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Preparation of drug loaded polymeric nanoparticles using AHP-DEA method

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ABSTRACT

We intend to fabricate drug loaded polymeric nanoparticles to overcome the limitations of curcumin in cancer treatment however, there are around eight reported methods to prepare polymeric nanoparticles. Selection of a appropriate method was a real challenge, as the selection of inappropriate method may lead to loss of resources. We used analytic hierarchy process in combination with data envelopment analysis method to select a appropriate nanoparticles preparation. Nanoprecipitation was identified as a appropriate method and implemented in the preparation of Curcumin loaded polymeric nanoparticles and the obtained nanoparticles were in the average particle size of 150 nm with polydispersity index of 0.2 and zeta potential of 30 mv. The study results concluded that the integration of analytical hierarchy process and data envelopment analysis has played a significant role in selecting a appropriate method for the nanoparticles preparation.

Keywords: Analytical Hierarchy Process,Curcumin, Data Envelopment Analysis, Nanoprecipitation, Polymeric Nanoparticle

INTRODUCTION

According to WHO, around 57 million deaths have occurred in 2008. Of which, 36 million (63%) deaths were due to non-communicable diseases such as cardiovascular diseases, diabetes and cancers. Of all non-communicable diseases, with more than 7.6 million deaths, cancer ranked third as the leading cause of death worldwide. The current statistics suggest that the cancer prevalence will continue to rise and may reach around 17 million cancer deaths by 2030. The major therapeutic approaches for the treatment of both localized and metastasized cancer is chemotherapy, which are being used alone or in combination with other forms of cancer therapies. However, systemic toxicity and multidrug resistance pose real concern over most potent chemotherapeutic agents. The systemic toxicity of potent chemotherapeutic agents can be reduced by various approaches but not completely preventable. In such cases, functional foods (i.e. foods that provide health benefits beyond basic nutrition) are the best alternatives for such potent chemotherapeutic agents. Curcumin is once such functional food isolated from *Curcuma longa*, which exhibits diverse health benefits including anti-cancer activity and has the ability to reverse the multidrug resistance. Curcumin is highly safe even at high doses but suffer some limitations including limited aqueous solubility, rapid systemic clearance, intestinal metabolism, hepatic metabolism, poor oral bioavailability and multidrug resistance. However, these limitations can be significantly overcome by Polymeric Nanoparticle

Drug Delivery System, which are being utilized to overcome several limitations of drug delivery systems. In Polymeric Nanoparticle Drug Delivery System, the drug is encapsulated in a non-toxic, biodegradable polymer and size of the drug particles are reduced in nanometer (nm) range. Polymeric Nanoparticle Drug Delivery System also exhibits potential advantages including drug stability, high carrier capacity, possibility of incorporation of both hydrophilic and hydrophobic drugs, possibility of various route of administration, controlled release of drug from the polymer matrix, reduced side effects of the drugs and the ability to incorporate multiple drugs into the polymer matrix. Fabricating curcumin in Polymeric Nanoparticle Drug Delivery System can overcome most limitations of curcumin. [1-12].

Hence, we intended to prepare curcumin polymeric nanoparticles to overcome the limitations of conventional curcumin in cancer treatment. However, there are around eight reported methods to prepare nanoparticles but the selection of a suitable method was a real concern, as the selection of an inappropriate method may lead to loss of material resources, financial resources and time of research.

Hence, we have decided to utilize the decision-making tool such as Analytical Hierarchy Process (AHP) in combination with Data Envelopment Analysis (DEA) in the selection of a suitable method for the preparation of curcumin polymeric nanoparticles. AHP is a multi-criteria decision-making tool which was developed by Dr. Thomas L. Saaty in 1970s and has been successfully implemented in many fields such as marketing, finance, education, public policy, economics, medicine, and sports to identify a suitable decision. AHP technique involves structuring multiple choice criteria into a hierarchy, assessing the relative importance of criteria, comparing alternatives for each criterion, and determining an overall ranking of the alternatives. DEA technique is a linear programming method used to measure the relative efficiency of decision making, which was first initiated in 1978 by Charnes, Cooper, and Rhodes in their operational research and later developed by Banker, Charnes, and Cooper in 1984. We have selected the combination of AHP and DEA because it is free rank reversal, which does not suffer from rank reversal, when an inappropriate alternative(s) is added or removed [12-21].

