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Applying Analytic Hierarchy Process (AHP) in the selection of best method for the preparation of solid dispersion as a carrier for the controlled drug delivery of Delayed Release tablets

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ABSTRACT

Novel drug delivery systems like controlled release, sustained release, prolonged release etc. is one of the best method for achieving therapeutic efficacy which helps to reduce frequency of drug administration. Solid dispersions are binary or ternary component system in which a solid matrix is used as a dispersed phase.It is used as a promising approach to improve the solubility of poorly soluble drugs. To achieve a better dissolution and bioavailability of poorly water insoluble drugs, it is necessary to select the best technique for the preparation of solid dispersions .This is influenced a number of factors like stability of drugs, solvent used, molecular arrangement etc. A study was conducted using five alternatives such as solvent evaporation technique (SET),Fusion method (FUM),Spray drying technique (SDT),Lyophilisation(LYZ),and super critical fluid technology(SFT).A set of alternatives were selected based on literature review, experiments, knowledge etc. The overall ranking of all techniques helps to select the best technique for the preparation of solid dispersion as a carrier .Based on priority ranking solvent evaporation technique is the most suitable method to achieve controlled drug release from delayed release tablets.

Key words: Multi-criteria decision making, Analytic Hierarchy Process, solid dispersions , Drug Delivery.

INTRODUCTION

During the past decade's most of the Pharmaceutical research activities have focused on the discovery and synthesis of the novel drugs and drug administration systems, by giving much importance to the controlled drug delivery systems (CDDS) [1,2].Oral ingestion is traditionally preferred route of drug administration, which is a convenient method to achieve both local and systemic effects. But conventional system does not achieve desired drug concentration at the target site, sometimes leads to excessive doses, variation in plasma concentration and leads to marked side effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period of time. Controlled drug delivery systems can provide a uniform concentration amount of drug at the absorption site can maintain the plasma concentration within a therapeutic range and minimizes the side effects and also reduces the frequency of administration.

To achieve controlled release of drugs via the oral cavity the different techniques are used such as osmotic systems which uses osmotic pressure as driving force, multiporous oral drug absorption systems (MODAS), microsphere technology, diffusion controlled matrix systems, Hydrogel systems, Gastric retention systems, Intestinal protective

drug absorption systems, pelletized pulsatile delivery systems, oral fast dispensing dosage forms, liposomes nanoparticles, colon-specific drug delivery [3-6].By using different polymeric systems as carriers ,helps to form solid dispersions ,which can be converted to delayed release tablets for achieving a controlled drug delivery for poorly soluble drugs.

A number of techniques are available for the preparation of solid dispersions, which includes solvent evaporation technique (SET),Fusion method (FUM),Spray drying technique (SDT),Lyophilisation(LYZ),and super critical fluid technology(SFT). The choice of an appropriate preparation technique depends upon the nature of polymer fixed and the site specific for the drug delivery, the choice of drug used, use of solvents, and duration of therapy. The method of preparation and its choice are equivocally determined by technique related factors like particle size, requirement, reproducibility of the release profile and method.

In solid dispersion technology, the overall goal is to achieve improve the dissolution of poorly soluble drugs, thereby enhances the bioavailability of drug and leads to better therapeutic efficacy. This is influenced by a number of factors like drug stability, excipients used, skill for operation, drug release, maximum yield of solid dispersion and preference to manufacturer. Selecting right design concept in the product development process is a crucial design. Inaccurate decision can cause the product to be redesigned or remanufactured. According to Xu*et al.*,[7] implementing appropriate evaluation and decision tool should be considered at the conceptual design stage that involves many complex decision-making tasks. One of the useful tools that can be employed at the conceptual design stage is analytic Hierarchy process (AHP). It is more rationale and appropriate to analyse both qualitative and quantitative parameters, to make a decision. When two or more alternatives are in hand and one has to select the best, then the appropriate approach is to use a multi-criteria decision making (MCDM) method, which involves all the factors that could influence solid dispersions in decision making process while choosing technique.

