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Selection of better method for the preparation of microspheres by applying Analytic Hierarchy Process

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Abstract

One of the most effective approaches for achieving novel drug delivery dosage forms such as sustained release, controlled release is microencapsulation. A number of techniques are available for the preparation of microspheres and the goal is to achieve reproducibility and consistency with good entrapment efficiency. This is influenced by a number of factors such as process information of the equipment and method, operation skill of the microencapsulator, sensitivity of the equipment etc. Hence it is important to incorporate all the factors that could influence microencapsulation in decision making process while choosing the best technique. In this study multi criteria decision making tool, analytic hierarchy process, is applied to make choice amongst alternative microencapsulation techniques [Solvent evaporation technique (SET)/ Co-acervation and phase separation (CAP) /Pan coating (PAN)/Spray drying and spray congealing (SPR)] and thereby opt the best technique. The composite score is used for the final ranking of the alternatives. The solution of the problem involves finding the composite score that reflects the relative priorities of all the alternatives at the lowest level of the hierarchy.

Key Words: Microencapsulation, Analytic hierarchy process, Multi Criteria Decision Making

Introduction

The last few decades have witnessed dramatic developments in pharmaceutical sciences. Much research effort in developing novel drug delivery systems has been focused on controlled release and sustained release dosage forms [1-3]. The pharmaceutical formulations with novel drug delivery systems have been introduced with the course of optimizing the bioavailability through the modulation of the time course of the drug concentration in blood [4,5].

All sustained and controlled release products show the common goal of improving drug therapy over that achieved with their non sustained and controlled release counter parts [6,7].

One of the more recent and interesting result of pharmaceutical research is the fact that absorption rate of a drug can be decreased by reducing its rate of release from the dosage form. The products so formulated are designed as sustained action, sustained release. Prolonged action, depot, retarded release, delayed action and timed release medication [8]. This has been due to various factors viz prohibitive cost of developing new drug entities, expiration of existing international patients, discovering of new polymeric materials suitable for prolonging the drug release, improvement in therapeutic efficacy and safety achieved by these delivery systems [9,10]. Various approaches are available for achieving novel drug delivery dosage forms such as targeted delivery system, nanoparticals, Prodrugs, transdermal system, ocular

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systems, intravaginal and intrauterine systems, injection and implants, microenapsulation, matrix devices, reservoir devices. One of the most effective approaches is microncapsulation of the drug [11].

A number of techniques are available for the preparation of microspheres that include co-acervation phase separation (CAP), solvent evaporation (SET), multiorifice centrifugal process (MCP), spray drying and spray congealing (SPR), polymerization (PM), pan coating (PAN), electrostatic deposition (ED) [12-20]. The choice of an appropriate microencapsulation techniques mainly depend on the nature of the polymer used. The drug intended use of the products, processing conditions involved in the manufacturing product and the duration of the therapy. The method of preparation and its choice are equivocally determined by technique related factors viz the particle size, requirement, reproducibility of the release profile and method.

In microencapsulation technique, the overall goal is to achieve reproducibility and consistency with good entrapment efficiency. This is influenced by a number of factors such as process information of the equipment and method, operation skill of the microencapsulator, sensitivity of the equipment etc,. Hence while choosing technique, consideration of cost factor alone may not be justifiable .It is more rational and appropriate to analyse both qualitative and quantitative parameters and then 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. It is important to incorporate all the factors that could influence microencapsulation in decision making process while choosing technique.

In the present case study analytic hierarchy process (AHP), a MCDM tool has been used to select the better technique Solvent evaporation technique(SET), Co –acervation and phase separation(CAP), Pan Coating(PAN) and Spray drying and spray congealing (SPR) for preparation of microspheres.

Analytic hierarchy process (AHP)

AHP developed by Saaty is one of the very effective MCDM Model [21]. This has been employed very successfully in many situations where a decision situation is characterized by a multitude of complementary and conflicting factors [22-24].

General methodology, excellent analytical-mathematical treatments of AHP are available in literature [22-26].

The basic steps of analytic hierarchy process model are given below [21].

1. List the set of different alternatives(Aj, 1<= i<=n)
2. Identify the factors that may be intrinsic as well as extrinsic, which may have an Impact on the selection of alternatives for Microencapsulation technique for microspheres formulation. For each of these impacts identify the criteria
   (Ci, 1<= i<=m) and the quantifiable indicates to the criteria for a possible measure.
3. Develop a graphical representation of the problem in terms of the overall goal, the factors, the criteria and decision alternatives. Such a graph depicts the hierarchy of the problem.