MATERIALS AND METHODS

Curcumin (97%, Sigma-Aldrich, India), Acetone (Analytical grade, S.D Fine Chemicals, India), Poloxamer (Grade 188, Sigma-Aldrich, India), Eudragit (Grade E 100, Degussa, India) were obtained and used as received without any further purification.

Methods for the preparation of polymeric nanoparticles

Eight potential alternatives or methods (Figure 1) for the preparation of polymeric nanoparticles were selected based on the studies published in peer reviewed Journals. A brief procedure for the preparation of polymeric nanoparticles by each method has been included in this paper.

S.No.	Potential alternatives/methods	Code
1.	Solvent Evaporation Method	A_1
2.	Salting-out Method	A_2
3.	Nanoprecipitation Method	A_3
4.	Dialysis Method	A_4
5.	Nano Spray Drying Method	A_5
6.	Desolvation Method	A_6
7.	Ionic Gelation Method	A_7
8.	Supercritical Fluid Technology	A_8

Figure 1: Potential alternative for the preparation of polymeric nanoparticles

Solvent Evaporation Method

Solvent evaporation method has been widely used in the preparation of both micro and nanoparticles. Briefly, drug and polymer were dissolved in water non-miscible organic solvent, which was then added to the aqueous phase containing

copolymer/surfactants (e.g. Poloxamer, Tween 80, and sodium dodecyl sulphate) under high energy homogenization to form an emulsion. Subsequently, the polymer in the emulsion undergoes precipitation, which encapsulates the drug in the polymer matrix resulting in the formation of nanospheres. The residual solvent in the formulation was then removed by increasing the temperature under reduced pressure [22, 23].

Salting-out Method

Salting-out method is a modified version of emulsion process to overcome the use of surfactants and chlorinated solvents that are toxic to physiological systems and hazardous to the environment. Briefly, drug and polymer were dissolved in water miscible organic solvent, which was then added to the aqueous phase containing stabilizer and salting-out agent (e.g. magnesium chloride, calcium chloride, magnesium acetate, sucrose) under constant stirring. Miscibility of organic solvent in the aqueous phase was prevented due to the presence of salting-out agent, which leads to the formation of emulsion. Addition of excess amount of distilled water in the emulsion enhances the diffusion of organic solvent into aqueous phase. Subsequently, the polymer in the emulsion undergoes precipitation, which encapsulates the drug in the polymer matrix and resulting in the formation of nanospheres. Residual solvent and salting-out agents were then removed by cross flow filtration technique [24, 25].

Nanoprecipitation Method

Nanoprecipitation method is very commonly used to prepare nanocapsules, which was first developed by Fessi. Briefly, drug and polymer were dissolved in water miscible organic solvent, which was then added to the aqueous phase containing stabilizer under mild stirring. The organic solvent was then diffused rapidly in to the aqueous phase, which decreases the interfacial tension between the aqueous and organic phase. Subsequently, deposition of polymer takes place in the interface between the aqueous and organic phase, which results in the formation of colloidal nanoparticles [26, 27].

Dialysis Method

Dialysis method is an effective technique to fabricate nanoparticles with narrow distribution and the basic principle is similar to nanoprecipitation method. Briefly, drug and polymer were dissolved in water miscible organic solvent, which was then placed inside a dialysis membrane/tube with appropriate molecular weight cut-off. Uniform volume of the organic phase diffuses out through the dialysis membrane/tube into the aqueous phase. The organic solvent was then diffused rapidly into the aqueous phase which decreases the interfacial tension between the aqueous and organic phase. Subsequently, deposition of polymer takes place in the interface between the aqueous and organic phase, which results in the formation of colloidal nanoparticles [28, 29].

Nano Spray Drying Method

In pharmaceutical industries, spray drying is a well known technique to produce powdered material from the liquid preparation. However, conventional spray dryers consist of rotary atomizer and pressure nozzle that produce powder in micron size. Hence, a new Nano Spray Dryer B-90 has been introduced by BÜCHI, Switzerland. Briefly, drug and polymer were dissolved in a suitable solvent with or without stabilizer to get a clear solution and filtered through a 0.45 µm syringe filter to avoid clogging. Filtered clear solution was then fed into the spray head by a pump. The drying gas was then allowed to enter from the top into the drying chamber and was heated up to the set inlet temperature. Piezoelectric driven actuator was then driven at around 60 kHz causing the spray mesh to vibrate and eject millions of precisely sized droplets with a very narrow distribution, which were gently dried into solid particles by the drying gas. The dried solid particles were then electrostatically charged and collected at the collecting electrode [30, 31].

