CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1256039

Available online at: http://www.iajps.com Research Article

SELECTION OF A SUITABLE METHOD FOR THE PREPARATION OF TADALAFIL MOUTH DISSOLVING TABLETS: MULTI-CRITERIA DECISION MAKING APPROACH

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Abstract:

Recent advances in Novel Drug Delivery Systems (NDDS) aim for designing dosage forms, convenent to be manufactured and administered, free of side effects, offering immediate release and enhanced bio availability, so as to achieve better patient compliance. Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop mouth dissolving tablets with improved patient compliance and convenience. Yet, dysphagia is the most common disadvantage of conventional tablets. Advantages of this drug delivery system include administration without water, anywhere, anytime, accuracy of dosage, easy portability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current marked this is seen to afflict nearly 35% of the general population and associated with a number of conditions, like parkinsonism, mental disability, motion sickness, unconsciousness, unavailability of water etc. To overcome such problems, certain innovative drug delivery systems, like 'Mouth Dissolving Tablets' (MDT) have been developed. These are novel dosage forms which dissolve in saliva within a few seconds, when put on tongue. Such MDTs can be administered anywhere and anytime, without the need of water and are thus quite suitable for children, elderly and mentally disabled patients.

Key words: *Analytical Hierarchy Process, Mouth dissolving tablets, Tadalafil*

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Please cite this article in press Shahul Hameed K M al., ***Selection of A Suitable Method for the Preparation of Tadalafil Mouth Dissolving Tablets: Multi-Criteria Decision Making Approach,*** *Indo Am. J. P. Sci, 2018; 05(04).*

INTRODUCTION:

However, the choice of an appropriate method depends upon various factors[1,2,3]. Hence, the solution of selecting the suitable method was a real concern, because selection of inappropriate method may lead to loss of materials resources, financial resources and time of research[5,6,7]. To achieve the goal of selecting the suitable method for the preparation of camptothecin loaded polymeric nanoparticles, there is a need of using a scientific approach Multi-Criteria Decision Making (MCDM) method[3,8]. The Analytical Hierarchy Process (AHP) can help in this regards [9,10]. The AHP is an operational research model first developed by Saaty in 1980, is a flexible multi-criteria decision making methodology that transforms a complex problem into a hierarchy with respect to one or more criteria[11,12]. One advantage of the AHP is that it is designed to handle situations in which the subjective judgements of individuals constitute an important part of decision process[13,14].

Thus, AHP technique involves structuring multiple choice criteria into hierarchy, assessing the relative importance of criteria, comparing alternatives for each criterion and determining an overall priority weight and ranking of the alternatives[15].The objective of the present study is to select the most suitable method for the preparation of camptothecin loaded polymeric nanoparticles from various methods available using analytical hierarchy process[16].

MATERIALS AND METHODS:

Analytical Hierarchy Process (AHP)

In this method, a simple hierarchical model consists of goal, criteria and alternatives are constructed [17,18]. AHP is composed of several previously existing but unassociated concepts and techniques, such as hierarchical structuring, pair-wise comparisons, the eigen-vector method for deriving weights and consistency considerations [19]. According to saaty, the method has three phases: 1) Decomposing, 2) Comparative Judgements, 3) Synthesizing. In *Decomposing phase*, the elements of decision problem are arranged in form of hierarchy [20]. The top elements of hierarchy is overall goal, the next level is the criteria which impact the goal directly, the next level is the operational sub-criteria, against which the decision alternatives of the lowest level of hierarchy can be evaluated and all the elements of a given level are assumed to be mutually independent [21]. In *Comparative Judgement Phase*, elements of one level of a hierarchy are compared pair-wise as to the strength of their influence on an element of the next higher level [22]. Saaty has suggested a scale of 1 to 9 when comparing two elements, with a score of 1 representing indifference between the two elements and 9 representing the overwhelming dominance of that element over the other[23]. These comparison leads to dominance matrices which are called pair-wise comparison matrices. The next phase is to *synthesize the priorities*, the simple hierarchical model which evaluates alternatives with respects to criteria and sub-criteria of overall goal [24]. The priorities of all alternatives with respect to each criterion are calculated. The overall priorities weights are calculated from pair-wise comparison matrix. Figure 1 shows the flow chart of the AHP methodology.