1. Analytic Hierarchy Process (AHP)

The AHP, developed at the Wharton school of business by saaty [8] is a powerful and flexible weighted scoring decision making process to help people set priorities and to make best decision. This technique is widely used to solve multi-criteria decision making in both academic research and industrial practice. General methodology, excellent analytical mathematical treatments of AHP are available in literatures [9-12].

AHP provides a way to rank the alternatives of a problem by deriving priorities. AHP gives a proven, effective means to deal with complex decision making and can assist with identifying and weighting selection criteria analysing the data collected for the criteria and expending the decision making process. The AHP is based on a matrix of pair wise comparisons between criteria, and it can be used to evaluate the relative performance of decision alternatives with respect to the relevant criteria.

The basic steps for the Analytic Hierarchy Process are given below [13].

1. List the set of different alternatives.
2. Identify the factors that may be intrinsic as well as extrinsic, which may have an impact on the selection of alternatives for formulation of solid dispersions. For each of these impacts identify the criteria and the quantifiable indicates to the criteria for a possible measure.
3. Develop a graphical representation of the problem to depict the hierarchy of the problem.
4. Assign weights to each alternative on the basis of its relative importance of its contribution to each criterion based on saaty's 9 point scale.
5. Once the pair wise comparison matrix has been formed for a criterion, the normalized priority of each alternative is synthesized.

This is done as follows:

✓ Sum the values in each column.
✓ Divide each element in the column by its column total which results in a normalized pair wise matrix.
✓ Compute the average of the elements in each row of normalized comparison matrix thus providing an estimate of the relative priorities of the alternatives. This result in a priority vector.

6. In addition to the pair wise comparison of the n alternative use the same pair wise comparison procedure to set priorities for all the criteria in terms of the importance of each in contributing towards the overall goal.
7. The priority vector is synthesized similar to step 5
8. Calculate the overall priority for alternatives
9. Choose the alternative that has the highest priority.

According to Saaty a key step in the AHP model is the establishment of priorities through the use of pairwise comparison procedure and the quality of the ultimate decision relates to the consistency of judgments that the

decision maker demonstrates during the pairwise comparisons. The consistency is determined using the eigen value ($M_W = \lambda_{max}$ W is solved).The eigenvector provides priority and eigen value measure of consistency index (CI) derived from the departure of λ_{max} from n is compared with corresponding average values for random entries yielding the consistency ratio (CR).

Here M = matrix; w=n dimensional eigenvector associated with the largest eigen value λ_{max} of the comparison matrix M.

Multiply each CI by the priority of the corresponding criterion and adding them together finds the consistency of the entire hierarchy. The result is then divided by the same type of expression using the random CI corresponding to the dimensions of each matrix weighted by the priorities as before.

Saaty has shown that λ_{max} is always greater than or equal to n, the closer the value of λ_{max} is n, the more consistent are the observed values of matrix. A zero value of CR would indicate perfect consistency whereas large values indicating increasing levels of inconsistency. The CR should be about 10% or less to be acceptable, if not, the quality of the judgment should be improved, perhaps by revising the manner in which questions are asked in making pairwise comparisons. If this should fail to improve consistency then, it is likely that the problem should be more accurately structured; that is, grouping similar elements under more meaningful criteria. The C*I* for a matrix of size is given by the formula.

$CI = (\lambda_{max}^{-n}/ (n-1)$

CR= C*I*/RI

Satty (based on large number of simulation runs) approximated random indexes (RI) for various matrix Sizes, n, as

Table 1: Random Index of Analytic Hierarchy Process

n	1	2	3	4	5	6	7	8	9	10	11
RI	0	0	0.58	0.90	1.12	1.24	1.32	1.41	1.45	1.49	1.51

Table 2: Saaty's nine point pairwise comparison scale

Intensity of Importance	**Definition**	**Explanation**
1.	Equal importance	Two activities constitute equally to the objective
3.	Moderate importance	Experience and judgment of one over another slightly favour one activity over another.
5.	Essential or Strong importance	Experience and judgment strongly favour one over Another
7.	Very strongly demonstrated importance	An activity is favoured very strongly over another; its dominance demonstrated in practice
9.	Absolute importance	The evidence favouring one activity over another is of highest possible order of affirmation
2,4,6,8	Intermediate values between adjacent scale values. If activity ***I*** has one of the above non zero numbers assigned to it when compared with activity ***j***, then ***j*** has the reciprocal value when compared with ***i***	When compromise is needed

