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http://www.ijcpa.in

July-September 2015

International Journal of
CHEMICAL AND PHARMACEUTICAL ANALYSIS

eISSN: 2348-0726 ; pISSN : 2395-2466

Research Article | Volume-2 | Issue-4 | Article ID: 697

# OPTIMIZATION OF SOLVENT SYSTEM DESIGN METHODOLOGY FOR FEASIBLE SEPARATION USING ALGORITHM: A COMPREHENSIVE REVIEW

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Received: 20 April 2015 / Revised: 22 May 2015 / Accepted: 25 June 2015 / Available online : 30 September 2015

## ABSTRACT

*Solvent system designing for chromatography is the most crucial point in pharmaceutical world. Designing and using certain systems with specific parameters can be done by optimization. "Eluotropic series" is not favourable tool for mobile phase optimization, as solvent proton acceptor, proton donor, dipole characteristic are not considerable while solvent strength plays a vital role in chromatographic separation which is used to estimate of a solvent's ability to cause migration of analyte Rf. This review gives a brief summary of solvent system designing via algorithm. The aim of optimizing the solvent composition is to achieve a more satisfactory separation of unknown structure & properties of uncharacterised polyherbal fraction that is essential for their ultimate identification. For instance, Trappe has given "Eluotropic Series" for column chromatography, where the solvents used can be based on accordance to their eluting effect. "Snyder triangle method" is used for optimization of mobile phase. L.R. Snyder classified the frequently used solvents in separation science. Later explored "Seven point optimization" by J. L. Glajch and Prisma model by Nyiredy. But presently "Simplex Method" and "Genetic algorithm" methods are mainly used for optimization of the solvent system designing. This review reflects the artifact of the optimum solvent system design via-model to algorithom. Also explained the map of whole parameter space in the alignment of solvent strength, retention factor and capacity factor for optimal solvent system for unknown polyherbal fraction. This constructive review provides a proof of concept for the methodology and current status that provides a systematic approach for appropriate solvent selection and design method, model, algorithom for feasible separation.*

***Keywords** – Optimization, Solvent system designing, Chromatography*

## 1. INTRODUCTION

Optimization of chromatographic separation is always an active research area because it is one of the key subjects for intelligent and automatic chromatographic separations. Many methods have been developed in order to optimize the parameters of interest in chromatography[1-5].

However, when sample composition becomes more complex, systematic optimization of the mobile phase becomes increasingly important. Well current research is going to be achieve its goal, by which we can get optimum separation systematically and the structures and properties of substances to be separated are not known just on the basis of marker. The choice of solvent or mixture of solvents used in chromatography is solely guided by two important factors i.e. the nature of the constituent to be separated (polar or non-polar).and the nature of process involved ("adsorption" or "partition" chromatography). New or improved mobile phase optimization methods for TLC have frequently been proposed in the literature. Some of them are based e.g. on the adaptation of window diagrams (COSTANZO 1997), while others rely on mathematical models and numerical methods (CIMPOIU et al. 1999, MALES and MEDIC-SARIC 2001). Several extensive reviews discussing the different optimization methods and their benefits and drawbacks have been published in recent years (SIOUFFI 1991, REICH and GEORGE 1997, ROZYLO and SIEMBIDA 1997, POOLE and DIAS 2000, GOCAN and CIMPAN 2004)[6]. As we know that so many methods have evolved but mainly i.e. Sequential simplex method, Genetic algorithm and solvent strength (via prism method) strategies are using for solvent system designing according to present review work.

So, to design a best solvent system for feasible separation is centrally important because global characterisation and holistic separation is pertaining in interest which shows intact quality control.