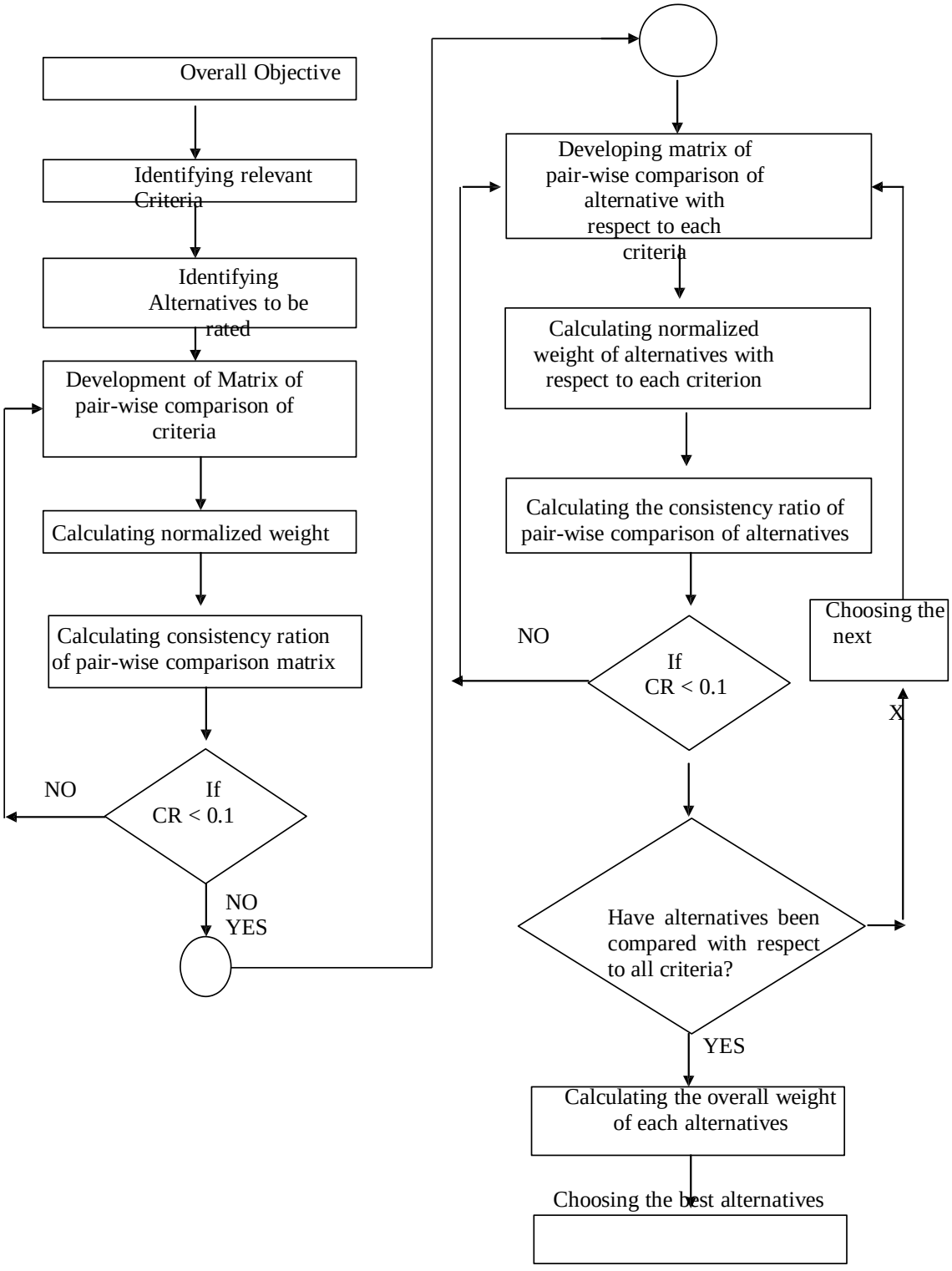

Chart 1: Flow chart for AHP Methodology

Table 2 shows a hierarchy model for the selection of suitable method for the preparation of tadalafil mouth dissolving tablets. The first level represents the goal of the problem. The objective of the model is divided into five main criteria such as Instrument, Process and Output and Cost in the second level. The third level consists four potential alternatives/methods Sublimation method (M1), Direct compression method (M2), Melt Extrusion Method (M3) and Freeze Drying Method (M4).

