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## Nano coenzyme Q<sub>10</sub> capsule

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### ABSTRACT

*The present study was conducted to develop nano CoQ<sub>10</sub> capsule. The experiment was designed accordingly ZEON F&D SOP for the nano CoQ<sub>10</sub> Capsule ZLL/F&D/041. Six formulations were carried for development of nano CoQ<sub>10</sub> capsule to check the overall acceptability. For the development of nano CoQ<sub>10</sub> capsule, experimental design with the active ingredient (nano CoQ<sub>10</sub> powder), lubricant, glidant, diluents and disintegrant produced different combinations that were studied using pre and post evaluation parameters. The methodology of nano CoQ<sub>10</sub> was carried out by dry mixing method. Capsule filling was performed by using hand capsule filling machine. Nano CoQ<sub>10</sub> was the main factor of the capsule, nano increase the bioavailability of CoQ<sub>10</sub> which possess significant role in various disease like, cardiac failure, ischemic heart disease, interaction with statins, hypertension, diabetes, neurodegenerative diseases, Parkinson's disease, Huntington's disease, Alzheimer's disease, cancer, aging, Down's syndrome, Periodontal Disease etc.*

**Keywords:** Nano, CoQ<sub>10</sub>, Capsule.

## 1. INTRODUCTION

The word capsule derived from the Latin word "CAPSULA" which means a small box and container<sup>1</sup>. Capsules are the form of solid dose in which the drug is either enclosed within a hard or soft soluble container or "shell". The shells are usually made of gelatin; however, they can also be made from starch or other suitable substances. The gelatin capsule shell can be soft or hard depending on their formulation. The capsule is intended to swallow completely by the patient<sup>2</sup>. Gelatin capsules, informally called gel caps or gelcaps, are composed of gelatin manufactured from the collagen of animal skin or bone. Gelatin is not derivable from ungulate hooves, which are composed of a different protein, (keratin). Vegetable capsules are composed of hypromellose, a polymer formulated from cellulose.

### 1.1 Types of the capsule

There are two types of capsules, "hard" and "soft". The hard capsule is also called "two pieces" as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the "cap" which fits over the open end of the longer piece, called the "body". The soft gelatin capsule is also called as "one piece"<sup>3</sup>. The administration of liquid and solid medicine encapsulate in hard gelatin capsules is one of the most often utilized dosage forms<sup>4</sup>.

### 1.2 Enzymes

Enzymes are biological catalysts. They increase the rate of chemical reactions taking place within living cells without themselves suffering any overall change. The reactants of enzyme-catalyzed reactions are termed substrates. Each enzyme is quite specific in character, acting on a particular substrate or substrates to produce a particular product or products<sup>5</sup>.

### 1.2.1 Coenzyme

Coenzymes are typically organic molecules that contain functionalities not found in proteins, while cofactors are catalytically essential molecules or ions that are covalently bound to the enzyme. Coenzyme example-Flavin, B<sub>12</sub>, thiamin pyrophosphate, lipoic acid, folate enzymes etc <sup>6</sup>.

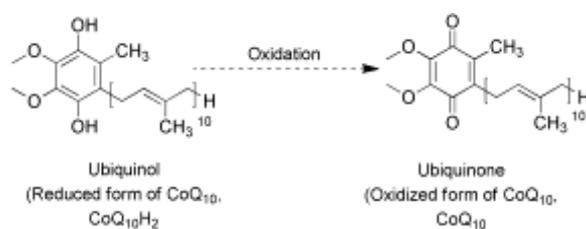
### 1.2.2 Coenzyme Q<sub>10</sub>

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) is a lipid-soluble molecule derived mainly from endogenous synthesis<sup>7</sup>. Coenzyme Q<sub>10</sub> was first discovered from beef mitochondria by Prof. Fredrick L. Crane and colleagues at the University of Wisconsin – Madison Enzyme Institute in 1957<sup>8</sup>. CoQ<sub>10</sub> is present in practically every cell in the human body.

Here, CoQ<sub>10</sub> performs two vital functions

- CoQ<sub>10</sub> is vital for energy production throughout the body.
- CoQ<sub>10</sub> as Ubiquinol provides powerful antioxidant protection.

From these two actions, CoQ<sub>10</sub> delivers nutritional support that expands to encompass whole-body health. When Ubiquinol donates its extra electrons, it “oxidizes” and transforms into CoQ<sub>10</sub> (ubiquinone). When CoQ<sub>10</sub> is able to gain more extra electrons, it becomes Ubiquinol<sup>9</sup>.



