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Development and evaluation of nano-encapsulated curcumin chewable tablets

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ABSTRACT

Herbal medicine is the oldest form of healthcare known to mankind and Turmeric is one of the oldest known herbs used in Asian countries since 2000 years ago. Curcumin is a plant-derived polyphenolic compound, naturally present in turmeric (Curcuma longa), has been the subject of intensive investigations on account of its various activities. In recent years, the potential pharmacological actions of Curcumin in inflammatory disorders, cardiovascular disease, cancer, Alzheimer's disease and neurological disorders have been shown. It is insufficiently absorbed in the human body, it has high metabolism speed and high elimination from the human body. For overcome these effects nano technology are applied on curcumin for enhancing the bioavailability of curcumin in the human body. Curcumin contains medical benefits. These benefits provided to a human in the form of a chewable tablet. Chewable tablets are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. Chewable tablets are a help to improved patient acceptance (especially pediatric) through pleasant taste, patient convenience; need no water for swallowing, absorption of the drug is faster, better bioavailability through bypassing disintegration (that increase dissolution), the large size of the dosage form is difficult to swallow. In such cases, chewable tablet offers advantages over it. The aim of this study was to develop a nanocurcumin chewable tablet which can provide promising results for curcumin to improve its biological activities. Tablet was evaluated for Weight variation test, Friability, Hardness and Time required for complete chewing and are found to be within acceptable limits.

Keywords: *Bioavailability, Chewable Tablets, Compression, Curcumin, Health, Turmeric.*

1. INTRODUCTION

Since ancient times, "Mother Nature" has been a fertile source of medicines used to treat human diseases. One of those remedies is the turmeric spice, which has been used for at least 2500 years, mainly in Asian countries. Turmeric is derived from the *Curcuma longa* L. plant, which belongs to the "Zingiberaceae" family (Mathew *et al*., 2005). The curcuminoids that belong to the group of "Diaryl-Heptanoids" are the main bioactive ingredients of turmeric. The most common curcuminoid present in turmeric is Curcumin, which has been consumed for medicinal purposes for thousands of years.Commercial curcumin is usually a mixture of three curcuminoids: *curcumin* (71.5%), demethoxycicin (19.4%) and *bisdemetoxicurcumin* (9.1%) (Pfeiffer *et al.*, 2003). Curcumin is a lipophilic polyphenol substance, which constitutes 2-5% of the turmeric powder (Kocaadam *et al*., 2015).

