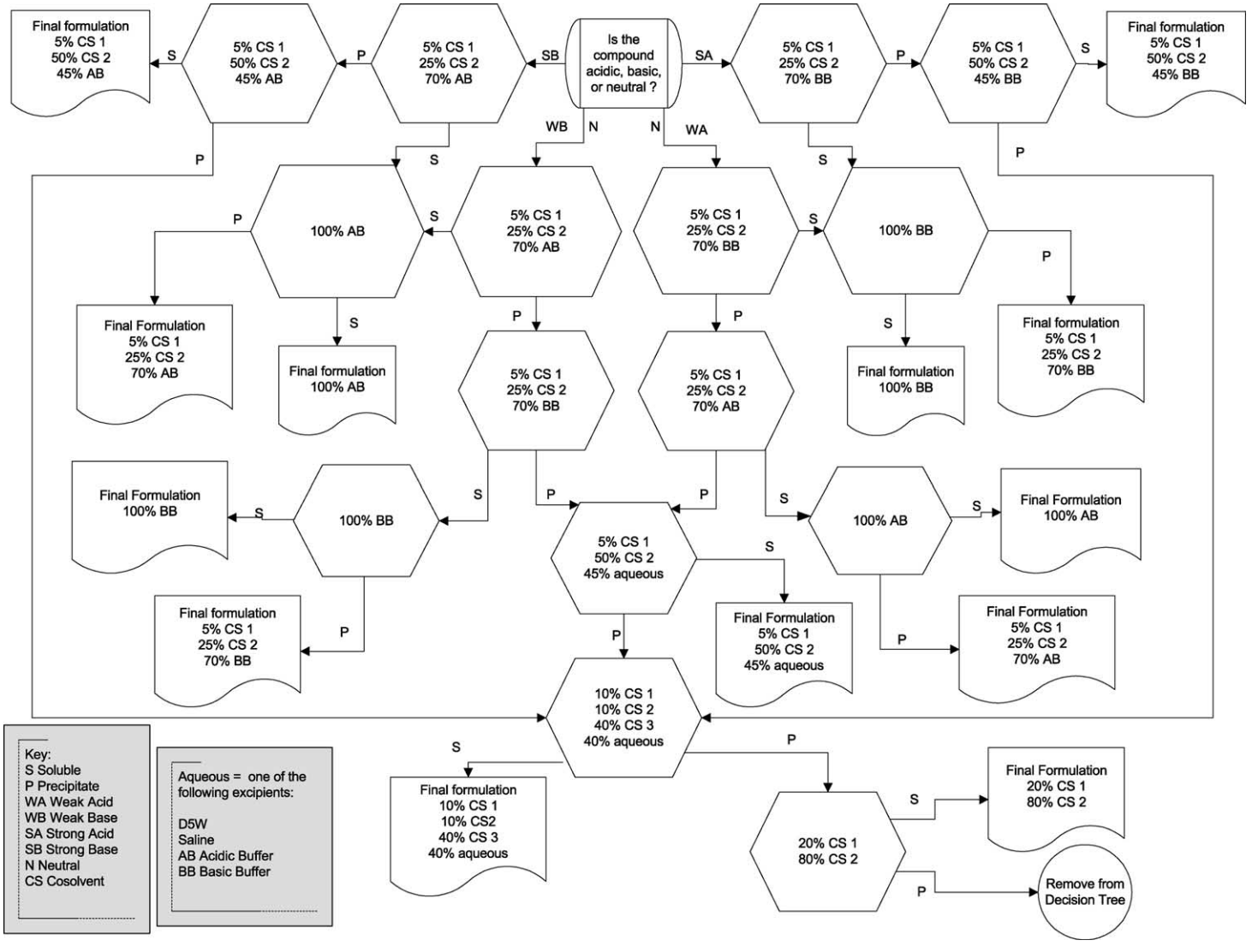
If a formulation contains over 60% cosolvent, the formulation must be approved by a veterinarian for animal safety prior to administration. Most animals tolerate one time dosing of high cosolvent containing formulations well.

