Multi criteria decision making to select the best method for the preparation of solid lipid nanoparticles of rasagiline mesylate using analytic hierarchy process

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Abstract

The objective of this study was to select best method for the development of rasagiline mesylate (RM) loaded nanoscale solid lipid particles using analytic hierarchy process (AHP). Improper method selection may lead to waste of time, loss of material and financial resources. One of the possibilities to overcome these difficulties, AHP was employed to find the suitable method. In the AHP, a decision of hierarchy was constructed with a goal, criteria, sub-criteria, and alternatives. After constructing the AHP, the expert choice software was used to compute the overall priority of criteria, sub-criteria and alternatives. The best alternative selected was based on the highest priority. Nanoscale solid lipid particles of RM was formulated by the selected microemulsion method (M4) and it shows the particle size, polydispersity index and zeta potential were within acceptable limits. Drug content and entrapment efficiency of the RM-solid lipid nanoparticles were 97.26% and 86.57%, respectively. This study concludes that the AHP was viable and effective tool for selecting a most suitable method for the fabrication of RM loaded nanoscale solid lipid particles.

key words: Criteria, desirability, dynamic sensitivity analysis, hierarchy

INTRODUCTION

Over the past few decades, nanostructured materials have been fascinating and challenging the world of science and technology due to their amazing role in producing novel shapes, structures and the unusual phenomena associated with these materials.[1] The London based largest nanotechnology consultancy company Cientifica Ltd. reported the development of nano based drug delivery expenditure was $3.4 billion in 2007 and approximately $26 billion in 2012 and in 2015 it is expected to be 220$.[2] The science and technology research in nanotechnology promises breakthroughs in the areas include manufacturing, medicine and healthcare, nanopharmaceuticals, biotechnology, nanoelectronics, information technology and National security.[3] The term "nanopharmaceuticals" covers drug discovery, design, development and delivery of drug. In pharmaceutical formulation development, 90% of the active ingredients exist in the form of solid particles.[4] Through the development in nanotechnology, it may conceivably to fabricate the drug loaded nanoparticles that can be used in numerous novel applications. Nanopharmaceutical is a promising approach to deliver the drug into brain for neurodegenerative disorders.[5] Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder of adult onset, after Alzheimer's disease and affecting 1-2% of general population. Rasagiline (N-propargyl-1-R-aminoindan) mesylate (RM) is a second-generation of propargylamine used for the treatment of PD.[6] RM is a novel irreversible monoamine oxidase type B-inhibitor, secondary cyclic benzylamine and indane derivative of antiparkinson drug.[7] Delivery of RM into brain is huge challenge because of unique property of blood brain barrier. Nanopharmaceutical have provided an effective way to overcome this difficulty and used to minimize the

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drug degradation upon administration, enhance the bioavailability and *in vivo* efficiency of many drugs, increase the specificity towards the cell, improved the stability of sensitive agents, increase the target efficiency and to control the release of drug.[2,8]

The fabrication of nanoscale solid lipid particles involved a wide variety of techniques such as, high pressure homogenization, microemulsion, solvent emulsification, double emulsion and solvent injection method with various degrees of quality, time, and expense. The difficulties associated with the selection of appropriate method for the development of nanoscale solid lipid particles are a crucial decision in the pharmaceutical formulations. Because, the selection of an inappropriate method may cause loss of material resources, time of research and its spiraling costs threaten to create novel drug developments are increasingly unaffordable to both pharmaceutical developing companies and consumers.[9] However, these problems can be significantly overcome by applying the analytic hierarchy process (AHP) and it introduced as a multi-criteria decision-making by Thomas L Saaty in 1970s.[10] This compensatory decision methodology can be implemented in the areas of planning, allocating resources, resolving conflicts, selecting the appropriate alternative, total quality management, method optimization, strategic marketing, evaluating the projects (agriculture, economics, transport, medicine, pharmaceuticals and finance sectors) and so forth.[11] AHP have advantages includes increasing the product quality and shorten the product development cycles.[12] AHP encompasses the following steps: (a) Structuring of the hierarchical decision problem. (b) Judgments matrix obtained based on pairwise comparison between criteria and alternative. (c) Consistency test must proceed until satisfactory (d) Synthesizing comparisons across various levels to obtain the final weights of alternatives.[13]

In this study, an appropriate method for the preparation of RM loaded solid lipid particles was selected by employing the AHP.[12,14-17]

In this study, the AHP is composed of four levels. Level 1 consists of the goal of choice of for selecting the most suitable method for the fabrication of drug loaded nanoparticles. Level 2 contains four main criteria, namely operational performance, machinery information, process output and production cost. Level 3 encompasses eleven sub-criteria, it represents different intensities of the criterion. Level 4 consists five alternatives, these can be used to reach the goal. The judgment on pairwise comparisons of the AHP is carried out by using Saaty's discrete 9-value scale method shows in Table 1.

