CHAPTER II
FRAMEWORK FOR FORMULATION DESIGN

In this section a framework for pesticide formulation design is presented. Figure 2.1 highlights the work-flow and the corresponding data-flow related to pesticide formulation design.

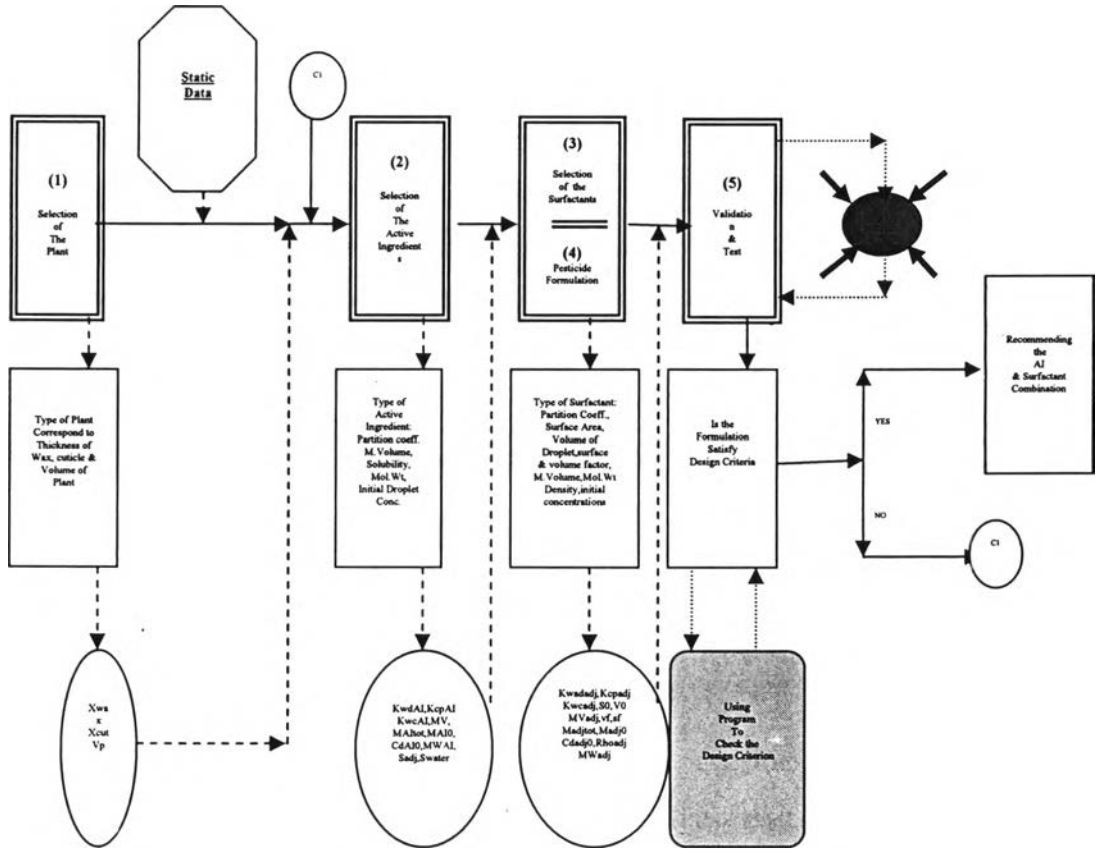

Figure 2.1 Framework for formulation design.

The design of a pesticide product can be defined as, "given a pesticide active ingredient, we need to identify the optimal pesticide formulation to be sold as a product for application on specific crops. For that, we need to identify the compounds (surfactants) that must be added in order to meet the specified performance criteria." A performance criterion might be the uptake of pesticide into the plant. The purpose of the framework is to guide the pesticide product designer through the different design stages and by providing methods and tools that can be

employed in their stages. The pesticide formulation framework is divided into three main sections:

1) Database

2) Model Preparation

3) Performance Evaluation Tools

The description of each section is as follows;

2.1 Database

The framework for formulation design will consist of several databases and one of them will be a database of plants, pesticides and surfactants with their characteristic properties. Initially it is important to know the type of plant for which one has to design the pesticide formulation. Table 4.1 shows a sample of plant species that are available in the database.