Desolvation Method

Polymeric nanoparticles were also prepared based on desolvation technique by changing the charge and hydrogen ion concentration or by addition of a desolvating agent such as ethanol or by addition of concentrated inorganic salt solutions. Briefly, drug was incubated with required amount of protein solution for about 1-2 hours at room temperature. Then the hydrogen ion concentration of the protein solution was adjusted suitably followed by addition of ethanol at the controlled rate of 1 ml/min under constant stirring at room temperature until the solution became turbid. The coacervate so formed

was hardened using 25% glutaraldehyde for about 2 hours to allow the cross-linking of protein [32, 33].

Ionic Gelation Method

Natural polymers such as chitosan and alginates have been studied extensively as carriers due to their permeation enhancing effect, enzyme inhibitory abilities and mucoadhesive property. Hence these polymers play a major role in the oral drug delivery system. Desolvation, emulsion cross-linking and spray drying methods have been tried to prepare chitosan nanoparticles. However, use of toxic chemicals in the oral drug delivery system poses a concern over its safety whereas, ionic gelation method takes place in aqueous environment and it is ideal for the oral drug delivery system. Briefly, drug and natural polymer were dissolved in water or in weak acidic medium based on the solubility of drug and polymer, which was then added drop-wise into the solution containing counter ions and stabilizer under constant stirring. The oppositely charged species undergoes complexation, which results in gelation and then precipitates to form spherical shaped particles. The resultant solution was then subjected to sonication, which reduces the particle size in nanometer range [34, 35].

Supercritical Fluid Technology

Supercritical fluid technology utilizes environment friendly solvent and prevents the use of organic solvent, which pose a real concern over the safety of the worker and consumers. Briefly, drug and polymer were dissolved in a suitable supercritical fluid at room temperature, which was then pumped into a pre-expansion tank using a syringe pump. In the pre-expansion tank, the solution was then heated isobarically to the pre-expansion temperature (40°C) at pre-expansion pressures (27.6 Pascal), which was then allowed to expand through nozzle into ambient air. The expanding solution experiences a high degree of supersaturation along with rapid pressure reduction, which results in nucleation and formation of well dispersed particles. Alternatively, the pre-heated solution was allowed to expand through nozzle into aqueous solution containing stabilizer, which results in controlled homogeneous nucleation and formation of uniform sized nanoparticles [36, 37].

