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Application of Analytical Hierarchy Process to Select Best Method for the Preparation of Antidiabetic Drug Loaded Nanoparticles

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Abstract
In this study, Analytical Hierarchy Process (AHP) was employed to select the best method for the preparation of Nateglinide (NTG)-loaded nanoparticles. There are various techniques available for the development of nanoparticles like Nanoprecipitation or Solvent displacement, Ionic gelation, Solvent evaporation method etc. and choosing the best method is a crucial one. AHP is one of the widely used multiple criteria decision making methods to solve the unstructured problems. It has unique advantages when important elements of the decision are difficult to compare or qualify. The following steps were involved in the AHP process: 1. Develop a hierarchy model, 2. Pair wise comparison of various alternatives and 3. Perform consistency verification. By using saaty's scale, pair wise comparisons were made to analyze the relative criteria. The best alternative selected was based on the highest priority. The result indicates that the built pair wise comparisons were reliable and also found that the solvent evaporation technique is best method for the nanoparticles preparation. Nateglinide-loaded ethyl cellulose nanoparticles were formulated by the selected solvent evaporation method and it shows the particle size, polydispersity index and zeta potential were within acceptable limits. Drug content and entrapment efficiency of the NTG-loaded Ethyl cellulose (EC) nanoparticles were 86.76 % and 81.06 %, respectively. This study concludes that the AHP was viable and effective tool for selecting a most suitable method for the fabrication of NTG-loaded EC nanoparticles.

Keywords: Antidiabetic, Hierarchy process, Nanoparticles (NPs), Nateglinide.

INTRODUCTION

Nanoparticles are solid colloidal particles ranging in size form 10-1000 nm (1μm), in which the active principle (drug or biologically active material) is dissolved, entrapped, and/or to which the active principle is absorbed or attached [1]. It is an effective nanocarrier platform for the delivery of hydrophobic and hydrophilic drugs. The development of smart Nanoparticles can deliver the drugs in controlled rate that provides better efficacy and lower toxicity for treatment of various diseases. The selection of the appropriate method for the preparation of nanoparticles depends on the physiochemical characteristics of the polymer and the drug to be loaded. On the contrary, the preparation techniques largely determine the inner structure, in vitro release profile and the biological fate of these polymeric delivery systems [2].

Diabetes mellitus is a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [3]. Orally administered antidiabetic drugs has some limitations, including low oral bioavailability due to degradation in the stomach, inactivation and digestion by proteolytic enzymes in the luminal cavity, poor permeability across the intestinal epithelium because of its high molecular weight and lack of lipophilicity [4]. Polymeric nanoparticles have been proposed as interesting colloidal systems that allow the enhanced therapeutic efficacy and reduction of toxicity and the large variety of antidiabetics drugs. Nanoparticles can also offer advantages like limiting fluctuation within the therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance [5].

Nateglinide is a new generation oral antidiabetic drug belonging to meglitinide category with short half life of about 1.5 hours. It reduces the blood glucose level by stimulating the insulin secretion of pancreas by blocking the ATP dependent potassium channel in pancreatic beta cells. Nateglinide is an amino acid derivative that induces an early insulin response to meals decreasing postprandial blood glucose levels, so it should be taken with meals and meal-time doses should be skipped with any skipped meal.

Nateglinide is a good candidate for controlled release due to the shorter half life and it can be achieved by the polymeric nanoparticle formulation. There are several techniques available for the development of polymeric nanoparticles

Table 1: Potential alternative for the preparation of polymeric nanoparticles.

Sl. No	Potential methods / alternatives	Code
01	Solvent Evaporation method	A_1
02	Nanoprecipitation method	A_2
03	Ionic Gelation method	A_3
04	Solvent displacement method	A_4
05	Salting out method	A_5

1. Solvent evaporation method

Nanoparticles can be prepared by solvent evaporation techniques and it involves two steps i.e. emulsification of polymer solution with drug and evaporation of polymeric solvent. The selected polymer (Ethyl cellulose, Cellulose acetate phthalate) and drug are dissolved in appropriate solvent and then dispersed into nano droplets in non solvent medium (water, Chloroform) containing surfactants (Tween 80, Poloxamer) by homogenization. This process is continued until the solvent is completely evaporated. Sizes of the nanoparticles are controlled by changing the stir speed, type of surfactants, temperature and viscosity of organic phase [6, 7].