Table 2.1 Total Thickness of Cuticular Layer of different Plant Species

Plant Species	Total (Cuticle + Wax) Thickness (nm)	Plant Species	Total (Cuticle + Wax) Thickness (nm)
Wheat	200	Pea	25
Field bean	100	Potato	100
Apple	25	Rape	130
Cotton	140	Spinach	100
Lemon	500	Strawberry	300
Maize	<10	Sugar Beet	200

The total thickness comprise of the wax and the cuticle layer in the leaf of the plant and it is assumed that 10% of total thickness is wax (Bell, 2003). The selection made on the type of the plant specie will give the necessary thickness of wax (X_{wax}) and cuticle (X_{cut}) that are needed in the models for performance evaluation. The volume of plant (V_p) is calculated using the assumption that the plant compartment has value of 1ml/droplet. The volume of each droplet used in the formulation is 0.2μL.

The static data shown in Figure 2.1 is the one that do not change despite of changes made in selection of type of pesticide or surfactant. It includes the volume of each droplet sprayed on leaf (0.2μL), its surface area (S0) and the time of uptake (tu).

The second step involves the selection of pesticide (Active Ingredient). It is the one, which controls the target pest due to its biological activity and therefore proper selection is very important. The values obtained are used in model preparation tool described in section 2.2 to predict parameters such as partition coefficient, solubility correlations. Table 2.2 shows sample pesticides, which are presently available in database with their properties that are required in the model.

Table 2.2 Pesticides & their Properties.

Pesticide (AI)	Molecular Weight	Water Solubility (g/l)	Log (P)	Associated Company
Phenylurea	136	4.1	0.8	LARS
Methyl Glucose	194	-	-3	Amersham Int., UK
Cyanazine	240	0.17	2.1	Shell, UK
Fluazifop-p-butyl	383	1.0e-03	4.5	Syngenta, UK
Permethrin	391	2.00e-04	6.5	Shell, UK

The third step involves selection of surfactant. Surfactants are basically added to increase the utility of the pesticide. Table 2.3 shows a sample of surfactants that are available in the database.

Table 2.3 Surfactants & their Properties

Surfactants	Code	Ethylene Oxide Content	Molecular Weight	Appearance
C13E6	AE6	6	464	liquid
C13E11	AE11	11	684	liquid
C13E15	AE15	15	860	semi-solid
C13E20	AE20	20	1080	Waxy solid

2.2 Design Model Preparation Tools

The physical properties of the pesticides and surfactants, which have not been measured experimentally or not available in the database such as McGowan Volume, partition coefficients, diffusion coefficients etc are estimated using the suit of models available and in the framework. The design/performance evaluation tools need these properties. The estimated values of these properties are as follows;

2.2.1 Partition Coefficients

a) Active Ingredient

The partition coefficients for active ingredient are calculated using the correlations given below (Bell, 2003).

$$\log K(wax/water) = \log P(oct) - 1 \tag{2.1}$$

$$\log K(cuticle/water) = -0.77 + 0.98 \log P(oct) \tag{2.2}$$

P (oct) is the partition coefficient between octanoi and water for the pure compound. The values for P (oct) are obtained from the literature (Stock et al.,,1993). The relationship between the three partition coefficients is given by the equation below:

$$\log K(wax/cuticle) = \frac{\log K(wax/water)}{\log K(cuticle/water)} \tag{2.3}$$

$\therefore$

$$\log K(wax/cuticle) = \frac{\log P(oct) - 1}{-0.77 + 0.98 \log P(oct)} \tag{2.4}$$

Using the correlations above and the value of log P (oct) available in database, the partition coefficient of some of pesticides are obtained and provided in table 2.4.

