FORMULATION DEVELOPMENT OF CURCUMIN (CURCUMA LONGA EXTRACT) BUCCAL DELIVERY SYSTEM (ORAL LIQUID SPRAY)

Bharathi Arigela[1]*, Kovida Chanumolu[2], Yamini Durga Talaparthi[2], Shriya suzan budha [3]

[1]Professor, Department of Pharmaceutics and Biotechnology, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh
[2]Students, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh
[3]Student, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh
***Corresponding author:**Department of Pharmaceutics,
KVSR Siddhartha College of Pharmaceutical Sciences,
Siddhartha Nagar,Vijayawada-10, Andhra Pradesh, India.

ABSTRACT

Background: The formulation aims to increase curcumin's oral bioavailability from Curcuma longa's rhizome. Curcuma longa rhizome colouring agent has anti-inflammatory, analgesic, and antioxidant properties. To tackle this problem, we created a curcumin formulation standardized to 95% potency in an emulsion that can be sprayed directly into the mouth.

Materials& Method: The materials under scrutiny are Turmeric extract containing 95% curcumin, Sorbitol solution (non-crystallizing) Sodium Benzoate, Polysorbate, Propylene Glycol, Glycerin, Acrysol K-140, Xanthan gum, Sucralose, Butylated Hydroxyanisole, Butylated Hydroxytoluene, Menthol crystals, Orange booster (IFF), Anhydrous citric acid, Distilled water.

Results and discussion: This formulation was centrifuged at 2000rpm for 10 minutes in three trials. One steady trail remained after centrifugation, whereas two unstable trails separated. Our rapid stability investigation requires only stable formulation.

Conclusion: We created an emulsion of curcumin standardized to 95% potency that may be sprayed into the mouth to deliver minute globules of curcumin. This aids oral inflammation and dental care. Curcumin is unstable and decomposes in light, heat, and air. We created the most stable oral spray of curcumin with polyoxy 40 hydrogenated castor oil's derivative in the optimal ratio and other substances. We also formulated the emulsion according to the spray device which is a new technique so that 1ml of the liquid formulation is equivalent to 7 sprays.

Key words: curcumin, oral bioavailability, anti-inflammatory, analgesic, antioxidant properties, liquid formulation.

1. INTRODUCTION: -

1.1 CURCUMIN: Curcuma longa plants generate turmeric's main curcuminoid, a bright yellow chemical. Turmeric intrigues cooks and medics. Ginger-family rhizomatous

herbaceous perennial turmeric (Curcuma longa). Turmeric, or Curcuma longa, has been utilized in Asian medicine for its anti-inflammatory, anticancer, antibacterial, and antioxidant qualities and its principal natural polyphenol, curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also known as diferulo[1]. The polyphenol curcumin targets multiple signalling molecules and acts on cells, promoting its many health benefits. Pain, metabolic syndrome, inflammation, and degenerative and inflammatory eye disorders may be treated[2]. Most of the therapeutic effects of curcumin supplementation are due to its anti-inflammatory and antioxidant properties[3]. Oral curcumin doesn't last long, which is bad. Despite its antioxidant and anti-inflammatory capabilities, it has a fast metabolism, minimal absorption, and rapid excretion. To increase curcumin bioavailability, researchers have explored different medications targeting these pathways[4]. These chemicals generally impede curcumin's metabolic pathway to boost bioavailability.

Curcumin comes from Curcuma longa, aromatic, phaeocaulis, manga, zedoria, and xanthorrhiza[5]. It comes in pills, tablets, ointments, energy drinks, soaps, and cosmetics. The FDA has designated curcuminoid : curcumin, bisdemethoxycurcumin, and demethoxycurcumin as "Generally Recognized as Safe"[6]. Clinical investigations have shown good tolerability and safety at dosages of 4000 to 8000 mg/day and up to 12,000 mg/day of 95% curcuminoid, including curcumin, bisdemethoxycurcumin, and demethoxycurcumin. Curcumin has a long-standing safety record. According to JECFA (The Joint United Nations and World Health Organization Expert Committee on Food Additives) and EFSA (European Food Safety Authority) studies, curcumin's Allowable Daily Intake (ADI) is 0-3 mg/kg body weight. Several trials on healthy participants have confirmed curcumin's safety and efficacy. Despite the well-established safety, some adverse effects have been documented. In a dosage response study, seven participants received 500-12,000 mg