**1.1 Background information**

The optimization of the chromatographic mobile phase proved to be possible when the number of experimental determinations of separation parameters for each compound is obtained for more than one distinct compositions of mobile phase, at least equal with the number of variable use in the mathematical model [7, 8]. The word optimum" is Latin, and means "the ultimate ideal;" similarly, optimus" means the best." Therefore, to optimize refers to try to bring whatever optimize we are dealing with towards its ultimate state. Optimization is Finding an alternative with the most cost effective or highest achievable performance under the given constrains, by maximizing desired factors and minimizing undesired ones. In comparison, maximization means trying to attain the highest or maximum result or outcome without regard to cost or expense[9]. There are so many optimization method i.e. Gradient-based Optimization ,Response Surface Methods ,Simplex Method as strong method, Random Search , Sampling Methods as weak and : Monte Carlo Simulated Annealing , Tabu Search , Evolutionary Optimization , Hybrid Methods as intermediate method[10, 11].

Literature search reveals a large number of published papers that describe various methods to optimize mobile phase. To emphasize on the importance and the opportunities of the simplex method, various older reviews papers are available in the literature. It is a fact that mobile phase optimization is the important steps that affect the quality of a separation in TLC method development[12]. Following methods can be used as an optional way:

*1.1.1 Random trial and error method*

Mobile phase components selection and optimization in many cases is done on a "trial and error" basis or the analyst's experience or following hints from a literature search[13, 14].Many authors did not discuss the solvent selection process but mentioned trial-and-error as the approach for mobile phase optimization[15-33].

*1.1.2 The Geiss's structural approach*

This approach for mobile phase optimization considers selectivity and solvent strength as independent factors With a Vario KS chamber, a type of chamber that permits rapid mobile phase optimization, Geiss used three strong solvents, i.e. methyl tert-butyl ether, acetonitrile and methanol. These solvents are diluted with a weaker solvent e.g. 1,2 dichloroethane to obtain a series of solvent strengths ranging up to 0.70, with a gradual intermediate increase of 0.05. From these solvents an appropriate solvent strength for separation is determined. The fine tuning is performed by blending solvent mixtures, which have the appropriate solvent strength, but a different selectivity [34].

*1.1.3 Window diagram*

This technique is easy to handle and any efficient statistical calculation program is able to determine the experimental parameters, and plot the corresponding graph of $Rf_{ij}$ against the solvent composition[35].

#### *1.1.4 Overlapping Resolution Map (ORM)*

The plotting of an overlapping resolution map is very long process. Derivation of an original resolution formula provides an equation that gives directly the solvent front migration distance required for the separation of various compounds. This equation is used to speed up 30 fold the drawing of overlapping maps[36].

#### *1.1.5 RSM(Response Surface Design)*

The design of experiments (DOE) is part of response-surface modeling (RSM) methodology. Experimental design can serve to develop multivariate calibration as a widely applied in chemometrics method. The principles of experimental design describe plan and conduct experiments at different combination of solvent to obtain the maximum amount of information (a response surface) in the fewest number of experiments. The principles of (RSM) can be used to fit a statistical model to the measure response surface.

The solvent strength throughout the parameter space is approximately constant & therefore, the separation time for all chromatograms within the parameter space should also be approximately constant. A response surface is constructed from the modelled retention surface using a suitable objective function. An estimate of the best mobile phase composition for the separation is made from the response surface. The sample is then chromatographed with the mobile phase composition and the quality of the chromatogram assessed. The quality of chromatograph are assessed by suitable objective function which is composed of Tertiary mixture (mobile phase composition) & nonlinear and linear plot (retention factor) .With the help of Response surface design is easier to model retention surface of individual multicomponent herbal fraction. To map the whole parameter space at reasonably selected intervals to locate the best separation. Response surface can be fitted by replacing the retention factor term with a suitable objective function and inherent problems with peak crossovers as the mobile phase composition is changed, resulted in this approach being largely replaced by the use of overlapping resolution map[37].

### 1.2 Aspects of the rationale behind solvent system design

Chromatography basically is not reproducible condition, because various factor such as humidity factor, temperature, etc affect the separation. On the contrary separation science also involved fuzziness, feasibility, intactness and flexibility. Under control conditions appropriate solvent system design is used to help phytoequivalence fingerprinting for authentify the uncharacterised multicomponent extract .Which make an obsolete data base for further prediction of unknown extract as well as control the continuous species variation.