4. Assign weights to each alternative on the basis of its relative importance of its contribution to each criterion. This is carried out through a pair wise comparison of the alternatives for each criterion. The scale of pair wise comparison (Table 1) may be used for preparing the pair wise comparison matrix elements M^k_{ij} for each criterion C_k (where M^k_{if} is evaluated when A_i is compared with A_j and Table 2 shows the general format of a pair wise comparison matrix.

5. Once the pair wise comparison matrix has been formed for a criterion C_k the normalized priority of each alternative is synthesized.

   This is done as follows:

   - Sum the values in each column of M^k.
   - 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 PM^k_1 denotes the priority for alternative A_i with respect to criterion C_k.

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. Let L_{ij} denote each element of the resulting pair wise comparison matrix, when C_i is compared with C_j.

7. The priority vector PL is synthesized similar to step 5(PL_i denotes the priority for criterion C_i

8. Calculate the overall priority for alternative A_i denoted by P_i as follows:

$$Pi = \sum_{k=1}^{m} PM^k 1x\, PL_k$$

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 he decision maker demonstrates during the pairwise comparisons. The consistency is determined using the eigenvalue ($M_W = \lambda_{max}$ W is solved). The eigenvector provides priority and eigenvalues give a measure of consistency of judgment. The 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 eigenvalue 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

Table 1. Saaty's nine-point 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	When compromise is needed
Reciprocals of above non zero	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***	

Table 2. 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

Table 3. Explanation for sub - attributes

1. Process Information [PI]			
	Production scale	[PS]	Lab scale, Pilot scale, Industrial scale
	Process condition	[PC]	Temperature, Stirring speed, Ph
2. Operation Skill [OS]			
	Technique	[MET]	Microencapsulation is a process whereby small discrete solid particles or liquid droplets are surrounded and enclosed by an intact shall
	Knowledge	[KN]	Refers to Microencapsulation theoretical background
	Training	[TR]	Hands on training on instrument
3. Supplier [SUP]			
	Availability	[AV]	How easily the machine can be procured.
	Experience	[EX]	Reputation of the Supplier
	Service	[SE]	Serving and maintenance facilities
	Spares	[SP]	Availability of spare parts
	Monopoly	[MO]	Vendor status single/Multi Vendor
4. Technical information [TEI]			
	Literature	[LT]	Scientific Journal, News, magazines updating current trends
	Manual	[MA]	Operational and service manual.
5. Technical Status [TES]			
	Establish Technique	[ET]	Standing of the technique in the global level research
	Growth	[GH]	Growth in the field of encapsulation technique
6. Machine [MAC]			
	Versatility	[VE]	Operational Flexibility, RPM, Encapsulation
	Complexity	[CO]	Complexity of the machine how easily one can handle the instrument

Table 4: Composite rating of techniques

#	Attributes	Notation	PR_WT	Sub-attributes	PR_WT	PR_WT			
						SET	CAP	PAN	SPR
1.	Process Information	PI	0.421						
				PS	0.25	0.591	0.247	0.049	0.110
				PC	0.75	0.559	0.323	0.058	0.058
2.	Operation skill	OS	0.261						
				MET	0.455	0.558	0.263	0.056	0.121
				KN	0.455	0.558	0.263	0.056	0.121
				TR	0.090	0.469	0.469	0.063	0.063
3.	Supplier	SUP	0.153						
				AV	0.334	0.530	0.311	0.096	0.061
				EX	0.333	0.450	0.450	0.049	0.049
				SE	0.111	0.450	0.450	0.049	0.049
				SP	0.111	0.450	0.450	0.049	0.049
				MO	0.111	0.438	0.438	0.081	0.040
4.	Technical information	TEI	0.094						
				LT	0.250	0.520	0.297	0.124	0.054
				MA	0.750	0.520	0.297	0.124	0.054
5.	Technical status	TES	0.046						
				ET	0.833	0.638	0.230	0.055	0.073
				GR	0.167	0.638	0.230	0.055	0.073
6.	Machine	MAC	0.025						
				VE	0.750	0.535	0.327	0.091	0.044
				CO	0.250	0.535	0.327	0.091	0.044
	Composite rating					**0.521**	**0.305**	**0.064**	**0.076**

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 to 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 *Cl* for a matrix of size n is given by the formula