2. Nanoprecipitation method

Nano precipitation method is one of the widely used methods to prepare the nanoparticles and it is also called as interfacial deposition method. It consists of two phase like solvent and non solvent phase. The solvent phase contains solvents or mixture of solvents (acetone, methylene chloride), polymer (Ethyl cellulose), drug and the non solvent phase contains film forming substance and surfactant. In the preparation, the organic phase i.e. solvent phase is added into non solvent phase (aqueous phase) slowly with optimum stirring and the nanoparticles are obtained as colloidal suspension. Factors influencing this preparation are organic phase injection rate and agitation of aqueous phase [6, 8].

3. Ionic gelation method

The principle of Ionic gelation method is interaction of the positively charged amino group with negative charged poly anion group like triphosphate and it facilitates the formation of coacervates in the range of nanometer. In this preparation, the chitosan is dissolved in the solvent like acetic acid containing surfactants. Then poly anion is added to the chitosan solution under mechanical stirring at room temperature. The size of the obtained nanoparticles is based on the ratio of chitosan and stabilizer [1, 9].

4. Solvent displacement method

This method involves the precipitation of polymer in organic solvent and diffusion of this solvent in to aqueous phase containing surfactant. In the preparation, drug and polymer are dissolved in a water immiscible solvent and poured into an aqueous solution with surfactant under mechanical stirring [6]. The nanospheres are formed by the solvent diffusion and the solvent is removed by vacuum. Size of the nanospheres is based the concentration of the polymer [10].

5. Salting out method

Salting out method is based on principle of separation of a water miscible solvent from aqueous medium through salting out effect. Nanoparticles are prepared by dissolving the polymer and drug in a solvent which can be emulsified into aqueous gel using the salting out agent (electrolytes) and stabilizers like hydroxyethyl cellulose. The obtained emulsion is diluted with aqueous solution to enhance the diffusion of solvent into aqueous medium; it indicates the formation of nanoparticles. There are several parameters which affects the preparation includes stirring rate, concentration of polymer and the type of stabilizers [6, 10]

Selection of better method for the preparation of nanoparticles is a crucial one because all the above methods have several advantages and disadvantages. So Analytical Hierarchy Process can be employed to select the suitable method for the preparation of antidiabetic drug loaded nanoparticles.

Analytical Hierarchy Process (AHP)

Analytical Hierarchy Process (AHP) is one of the useful tools in selecting the suitable method for the preparation of antidiabetic drug loaded nanoparticles which was developed by Saaty [11]. The AHP is designed to structure a decision process in a situation affected by multiple independent factors [12]. Multi-criteria analysis is used to make comparative assessment of alternatives and permits several criteria to be taken simultaneously in a complex situation. In this study, a complex problem can be divided into several sub problems that are organized according to hierarchical level where each level denotes a set of criteria related to each sub-problems. The top, intermediate and bottom level represents the goal of problem, factors of the respective upper levels and alternatives considered respectively [11, 13-15].

METHODOLOGY

The AHP methodology has been accepted by the International scientific community as a robust and flexible multi criteria decision making tool and it is widely used multiple criteria decision making methods to solve the unstructured problems. It has unique advantages when important elements of the decision are difficult to compare or qualify. The following steps were involved in the AHP process: 1. Develop a hierarchy model, 2. Pair wise comparison of various alternatives, and 3. Perform consistency verification [16 - 20].

1. Develop a hierarchy model

To make a decision in an organised way, AHP is used to break down a complex multi-criteria decision-making problem into a hierarchy, consisting of the interested criteria, sub criteria and considered alternatives. A complex four-level hierarchy decision model was constructed and shown in Fig. 1. The first level denotes the goal with three main criteria in the second level, eight sub-criteria in the third level and five method/alternatives for the preparation of antidiabetic drug loaded nanoparticles in the fourth level.