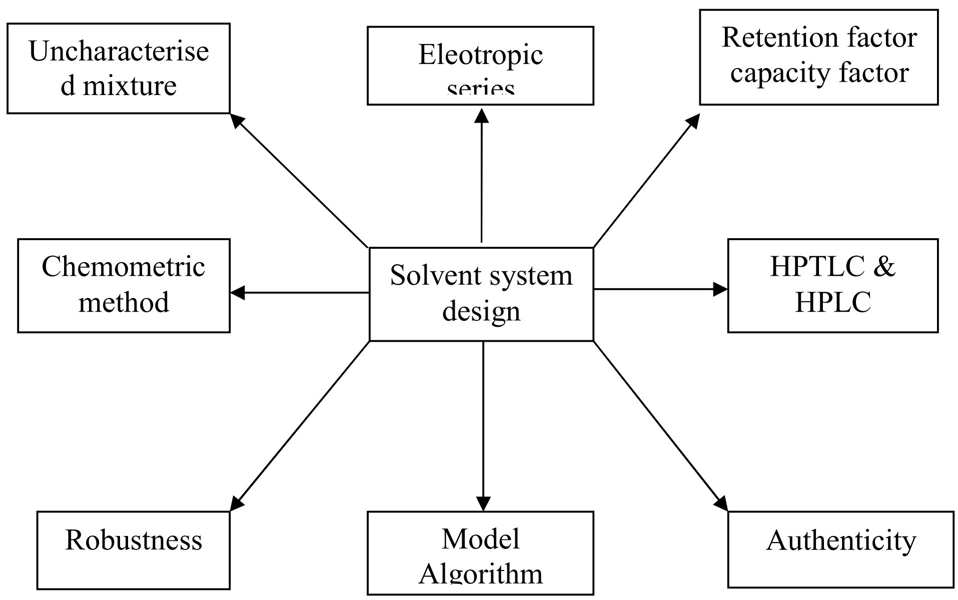
An important task in separation of compounds from a mixture by chromatography is choosing of the proper mobile phase because solvent has a double function in chromatography that they are responsible for transporting the sample and for creating the separation system and the solvent's strength determines its ability to transport the sample through the system as given in scheme 1. The objective of this review is to describe algorithm that is able to guide a user through the selection/design of the best possible solvent for feasible separation of multicomponent fraction.

## 2. COMMON OPTIMIZATION TECHNIQUE FOR SOLVENT SYSTEM DESIGN METHODOLOGY

A total chromatographic optimization system develops to undersign of both mobile phase composition and the analysis time (or migration distance). Here systemically explained some optimization technique. Optimization method is more specific concerning the sample and measuring condition. A model is a description of the data properties, and an algorithom is a detailed set of instructions for accomplishing a computational task [38].

### 2.1 Models used for solvent system designing

*2.1.1 Synder solvent selectivity triangle*: Snyder based his solvent characterization scheme on Rohrschneider's gas–liquid partition coefficients for three test solutes – ethanol, dioxane, and nitromethane – in 82 common solvents[39]. The solutes were chosen to probe the ability of each solvent to participate in proton accepter, proton donar,and dipolar interaction. In snyder system , proton donar characteristic actually refers to a solvent's ability to interect with a proton accepter(dioxane). It is not an actually proton donar capability, and thus a solvent(or solute) can be classified as a proton donar even though it contains no protons. The same qualification is applies to proton accepters, which are classified as such based on an ability to interect with a proton donar(ethanol)[40].