This study consisted an objective to select the most appropriate method between five alternatives, namely the double emulsion, solvent emulsification/evaporation,

high pressure homogenization, microemulsion and solvent injection method. These alternatives and their brief process encompassed here. The selected alternatives for the fabrication of RM loaded nanoscale solid lipid particles is listed in Table 2.

High pressure homogenization

High pressure homogenization is a reliable and powerful method, used for the preparation of solid lipid nanoparticles (SLN). Briefly, the solid lipid (glyceryl monostearate, palmitic acid and stearic acid) and drug are heated above the melting point of the lipid. An aqueous phase containing surfactant (polyethylene-polypropylene glycol and polysorbate 80) is added drop by drop into the melted lipid under high-speed stirring to make the emulsion. Then, the hot emulsion is homogenized by high pressure homogenization at the same temperature. The obtained hot o/w emulsion is immediately cooled in an ice bath, to solidify nanoparticles.[18,19]

Microemulsion technique

Microemulsion technique is a simple method used to prepare SLN, which was first introduced by Gasco.[20] Microemulsions are clear, thermodynamically stable and possibility to incorporate both hydrophilic and/or lipophilic drugs. In this method, the drug is added into melted lipid (stearic acid and palmitic acid). The aqueous phase containing surfactant (polyethylene-polypropylene glycol) and co-surfactant (polysorbate 80) is added drop wise into the lipid phase, under magnetic stirring to obtain a clear microemulsion. The warm o/w clear emulsion is dispersed

Table 1: Saaty's pair-wise comparison nine point scale for AHP preference

Scale	Numerical rating	Reciprocal
Extremely importance	9	1/9
Very to extremely strongly importance	8	1/8
Very strongly importance	7	1/7
Strongly to very strongly importance	6	1/6
Strongly importance	5	1/5
Moderately to strongly importance	4	1/4
Moderately importance	3	1/3
Equally to moderately importance	2	1/2
Equally importance	1	1

AHP: Analytic hierarchy process

Table 2: Alternatives for the fabrication of drug loaded nanoscale solid lipid particles

Potential alternatives/method	Code
Double emulsion method	M1
Solvent emulsification/evaporation	M2
High pressure homogenization method	M3
Microemulsion method	M4
Solvent injection method	M5

into cold distilled water under probe sonicator to solidify the nanoparticles.[21,22]

Solvent emulsification/evaporation

Solid lipid nanoparticles are also fabricated based on the emulsification solvent diffusion technique. In this method, the drug and chosen lipid is dissolved in water immiscible organic solvent (cyclohexane, chloroform, and dichloromethane), which is then emulsified in an aqueous solution containing stabilizer under stirring. Then the organic solvent evaporated under high pressure homogenizer and reduced pressure. The SLN obtained by the precipitation of lipid in an aqueous phase. The most important advantage of this technique is avoidance of any thermal stress during the fabrication.[23,24]

Double emulsion method

Double emulsion technique is primarily used for hydrophilic drugs, the encapsulated hydrophilic drug with stabilizer to prevent drug separation to external aqueous phase during evaporation in the external aqueous phase of w/o/w double emulsion. Briefly, the drug is dissolved in an aqueous solution, which is then emulsified in an aqueous phase containing stabilizer under stirring. The obtained preemulsion is dispersed into an aqueous phase containing hydrophilic emulsifier under stirring and resulting in formation double emulsion SLN.[25]

Solvent injection method

Solvent injection method is a novel approach to formulate SLN and the preparation based on precipitation from the dissolved lipid in solution. In this method, the solid lipid is dissolved in the aqueous miscible/immiscible organic solvent (ethanol, acetone, isopropanol), which is injected through an injection into an aqueous phase containing with or without surfactant under stirring. The excess lipid is filtered through filter paper. The aqueous phase containing an emulsifier helps to form lipid droplets at the site of injection and stabilize SLN until solvent dispersion is complete by reducing the surface tension between water and solvent.[26,27]

METHODS

Construction of model

The AHP was developed based on the literature review. In this study, a four level hierarchy model was employed as illustrated in Figure 1. In the four levels AHP described below:
- Overall goal of the decision
- Identify the relevant criteria
- The criteria further divided in sub-criteria
- Develop pair wise comparison matrix
- Calculate overall priority ranking
- Select the best alternative.