Table 3: Format of pair wise comparison matrix

Evaluation Criteria	**C1**	**C2**	**C3**	**Cm**
C1	1	Reciprocal of entries below the diagonal		
C2	Degree of preferences of C2 versus C1	1		
C3	C3 versus C1	C3 versus C2	1	
Cm	C3 versus C1	Cm versus C2	Cm versus C3	1

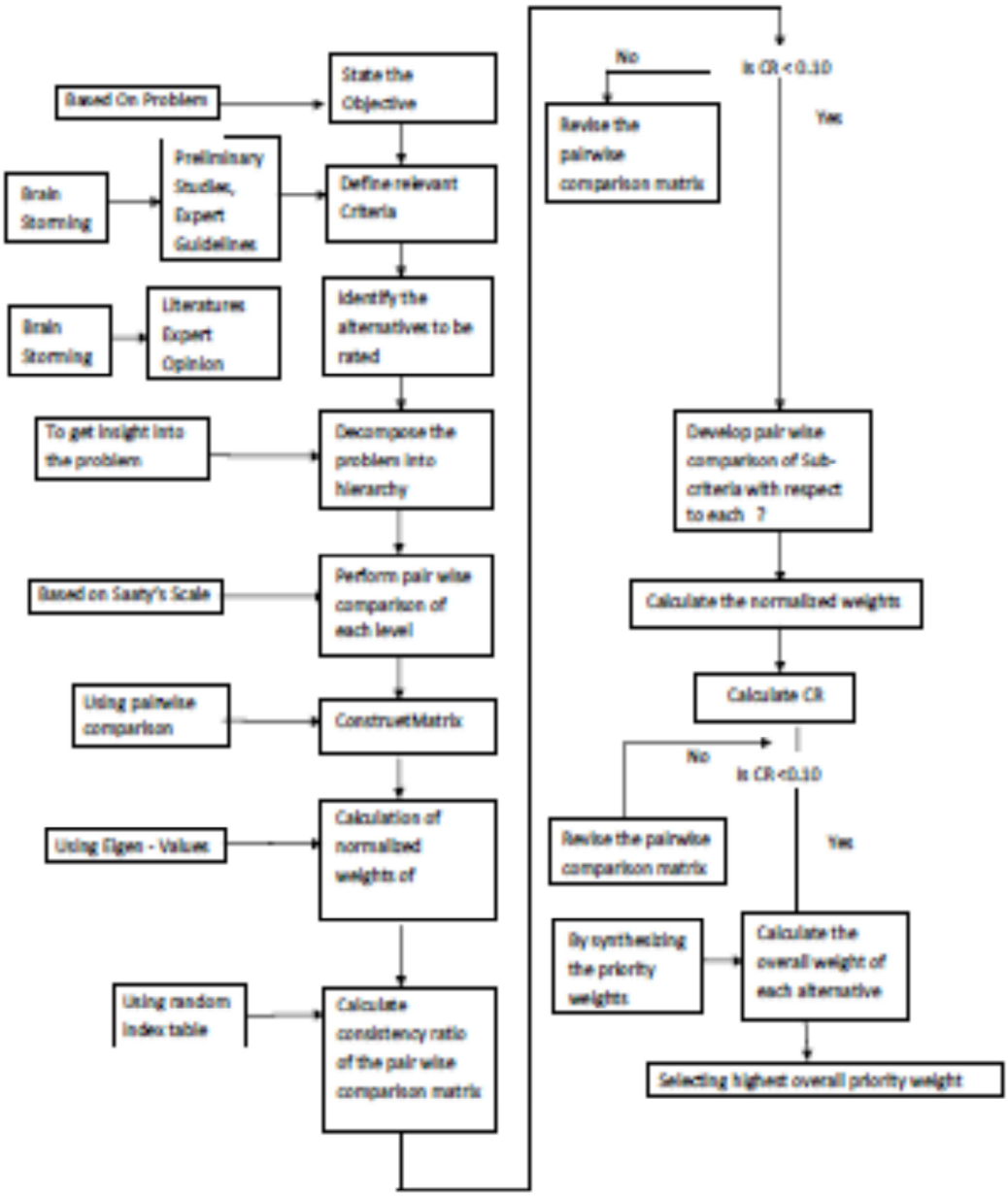

Fig. 1. The AHP methodology is depicted in the form a flow chart

2. Methodology and Experimental Work

The aim of the study is to select the best method for the preparation of solid dispersions as a carrier for manufacturing of solid dispersions as a carrier for manufacturing of delayed release tablets for controlled release .The different methods used are solvent evaporation technique (SET),Fusionmethod (FUM),Spray drying technique (SDT),Lyophilisation(LYZ),and super critical fluid technology(SFT).The following is the step by step description of the procedures used to select the best method.

STEP 1: DEFINE THE PROBLEM [14]
A case study for this research is to select the best method for preparation of solid dispersions choose the most suitable method by using AHP.

STEP 2: DEVELOP A HIERARCHY MODEL
In this section, the hierarchy model for structural design concept decisions using AHP is introduced. A four level hierarchy decision process is displayed in figure 2 and is described below.

Level I: Initially, the objective or the overall goal of the decision is presented at the top level of the hierarchy. Specifically, the overall goal of this application is to "select the best method for preparation of solid dispersions".