**Scheme 1:** An illustrative flowchart described for solvent system designing

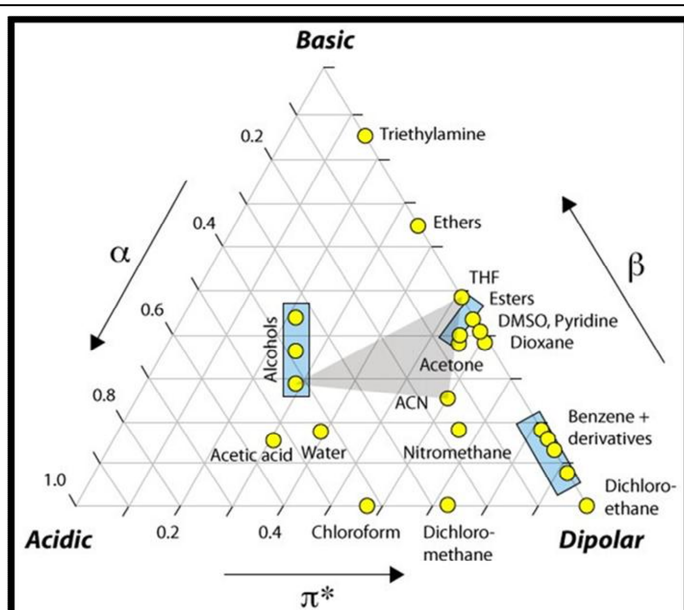



**Fig 1:** Snyder's solvent selectivity triangle (Johnson A.R., Vitha M.F., J. Chromatogr. A 2011,1218: 556–586).

*2.1.2 PRISMA model:*

The "PRISMA" mobile phase optimization model was developed by Nyiredy et al. in 1985. The model formanual selection of solvents and optimization of the mobile phase was developed first for thin-layer chromatography. The system is a structured trial and error method consisting of three parts. In the first part the basic conditions, i.e. Stationary phase, Vapor phase and individual solvents for the optimization process, are selected. The second part is the optimization of the mobile phase composition using the previously selected solvents, and the third part involves the selection of development mode and chromatographic technique, and the transfer of the optimized TLC mobile phase to the various analytical and/or preparative planar and column liquid chromatographic techniques as shown in Fig. No.2[41].