Structuring the hierarchy of criteria and sub-criteria

In this study, the main criteria selected namely operational performance, machinery information, process output and production cost. These criteria are further divided into the third level, namely sub-criteria. The first criteria of operational performance have four sub-criteria namely, Performance monitoring capability, ease of operation, fault diagnosing capabilities and scale up. The second criteria of machinery information contain three sub-criteria, availability of machinery, operating procedure and machinery back-up. The third criteria of process output further divided into two sub-criteria, accuracy and reliability. The fourth criteria has two sub-criteria namely, price and payment system.

Pairwise comparison matrix

The Expert Choice Software (version 11) was used for pairwise comparison of criteria, sub-criteria and alternatives. This software provides various options for comparing criteria, sub-criteria and alternatives: Numerical, verbal and graphical. In this work, we decided to use numerical scale between 1 and 9 (Saaty's scale) and this scale used to assign the weights for criteria, sub-criteria and alternatives. In the first step, the comparison has been made between criteria and sub-criteria. In next step, each alternative were compared with criteria and sub-criteria and then calculated the overall priority weights of criteria, sub-criteria and alternatives.

Calculation of priorities and sensitivity analysis

Expert choice (version 11) was used to calculate the priority and sensitivity analysis by user-friendliness. This sensitivity analysis used to check how sensitive the alternatives in case any changes in criteria weights. Here, we can see that each alternatives priority and weights of each criteria. The sensitivity analysis graph describes, how the alternatives perform with respect to all criteria as well as overall.

Preparation of rasagiline mesylate loaded solid lipid nanoparticles

Rasagiline mesylate was generous gift from Orchid Health Care Pvt. Ltd. (Chennai, India). Stearic acid and Tween 80 were obtained from SD Fine Chem Ltd. (Mumbai, India). High performance liquid chromatography (HPLC) grade Acetonitrile and Lutrol were purchased from Sigma Aldrich (Bangalore, India) and Signet Chemicals Lab (India), respectively. The analytic grade chemicals and reagents were used for all the experiments. Double distilled water was used after filtration through a 0.45 μm membrane (cellulose acetate).

Rasagiline mesylate loaded nanoscale solid lipid particles were prepared by microemulsion technique. In this method, the lipid phase containing stearic acid was heated at 69-70°C and the drug was added in the melted lipid. Lipid phase was added drop wise into aqueous phase containing surfactant
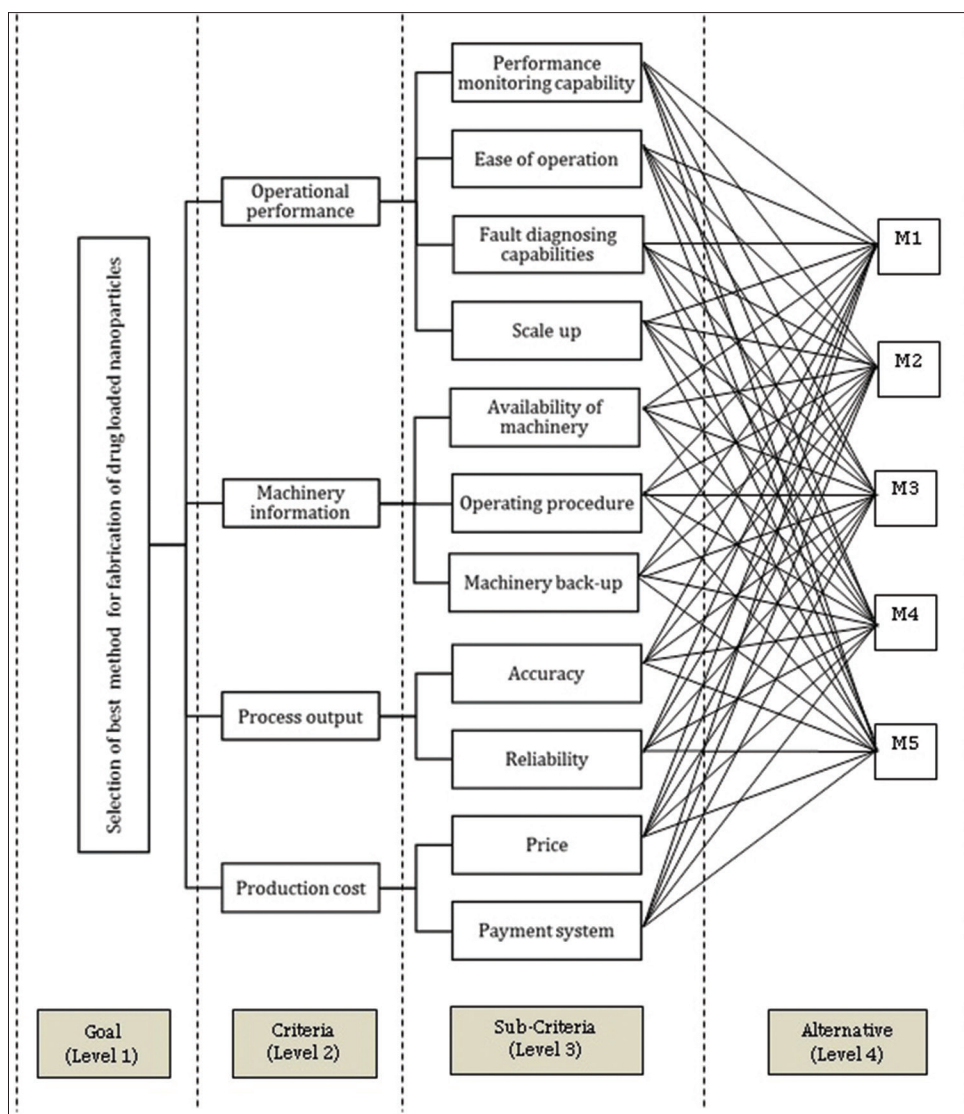
Figure 1: Four level hierarchy model for selection of best method for fabrication of rasagiline mesylate loaded solid lipid nanoparticles