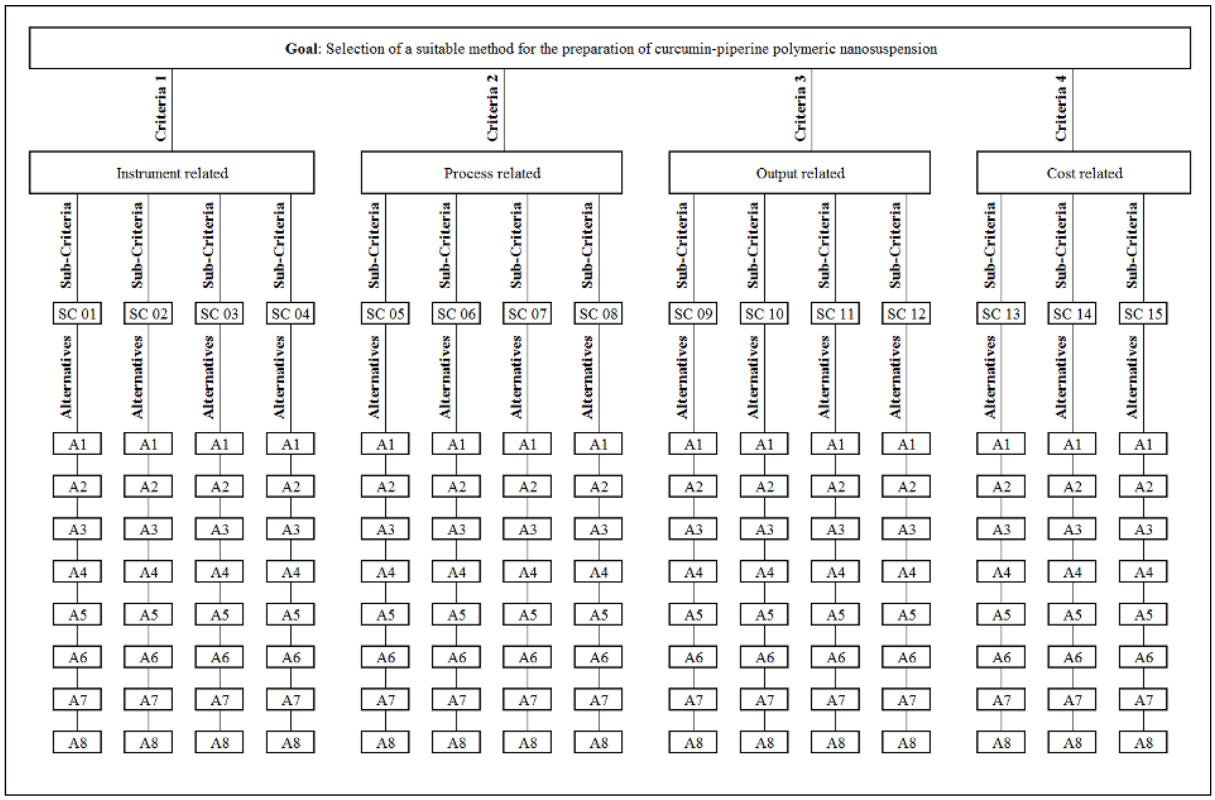

Fig. 2: Hierarchy model for the selection of a suitable method for the preparation of polymeric nanoparticles

Hierarchy model

To make a decision in an organised way, a hierarchy model (Fig.2) was developed with four levels. Goal in the first level, four main criteria in the second level, 15 sub-criteria in the third level and 8 potential alternatives/methods for the preparation of polymeric nanoparticles in the fourth level.

Main criteria and sub-criteria

To assess the potential alternatives, four main criteria and fifteen sub-criteria (Fig. 3) were selected based on the most crucial and significant issues in the preparation of polymeric nanoparticles and also based on following five principles for the preparation of safe nanoproducts (a) Size reduction in nanometer range and change of surface characteristic of drug should not alter the functionality of the drug and should not be toxic to human and environment, (b) Toxic chemicals used in the preparation should be replaced with suitable non-toxic alternative chemicals, (c) Intentional bonding of atoms or molecules to nanoparticles should preserve the desired product properties and devoid of toxicity, (d) Highly toxic drugs should be enclosed or encapsulated using non-toxic polymers to reduce the toxicity of the drug and (e) If not possible to avoid the use of toxic chemicals, use limited quantities of the toxic chemicals [38].

Main Criteria	Sub-Criteria	
	Code	Description
Instrument related	SC01	Availability of instrument in the academic institute.
	SC02	Backup for the instrument in case of repair, breakdown etc.
	SC03	Simple operating procedure.
	SC04	Precise performance of instrument's in-built parameters.
Process related	SC05	Minimum number of excipients for the preparation.
	SC06	Simple process for the preparation.
	SC07	Minimum influenceable parameter during the process.
	SC08	Possibility to transfer the technology from lab to industry.
Output related	SC09	Minimum average particle size with optimal zeta potential.
	SC10	Minimum polydispersity index.
	SC11	Maximum product output per operation.
	SC12	Reproducible result.
Cost related	SC13	Minimum cost, if prepared in the academic institute.
	SC14	Minimum cost, if prepared outside the academic institute.
	SC15	Minimum cost, if the preparation is out-sourced.

Figure 3: Main criteria and sub-criteria for the selection of suitable method

Determination of priority weights and ranking

Pair-wise comparisons were made using Saaty's scale (Fig. 4) to evaluate the relative importance of criteria and to compare the alternatives for each criterion. During pair-wise comparison, weights were assigned as follows. If criteria/alternative i and j are equally important, then the corresponding weights will be $a_{ij} = w_i/w_j = 1$; $a_{ji} = w_j/w_i = 1$. Consistency Ratio (CR) was calculated for each pair-wise comparison matrix and a value ≤ 0.1 are considered acceptable, which indicates that the judgments/weights allotted are reasonable. In the DEA process, potential alternatives were named as Decision Making Units (DMU) and the overall priority weights of sub-criteria were grouped under corresponding four main criteria, which were then subjected to DEA process to determine the efficiency of decision making [13, 14, 19, 21].