Main Criteria

Choosing the potential alternatives for the preparation of tadalafil mouth dissolving tablet as well as selecting the related main criteria (Table 1) are based on the five principles for the preparation of safe Tablets. More specifically, the main principles are as follows: 1) Reducing the side effects of drug without altering the function of drug. 2) Replacing the use of toxic chemicals used in the preparation with suitable nontoxic chemicals. 3) Use of nontoxic excipients to reduce the toxicity of the drug, 4) Use of limited quantity of toxic chemicals, when the use of the toxic chemical cannot be avoided. four potential methods or alternatives selected for the preparation of tadalafil mouth dissolving tablet are given in Table 2. A brief procedure of each method is being discussed below [25].

Table 1: Main criteria for the selection of suitable method.

	Criteria
C01	Minimum number of excipients for the preparation
C02	Simple process for the preparation
C03	Possibility to transfer the technology from lab to industry
C04	Reproducible result
C05	Minimum cost, for the preparation

Table 2: Potential alternatives for the preparation of tadalafil mouth dissolving tablet.

	Methods
M_1	Sublimation Method
M_2	Direct compression method
M_3	Melt extrusion Method
M_4	Freeze Drying Method

Determination of Priority Weight and Ranking

Figure 2 shows the proposed hierarchy model for selecting the suitable method, where the first level is the overall objective. The figure also shows the five main criteria in the second and five alternatives in the last level. Assessment of the criteria weights are developed using the pair-wise comparison. According to AHP method, the elements of one level are pair-wise compared with the elements of next higher level resulting in a number of pair-wise comparison matrixes. The pair-wise comparisons were made using the saaty's scale (Table 3). The pair-wise comparison weights of the ith criteria against the jth criteria are assigned as follows

Consistency Ratio (CR)

The Consistency ratio is calculated to determine inconsistencies in the evaluation. The value of all above pair-wise comparison matrix should be lower than 0.1, indicating that the expert's judgements/weights allotted are reasonable. In order to calculate the consistency ratio, eigen-value λmax is obtained from the matrix A. The degree of consistency (CI) can be estimated as shown in the following expression[26,27].

$$CI = \lambda max - n / n - 1$$

Consistency ratio (CR) can be calculated from the relation of the consistency index (CI) and the random consistency index (RI). The RI value is obtained from Table 4 and the value depends on the value of n.

$$CR = CI / RI$$

RESULTS AND DISCUSSION:

Pair-wise comparison matrix (Figure 1 to 3) was constructed by assigning the weights to all the elements using the saaty's scale. All the constructed pair-wise comparison matrixes were found to be consistent, as the consistency ratio was < 0.1. Hence, the weights allotted were reasonable. From the pair-wise comparison matrix, priority weights from each criterion are calculated and ranks are assigned based on overall priority weights.

Table 3: Pair-wise comparison for criteria preferences

Criteria	C01	C02	C03	C04	C05
C01	1	1/9	1/7	1/5	1/3
C02	9	1	3	5	7
C03	7	1/3	1	3	9
C04	5	1/5	1/3	1	9
C05	3	1/7	1/9	1/9	1
CI: 0.0534; CR: 0.1382; λ_{max}:5.6136					

Table 4: Pair-wise comparison for the criteria C01

Methods	M_1	M_2	M_3	M_4
M_1	1	1/3	5	3
M_2	3	1	9	5
M_3	1/5	1/9	1	1/3
M_4	1/3	1/5	3	1
CI: 0.0252; CR: 0.0284; λ_{max}: 4.0757				

Table 5: Pair-wise comparison for the criteria C02

Methods	M_1	M_2	M_3	M_4
M_1	1	1/3	5	3
M_2	3	1	9	5
M_3	1/5	1/9	1	9
M_4	1/3	1/5	1/9	1
CI: 0.0679; CR: 0.4134; λ_{max}: 5.1038				

Table 6: Pair-wise comparison for the criteria C03

Methods	M_1	M_2	M_3	M_4
M_1	1	1/3	5	3
M_2	3	1	9	5
M_3	1/5	1/9	1	1/3
M_4	1/3	1/5	3	1
CI: 0.0252; CR: 0.0284; λ_{max}: 4.0757				

Table 7: Pair-wise comparison for the criteria C04

Methods	M_1	M_2	M_3	M_4
M_1	1	1/3	5	3
M_2	3	1	9	5
M_3	1/5	1/9	1	1/3
M_4	1/3	1/5	3	1
CI: 0.0252; CR: 0.0284; λ_{max}: 4.0757				