Table 2.4 Estimated Partition Coefficients for some Pesticides & Surfactants

Active Ingredient	LogP (oct)	KwdAI (Wax/Water)	KcpAI (Cuticle/Plant)	KwcAI (Wax/Cuticle)
Methylglucose	-3	1.00e-04	1.95e-04	0.512861
Permethrin	6.5	316227.8	398107.2	0.794328
Phenylurea	0.8	0.630957	1.032761	0.610942
Cyanazine	2.1	12.58925	19.40886	0.648634

b) Surfactants

The logarithms to the partition coefficients for some of the surfactants were given by Bell (2004), which is given in table 2.5.

Table 2.5 Logarithmic partition coefficients for surfactants

Surfactants	LogK (wax/water)	LogK (Cuticle/Water)
C13E6	2.93	3.96
C13E11	1.78	3.12
C13E15	0.86	2.46
C13E20	-0.29	1.62

Using the relation between the three partition coefficients given in equations (2.1), (2.2) & (2.4) the values obtained for partition coefficient of surfactants are given in table 2.6.

Table 2.6 Partition coefficients for surfactants

Surfactants	Kwdadj	Kcpadj	Kwcadj
C13E6	851.138038	9120.108394	0.0933254
C13E11	60.2559586	1318.256739	0.0457088
C13E15	7.2443596	288.4031503	0.0251189
C13E20	0.51286138	41.68693835	0.0123027

2.2.2 McGowan Volumes

The McGowan Volumes (MV) has been calculated using ProPred from ICAS software package for both pesticides and surfactants and are given in table (2.7) & table (2.8) respectively.

Table 2.7 McGowan Volume for Pesticides

Active Ingredient	McGowan Volume (cm^3/mol)
Methyl glucose	133.85
Permethrin	281.86
Phenylurea	107.26
Cyanazine	177.43

Table 2.8 McGowan Volume for surfactants

Surfactants	McGowan Volume (cm^3/mol)
C13E6	404.2
C13E11	574.45
C13E15	710.65
C13E20	880.9

2.2.3 Initial Concentrations in Droplet

a) Active Ingredient

In order to calculate the initial concentration of pesticide in droplet the pesticide solubility is taken from literature (Stock et al., 1993) and converted from g/l to mol/m^3. The total number of moles deposited on the leaf is calculated as:

$$M_{AI,total} = \frac{pestrate}{MW_{AI}}.V_{droplet} \quad (2.5)$$

Where $M_{AI,total}$ is the total number of moles of pesticide, *pestrate* denotes the pesticide rate in g/l, MW_{AI} is the molecular weight and $V_{droplet}$ is the volume of droplet in liters.

The total pesticide concentration (including both dissolved and solid matter in the droplet) is calculated as:

$$C_{dAI,total} = \frac{M_{AI,total}}{V_{droplet}} = \frac{pestrate}{MW_{AI}}.1000.\left(\frac{L}{m^3}\right) \quad (2.6)$$

If the concentration is smaller than the solubility limit than all of the pesticide will be dissolved at the beginning of the simulation and the starting concentration, $C_{dAI,0}$ will be equal to the calculated total concentration but if the total pesticide concentration is greater than the solubility limit some of the pesticide will be solid at the beginning of the simulation. In this case the starting concentration will be equal to the saturation concentrations of pesticides. The number of moles of solid pesticide than present in droplet is calculated as:

$$M_{AI,0} = M_{AI,total} - C_{dAI,0}.V_{droplet} \quad (2.7)$$

The calculated values of parameters for some of the pesticides using above correlations are given in table 2.9.