S. No.	Importance	Weights	
		i^{th} Vs j^{th} ($a_{ij} = w_i/w_j$)	j^{th} Vs i^{th} ($a_{ij} = w_j/w_i$)
1.	Equally important	1	1
2.	Equally to moderately more important	2	1/2
3.	Moderately more important	3	1/3
4.	Moderately to strongly more important	4	1/4
5.	Strongly more important	5	1/5
6.	Strongly to very strongly more important	6	1/6
7.	Very strongly more important	7	1/7
8.	Very strongly to extremely more important	8	1/8
9.	Extremely more important	9	1/9

Fig. 4: Saaty's scale

RESULT AND DISCUSSION

Weights were assigned to all pair-wise comparisons using Saaty's scale and matrices were constructed. All constructed pair-wise comparison matrices were consistent, as the consistency ratio of all the matrix was ≤ 0.1. Hence, the weights allotted were reasonable. Fig 5 shows the overall priority weights, consistency ratio and ranking of sub-criteria**.** Out of 15 sub-criteria, SC09 received the maximum priority weight (0.1427) followed by SC10 with 0.1310 and SC12 with 0.1187. However, SC05 has received the least priority weight (0.0213). With respect to main criteria, output related criteria received the maximum priorities weights, as the first three maximum priority weights of sub-criteria belong to output related criteria and results signify the importance of output related parameter in the preparation of polymeric nanoparticles.

Main Criteria	Sub-Criteria	Overall Priority Weights	Rank
Instrument related	SC 01	0.0453	10
	SC 02	0.0358	13
	SC 03	0.0401	11
	SC 04	0.0974	04
Process related	SC 05	0.0213	15
	SC 06	0.0371	12
	SC 07	0.0544	07
	SC 08	0.0862	05
Output related	SC 09	0.1427	01
	SC 10	0.1310	02
	SC 11	0.0595	06
	SC 12	0.1187	03
Cost related	SC 13	0.0318	14
	SC 14	0.0494	08
	SC 15	0.0494	09

Fig 5: Overall priority weights and ranking of sub-criteria

Fig 6 shows the priority weights and ranking of potential alternatives obtained by AHP. Out of 8 methods, nanoprecipitation (A_3) received the maximum overall priority weights (0.2219) followed by supercritical fluid technology (A_8, 0.1550) and dialysis method (A_4, 0.1294). However, desolvation method (A_6) received the least overall priority weights (0.0652).

Criteria	Potential alternatives/Methods for the preparation of polymeric nanoparticles							
	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
SC 01	0.0033	0.0074	0.0150	0.0034	0.0014	0.0047	0.0089	0.0013
SC 02	0.0017	0.0071	0.0129	0.0017	0.0015	0.0033	0.0063	0.0014
SC 03	0.0021	0.0066	0.0141	0.0021	0.0019	0.0037	0.0078	0.0017
SC 04	0.0190	0.0065	0.0067	0.0106	0.0203	0.0049	0.0067	0.0226
SC 05	0.0032	0.0017	0.0035	0.0036	0.0012	0.0019	0.0033	0.0030
SC 06	0.0022	0.0062	0.0117	0.0039	0.0020	0.0026	0.0065	0.0020
SC 07	0.0061	0.0065	0.0148	0.0065	0.0027	0.0030	0.0118	0.0031
SC 08	0.0129	0.0052	0.0083	0.0101	0.0189	0.0037	0.0048	0.0224
SC 09	0.0154	0.0099	0.0403	0.0236	0.0083	0.0078	0.0104	0.0269
SC 10	0.0068	0.0096	0.0306	0.0225	0.0170	0.0071	0.0106	0.0268
SC 11	0.0087	0.0048	0.0063	0.0048	0.0136	0.0030	0.0036	0.0147
SC 12	0.0076	0.0092	0.0172	0.0263	0.0190	0.0061	0.0093	0.0239
SC 13	0.0024	0.0048	0.0101	0.0020	0.0015	0.0031	0.0067	0.0014
SC 14	0.0036	0.0076	0.0154	0.0040	0.0022	0.0049	0.0098	0.0018
SC 15	0.0035	0.0088	0.0148	0.0044	0.0023	0.0054	0.0084	0.0019
Overall priority weights	0.0984	0.1017	0.2219	0.1294	0.1137	0.0652	0.1148	0.1550
Rank	7	6	1	3	5	8	4	2

Fig 6: Priority weights and ranking of potential alternatives

Fig 7 shows the efficiency scores of the eight alternatives obtained by DEA technique. Out of 8 DMU's, DMU 3 (Nanoprecipitation method) has received 100% efficiency and it is the only efficient DMU, followed by DMU 8 (Supercritical fluid technology) with 97.8% efficiency and DMU 4 (Dialysis method) with 81.8 % efficiency. However, DMU 6 (Desolvation method) achieved the least efficiency with 34.1 %. AHP in combination with DEA methods has identified nanoprecipitation as suitable methods for preparation of polymeric nanoparticles.