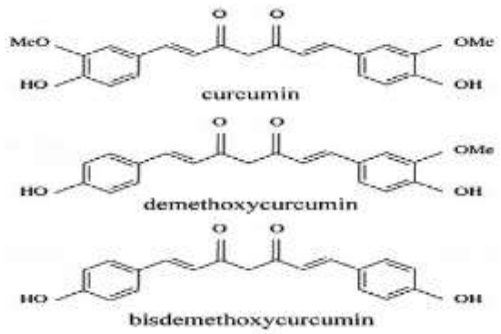

Figure 1.Structural formula of three curcuminoids

The phenolic groups in the structure of curcumin explain the ability of curcumin to eliminate oxygen-derived free radicals. The free radicals which can be eliminated by curcumin are hydroxyl radical, singlet oxygen, superoxide radical and nitrogen dioxide. (Louay *et al.*,2014) Curcumin shows strong antioxidant activity, as compared to vitamins C and E (Labban *et al*., 2014). Oral bioavailable formulations of curcumin were safe for a human at the dose of 500 mg two times in a day for 30 days. In addition, curcumin is known as a generally recognized as a safe substance. Turmeric and curcumin are nontoxic for human, especially in oral administration. Extraction of curcuminoids from turmeric powder or turmeric with the help of methanol as a solvent was carried out and curcuminoids were isolated in the form of crystals with 95 %purity and 75% yield. The isolated crystals show very good anti-inflammatory activity against %inhibition of oedema. (Patil*et al*., 2011). The chemical denotation of curcumin is 1, 7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1, 6-diene-3, 5-dione or dipheruloylmethane; while its chemical formula is $C_{21}H_{20}O_6$ (Deogade *et al*., 2015). Curcumin is not soluble in water at acidic and neutral pH; however it is soluble in acetone, methanol, and ethanol. It is stated that *curcumin*is sensitive to light and therefore it is recommended that biological samples containing curcumin are to be protected from light. (Prasad *et al.*, 2014). Due to its insufficient absorption by the body, high metabolism speed and high elimination from the body, curcumin has a limited bioavailability in the body. The low bioavailability of curcumin limits significantly the therapeutics effects of this component (Devassy.,2015). Subsequently, several nano-based methodologies are being created to improve the bioavailability of curcumin and decrease the apparent poisonous quality. Nanoparticlebased delivery systems will probably be suitable for highly hydrophobic agents like curcumin circumventing the pitfalls of poor aqueous solubility.(Bisht*et al* in 2007 reported the synthesis, physicochemical characterization and cancer related application of a polymer-based nanoparticle of curcumin namely "nanocurcumin" with less than 100 nm size. Nanocurcumin was found to have similar *invitro* activity as that of free curcuminin pancreatic cell lines. In ancient times, curcumin appeared in the Ayurveda medical treatment methods applied in India, used in the treatment of injuries, skin diseases, eye infections, ambustions and acne.Curcumin is also an important component of traditional treatment methods called JiaweiXiaoyao in China, and it has been used for the treatment of various diseases like dyspepsia, stress, depression for thousands of years. In the last 30 years, curcuminwas shown to have a therapeutic effect against cancer, auto-immune diseases, metabolic diseases, neurological diseases, cardiovascular diseases, lung diseases, liver diseases and a variety of other inflammatory diseases.

Table1.Diseases of different body systems taking effects from curcumin (Noorafshan *et al*., 2012)

Nervous system	**Alzheimer'sdisease Parkinson's disease Brain tumor Multiple sclerosis Neurodegenerative disorders**
Respiratory system	**Lungcancer, Inflammatorylungdiseases ,Pneumonia (anti-bacterial effect)**
Cardiovascular system	**Cardiomyopathy Oxidative heart injuryCardiac hypertrophy Myocardial infarction**
Urinary system	**Renal tubular fibrosis Inflammatory kidney diseases Oxidative kidney injury**
Reproductive system	**Toxin induced oxidative Tumors of reproductive system Dysmenorrhea**
Digestive and hepato-biliary system	**Tumors, GI ulcers, Inflammatory bowel disease,Cirrhosis Jaundice, Hepatic injuries (ex. Drug induced), Oxidative damage**
Musculoskeletal system and Skin diseases	**Inflammatory diseases (ex. Osteoarthritis), Oxidative stress, Ischemic damage, Insulin resistance,**
Endocrine system	**Diabetes, Hypothyroidism, Endocrine tumors**

In a study by Renu *et al*., 2015, they defined chewable tablets that must be broken and chewed between the teeth before ingestion. These tablets are given to children who have difficulty swallowing and to adults who do not like to swallow. These tablets are

intended to gently disintegrate in the mouth at a moderate rate with or without actual chewing; the characteristically chewable tablets have a smooth texture after disintegration, are pleasant in taste and leave no bitter or unpleasant taste. Geriatric and pediatric patients and patients who travel and may not have quick access to water need easy-to-swallow dosage forms, such as chewable tablets. A flavoring agent is included to make it more palatable. Several factors involved in the formulation of chewable tablets. The main formulation factors are flow, lubrication, disintegration, organoleptic properties, compressibility, compatibility, and stability, which are common to normal (swallowed) and chewable tablets.

Nano curcumin dose provides in the form of chewable tablets because improved patient acceptance (especially pediatric) through pleasant taste, patient convenience; need no water for swallowing, absorption of the drug is faster, better bioavailability through bypassing disintegration (that increase dissolution), the large size of the dosage form is difficult to swallow. In such cases, chewable tablet offers advantages over it.

2. METHODOLOGY

The present investigation entitled "Development and Evaluation of Nano Curcumin Chewable Tablets" was carried out in the laboratory of Formulation and DevelopmentDepartment at ZEON Life sciencesPvt Ltd., Himachal Pradesh in the academic year 2017-18.