Table 2.9 Calculated model parameters for four pesticides

Active Ingredient	C_{dAI0} (mol/m^3)	$M_{AItotal}$ (mol)	M_{AI0} (mol)
Methyl glucose	2.57732	5.15464e-10	0
Permethrin	5.12e-04	2.55754e-10	2.55652e-10
Phenyl urea	3.676471	7.35294e-10	0
Cyanazine	0.708333	4.16667e-10	2.75e-10

b) Surfactants

The droplet concentrations of the surfactants are very important parameters for the model. Samples calculations have been performed for the

surfactants available in the database. The equations used are very similar to the ones used for pesticides. The starting droplet concentration of surfactants (adjuvant) are checked against their critical micellar concentration and if the calculated ones are more than critical micellar concentration than initial droplet concentration is set equal to the critical micellar concentrations.

The total number of moles of surfactant is calculated as:

$$M_{adj,total} = \frac{surfrate}{MW_{adj}}.V_{droplet} \tag{2.8}$$

Where $M_{adj,total}$ is the total number of moles of surfactant (adjuvant), *surfrate* denotes the surfactant rate in g/l, MW_{adj} is the molecular weight and $V_{droplet}$ is the volume of droplet in Liters.

The total surfactant concentration (including both dissolved and solid matter in the droplet) is calculated as:

$$C_{dadj,total} = \frac{M_{adj,total}}{V_{droplet}} = \frac{surfrate}{MW_{adj}}.1000.\left(\frac{L}{m^3}\right) \tag{2.9}$$

The number of moles of solid surfactant than present in droplet is calculated as:

$$M_{adj,0} = M_{adj,total} - C_{dadj,0}.V_{droplet} \tag{2.10}$$

$C_{dadj,0}$ is starting concentration in the droplet which is equal to cmc in cases when $C_{dadj,total}$ >cmc.

Table (2.10) shows the calculated model parameters for surfactants that are available in database.

Table 2.10 Calculated model parameters for surfactants

Surfactants	Surfactant Rate (g/l)	C_{dadj0} (mol/m^3)	$M_{adjtotal}$ (mol)	M_{adj0} (mol)
C13E6				
	0.2	0.0187	8.62069e-11	8.24669e-11
	1	0.0187	4.31034e-10	4.27294e-10
	5	0.0187	2.15517e-09	2.15143e-09
C13E11				
	0.2	0.0527	5.84795e-11	4.79395e-11
	1	0.0527	2.92398e-10	2.81858e-10
	5	0.0527	1.46199e-09	1.45145e-09
C13E15				
	0.2	0.1207	4.65116e-11	2.23716e-11
	1	0.1207	2.32558e-10	2.08418e-10
	5	0.1207	1.16279e-09	1.13865e-09
C13E20				
	0.2	0.18518519	3.70370e-11	0
	1	0.3405	1.85185e-10	1.17085e-10
	5	0.3405	9.25926e-10	8.57826e-10

2.2.4 Droplet Surface Area

The contact angle and hence surface area covered by the droplet are dependent on the surfactant, which has been used. It is assumed that the concentration has no influence on the covered surface area. The listed contact angles and droplet areas are estimate given by Bell (2004), as they have not been available in literature. Table 2.11 shows the estimated contact angles and surface area of some of surfactants.

Table 2.11 Estimated contact angles and surface area of surfactants.

Surfactant	Contact Angles (degrees)	Droplet surface area, S0 (m^2)
C13E6	30-70	1.31e-06
C13E11	90	6.56e-07
C13E15	105	4.92e-07
C13E20	120	3.28e-07
None	0	1.59e-07

2.2.5 Diffusion Coefficient

Data collected from the literature has been used to develop special correlations for diffusivity coefficients. The following final models (Bell, 2004) have been analyzed.

(2.11)

$$\log D_{AI,wax} = -16.449 - 0.00227 * MV_{AI} + 0.1266 * C_{adj} \quad (2.12)$$

$$\log D_{AI,cutin} = -13 - 0.01 * MV_{AI}$$

$$\log D_{adj,wax} = -13.02 + 0.01363 * C_{adj} - 0.01398 * MV_{adj} \quad (2.13)$$

$$\log D_{adj,cutin} = -10.23 - 0.015 * MV_{adj} \quad (2.14)$$

Where;

D_{adj} and D_{AI} are diffusivity for surfactant and pesticide respectively in wax and cutin.