DMU	Overall priority weights of main criteria				Dummy Input	Efficiency	Rank
	Instrument Related	Process Related	Output Related	Cost Related			
DMU 1	0.0261	0.0244	0.0385	0.0095	1	63.7 %	6
DMU 2	0.0276	0.0196	0.0335	0.0212	1	56.7 %	7
DMU 3	0.0487	0.0383	0.0944	0.0403	1	100 %	1
DMU 4	0.0178	0.0241	0.0772	0.0104	1	81.8 %	3
DMU 5	0.0251	0.0248	0.0579	0.0060	1	64.8 %	5
DMU 6	0.0166	0.0112	0.0240	0.0134	1	34.1 %	8
DMU 7	0.0297	0.0264	0.0339	0.0249	1	68.9 %	4
DMU 8	0.0270	0.0305	0.0923	0.0051	1	97.8 %	2

Fig 7: Ranking of potential alternatives using DEA technique

Nanoprecipitation method was implemented in the fabrication of curcumin polymeric nanoparticles. Briefly, Curcumin and Eudragit E 100 were dissolved in acetone using bath sonicator (40 kHz, Lark, India), which was then poured into the distilled water containing poloxamer 188 as stabilizer under mild stirring (500 rpm, Remi, India) for 3 hours which results in the formation of colloidal nanoparticles. The average particle size and polydispersity index of the colloidal nanoparticles was measured using

Zetasizer (Malvern Instrument, UK) .The average particle size of curcumin nanoparticle was 150 nm with 0.2 polydispersity index and zeta potential was around 30 mV.

Most conventional potent chemotherapeutic agents produce moderate to severe adverse effects as it targets both rapidly proliferating cancerous cells and normal cells. However, these adverse effects can be significantly minimized or prevented by polymeric nanoparticles, which target the cancer cell either by passive targeting or by active targeting. However, active targeting requires ligands, which are coupled with nanoparticles and receptors for the ligands to bind at the cancer site whereas, in passive targeting, polymeric nanoparticles below 150 nm can be highly permeable to the cancer cells, as the cancer cells are leaky with gap of minimum 150-200 nm between the adjacent endothelial cells. However, normal tissue vasculatures are lined with tight endothelial cells, which prevent the entry of nanoparticles and thereby preventing the adverse effect due to chemotherapeutic agents [4]. Prepared curcumin nanoparticles was in the average particle size of 150 nm which is around the leaky cancer cells (150-200nm). Hence, this formulation is expected to reach the cancer cells by passive diffusion.

Aggregation of polymeric nanoparticles in the storage container tends to decrease the stability of the formulation. Similarly, aggregation of polymeric nanoparticles in the intestinal gut tends to decrease the oral bioavailability. The charges on the polymeric nanoparticles are likely to play a crucial role in the aggregation. Higher numbers of either positive or negative charges keep away each other, which in turn prevent the aggregation. These charges are measured and expressed as zeta potential. Nanoparticless with zeta potential below ±5 mV experience pronounced aggregation, zeta potential below ±20 mV have limited stability, zeta potential greater than ±30 mV are physically stable and zeta potential greater than ±60 mV demonstrate excellent stability. However, zeta potential greater than ±30 mV is considered ideal and acceptable. Prepared curcumin nanoparticles showed a zeta potential of 30 mV which is considered as physically stable and this formulation is expected to be stable both during its storage.

CONCLUSIONS

In this research, we studied the problem of selecting a appropriate method for the preparation of curcumin polymeric nanoparticles. We have used analytic hierarchy process in combination with data envelopment analysis to select a appropriate method and the results suggested nanoprecipitation method would be a suitable method. Subsequently, nanoprecipitation method was implemented to prepare curcumin nanoparticles and the results revealed that the particle size, polydispersity index and zeta potential were within acceptable limits. The study concludes that the integration of analytical hierarchy process and data envelopment analysis has played a significant role in selecting a appropriate method for the preparation of nanoparticles.

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