Table 2. Formulation of chewable tablets

S No.	INGREDIENTS
1.	nanocurcumin
2.	Diluent
3.	Binder
4.	Lubricant
5.	and adhering agent
6.	sweetening agent (sucralose)
7.	flavoring agent (black salt)
8.	malic acid
9.	Glidant

2.1 Development of chewable tablets

The formulation was prepared in a step wise manner as follows:

Step 1: Dispense of all the materials according to the bill of materials in the accurate amount.

Step 2: Collection of the entire material was in the clean polybag.

Step 3: Binding agent was taken and dissolved in the isopropyl alcohol (IPA) because it is not soluble in the purified water.

Step 4: After making a binding solution, it was kept separately.

Step 5: Take active agent (nanocurcumin) and mix it with a binding solution in the harmonized way carefully.

Step 6: Mixing of the binding solution was done with active agent at least 10-15 min.

Step 7: Continuous mixing was done until the granular powder is not formed.

Step 8: Drying the granules at 60 ^{0}C in the tray dryer for 1-2hrs, meanwhile the IPA was evaporated.

Step 9: Checking the LOD (Loss on Drying) of dried material.

Step 10: Sifting the dried material with the help of 20 mesh sifter.

Step 11: After sifting, the sifted materials, and collection in the clean polybag.

Step 12: Keeping the sifted material separately.

Step 13: Taking all the lubricants and glidants in the clean poly bag.

Step 14: Sifting the lubricants and glidants through the 40 mesh sieves.

Step 15: Adding the sifted lubricants in the step 12 material and mixing it properly for at least 15-20 min.

Step 16: Keeping all collected material in the clean poly bag.

2.2 Raw materials

2.2.1 Nano curcumin: It was the active agent of the chewable tablet which was provided by the Formulation and Development Department.

2.2.2Diluents: Diluents are fillers used to make the required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk. The secondary reason is to provide better tablet properties such as improve cohesion, to permit the use of direct compression manufacturing or to promote flow.

A diluent should have following properties:

- They must be non-toxic
- They must be commercially available in acceptable grade
- Their cost must be low
- They must be physiologically inert
- They must be physically & chemically stable by themselves & in combination with the drugs.
- They must be free from all microbial contamination.
- They do not alter the bioavailability of the drug.
- They must be color compatible.
-

2.2.2 Binder: These materials are added either dry or in wet- form to form granules or to form cohesive compacts for a directly compressed tablet.

2.2.3Lubricants: Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation.

2.2.4 Glidants: Glidants are added to promote the flow of granules or powder material by reducing the friction between the particles

2.2.5 Flavouring agent: For nanocurcumin chewable tablet – black salt flavor in powder from being used

2.2.6 Sweetening agent: For a chewable tablet, sucralose is used. It gives the sweet and sour flavor.
Granulespowder is ready for compression by 8 stations rotary press tablet compression machine.

Figure 1: Developed nano curcumin chewable tablets

2.3 Evaluation of granular powders

2.3.1 Angle of repose: The angle of repose of the powdered blend was determined by the funnel method. The accurate weight granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured using the following equitation.

$$Ø = tan^{-1} (h/r)$$

Where h and r are the height and radius of the powder pile respectively.

2.3.2 Bulk & tapped density: Both loose bulk density (LBD) and tapped density were determined, A quantity of the powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder, After the initial volume was absorbed, the cylinder was allowed to fall under its one weight onto a hard surface. From the height of the 2.5 cm. LBD and TBD were calculated using the following formulas.

$$LBD = \frac{weight\ of\ powder}{Volume\ of\ the\ packing}$$

2.3.3 Compressibility index: The compressibility of the powdered blend was determined by Carr's compressibility index.

$$Carr's\ index\ (\%) = (TBD - LBD)\ /TBD \times 100$$

2.3.4 Moisture Content: Moisture content: the amount of moisture present in granules called moisture content.

2.4 Evaluation of tablets (sensory & physic-chemical estimation)

2.4.1 Odour: It also a sensory attribute for the quality of tablets.

2.4.2 Taste: Physiologically, taste is a sensory response resulting from a chemical stimulation of the taste buds on the tongue. There is four basic type of taste; salty, sour, sweet and bitter. This product contains sweet and sour taste.