MV_{adj}, MV_{AI} are McGowan Volumes of surfactant and pesticide respectively.

C_{adj} is concentration of surfactant.

The analysis of the candidate mixture needs a number of physical properties and data. Models used for them were described above. The fourth step in the formulation design is to generate candidate mixtures and test them for feasibility through there models. Once all the selection is made than all the corresponding data goes into the performance evaluation tools where the necessary simulations are performed to validate the design. The next section will describe about the performance evaluation tools that are needed to process the selected data and estimate the uptake behavior of the selected combination of pesticide and surfactant.

2.3 Design/Performance Evaluation Tools

This section will focus on how we can combine various tools within the framework in order to obtain pesticide-formulated product. Figure 2.2 shows a diagrammatic representation of tools which when combined together can result in an efficient formulation Design.

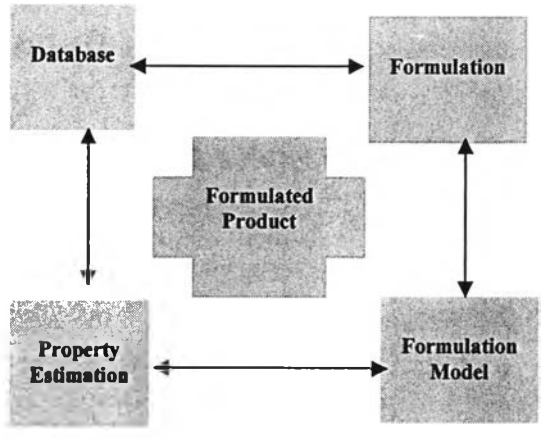

Figure 2.2 Diagrammatic Representation of Tools used in Formulation Design

The first step in the framework is the selection of Plant specie as such the tool employed to handle this is the database of various plant species available within the framework and also discussed in section 2.1. Once the type of plant and its property is known the next step is to select the pesticide for which the formulation is desirable. Database of pesticide combined with property estimation tools will assist in providing necessary data values corresponding to the pesticide selection. The property estimation tools used in this framework with there function are given in table 2.12.

Table 2.12 Property Estimation Tools and their functions

Tools	Function
ProPred	Pure component Property estimation
ICAS-Utility	Phase Diagrams
SoluCalc	Solid Solubility
Polymer Sol.	Diffusivity, Solubility

The third step involves the selection of surfactant that should be combined with the selected pesticide. A list of various surfactants will be made available to the user and once the selection is made the database together with property estimation tool will provide necessary data but it also very important what should be the characteristic property of given formulation that is to know what type and in what amount the surfactant should be added so that the desired properties of pesticide formulation product is matched and to do this CAM^{b}D (Computer Aided Mixture^{blend} Design)(Gani, 2004) methodology will be used. Only candidate mixtures generated apriori, will be investigated and therefore the CAM^{b}D approach, which will need further development for pesticide formulation design, is not discussed further. The final step involves the validation and test of formulation so as to see whether it satisfies the design criteria or not. The tool to perform this will be the Formulation Model. The model can be control release model or Uptake Model.

A mathematical model that can predict the delivery of the AI from a fabricated device is required in the above framework in order to optimize the design of the product (that contains the pesticide formulation) with respect to the amount of pesticide that will be available in the environment where it is released.

A mathematical model for the release of an AI from a microcapsule device (or solution of microcapsules) has been previously developed and validated (Muro-Suñé, 2004a). This model accounts for the number of microcapsules and their sizes through a normal distribution function of the microcapsule radii. The release is modelled with the equations for non-constant activity source (Comyn, 1985), which are derived from Fick's law of diffusion and provide the variation of the AI concentration with time, from which the percentage of release of the AI into the environment is obtained. This model applies for the case where the AI is available in solution below saturation. More details of the control release model can be obtained from the author (Muro-Suñé, 2004).