and co-surfactant, which heated at same temperature. The mixture was stirred magnetically (Remi, India) at 500 rpm for 10-15 min to facilitate o/w emulsion formation. The resulting o/w emulsion was dispersed into cold distilled water under probe sonicator (Lark, India) for 20 min to solidify the nanoparticles.

Characterization of rasagiline mesylate loaded solid lipid nanoparticles

The prepared RM-SLNs process yield was determined by using formula (process yield = [practical yield/theoretical yield] × 100)[28] and the average particle size, polydispersity index (Pdi) and zeta potential were measured using Zetasizer version 6.20 (Malvern zetasizer, Malvern Instrument, UK) Figure 2. Pdi, a parameter calculated from the width of the particle size of distribution by using equation = D (0.9) - D (0.1)/D (0.5). Where, D (0.9), D (0.5) and D (0.1) are corresponding to particle size immediately

above 90%, 50% and 10% of the sample.[29] The measuring range of the Malvern Mastersizer is from 0.02 μm to 2000 μm. The determination of drug content and drug entrapment efficiency of RM-SLNs analyzed by HPLC method (Thermoscientific, Spectra System P-4000, USA) using ultraviolet detector (Kromosil 100) and C18 column (particle size 5 μm, 250 mm × 4 mm). The detection of wavelength was 265 nm. The energy expenditure (EE) was calculated by using the equation (EE = total drug (assay) - free drug/total drug × 100).

RESULTS AND DISCUSSION

Analytic hierarchy process was used for assessing the most appropriate method for fabrication of RM loaded nanoscale solid lipid particles among the five alternatives. The overall objective of the decision problem focused in the

top-level of hierarchy. The middle level consists the various criteria, each criterion were broken down into sub-criteria and the end level of the hierarchy consists of alternatives, which used to reach the goal. After constructing the AHP, the expert choice software used to compute the pair wise criteria and sub-criteria. The constructed each pairwise comparison matrix were consistent, as the consistency ratio was ≤0.10 reported by expert choice. Table 3 exhibits the composite priority weights for criteria and sub-criteria and alternatives.

Among four criteria, the process output criteria has received maximum priority weights (0.379) followed by production cost (0.243), operational performance (0.197) and machinery information (0.182). Every criteria was given some priorities based on their importance one to another with the help of the satty scale. The criteria are the compared pair wisely with each other and with respect to the alternatives and to the goal. The one which score more would be the best part as per the satty rule. As per that, the criteria process output which scored 0.379 was considered to be the best criteria. The machinery information priority weights were smaller than the rest of other criterion. Out of eleven sub-criteria, price received the maximum priority weight (0.667) followed by accuracy with 0.500, reliability with 0.500, machinery back-up with 0.443, availability of machinery with 0.378,

payment system with 0.333, fault diagnosing capabilities with 0.312, performance monitoring capability with 0.286, scale up with 0.280, operating procedure with 0.169 and ease of operation with 0.127. The sub-criteria ease of operation has received the least priority weight, with respect to main criteria process output criteria priorities weight was higher than the rest of other criteria, as the maximum priority weight of sub-criteria being the main criteria of production cost and the results indicates the production cost parameter has a strong influence in the preparation of RM-SLN.