and were observed for 72 hours. They had diarrhea, headache, rash, and yellow stool. In another trial, some participants who took 0.45 to 3.6 g of curcumin per day for one to four months suffered nausea and diarrhea, as well as an elevation in serum alkaline phosphatase and lactate dehydrogenase levels.[7]. Curcumin prevents lipid peroxidation including DNA damage by scavenging hydroxyl radicals, superoxide anion, as well as single-molecule oxygen. Curcumin inhibits inflammation and cancer via altering signalling molecules. In vitro, curcumin inhibits protein kinases, c-Jun/AP-1 activation, prostaglandin production, and COX-2 activity and expression, influencing development, differentiation, and malignancy [8].

1.2 Buccal drug delivery: Bioadhesive medicine delivery formulations were introduced in 1947 when dental adhesive powder and gum tragacanth attached penicillin to the oral mucosa. Medical drug delivery via mucoadhesive systems has gained in popularity [9]. Low bioavailability, gastrointestinal intolerance, inconsistent absorption, or pre-systemic clearance of other delivery routes render some drugs useless. Buccal delivery of systemic drugs is appropriate due to oral effects. This system administers medication through the mouth's buccal mucosa. Retentive doses of the therapeutic ingredient were easiest to deliver locally and systemically through the buccal cavity mucosa. Mucosa is permeable due to its extensive blood supply.[10]

- It has more surface area than sublingual mucosa.
- Improved compliance with parental instructions
- Easy administration and removal in case of toxicity
- Suitable for unconscious or comatose patients
- It does not do acid/enzyme or first-pass metabolism.

- It penetrates faster than skin and TDDS [11].

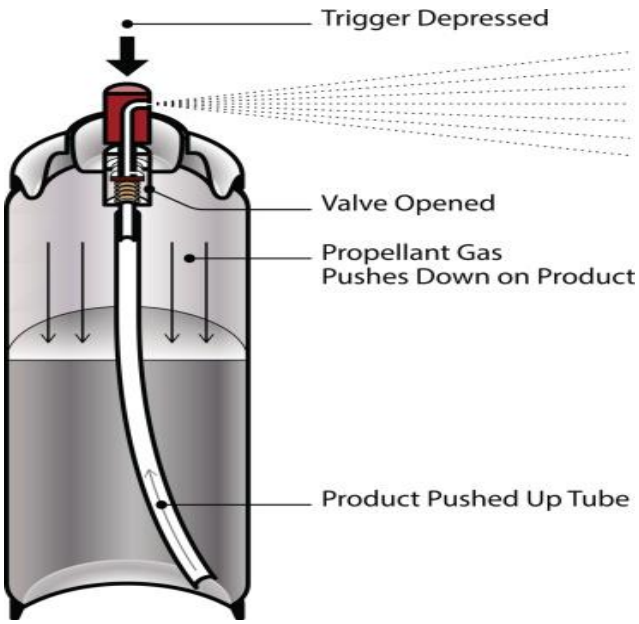

Figure 1: Cross section of the spray device

1.3 METHOD OF WORKING OF SPRAY DEVICE: A dip tube is inserted into the spray bottle containing 30 servings of oral liquid**.** Housing is connected to a dip tube and dose-controlling glass ball. Figure 1 shows the cross section design of the spray device.The glass ball moves up and down to control the particular amount of liquid per spray according to the actuator spray device action. The long spring controls the up and down movement of the glass ball for the release of liquid from the container as per the movement of the actuator spray device [12] Closure is like a screw cap that holds the piston and liquid-filled bottle. The needle-like arrangement is to connect the piston and the spring to move the glass ball according to the action of the actuator. The piston is for controlling the movement of the stem in the device for sucking and releasing liquid as per

the glass ball movement. The components work as a short spring to hold the piston with the stem , The Gasket is the outer cover of the stem and the O ring is the outer cover of the stem . Stem is to move up and downwards to suck the liquid according to the movement of the actuator. The actuator is to control and sprays liquid, which is operated manually with a finger. Insert is attached to spray nozzle to control and release liquid in the form of fine spray. Over cap is to cover the whole spray device to avoid external contamination [13]