2.4.3 Diameter: It was measured by using vernier calliper scale.

$$Diameter = \frac{Total\ diameter}{No.\ of\ tablets}$$

2.4.4 Thickness: The thickness of individual tablet is measured with a micrometer, which given us information about the variation between tablets. Tablets should be within ± 5 % variation of a standard value.

$$Thickness = \frac{Total\ thickness}{No.\ of\ tablets}$$

2.4.5 Weight variation test: Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and the standard deviation was calculated. IP limit forweight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is± 7.5% and more than 300 mg is ± 5%.

$$PD = \frac{(W\ avg) - (W\ initial)}{(W\ avg) \times 100}$$

Where PD= Percentage deviation

W avg = Average weight of the tablet,

W initial = Individual weight of the tablet.

2.4.6 Hardness: The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester. The Pfizer tester is commonly used

2.4.7 Time required for complete chewing: In this estimate that how much time are required for chewing of a chewable tablet.

2.4.8 Friability: The friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of absorption and shocks in a plastic chamber revolving at a height of 6 inches in each revolution. A pre-weighted sample of taste was placed in the friability and was subjected to 100 revolutions. Tablets were degusted using a soft muslin cloth and reweighted. The friability (F) is given by the formula.

$$F = (1\text{-}w_0/w) \times 100$$

Where w_0 is the weight of the tablets before the test and w is the weight of the tablets after the test.

3. RESULTS AND DISCUSSION

3.1 Evaluations of granule powder: The granule powder thus prepared was evaluated and the results obtained are given in table 3. Granule powders having an angle of repose value less than $25^{0,}$ showed excellence flow. Powder density was found below 1, which indicated the good quality of the powder. The value of % compressibility is found to be 9.25 which indicate the better ability of flow. The moisture content of powder was found below 3% which indicated the powder stickiness problem in compressor machine.

Table 3.Evaluation of granules powder

S No.	Parameters	Observation
1.	angle of repose	28.51^0
2.	moisture content	2.26%
3.	bulk density	0.53 g/ml
4.	tapped density	0.68 g/ml
5.	compressive index	9.52 g/ml

3.2 Evaluation of tablets: The tablets thus prepared were evaluated and the results obtained are given in Table 4.Organolaptic properties like color, odor and taste were found to be acceptable. Tablet showed % weight variation within given limit (120 mg is ± 10%, 120 mg to 300 mg is± 7.5% and more than 300 mg is ± 5 %.). Friability was found to be below it gives the better handling property of tablets. Hardness value was found to be in the range of 10-15 kg/cm^2. The time required for complete chewing is 5-15 min. the thickness of tablets is 6-7mm and diameter is 13-15mm.

Table 4.Evaluations of granule powder

S No.	Parameters	Observation
1.	weight variation	893.9mg ± 5%.
2.	hardness	12.8kg/cm^2
3.	thickness	6.47mm
4.	diameter	13.50mm
5.	friability	0.14%
6.	the time required for chewing	5-9 min

4. CONCLUSION

The present study was conducted to increase the bioavailability of curcumin in the human body to enhance its effect. This study was focused to make ananocurcuminchewable tablet. These tablets are also very cost effective and can give to the children who have difficulty in swallowing and to the adults who dislike swallowing. Chewable tablets are a help to improved patient acceptance through pleasant taste, patient convenience. This formulation of nanocurcumin chewable tablet will increase the bioavailability of curcumin which results in better absorption of curcumin in the human body. This will enhance the effectiveness of nanocurcumin chewable tablet was successfully develop. It is yellowish in color with the pleasant odor and taste. Its flavor is sweet and sour due to this combination of taste it will attract the children's also. The evaluation of granules and tablets indicate successful formulation of chewable tablet. This chewable tablet meets all the standard limits

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