The obtained priority weights of sub-criteria and their ranking depicted in Figure 3. It can be seen that the price (sub-criteria) occupied the topmost rank, the top rank being the main criteria of production cost, followed by reliability, accuracy, machinery back-up, availability of machinery, payment system, fault diagnosing capabilities, scale up, performance monitoring capability, operating procedure and ease of operation. There are also two criteria namely, operational performance and process output criteria were received same ranking. The AHP analysis exhibits that alternative M4 (microemulsion method) is the most suitable method for the preparation of RM loaded nanoscale solid lipid particles and the alternatives M5, M1, M3, and M2 are feasible respectively.
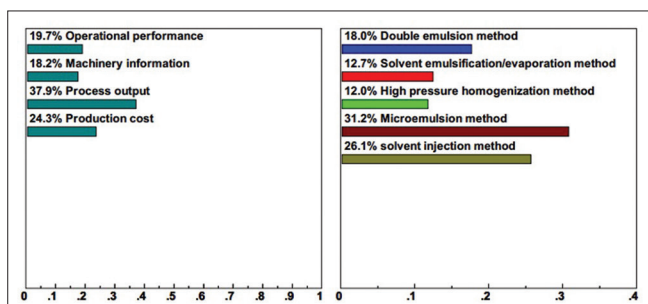
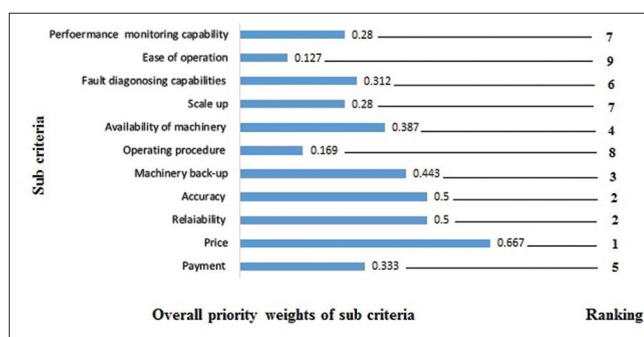

Figure 2: Dynamic sensitivity analysis graph

Figure 3: Overall priority weights and ranking of sub-criteria

Table 3: The composite priority weight for criteria, sub-criteria and alternatives

Criteria	Priority weights	Sub-criteria	Priority weights of sub-criteria	Priority weights				
				M1	M2	M3	M4	M5
Operational performance	0.197	Performance monitoring capability	0.286	0.104	0.118	0.143	0.396	0.239
		Ease of operation	0.127	0.114	0.140	0.163	0.303	0.280
		Fault diagnosing capabilities	0.312	0.178	0.144	0.121	0.309	0.248
		Scale up	0.280	0.247	0.114	0.123	0.269	0.247
Machinery information	0.182	Availability of machinery	0.378	0.231	0.188	0.083	0.263	0.231
		Operating procedure	0.169	0.276	0.100	0.092	0.276	0.256
		Machinery back-up	0.443	0.244	0.112	0.112	0.288	0.244
Process output	0.379	Accuracy	0.500	0.214	0.112	0.122	0.308	0.244
		Reliability	0.500	0.174	0.121	0.121	0.309	0.275
Production cost	0.243	Price	0.667	0.107	0.122	0.122	0.359	0.289
		Payment system	0.333	0.88	0.155	0.144	0.321	0.292

The obtained sensitivity investigation results were shown in the Figure 4. This analysis was conducted to investigate the effect of the various criteria on the final decisions. In the performance sensitivity analysis graph, left vertical- axis signify the weight of the main criteria and the right vertical axis gives the priority of each alternative. This investigation can help to decision makers to identify the strength and weakness of the alternatives.

The dynamic sensitivity was used to identify the changes in the criteria weights and these results can cause changes of the final ranking. Figure 2 shows that no sensitive change has been occurring in the ratings of alternatives, while changing the priorities of operational performance, machinery information, process output, and production cost. The graph exhibits that how the alternatives perform with respect to all objectives as well as overall.