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

$$CR = CI/RI$$

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

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

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

METHODOLOGY AND EXPERIMENTAL WORK

The case study was conducted with an objective to choose the better system between four alternatives, namely SET, CAP, PAN and SPR, for carrying out microencapsulation. To identify major system evaluation criteria, a group was constituted and a brainstorming session was conducted. The active participants of the group were selected based on their expertise and experience in

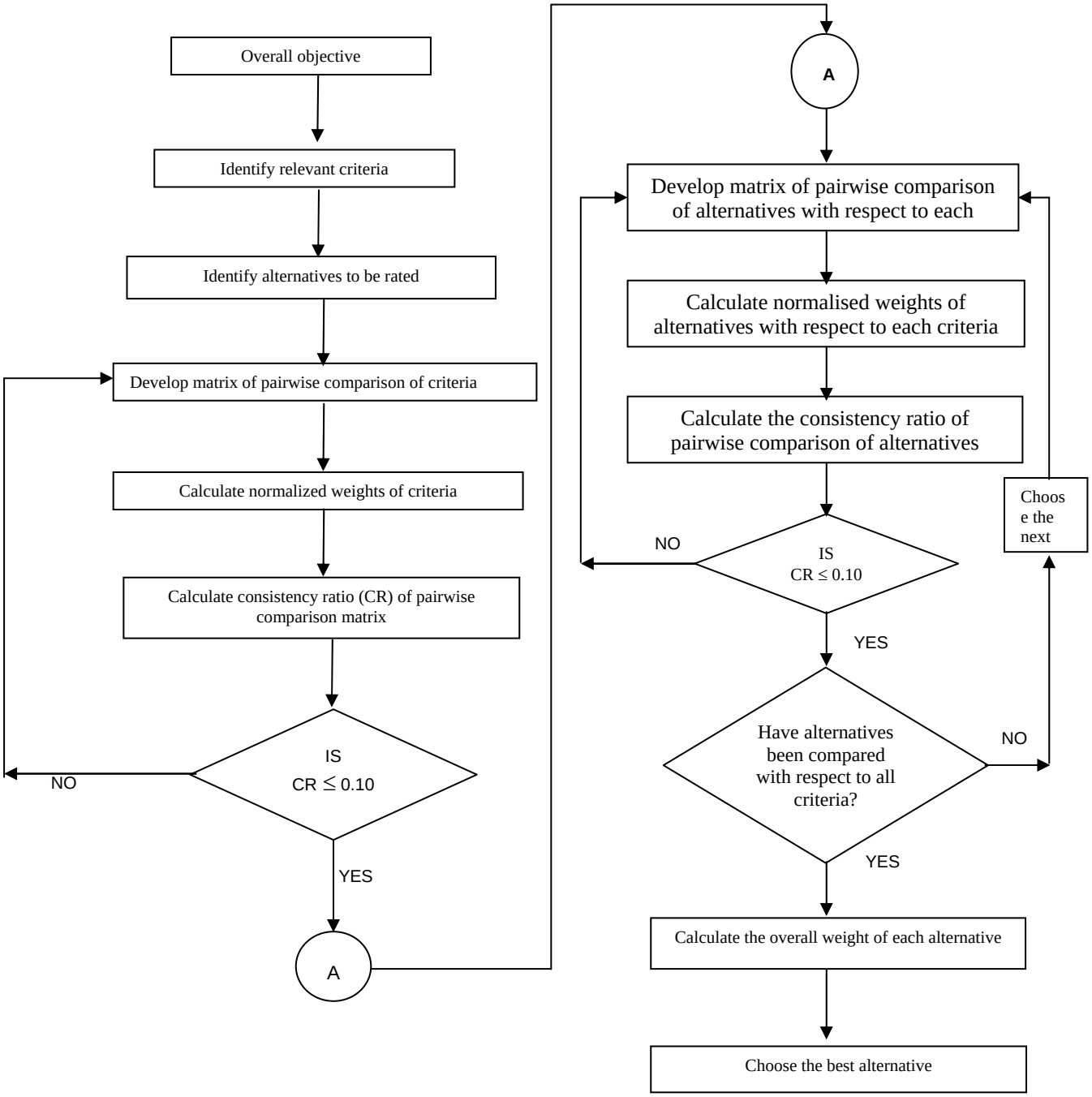

Figure 1. Flow chart for AHP methodology

microencapsulation technique and a group leader with good experience in brainstorming technique and decision-making [20] (in this case the group leader is well experienced and knowledgeable in microencapsulation technique). The group leader is also familiar with AHP model. After this exercise the group identified the factors/attributes such as Process Information (PI) of the equipment and method, Operational skill (OS) of the microencapsulator, supplier (SUP) of the equipment, technical information (TEI) about the equipment, technical status (TES) of the equipment, machine (MAC) inbuilt operational flexibility, etc. Table 3 gives an explanation for the attributes.