**Fig-1: Oxidized and reduced form of ubiquinone<sup>10</sup>.**

CoQ<sub>10</sub> is highly lipophilic molecule composed of a 1,4-benzoquinone. The Q refers to the quinone chemical groups and the 10 refers to the number of isoprenyl chemical subunits in its tail. CoQ<sub>10</sub> belongs to a group of compounds that are characterized by their quinone moieties in addition to the length and composition of their hydrophobic tails<sup>11</sup>. Its molecular formula is C<sub>59</sub>H<sub>90</sub>O<sub>4</sub> and its molecular mass 863.34g/mol<sup>8</sup>. CoQ<sub>10</sub> is an obligatory member of the respiratory chain in the mitochondria of all cells. Therefore, it is an essential ingredient in the formation of adenosine triphosphate (ATP), the source of energy in most cellular processes<sup>12</sup>.

### 1.2.3 Occurrence

Coenzyme Q has been found in both microorganisms and plants, as well as in animals. The highest concentrations in human tissues are found in heart, liver and kidney, approximately 110, 60 and 70 μg/g tissue, respectively, and the lowest concentration, 8 μg/g, in lung<sup>13</sup>.

### 1.2.4 Most frequent physiologic and clinical applications of coenzyme Q<sub>10</sub>

Physiologic and clinical applications -

- Human coenzyme Q<sub>10</sub> deficiencies
- Mitochondrial diseases
- Fibromyalgia
- Cardiac failure
- Ischemic heart disease
- Interaction with statins
- Hypertension
- Diabetes
- Neurodegenerative diseases
- Parkinson's disease
- Huntington's disease
- Alzheimer's disease
- Cancer Aging
- Periodontal Disease<sup>14</sup>

### 1.3 Nanotechnology

Nano particles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Nanoparticles sized between 1 and 100 nanometres<sup>15</sup>.

Coenzyme Q<sub>10</sub> is an antioxidant and essential molecule for the proper growth of every cell in the body, It is a very hydrophobic drug resulting in poor bioavailability and poor delivery significance. The main problem in the delivery of the coenzyme Q<sub>10</sub> is that it is a very insoluble molecule in the water several nanotechnology-based formulations have been prepared for the effective delivery of the coenzyme Q<sub>10</sub>. The main advantage of these nano delivery systems is modulation of the pharmacokinetic properties of the coenzyme Q<sub>10</sub> to enhance its bioavailability<sup>16</sup>.

## 2. METHODOLOGIES

The nano coenzyme Q<sub>10</sub> capsule formulation was carried out in the Department of Research and Development at Zeon Life sciences Ltd. Paonta Sahib, Himachal Pradesh in the academic year 2017-2018.

### 2.1 Raw materials

Various factors were looked while designing the dosage form in capsules. A normal capsule formulation contains only glidants, lubricants, diluents, and disintegrants.

#### 2.1.1 Nano coenzyme Q<sub>10</sub>

It was the active agent in the formulation of CoQ<sub>10</sub> Capsule.

#### 2.1.2 Lubricants

Lubricants were used to help in smooth running of a high-speed automatic capsule filling machine facilitating the powders do not stick to the tamping pins and dosing disc<sup>17</sup>. A lubricant, an additive to reduce friction, was an essential component of a drug formula since lubrication was often required to ensure the success of pharmaceutical manufacturing<sup>18</sup>.

Eg: Magnesium stearate, Stearic acid, Polyethylene glycol.

#### 2.1.3 Glidants

They helped in the powder in granulation form or pellets form to flow from the hopper to the empty hard capsules<sup>17</sup>.

Eg: Talc powder, Aerosil (colloidal silicon dioxide)

#### 2.1.4 Disintegrates

Disintegrating agents were substances included in capsule hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids<sup>19</sup>. Eg: Cross povidone, Sodium Starch glycolate, Croscarmellose Sodium .

#### 2.1.5 Diluents

Diluents were used to cover up the fill volume or weight of the capsules<sup>17</sup>. Eg: Micro crystalline cellulose, lactose, tricalcium phosphate.

## 2.2 Experimental design

The experiment was designed accordingly zeon f&d sop for the nano coq10 capsule zll/f&d/041. Six trials were performed to optimization of nano CoQ<sub>10</sub>.

**Table-1: Experimental design for formulation of nano CoQ<sub>10</sub> capsule**

Excipients	Formulation (%)					
	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>
Nano COQ10	91	45	26.5	84.8	88.5	88.5
Glidant [1]	1.5	0.8	0.8	1	1.05	1.05
Lubricant	1.5	0.8	0.8	1	1.05	1.05
Diluent [1]	0	49	67.5	8.5	8.9	0
Diluent [2]	0	0	0	0	0	8.9
Disintegrat e	1	5	5	4.3	0	0
Glidant [2]	5	0.4	0.4	0.5	0.5	0.5

## 2.3 Manufacturing steps

### 2.3.1 Process flow chart for capsule preparation

#### Step 1-Dispensing

All material was dispensed (Recipient 1-6) according to BOM (Bill Of Material).