Level II &Level III

Table 4: Explanation of Sub-attributes

Sl.No.	Main Criteria	Sub Criteria	Explanation
1	Drug Stability	Production method (PM)	Application in laboratory ,industry etc.
		Processing Condition(PC)	Ease in preparation, Handling of machines, temperature ,solvent etc.
2	Excipients	Availability (AV)	Procurement and supply
		Techniques(TQ)	How solid carriers can form a dispersed phase
		Cost of production (CP)	Materials, machines ,labour etc.
3.	Drug Release	Particle size (PS)	Formation of fine particles
		Molecular arrangement (MA)	Crystalline or amorphous form
		Wettability (WT)	Mechanism of drug release
		Rate of dissolution (RD)	Refers to dissolution theoretical background
		Type of system (SY)	Standing of technique for the global level
4.	Technical Skill	Knowledge (KN)	Refers to the theoretical background elated to literature, experiments etc.
		Complexity (CO)	How easily the method can be applied
5.	Product Yield	Carriers (CA)	Compatibility, processing, ease of solvent removal.
		Experience(EP)	Reputation of the supplier.
6.	Preference to manufacturer	Reproducibility (RP)	Flexibility in operation, drug entrapment
		Final Product (FP)	Complexity and handling of equipment, training hands.

Level IV
Finally, at the lowest level of the hierarchy, the design methods for the preparation of solid dispersions are included.