Table 2: Main criteria and sub-criteria for the selection of suitable method

CRITERIA	SUB CRITERIA
Technological Aspects	Literature Review
	Equipment Availability
	Equipment Back up
Operational Aspects	Ease of Operation
	Reliability
	Accuracy
Economic Aspects	Cost of ingredients
	Operation Cost

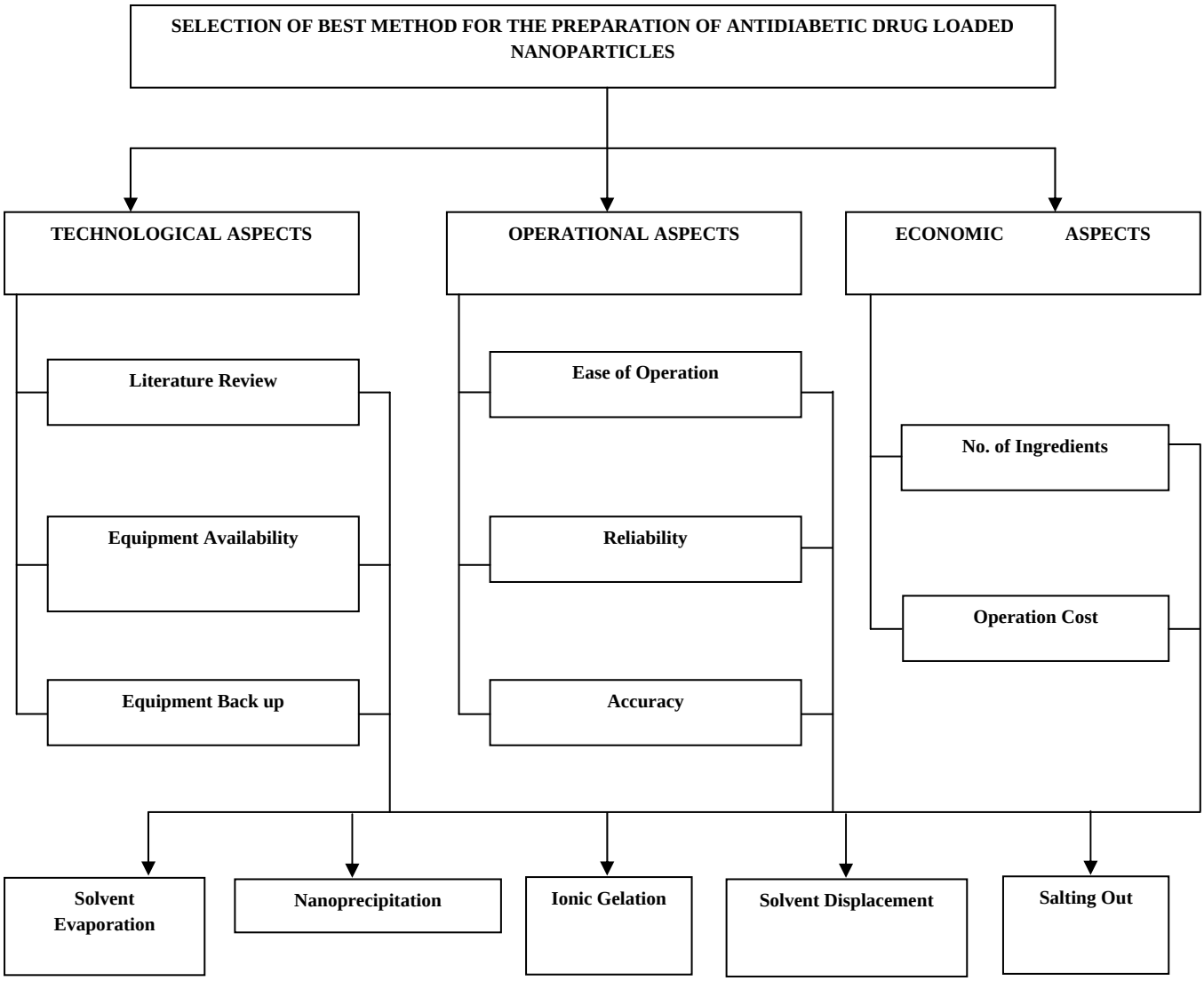

Fig. 1: Hierarchical model for the selection of best method for the preparation of antidiabetic drug loaded nanoparticles.