#### Step 2 – Sifting

The dispensed active ingredient was pass through 20 mesh sieve and lubricants, glidants, diluents were pass through 40 mesh sieve



#### Step 3 – Mixing



All sifted ingredients were collected in a fresh polybag and mixed properly



Bulk Density (g/ml) and LOD Of blend were calculated capsules were filled with hand capsule filling machine

## 2.4 Bulk density

Both loose bulk density (LBD) and tapped density were determined, A quantity of the powder from each formula was introduced into a 10 ml measuring cylinder, After the initial volume was absorbed, the cylinder was allowed to fall under its own weight onto a hard surface. From the height of the 2.5 cm. LBD and TBD were calculated using the following formulas.

$LBD = \text{weight of powder} / \text{volume of the packing.}$

$TBD = \text{weight of powder} / \text{tapped volume of the packing.}$

## 2.5 Capsule filling

Hand operated and electrically operated machines are in practice for filling the capsules but for small and quick dispensing hand operated machines are quite economical. The machine can be “tapped” to spread the powder and drop it down into the capsule bases. A small device consists of many “pegs” on a handle can be used to tamp the powder into the capsule bases gently and evenly. Any remaining powder then unfolds equally over and into the capsule bases and tamped. These procedures are repeated until all of the powder is within the capsules. The capsule caps are then fitted over the machine, fixed in place, and the filled capsules removed, dusted using a clean cloth, and packaged<sup>20</sup>.



**Fig- 2: Capsule hand filling machine**

## 2.6 Parameter for Analysis Of Nano CoQ<sub>10</sub> 10 capsule-

### 2.6.1 Appearance

Capsules produced on a small or a large scale should be uniform in appearance. Evidence of physical instability is demonstrated by gross changes in appearance, including hardening or softening, cracking, swelling, mottling, printing mistake or discoloration of the shell. Defective capsules should be rejected<sup>21</sup>.

**2.6.2 Size and Shape-** Hard capsules were made in a range of sizes, the standard industrial ones in use today for human medicines range from size from 000 (the largest, 1.40 ml) to 5 (the smallest, 0.13ml) are commercially available <sup>21</sup>.

**2.6.3 Lock length** -Ten individual capsules were taken from formulation trial batch and lock length was measured manually by using vernier calipers and an average of ten capsules was noted <sup>1</sup>.

### 2.6.4 Weight variation test

Ten capsules were individually weighted and the content was removed. The emptied capsule was individually weighed and the net weight of the contents was calculated by subtraction and the percent weight variation was calculated by using the following formula.  $\text{Weight variation} = (\text{weight of capsule} - \text{Average weight}) / \text{Average weight of capsule} \times 100$  Weight variation should not be more than 7.5%<sup>4</sup>.

### 2.6.5 Disintegration test

The capsules were placed in basket-rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°C. To fully satisfy the test, the capsule should disintegrate completely into a soft mass having no palpably firm core without any fragments of the gelatin shell. If one or two capsules fail, the test should be repeated on additional of 12 capsules. Then, not fewer than 16 of the total 18 capsules tested should disintegrate completely<sup>1</sup>.

## 3. RESULTS AND DISCUSSION

The capsules were formulated by using nano CoQ10 powder. There were six formulations which were formulated and evaluated.

### 3.1 Pre capsule filling studies

#### 3.1.1 Bulk Density

**Table -2: Bulk Density of all formulated blends**

S.no	Formulation	Bulk density (g/ml)
1	F <sub>1</sub>	0.28
2	F <sub>2</sub>	0.41
3	F <sub>3</sub>	0.42
4	F <sub>4</sub>	0.58
5	F <sub>5</sub>	0.60
6	F <sub>6</sub>	0.63

#### 3.1.2 Loss on drying

The moisture content of formulated blend with nano CoQ10 91%, 45%, 26.5%, 84.8%, 88.5% varied significantly from each other and ranged from 2.5% to 4.1%.

**Table- 3: LOD of all formulated blends**

S.no	Formulation	LOD (%)
1	F <sub>1</sub>	2.5
2	F <sub>2</sub>	3.6
3	F <sub>3</sub>	2.9
4	F <sub>4</sub>	4.1
5	F <sub>5</sub>	3.9
6	F <sub>6</sub>	3.8

### 3.2 Post capsule filling parameters

#### 3.2.1 Net powder contains

Table 4 shows net powder content of F1 to F6. We can clearly observe that maximum powder content was found to be in the case of F6; this formulation could show a better powder content range.