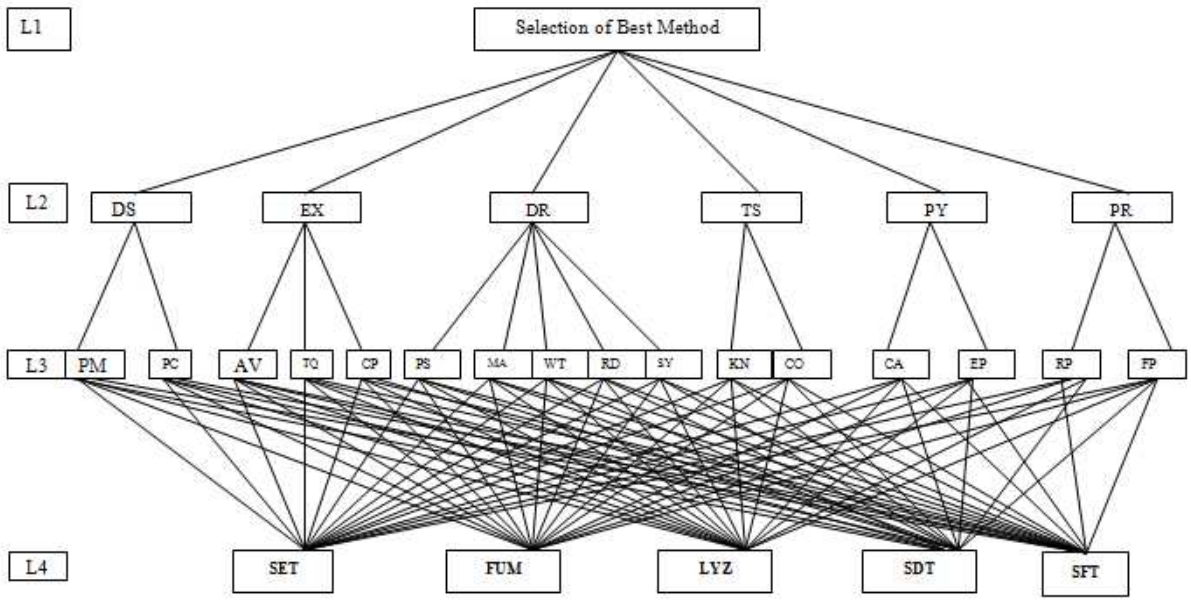

Fig. 2. AHP Hierarchy structure for solid dispersion Formulation Technique

STEP 3: CONSTRUCT A PAIR -WISE COMPARISON MATRIX

One of the major strengths of AHP is the use of pair-wise comparison to derive accurate ratio scale priorities .Pair-wise comparisons are fundamental to AHP methodology [15].Then a pair-wise comparison matrix (size nxn) is constructed for the lower levels with one matrix in the level immediately above; This generates a matrix of relative rankings for each level of hierarchy. The number of matrices depends on the number of elements at each level.

STEP 4: PERFORM JUDGMENT OF PAIR-WISE COMPARISON

Pair-wise comparison begins with comparing the relative importance of two selected items. There are *n*x*(n*-1*)* judgments required to develop the set matrices in step 3. The decision makers have to compare or judge each element by using the relative scale pairwise comparison as shown in Table 2. The judgments are decided based on the decision makers' or users' experience and knowledge. The scale used for comparisons in AHP enables the decision maker to incorporate experience and knowledge intuitively. To do pairwise comparison, for instance as shown in Table 5. Reciprocals are automatically assigned to each pair-wise comparison.

Table 5: Pair wise Comparison with respect to overall goal

	DS	EX	DR	TS	PY	PR	Priority Vector
DS	1	3	3	5	8	9	0.403
EX	1/3	1	3	5	7	8	0.269
DR	1/3	1/3	1	3	5	7	0.161
TS	1/5	1/5	1/3	1	3	8	0.099
PY	1/8	1/7	1/5	1/3	1	3	0.043
PR	1/9	1/8	1/7	1/8	1/3	1	0.024

STEP 5: SYNTHESIZING THE PAIRWISE COMPARISON

To calculate the vectors of priorities, the average of normalized column (ANC) method is used. ANC is to divide the elements of each column by the sum of the column and then add the element in each resulting row and divide this sum by the number of elements in the row *(n).*This is process of averaging over the normalized column.

$$W_i = \frac{1}{n}\sum_{j=1}^{n} \frac{a_{ij}}{\Sigma_i^n a_{ij}}, i, j = 1,2, \dots n \qquad (1)$$

STEP 6: PERFORM THE CONSISTENCY

Since the comparisons are carried out through personal or subjective judgments, some degree of inconsistency may be occurred. To guarantee the judgments are consistent, the final operation called consistency verification, which is regarded as one of the most advantages of the AHP, is incorporated in order to measure the degree of consistency among the pairwise comparisons by computing the consistency ratio (13).