Table 3: Pair comparison evaluation scale

Relative importance	Description
1	Equally important
2	Equally to moderate more important
3	Moderately more important
4	Moderately to strongly more important
5	Strongly more important
6	Strongly to very strongly more important
7	Very strongly more important
8	Very strongly to extremely more important
9	Extremely more important

2. Pair wise comparison of various alternatives

Pair-wise comparisons were made using Saaty's scale [Fig. 2 - Fig. 10] to evaluate the relative importance of criteria and to compare the alternatives for each criterion [21]. Table 3 displays the meaning of the comparison scale used in the weighting of two elements. In the case of interdependencies, components with the same level are viewed as controlling components of each other [12]. Prioritization procedure starts in order to determine the relative importance of the criteria within each level. This vector corresponds to the main eigenvector of the comparison matrix [11, 13]. The pairwise comparisons generate a matrix of relative rankings for each level of the hierarchy [22]. The supermatrix obtained in this step is called the initial supermatrix and it contains all the eigenvectors that are derived from the pairwise comparison matrixes of the model.

3. Perform consistency verification

Since the comparisons are carried out through personal or subjective judgments, some degree of inconsistency may occur [22]. Consistency verification of the judgements is one of the most advantageous features of AHP. The consistency is determined by the consistency ratio (CR). Consistency Ratio (CR) is calculated for each pair-wise comparison matrix and a value ≤ 0.1 are considered acceptable, which indicates that the judgments/weights

allotted are reasonable (MOO). Consistency ratio (CR) is the ratio of consistency index (CI) to random index (RI) for the same order matrices [22]. A sensitivity analysis can be performed in order to improve the quality of the final results of the evaluation [13].

4. Preparation of Nateglinide loaded polymeric nanoparticles

Nateglinide (NTG) was obtained as a gift sample from Glanmark Pharmaceutics Ltd, Mumbai. Ethyl cellulose (EC) was received from Himedia Laboratories, Mumbai. The following materials were procured from the indicated suppliers and used as received: Polyvinyl alcohol (PVA) (Fourrts India Laboratories Pvt Ltd, Chennai), Methanol (Qualigens Fine Chemicals, Mumbai), Acetone (SD Fine Chemicals, Mumbai) and all other materials and reagents used were of analytical grade.

The NTG-loaded EC nanoparticles were prepared by the solvent evaporation method.

NTG and EC were dissolved in mixture of methanol with acetone in 1:2 ratio using a vortex shaker to form homogeneous organic phase of NTG and EC. This solution was added drop by drop into aqueous phase polyvinyl alcohol using mechanical stirrer at 1000 rpm for 3 hrs to prepare a suspension and evaporated the organic phase followed by magnetic stirring for 2 hrs under atmospheric pressure at room temperature. The solution was centrifuged at 15,000 rpm for 15 min to form the emulsion. After centrifugation the supernatant was excreted and the pallets obtained were washed by using the same volume of distilled water as of the supernatant and again centrifuged at 15,000 rpm for 5 min. The precipitates was washed thrice with distilled water and freeze-dried to get the powdered nanoparticles.

4. Characterization of Nateglinide loaded polymeric nanoparticles

The prepared NTG-loaded EC nanoparticles were characterized by particle size, polydispersity index (PDI), the measuring range of Malvern Mastersizer is from 0.02 µm to 2000 µm and zeta potential was measured using by Malvern zetasizer (MAL 1054413 Zetasizer Version 6.20 Instruments, UK). Process yield of the formulation was determined by using formula (Process yield = [Practical yield / Theoretical yield] × 100). The drug content and drug entrapment efficiency of fabricated NTG-loaded EC nanoparticles were analyzed by HPLC method (Hypersil ODS C_{18} (average particle size 5 mm) column (250mm, 4.6mm). The detection of wavelength was 210 nm.