By applying the solubilization strategies with proper choice of acceptable cosolvent(s) and aqueous buffer, this laboratory was able to formulate over 80% of the discovery compounds submitted for evaluation with vehicles containing at least 20% of an aqueous component. Almost 60% of the discovery formulations contained approximately 50% aqueous vehicle. A population consisting of approximately 11% of all compounds surveyed could not be formulated with these strategies, which may, in part, be attributed to poor intrinsic aqueous solubility values. A second potential contributor to the population of non-formulatable compounds is the difficulty of formulating cassettes of compounds. In these instances, the possibility exists that one compound may not be able to be dissolved in a particular cassette grouping. When this happens, the entire study is removed from the formulation scheme and all compounds in that particular cassette are considered non-formulatable by these solubilization strategies. Difficulties arising from the formulation of cassettes of compounds may therefore have artificially increased the population of non-formulatable test subjects. Although 11% of all discovery compounds evaluated did not successfully pass through the initial formulation strategy and in vivo screen test, the information generated by this laboratory can still make a positive contribution for discovery research. Difficult to formulate compounds are re-evaluated and re-modified by the discovery team to obtain better drug like properties.

Based on the formulation information of 317 compounds and the solubilization approaches described earlier, a discovery formulation decision tree is proposed and displayed as Scheme 1. As can be seen from the scheme, there are four pathways to formulate discovery compounds after an initial assessment of their functional group properties. These routes are categorized as strong acid (SA), strong base (SB), weak acid (WA), and weak base (WB). Since the acceptable pH is ranged from 4 to 9, discovery compounds with pK_a values lower than 4 and higher than 9 are considered strong acids and bases, respectively. Compounds are considered weak acids or bases if their pK_a values are between 4 and 9. A neutral compound does not ionize in either acidic or basic buffers. It may be formulated by either the WA or WB route. Zwitterinoic compounds are treated as a monoacid or monobase and formulated by one of the four routes depending on the pK_a values of the functional groups within the compound.

After receiving a formulation request from the discovery team, the discovery scientist must assess acidity or basicity based on structural information and identify a formulation route to be used for the particular compound. Once this initial assessment is completed, the zone 2 solvent system, 30% cosolvent(s) and 70% aqueous buffer, is utilized to begin formulation development. The content of organic solvent in these vehicles may be unnecessarily high and aggressive if the discovery compounds are strongly acidic/basic compounds or highly water-soluble. However, this approach is intended to generate an acceptable formulation as quickly as possible in an effort to save limited quantities of discovery compound for further experiments. The outcome of the first formulation test triggers optimization with a less aggressive vehicle (zone 1 solvent system) or, alternatively, use of a much more aggressive series of vehicles (zones 3–5 solvent systems) to solubilize the compound. If compounds cannot be successfully formulated following this scheme, they are removed from the high-throughput paradigm and additional solubilization strategies are considered to identify plausible injectable vehicles.

Choice of cosolvent and buffer comprising a particular vehicle in any formulation zone is empirical in nature. It is believed that combined use of the buffers and cosolvents listed in Tables 2 and 3, respectively, is suitable for solubilizing a wide range of chemical entities. As a result, we recommend that the formulation scientist both consider the molecular structure and consult with members of their therapeutic area team to choose appropriate solvents for a particular pharmacokinetic/pharmacodynamic model. For example, high concentrations of ethanol may be unsuitable for CNS related programs due to its intoxicating effects and the hemolytic effect of propylene glycol (Krzyzaniak et al., 1997) might render it a liability for cardiovascular programs. In cases where particular excipients may be excluded, replacements may be empirically chosen that provide similar solubilization properties with



Scheme 1. Discovery formulation decision tree.

limited side effects that may be detrimental to particular models.

It seems that there is a contradiction between balancing the speed of throughput formulation and the usage of vehicle. If time is the most important factor driving discovery research, there is no compelling reason to optimize discovery formulation. Moderate to high concentrations of organic solvent should be used for formulation development and in vivo dosing. On the other hand, laboratory animal safety is also important. Therefore, vehicle optimization can ensure that the experimental animal will not encounter fatal side effects during the in vivo data collection period. The proposed scheme can serve as a tool of balancing speed and safety. Use of the proposed formulation tree can also provide a consistent formulation strategy across in vivo discovery screening for different animal species. This consistency can ensure that discovery teams are able to compare data generated from different animal species without formulation vehicle variable confounding the results. Scheme 1 enables the discovery formulator to deliver formulations in a high throughput manner regardless the availability of physicochemical properties. The proposed scheme can be applied to rapid (less than 3 days) early pre-clinical formulation development for both singular and cassette dosing with concentrations ranging from 0.35 to 3 mg/ml.

5. Conclusion

Over 300 compounds were formulated by this laboratory in the year 2000. Simple pH adjustment, cosolvent addition, and the combination of these approaches were adequate to formulate the majority of these compounds. Based on the formulation database generated by this laboratory, a decision tree for early discovery formulation is proposed, that allows for relatively high throughput while conserving the limited amounts of discovery compounds.

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