The consistency is determined by the consistency ratio (CR) to random index (RI) for the same order matrices. To calculate the consistency ratio (CR), there are three steps to be implemented as follows:

6.1 Firstly, Calculate the Eigenvalue (λ_{max})

To calculate the eigenvalue (λmax), multiply on the right matrix of judgments by the priority vector or eigenvector, obtaining a new vector.

6.2 Secondly, Calculate the Consistency Index (CI)

CI=(λ_{max}-n)/(n-1)

Where n is the matrix size

6.3 Finally, Calculate the Consistency Ratio (CR).

The CR can be calculated using the formula

CR=CI/RI

Selecting the appropriate value of random index (RI), for the matrix size of five using Table 1. Then calculate the consistency ratio (CR), CR=CI/RI

As the value of CR is less than 0.1, the judgments are acceptable. If CR>0.1, the judgments are inconsistent. To obtain a consistent matrix, judgments should be reviewed and improved.

STEP 7: PREFORMED FOR ALL LEVELS IN THE HIERARCHY MODEL

The consistency tests for the sub-criteria and alternatives must be performed. As the value of CR for all sub criteria and alternatives in less than 0.1, the judgments are acceptable.

Table 6: Pair wise comparison for the sub criteria to DRUG STABILITY

	PM	PC	Priority vector
PM	1	5	0.833
PC	1/5	1	0.167

Table 7: Pair wise comparison for the sub criteria to excipients

	AV	TQ	CP	Priority vector
AV	1	3	5	0.607
TQ	1/3	1	5	0.303
CP	1/5	1/5	1	0.090

Table 8: Pair wise comparison for the sub criteria to drug release

	PS	MA	WT	RD	SY	Priority vector
PS	1	1	3	5	7	0.372
MA	1	1	3	3	5	0.321
WT	1/3	1/3	1	3	5	0.171
RD	1/5	1/3	1	3	5	0.092
SY	1/7	1/5	½	1/3	1	0.044

Table 9: Pair wise Comparison for the sub criteria to Technical skill

	KN	CO	Priority vector
KN	1	5	0.833
CO	1/5	1	0.167

Table 10: Pair wise Comparison for the sub criteria to Product yield

	CA	EP	Priority vector
CA	1	3	0.751
EP	1/3	1	0.249

Table 11: Pair wise Comparison for the sub criteria to Preference to manufacturer

	RP	FP	Priority vector
RP	1	5	0.833
FP	1/5	1	0.167

STEP 9: PRIORITY VECTOR FOR ALL THE CRITERIA TO SUB CRITERIA

After the consistency calculation for all the levels is completed, the formation of matrix and further calculation of all the criteria to sub criteria is performed, its new vector is calculated, the consistency index and consistency ration is also estimated.

STEP 10: DEVELOP OVERALL PRIORITY RANKING the consistency calculation for all levels is completed, further calculation of overall priority vector is to select the best method for the preparation of solid dispersions. Table 12 represents the overall rating of each method of preparation.

The Figure 2 shows AHP for choosing the best technique for the preparation of solid dispersions. It represents four levels of Hierarchy .The highest level L-1 is the focus of the problem. This is intern split into a set of attributes DS,EX,DR,TS,PY and PR. Corresponding to an intermediate level of hierarchy.L-2 represents another set of Sub-attributes such as HP, CO etc. Corresponding to a lower level of hierarchy L-3, the last level hierarchy L-4 consists of the decision alternative, SET, FUM, LYZ, SDT and SFT.

Using the AHP model the priority weights, PRWT to the attributes and Sub-Attributes are calculated.