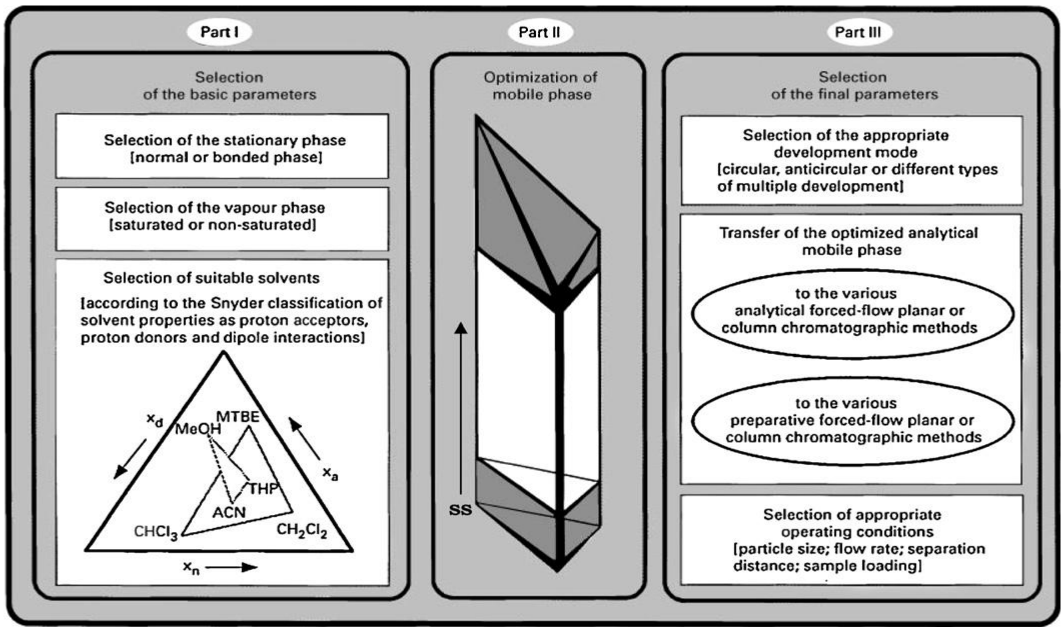
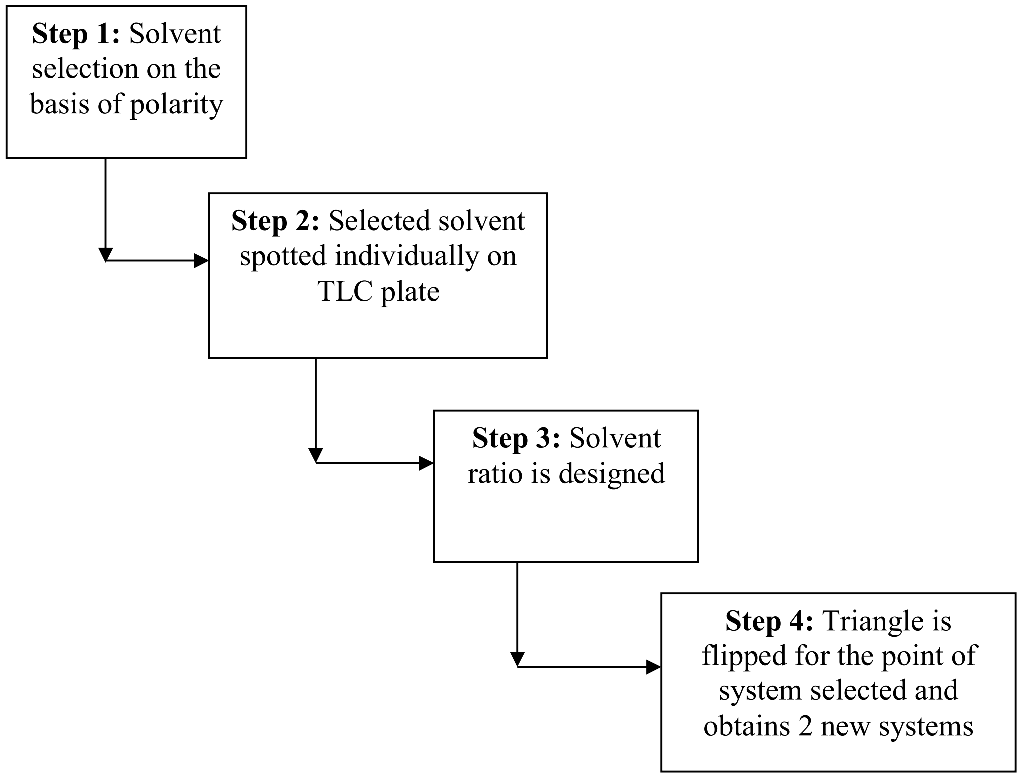



**Fig 2:** Selection of optimize mobile phase through Prism model

## 2.2 Algorithm used for solvent system designing

2.2.1 Sequential simplex method: the definition of simplex is best defined as geometric figure in which the number of points equal to one or more than the number of factors. In order to give a triangle or a tetrahedron, simplex is carried out by either using two factors or three factors respectively. This method accepts point showing best response and rejects points showing worst response, the triangle is flipped at the point of acceptance to give mirror image of the previous triangle, thus forming a new triangle[42]. This method can be repeated in order to obtain best results as given in scheme 2.

This method mainly aims at finding the local maxima of solvent system and the chromatographic response factor like Rf and hRf and to reduce the effect of matrix in separation. Further application for the simplex method is that it is widely used for solving linear programs and optimization of mobile phase. Previously work done by different researchers is given in table no.1.