Table 1: specifications of spray device

1.	Length of the container	121.5mm ± 1mm
2.	Width of the container	75mm ± 1mm
3.	Height	30mm ± 1mm
4.	Thickness	650 micrometer (Tolerance ± 10%)
5.	Weight	6 gsm ± 1gm
6.	Colour shade	Milky white
7.	Material of construction	High impact polystyrene

2. AIMS AND OBJECTIVES

2.1 AIM: The aim of the study is the Formulation development of Curcumin (Curcuma longa extract) Buccal delivery system (oral liquid spray) and evaluation.

2.2 OBJECTIVE: - The primary aim of the formulation is to enhance the oral bioavailability of curcumin, the pigment derived from the rhizome of Curcuma longa. This is a natural colouring agent derived from the rhizome of Curcuma longa, exhibiting therapeutic properties such as anti-inflammatory, analgesic, and antioxidant effects. Oral tablet and capsule formulations currently in the market exhibit low absorption and bioavailability due to numerous molecular biotransformation and first-pass metabolism. To address this issue, we developed a curcumin formulation standardized to 95% potency in an appropriate emulsion, enabling administration as a spray that delivers tiny globules of curcumin straight into the oral cavity.

3. MATERIALS AND METHODS

3.1 List of materials/reagents used in the study

Table 2: List of ingredients

s.no	Chemical name	Function
1.	Turmeric extract – 95% curcumin	Active pharmaceutical ingredient (API)
2.	Sorbital 70% solution (non-crystallizing)	Bulking agent
3.	Sodium benzoate	Antimicrobial agent
4.	Polysorbate 80	Surfactant

5.	Propylene glycol	Preservative
6.	Acrysol k – 140	Emulsifier
7.	Xanthan gum	Viscosity modifier
8.	Sucralose	Sweetening agent
9.	Butylated hydroxy anisole	Anti-oxidant
10.	Butylated hydroxyl toluene	Anti-oxidant
11.	Menthol crystal	Flavouring agent
12.	Orange booster	Flavouring agent
13.	Citric acid anhydrous	PH modifier
14.	Glycerin	Sweetening & tonicity
15.	Purified water to produce	Vehicle

3.2 EXPERIMENT METHOD

Table 3: Formula For 1000ml Batch Size

S.NO	**Chemical name**	**Batch number 21059**	**Batch number 21059 A**	**Batch number 21059 B**
1.	Turmeric extract – 95% curcumin	25 g	25g	25g

2.	Sorbitol 70% solution (non-crystallizing)	480g	480 g	480 g
3.	Sodium Benzoate	2g	2g	2g
4.	Polysorbate 80	54 g	54g	54g
5.	Propylene glycol	70 g	70g	70g
6.	Glycerin	50g	50g	50g
7.	Acrysol K- 140	30 g	25gm	20gm
8.	Xanthan gum	0.2 g	0.2g	0.2g
9.	Sucralose	2g	2g	2g
10.	Butylated Hydroxy Anisole	0.05mg	0.05mg	0.05mg
11.	Butylated Hydroxy Toluene	0.05mg	0.05mg	0.05mg
12.	Menthol crystal	0.7g	0.7g	0.7g
13.	Orange booster (IFF)	2.5ml	2.5ml	2.5ml
14.	Citric acid anhydrous	2 ml	2ml	2ml
15.	Purified water	Up to 1000ml	Up to 1000ml	Up to 1000ml