RESULTS AND DISCUSSION

In this study, AHP the widely used Multi Criteria Decision Making method was applied to select the best method for the preparation of antidiabetic drug loaded nanoparticles. The saaty scale was used to assign weights to all pair wise comparisons [Fig. 2 - Fig. 10]. The consistency ratios for the entire matrix were found to be consistent, as the ratio of the matrix was ≤ 0.1. Fig. 11 shows the overall priority weights obtained from the AHP method. Out of 5 alternatives, solvent evaporation method (A_1) received the maximum overall priority weights (0.471) followed by nanoprecipitation method (A_2, 0.168), salting out method (A_5, 0.160) and solvent displacement method (A_4, 0.108). However, Ionic Gelation method (A_3) received the least priority weight of (0.093). The sensitivity investigation of the decisions made is shown in the Fig. 12.

Table 4 shows the representation to formulated NTG-loaded EC nanoparticles results. The formulated NTG-loaded EC nanoparticles were characterized by the average mean particle sizes [Fig. 13] and the PDI was calculated based on the volumetric distribution of particles and provide the information about the homogeneity of particle size distribution. NTG-loaded EC PDI was 0.312 and it shows narrow size distribution. The values of zeta potential more positive than 30 mV or more negative than 30 mV are electrochemically stable. NTG-loaded EC nanoparticles zeta potential value was -14.4 mV [Fig. 14], which shows the electrochemical stability of the formulations. The percentage process yield obtained was 81.46 %. The drug content and drug entrapment efficiency were found 86.76 % and 81.06 % respectively for the developed nanoparticles.

	Technological Aspects	Operational Aspects	Economic Aspects
Technological Aspects		1.0	1.0
Operational Aspects			2.0
Economic Aspects	Incon: 0.05		

Fig. 2: Pairwise comparison of the general criteria with reference to the selection of best method for the preparation of antidiabetic drug loaded nanoparticles.

	Solvent Evaporation	Nanoprecipitation	Ionic Gelation	Solvent Displacement	Salting Out
Solvent Evaporation		7.0	5.0	3.0	2.0
Nanoprecipitation			3.0	2.0	1.0
Ionic Gelation				2.0	2.0
Solvent Displacement					2.0
Salting Out	Incon: 0.06				

Fig. 3: Pairwise comparison matrix of the alternative with reference to literature review

	Solvent Evaporation	Nanoprecipitation	Ionic Gelation	Solvent Displacement	Salting Out
Solvent Evaporation		8.0	6.0	4.0	2.0
Nanoprecipitation			2.0	4.0	6.0
Ionic Gelation				2.0	4.0
Solvent Displacement					3.0
Salting Out	Incon: 0.02				

Fig. 4: Pairwise comparison matrix of the alternative with reference to equipment availability

	Solvent Evaporation	Nanoprecipitation	Ionic Gelation	Solvent Displacement	Salting Out
Solvent Evaporation		6.0	4.0	2.0	2.0
Nanoprecipitation			2.0	3.0	2.0
Ionic Gelation				2.0	2.0
Solvent Displacement					2.0
Salting Out	Incon: 0.06				

Fig. 5: Pairwise comparison matrix of the alternative with reference to equipment backup

	Solvent Evaporation	Nanoprecipitation	Ionic Gelation	Solvent Displacement	Salting Out
Solvent Evaporation		7.0	6.0	5.0	3.0
Nanoprecipitation			4.0	3.0	1.0
Ionic Gelation				2.0	1.0
Solvent Displacement					2.0
Salting Out	Incon: 0.09				

Fig. 6: Pairwise comparison matrix of the alternative with reference to ease of operation

	Solvent Evaporation	Nanoprecipitation	Ionic Gelation	Solvent Displacement	Salting Out
Solvent Evaporation		6.0	5.0	4.0	3.0
Nanoprecipitation			4.0	3.0	2.0
Ionic Gelation				1.0	2.0
Solvent Displacement					2.0
Salting Out	Incon: 0.07				

Fig. 7: Pairwise comparison matrix of the alternative with reference to reliability

	Solvent Evaporation	Nanoprecipitation	Ionic Gelation	Solvent Displacement	Salting Out
Solvent Evaporation		7.0	6.0	4.0	2.0
Nanoprecipitation			3.0	2.0	2.0
Ionic Gelation				1.0	2.0
Solvent Displacement					2.0
Salting Out	Incon: 0.05				