Table 8: Pair-wise comparison for the criteria C05

Methods	M_1	M_2	M_3	M_4
M_1	1	1/3	5	3
M_2	3	1	9	5
M_3	1/5	1/9	1	9
M_4	1/3	1/5	1/9	1
CI: 0.0679; CR: 0.4134; λ_{max}: 5.1038				

Table 5 shows the overall priority weight and ranking of potential four alternatives obtained from AHP methods. Out of four alternatives, the second alternative direct compression method received a highest overall priority weight of 0.567 followed by sublimation method with 0.2544, Melt extrusion method with 0.0977. However, the freeze drying method received the least overall priority weight of 0.0809. The sensitivity investigation of the decisions made is shown in the Figure 1.

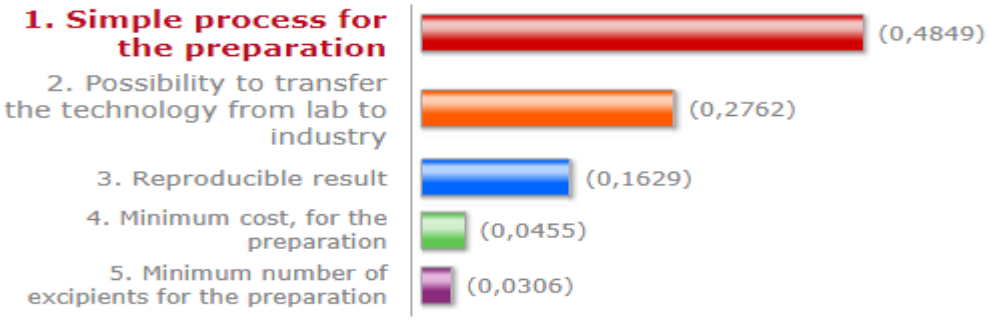

Fig. 1: Priority weights and ranking of criteria preferences

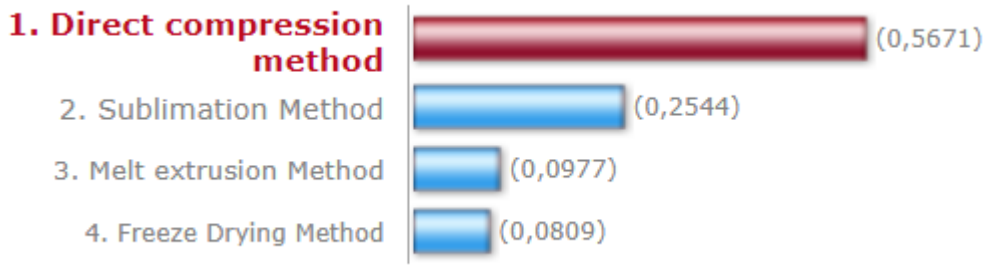

Fig.2: Priority weights and ranking of methods

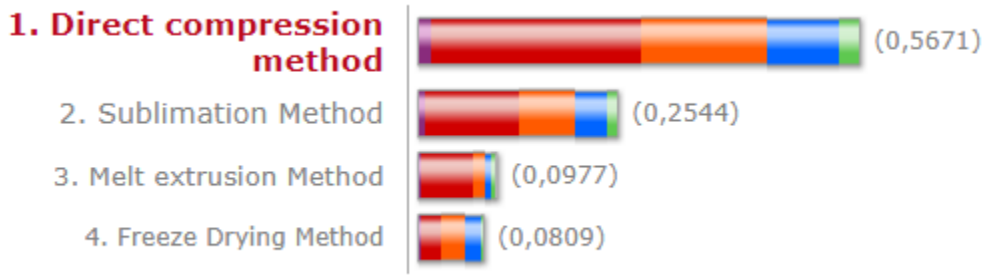

Fig.3: Priority weights and ranking of methods with criteria structure

CONCLUSION:

In the present study, we investigated the problem of selecting the suitable method for the preparation of camptothecin loaded polymeric nanoparticles using a tadalafil mouth dissolving tablets implementing the analytical hierarchy process. This paper proposed a hierarchy model consisting of five main criteria with four alternatives. Expert choice software was used to compute the overall priority weight of each alternative. The results of the study revealed that the direct compression method is the most suitable method for the preparation of tadalafil mouth dissolving tablets with the highest overall priority weight of 0.5671 than any other methods.

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