3.3 METHOD OF PREPARATION FOR BATCH 21059: As mentioned in Table 2 and 3 Weigh 25g of curcumin, add 50g of tween-80, 30g of acryl-k-140, 50g of glycerin, and 50g of propylene glycol, and mix thoroughly. Measure 0.2g of xanthan gum, dissolve it in 4g of tween-80, add 200 ml of hot water and 2g of sodium benzoate, cool it, and transfer the combination into the xanthan gum and tween-80 mixture, set it aside, and cool the mixture [14]. After cooling, transfer the mixture to a 1-litre vessel and continue stirring. Add 480

grams of sorbitol to the aforementioned mixture. Weigh 2gm of sucralose, dissolve it in 10ml of water, and transfer it to a 1-litre jar. Weigh 0.05 mg of butylated hydroxy toluene and 0.05 mg of butylated hydroxy anisole. Crush it with 10 gm of propylene glycol and place it into the mixing vessel[15].Smash 0.7 gm of menthol crystal, dissolve it with 10 gm of propylene glycol, and transfer it to the mixing bowl. Add 2.5 ml of an orange booster to the mixture, then add water to get the volume up to 1 litre. Check the pH. pH is 6.95, and the pH range is 3.5 to 5. Adjust the pH by adding 2 grams of citric acid by dissolving it in a small amount of water, adding it into the above solution stirring it, and then checking the pH [16]. After adding citric acid, the pH is 4.35. Now, the formulation should be exposed to centrifugation at 2000 rpm/10 min. [17]

3.4 METHOD OF PREPARATION FOR BATCH 21059 A: Combine 25g curcumin, 50g tween-80, 25g acrysol K-140, 50g glycerin, and 50g propylene glycol. Mix thoroughly. Dilute 0.2g of xanthan gum in 4g of tween-80. Add 200ml of hot water and 2g of sodium benzoate. Cool and transfer to the xanthan gum and tween-80 mixture. Set aside to cool. After cooling, transfer the mixture to a 1-liter vessel and continue stirring. Add 480 grams of sorbitol to the aforementioned mixture. Dissolve 2gm sucralose in 10ml of water and transfer to a 1-litre bottle. Weigh 0.05 mg of butylated hydroxy toluene and 0.05 mg of butylated hydroxy anisole. Crush it with 10 gm of propylene glycol and put it in the mixing vessel. Crush 0.7 gm of menthol crystal, dissolve it with 10 gm of propylene glycol, and transfer it to the mixing bowl. Add 2.5 ml of the orange booster to the mixture, then add water to make it up to 1 litre. Check the pH. pH is 6.95, and the pH range is 3.5 to 5. Now, correct the pH by dissolving 2 grams of citric acid in a tiny amount of water, transferring it to

the aforementioned solution, and stirring it. Check the pH. After adding citric acid, the pH is 4.35. Now the formulation should be submitted to centrifugation with 2000 rpm/10 min

3.5 METHOD OF PREPARATION FOR BATCH 21059 B: Weigh 25g of curcumin, add 50g of tween-80, 20g of acrysol k-140, 50g of glycerin and 50g of propylene glycol mix them all and 0.2g of xanthan gum, dissolve it in 4g of tween -80, add 200ml of boiled water and 2g of sodium Benzoate, cool it and transfer them into xanthan gum and tween-80 mixture, keep it aside and cool the mixture. After cooling transfer the mixture into to 1 litre vessel and keep stirring. Add 480 gm of sorbitol and transfer it into the above mixture. Weigh 2gm of sucralose dissolve it in the 10ml of water and transfer it into the 1 litre vessel. Weigh 0.05mg of Butylated hydroxyl toluene and 0.05mg of Butylated hydroxy anisole crush it by adding 10 gm of propylene glycol, and transfer it into the mixing vessel. Crush 0.7 gm of menthol crystal and add 10 gm of propylene glycol dissolve it and transfer it into the mixing vessel. Add 2.5 ml of orange booster to the mixture, adjust the volume to 1 litre with water, and check the pH. Ph is 6.95 and the limit of the pH. is 3.5 – 5. Now adjust the pH by adding 2 gm of citric acid, dissolving it in a small amount of water, transferring it to the above solution, and stirring it. Then, check the pH. After the addition of citric acid, the pH is 4.35. Now the formulation should be submitted to centrifugation with 2000 rpm/10min.

3.6 ASSAY:

3.6.1 Buffer preparation:

3.6.2 Mobile phase: It is a mixture of 35 volumes of tetrahydrofuran and 65 volumes of a buffer solution prepared by dissolving 10g of citric acid in 1000ml of water, adjusted to pH 3.0 with dilute ammonia solution.