Fig. 8: Pairwise comparison matrix of the alternative with reference to accuracy

	Solvent Evaporation	Nanoprecipitation	Ionic Gelation	Solvent Displacement	Salting Out
Solvent Evaporation		2.0	4.0	6.0	8.0
Nanoprecipitation			3.0	5.0	7.0
Ionic Gelation				2.0	4.0
Solvent Displacement					1.0
Salting Out	Incon: 0.02				

Fig. 9: Pairwise comparison matrix of the alternative with reference to no. of ingredients

	Solvent Evaporation	Nanoprecipitation	Ionic Gelation	Solvent Displacement	Salting Out
Solvent Evaporation		9.0	6.0	3.0	1.0
Nanoprecipitation			2.0	2.0	2.0
Ionic Gelation				2.0	2.0
Solvent Displacement					4.0
Salting Out	Incon: 0.09				

Fig. 10: Pairwise comparison matrix of the alternative with reference to operation cost

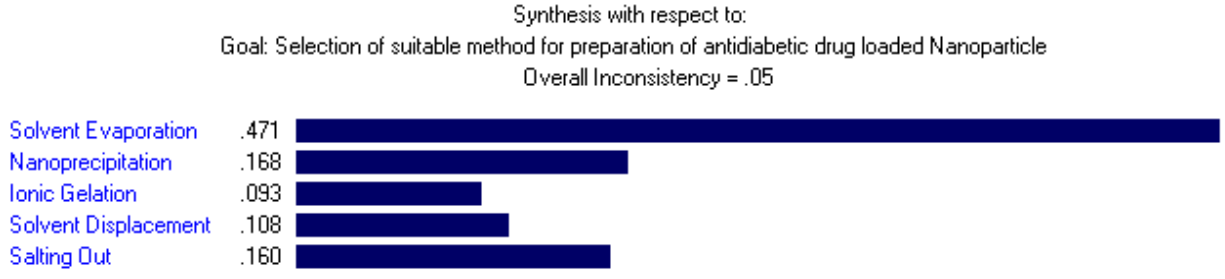

Fig. 11: Overall priority weight for alternatives

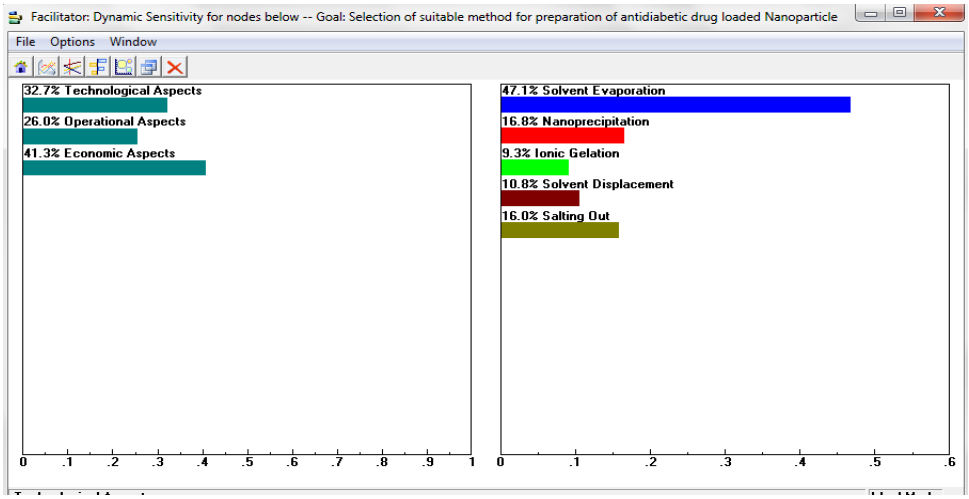

Fig. 12: Sensitivity Analysis

Table 4: Characterization of nateglinide loaded polymeric nanoparticles

Formulation	Particle size (nm)	PDI	Zeta potential (mV)	Process yield (%)	Drug content (%)	Entrapment efficiency (%)
NTG-EC NPs	108	0.312	−14.4	81.46	86.76	81.06 %