**Scheme 2:** Illustration of the main step of solvent system methodology via simplex method

**Table 1: Work done by different researchers by using simplex technique for solvent system designing**

| Previously work done by researchers | Year | Reference |
|---|---|---|
| The optimization of information obtained by multicomponent chromatographic separation using the simplex technique. | 1975 | 43 |
| The use of simplex method in the optimization of chromatographic separation | 1979 | 44 |
| Use of sequential simplex algorithm for improved separation in automated liquid chromatography methods development. | 1983 | 45 |
| Application of sequential simplex. Optimization to formulation development. Optimization of the mobile phase in TLC by the simplex method. | 1984 | 46 |
| Simplex optimization of HPLC seperations. | 1989 | 47 |
| Optimization of separation in supercritical fluid chromatography using a modified simplex algorithm. | 1990 | 48 |

2.2.2 Genetic algorithm: Genetic algorithm is an optimization algorithm that mimics the mechanisms of natural selection described by genetics and the Darwinian theory of evolution. As a global-searching algorithm, genetic algorithm makes use of artificial intelligence to obtain the solution of rather complex problems, so it has been widely applied in resolving combinatorial optimization problems[49], and attempter problems [50]due to their parallelism and effective utilization of global information. However, up to now, there are a few reports on the application of genetic algorithm in optimization of chromatography. Genetic algorithm has been applied in prediction for chromatographic retention by Zhang et al. The field of GAs is relatively young. The first applications were reported around 1960 when Holland introduced the method. It is however only since the 1980s that the number of publications increases exponentially, mainly due to advances in the computer technology. In 1985 the first conference on GAs took place and the first textbook appeared in 1989. Sandra babic, Alka J.M.Horvant, and Marija Kastelan-Macan has used Genetic algorithm to Optimize TLC Separation[51.]

**2.3 Instrumentation**

*2.3.1 HPTLC*

High-performance thin-layer chromatography is an advanced form of instrumental TLC, which does not only include the use of high performance adsorbent layers (e.g. silica gel with refined uniform particles, approximately 5 µm in diameter, as compared to 12µm in TLC), but also adopted instrumentation e.g. the development chambers. It usually also implies a standardized methodology for development, optimization, documentation and the use of the ''appropriateness'' validated methods. The HPTLC technique is applied in qualitative and quantitative separations of compounds in mixtures, where the quantitative mode operates in a more optimized way (standardized with a given procedure), hence, applicable in the assay of compounds in samples.

It a displacement model according to Snyder a surface phase (monolayer) & mobile phase (significance prediction of solvent strength) which integrate competitive solute-solvent interaction. On the contrary selectivity is the alignment of mobile phase optimization[52].

*2.3.2 HPLC*

High performance liquid chromatography is a separation method that separates all analytes as quickly as possible. It takes shorter analysis time, less eluent consumtion, less sample amount needed. Chromatography resolution is basically product of Efficiency, Retention, and Selectivity. HPLC theory helps to understand how to conduct a method speedup systematically. In contextual rapid separation LC is composed of four compartments Hardware, Software, Tools, Chemistry. Isocratic and gradient elution method are complementary separation technique .Isocratic methods are generally preferred because of convenience, simplicity and reproducibility, but are inappropriate for sample containing components with a wide retention range. Gradient methods are also preferred for the revere-phase in separation of macromolecules. The characteristic feature of gradient elution is the programmed increase in mobile phase solvent strength during the separation. Changes in solvent strength are accompanied by a simultaneous change in selectivity for many compounds. The gradient elution provides an effective means of selectivity optimization. The algorithm technique of optimizing mobile phases for liquid column chromatography using various designs (OMP, RSM, etc) is transformed into a non-statistical multifactor optimizing method. The optimized parameters are the binary (tertiary) solvent composition, mobile phase flow rate, and analysis time. The main goal is to obtain the fastest analysis of uncharacterized mixer extract compatible with the desired separation.(**Reff-essence of chromatography**)53

**3 APPLICATION OF OPTIMIZATION TECHNIQUE IN SOLVENT SYSTEM DESIGNING**

The field of optimization is broad and has applications in all areas of pharmaceutical science. Basically it is used to improve the separation between all single representing the individual components of mixture., to obtain a chromatogram in each peak corresponds to one component only and also it gives idea about using ternary or quaternary mobile phase given in Table 2.