In Table 3, under each attribute sub-attributes were associated for example under the attribute Process Information sub-attributes such as production scale and process condition are considered since these sub-attributes contribute a lot in achieving the overall goal to formulate microspheres with reproducibility and consistency release profile. Figure 2 shows the AHP hierarchy for choosing the best technique for Microencapsulation. It represents four levels of hierarchy. The highest level, [L 1], is the focus of the problem. This is turn is split into a set of attributes, PI, OS,SUP, TEI, TES and MAC corresponding to an intermediate level of hierarchy [L 2]. This in turn into another set of sub attributes such as PS, PC etc., corresponding to a lower level of hierarchy, [L 3], the last or the lowest level of hierarchy, [L4], consists of the decision alternative, PAN/SPR, of the technique.

Using the AHP model the priority weights, [PR_WT], to the attributes and sub-attributes are calculated[24].

RESULTS AND DISCUSSION

In the case study, AHP technique was applied to make choice amongst alternative microencapsulation techniques (SET/CAP/PAN/SPR) and thereby opt the best technique. The composite score is used for the final ranking of the alternatives. The

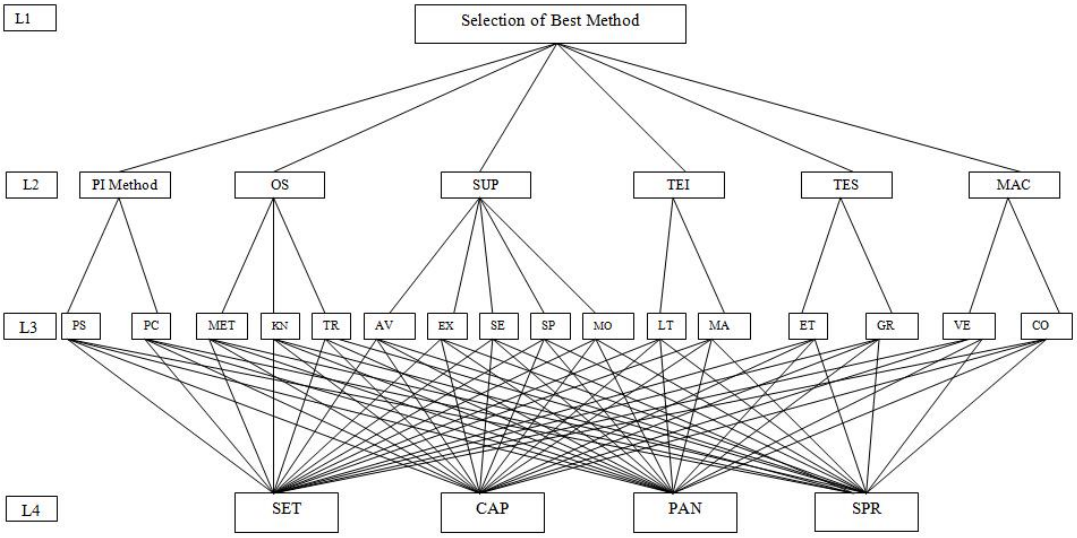

Figure 2. AHP Hierarchy structure for Microencapsulation Technique selection

solution of the problem involves finding the composite score that reflects the relative priorities of all the alternatives at the lowest level of the hierarchy. The composite score favored the selection of SET (score=0.521) over CAP (score=0.305), PAN (score=0.064), SPR (score=0.076) for microencapsulation technique.

CONCLUSION

In today competitive scenario, an effective framework for formulation of microspheres using AHP as MCDM tool is presented in this case study here. This approach is a systematic one and it includes both quantitative and qualitative factors. Software for computing priority weights can be easily developed else commercial software (expert choice) is available. The factors considered here are illustrative only and these may vary from case to case .The proposed approach can be extended to other situations like selection of alternatives such as tablets formulation machines, characterization technique such as pharmacokinetic studies, release behavior, drug content, microbial versus instrumental for the determination of potency of antibiotics, blenders for mixing powders, liquid, semisolids and site selection for pharmaceutical plants.

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