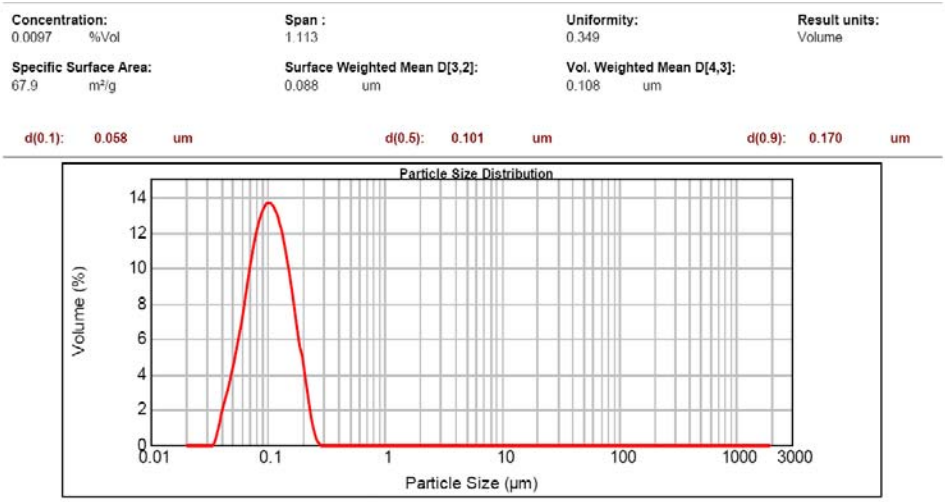

Fig. 13: Particle size distribution of nateglinide loaded polymeric nanoparticles

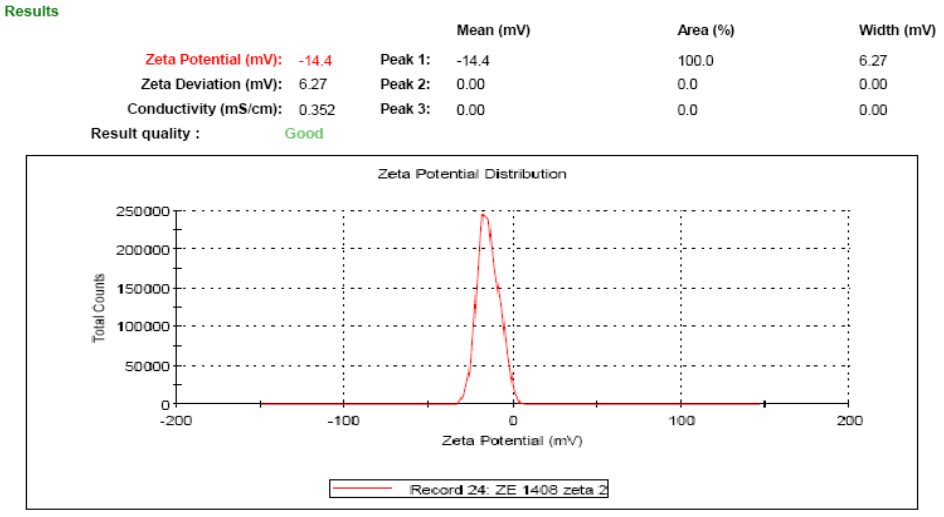

Fig. 14: Zeta potential distribution of nateglinide loaded polymeric nanoparticles

CONCLUSION

The paper illustrates the difficulties in the selection of the best method for the preparation of antidiabetic drug loaded nanoparticle. The selection of an unsuitable method may lead to loss of material resources, financial resources and time of research. To overcome this, a hierarchy was constructed with three criteria, eight sub-criteria and five alternatives. The assessment of the alternative was performed through Multi Criteria Decision Making Analysis and the software used for computing the priority weights for alternatives was expert choice. It shows that the solvent evaporation method is the best method for the preparation of antidiabetic drug loaded nanoparticles with the highest overall priority weight of 0.471.

Based on this decision, solvent evaporation method was used to prepare the NTG-loaded EC nanoparticles and characterised for Particle size, PDI, Zeta potential, Drug content and Entrapment efficiency. The result that shows the particle size, PDI and zeta potential were within the appropriate limits. The drug content and entrapment efficiency showed 86.76 % and 81.06 % respectively. This study resolves that the AHP is a possible and effective tool for selecting a most suitable method to formulate for NTG-loaded EC nanoparticles.

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