The percentage process yield of 83.60 was obtained for RM-loaded SLNs. Table 4 shows the Characterization of fabricated RM-loaded SLNs results. The average mean particle sizes of RM-SLNs was 248.70 nm [Figure 5] and the Pdi was calculated based on the volumetric distribution of particles and provide the information about the homogeneity of particle size distribution. RM loaded SLN Pdi was 0.481, it indicates the narrow size distribution. The values of zeta potential more positive than 30 mV or more negative than 30 mV are electrochemically stable. RM loaded SLN zeta potential value was - 35.5 mV [Figure 6], which shows the electrochemical stability of the formulations. This result can be minimizing the aggregation/flocculation between the particles.

CONCLUSION

In this study, we investigated the difficulties in the selection of the best method for the preparation of RM loaded SLN. The selection of an unsuitable method may lead to loss of material resources, financial resources and time of research. To overcome these difficulties, we applied the AHP method, which can be used to evaluate and select the best alternative based on the criteria and sub-criteria aspects of decision. The AHP analysis exhibits that alternative M4, the microemulsion method, is the most suitable method for the preparation of RM loaded nanoscale solid lipid particles. The microemulsion method was implemented to fabricate RM-SLNs and

the results revealed that the particle size, Pdi and zeta potential were within acceptable limits. Drug content and entrapment efficiency of the RM-SLNs was 97.26% and 86.57%, respectively. This study concludes that the AHP is a viable and effective tool for selecting a most suitable method for the fabrication of RM loaded nanoscale solid lipid particles.
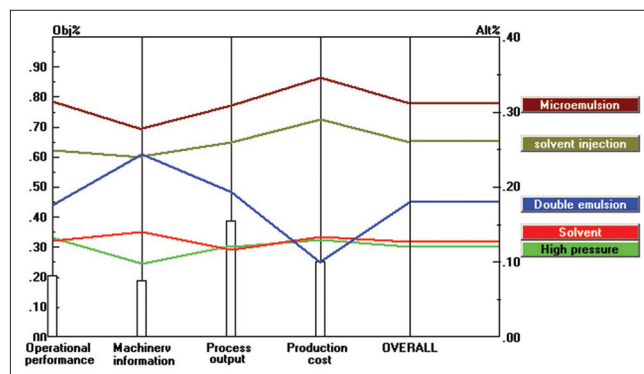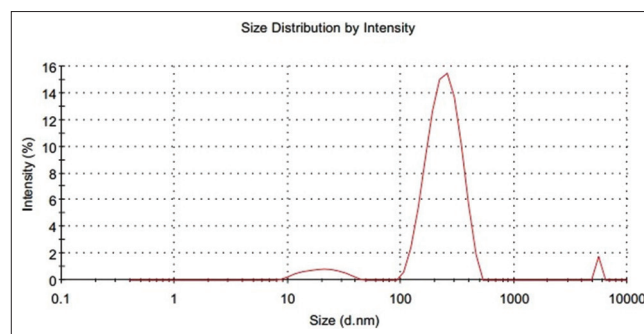

Figure 4: Performance sensitivity graph

Figure 5: Particle size distribution of rasagiline mesylate solid lipid nanoparticles
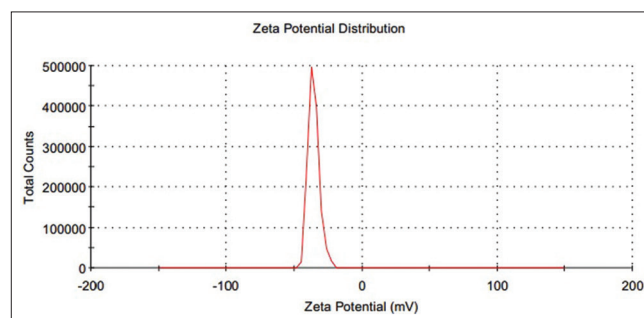

Figure 6: Zeta potential distribution of rasagiline mesylate solid lipid nanoparticles

Table 4: Characterization of fabricated RM-loaded SLN

Formulation code	Process yield (%)	Particle size (nm)	Pdi	Zeta potential (mV)	Drug content (%)	Entrapment efficiency (%)
RM-SLN	83.60	248.7	0.481	−35.5	97.26	86.57

Pdi: Polydispersity index, RM-SLN: Rasagiline mesylate-solid lipid nanoparticles

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