The mobile phase optimization process proved to be able to provide accurate, precise and reproducible method of characterization and analysis of chromatographic parameters via following methods:

3.1 Solvent system designing for “Kutaz dadim kwath” using Sequential Simplex Method: [54]

For kutaz dadim kwath solvent system was designed by using triangle method in which 7 solvent system was designed . so, finally best separation was found Toulene : Dichloromethane : Ethyl acetate(4.3: 5: 2.5). This system has been selected due to the reason that it shows the maximum solute run.

3.2 Optimization of mobile phase by “Simplex method” with special reference to Guggulu (*COMMIPHORA WIGHTII*):[55]

According the previous available references for chromatographic separation of Guggulu mobile phase- Petroleum ether: ethyl acetate: methanol (6: 2: 0.5v/v/v) was used. But in this article petroleum ether was replaced by benzene because PE is mixture of crude components, its diaelectrical potential can vary and its strength is also not fix it may vary. While benzene is purified, its diaelectrical potential is fix and strength is also fixed.. and The final optimize solvent system was Benzene: ethyl acetate: methanol 6.9 : 1.8 : 1.3 (v/v/v). Depending upon the response of the solvents towards the separation of components, the nature of the solvent was decided as Benzine- promoter Ethyl acetate -modifier & MeOH as suppresser.

**Table 2: Different application of optimization technique in Pharmaceutical Sciences**

| S. No | Research envisaged | Instrumental technique | Chemometric analysis (Optimization) | References |
|---|---|---|---|---|
| 1 | Development of Suitable Solvent system for downstream processing of Biopolymer Pullulan Using Response surface methodology. | TLC & HPTLC | D-Optimal design | 56 |
| 2 | Comparison of optimization methods in planar chromatography | HPTLC& TLC (Spotting Technique) | Overlapping Resolution Map | 57 |
| 3 | Planar chromatographic method development using the Prisma optimization system and flow charts | HPTLC &TLC | Prisma method | 58 |
| 4 | Separation of tropane alkaloids by TLC,HPTLC and OPLC method | TLC,HPTLC,OPLC | Prisma method | 59 |
| 5 | Normal phase 2D TLC separation of flavonoids and phenolic acids from betula sp. Leaves | TLC | Prisma method | 60 |
| 6 | The application of TLC to the determination of phenol residues in water. | TLC | Prisma method | 61 |
| 7 | The main saponins from aerial parts and the roots of solidago virgaurea subsp.Virgourea | TLC & HPTLC | Prisma method | 62 |
| 8 | HPTLC and OPLC separation and detection of prostaglandin esters using 4-bromomethyl-7-methoxycoumarin (BrMMC). | HPTLC-OPLC | Prisma method | 63 |
| 9 | An alternative solvent system for the separation of anthraquinone aglycones from rhubarb on silica thin layer | TLC | Prisma method | 64 |
| 10 | Effective systems for the separation of pharmaceutically important estrogens by thin layer chromatography. | TLC | Prisma method | 65 |

3.3 Authenticity: Homogeneous authenticity is the important step to assess the quality of plant medicine. Each crude mixture of herbal fraction contains certain nature of constituents. Optimum solvent system design governs reliable pattern of chromatographic separation. Therefore validate algorithom can be analyzed to identify medicinal plants and distinguished the spurious, adulterant. Furthermore, not only can authenticity be identified but substitutes can also be searched according to the theory that ''herbs containing the same properties have similar potency''.

## 4. SOME SUGGESTIONS AND CONCLUSION:

The optimization procedure opens a new pathway in analyzing and characterization of chromatographic parameters of TLC analysis by using mixture solvents. The algorithm and other method as mentioned are simple and rapid for optimization and many mobile phase compositions can be evaluated simultaneously. The advantage of these optimization methods is that optimum composition of mobile phase can be easily obtained.

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