Table 12: Composite rating for techniques

S.NO	ATTRIBUTES	NOTATION	PR_WT	SUB ATTRIBUTES	PR_WT	SET	FUM	LYZ	SDT	SFT
1	DRUG STABILITY	DS	0.403	PM	0.833	0.511	0.297	0.096	0.057	0.038
				PC	0.167	0.508	0.318	0.069	0.069	0.035
2	EXCIPIENTS	EX	0.269							
				AV	0.607	0.51	0.293	0.111	0.052	0.034
				TQ	0.303	0.545	0.215	0.13	0.073	0.038
				CP	0.09	0.511	0.248	0.121	0.08	0.04
3	DRUG RELEASE	DR	0.161	PS	0.372	0.484	0.299	0.115	0.064	0.038
				MA	0.321	0.391	0.391	0.071	0.094	0.053
				WT	0.171	0.401	0.375	0.11	0.084	0.031
				RD	0.092	0.421	0.394	0.064	0.064	0.057
				SY	0.045	0.374	0.349	0.154	0.087	0.037
4	TECHNICAL SKILL	TS	0.099	KN	0.833	0.479	0.29	0.131	0.062	0.039
				CO	0.167	0.447	0.302	0.138	0.07	0.043
5	PRODUCT YIELD	PY	0.043	CA	0.751	0.493	0.281	0.121	0.074	0.031
				EP	0.249	0.559	0.228	0.111	0.069	0.034
6	PREFERENCE TO MANUFACTURER	PR	0.024	RP	0.833	0.484	0.316	0.109	0.058	0.033
				FP	0.167	0.458	0.33	0.119	0.06	0.033
	COMPOSITE RATING					**0.495**	**0.297**	**0.105**	**0.064**	**0.038**

RESULTS AND DISCUSSION

From the study, AHP technique helps to select the best choice amongst alternative for the preparation like SET, FUM, SDT, LYZ, and SFT. From the **table 12** the overall ranking of techniques of all the alternatives, the problem involves the finding of composite scores reflects the relative priorities of all the alternatives at the lowest level of the hierarchy. The rating of SET (0.495), FUM (O.297), SDT (0.105), LYZ (0.064), SFT (0.038) for the preparation of solid dispersions. The score shows the selection of solvent evaporation technique for the preparation of solid dispersions. Among the criteria in the best method for selection criteria was the drug stability, drug release and preference for the manufacturer ; solvent evaporation technique can offer desirable release rate and dissolution profiles for the development of oral controlled drug delivery.

CONCLUSION

The AHP is a versatile decision aid which can handle problems involving both multiple objectives and uncertainty. This paper presents the methodology of, evaluating and selecting the most appropriate method for developing the best technique for the preparation of solid dispersions as a carrier for delayed release tablets. The hierarchy presented in this article gives an illustration of different factors for the best method in the preparation of solid dispersions .The different methods for the preparation of solid dispersions is complicated. This technique is based on the criteria and sub-criteria aspects of a design. The table 5 to table 11 presents the Eigen vector values from which we can select the correct method for the preparation of solid dispersions.

AHP has got many applications in pharmaceutical industries in determining the process's priority, hazard and probability of risk. AHP helps the pharmaceutical industry to create the best practice for the proper configuration during the production and development of targeted dosage forms. Hence AHP can be applied to for the design and fabrication of solid dispersions in the work stream of industrial manufacturing area. The therapeutic efficacy of a drug depends upon the release mechanism and bioavailability of drug from the drug delivery system. Therefore AHP technique can alleviate the different problem to the manufacturer before the formulation of new dosage form.

The above observation suggest that multi-criteria decision making (MCDM) method should be used as decision support tool .This is still critical and very valuable in many scientific, Pharmaceutical and engineering applications. This study is not limited to the evaluation of preparation of solid dispersions, it can also be applied to other areas such as validation and method development of new drug moieties, extraction methods used for herbal drugs, Pharmacological screening of drugs, in tableting technologies, preparation of targeted drug delivery systems like liposomes, nanoparticles, microspheres, niosomes etc. In further studies Fuzzy-AHP model is also employed for generating better result. The market for the new drug delivery systems has come long way for the targeted drug delivery technologies for tumour cells, sustained release dosage forms, controlled release dosage forms for the incorporation of drug molecules.

Conflict of Interest

Authors have no conflict of interest.

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