**Table -4: Net powder contain per capsule**

Formulation	Claim weight (mg/capsule)	Results
	Net powder contains	Net powder contain (mg)
F <sub>1</sub>	390±7.5% (360-419)	322
F <sub>2</sub>	410±7.5% (379.25- 440.75)	365
F <sub>3</sub>	430±7.5%	385

	(397.75-462.25)	
<b>F<sub>4</sub></b>	585±7.5% (541.12-628.87)	530
<b>F<sub>5</sub></b>	610±7.5% (564.25-655.75)	550
<b>F<sub>6</sub></b>	660±7.55 (610.5-709.5)	630

### 3.2.2 Weight variation

Table 5 shows the weight variation of F<sub>1</sub> to F<sub>6</sub>, we can clearly observe that in F<sub>1</sub> to F<sub>6</sub>, the weight of per capsule was found different according to the claim, But the weight of capsules was found satisfactory in the F<sub>6</sub> formulation.

**Table- 5: Weight variation per capsule**

<b>Formulation</b>	<b>Claim weight /capsule(mg)</b>	<b>Results</b>
	<b>Filled capsule weight</b>	<b>Filled capsule weight</b>
<b>F<sub>1</sub></b>	508±7.5% (469.9-546.1)	440
<b>F<sub>2</sub></b>	528±7.55 (488.4-567.6)	483
<b>F<sub>3</sub></b>	548±7.5% (506.9 -589.1)	503
<b>F<sub>4</sub></b>	703±7.5% (650.27 - 755.72)	648
<b>F<sub>5</sub></b>	728±7.5% (673.4-782.6)	668
<b>F<sub>6</sub></b>	778±7.5% (719.65- 836.35)	748

### 3.2.3 Locked length

**Table -6: Locked length of all formulation**

<b>Formulation</b>	<b>Standard locked length (±0.76mm)</b>	<b>Results (Locked length) (mm)</b>
F <sub>1</sub>	23.30±0.76	23.14
F <sub>2</sub>	23.30±0.76	23.40
F <sub>3</sub>	23.30±0.76	23.24
F <sub>4</sub>	23.30±0.76	23.31
F <sub>5</sub>	23.30±0.76	23.42
F <sub>6</sub>	23.30±0.76	23.32

Table 6 shows the Locked Length of F<sub>1</sub> to F<sub>6</sub>. Locked length of the capsule was found satisfactory according to claim.

### 3.2.4 Disintegration test

Table 7 shows disintegration time of F<sub>1</sub> to F<sub>6</sub>. we can clearly observe that the maximum disintegration time was found to be in the case of F<sub>5</sub> and F<sub>6</sub>, 12 min 40 sec and 12 min 38 sec respectively and minimum weight variation was found to be in case of F<sub>2</sub>. Disintegration time was found the maximum in F<sub>5</sub> and F<sub>6</sub> this was due to the absence of disintegrants in the formulation.

Table -7: Disintegration time for capsules

Formulation	Disintegration Time (min)
F <sub>1</sub>	8 min 10 sec
F <sub>2</sub>	7 min 8 sec
F <sub>3</sub>	8 min
F <sub>4</sub>	9 min 48 sec
F <sub>5</sub>	12 min 40 sec
F <sub>6</sub>	12 min 38 sec

#### 4. CONCLUSION

A nano CoQ<sub>10</sub> capsule was successfully developed. A Nano CoQ<sub>10</sub> capsule posses light yellowish granular powder. Nano CoQ<sub>10</sub> was the main factor of the capsule , Nano increase the bioavailability of CoQ<sub>10</sub> which posses significant role in various disease like mitochondrial diseases, cardiac failure, ischemic heart disease, Interaction with statins, hypertension, diabetes, neurodegenerative diseases, parkinson's disease, huntington's disease, alzheimer's disease, cancer, aging, Down's syndrome, Periodontal disease etc.

Other main ingredients in the formulation

Lubricants- They helped in the smooth running of capsule filling machine facilitating the powders did not stick to the tamping pins and dosing disc.

Diluents were added to the formulation to increase the bulk volume of the material. The selection of the diluents would depend on the type of plasticity of material to be used. In general, a direct compression formulation would require diluents with good flow and compaction properties.

Disintegrants agents were added to capsule formulations to promote the breakup of the capsule "slugs" into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance.

The system was found to be satisfactory in terms of release of the drug within 15 min. All pre and post parameter of the capsule was found satisfactory in terms of Bulk Density, moisture Content , weight and Locked length.

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