3.6.3 Test solution: Reflux about eq. to 150mg of Curcuma longa extract under examination with 50 ml of methanol in a water bath for 15 min, cool, and filter. Reflux the residue further with 5 x 25 ml of methanol, cool, and filter. Combine all the filtrates and concentrate to 100 ml. Add 5 ml to 50 ml methanol [18].

3.6.4 Packaging: The formulated solution is Filled in a 100ml bottle sealed in a bottle sealing machine and subjected to analysis

4. Results and Discussion: In this study, we performed three trials as shown in Fig 2,3,4 for this formulation, these formulations underwent centrifugation at 2000rpm speed for 10 minutes. After centrifugation out of three only one trail shown in Fig 1 was stable. which was not separated and another two got separated which were unstable. Table 4 shows the Observed values of HPLC peak Areas, and retention time of Curcumin oral spray sample and standard and Figs 5&6 depicts the graphical presentation. we took a few parameters to check the curcumin oral spray sample solution as mentioned in Table 5. Only stable formulation is necessary for our study, which is subjected to accelerated stability studies.

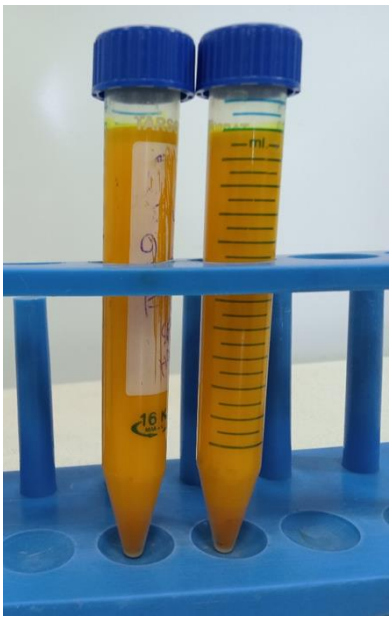

Fig 2: Stable formulation (Batch 1)

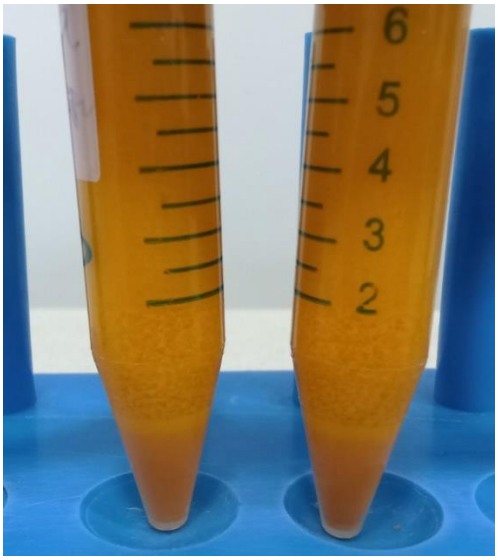

Fig 3: unstable formulation (Batch 2)

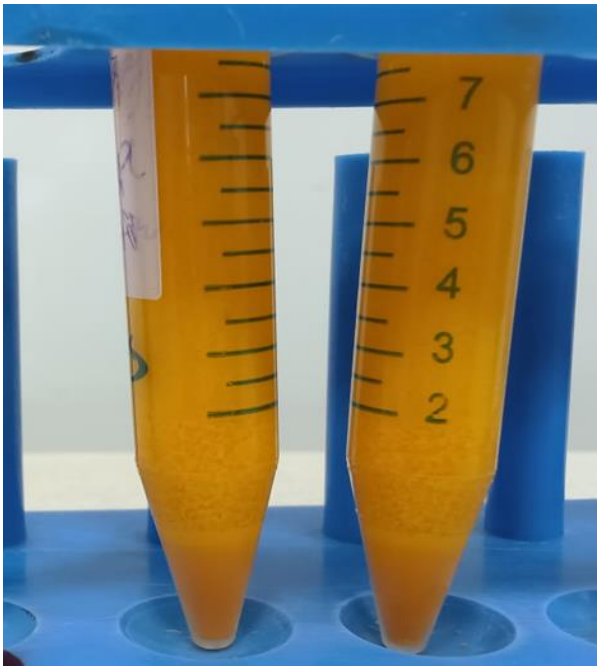

Fig 4: unstable formulation (Batch 3)

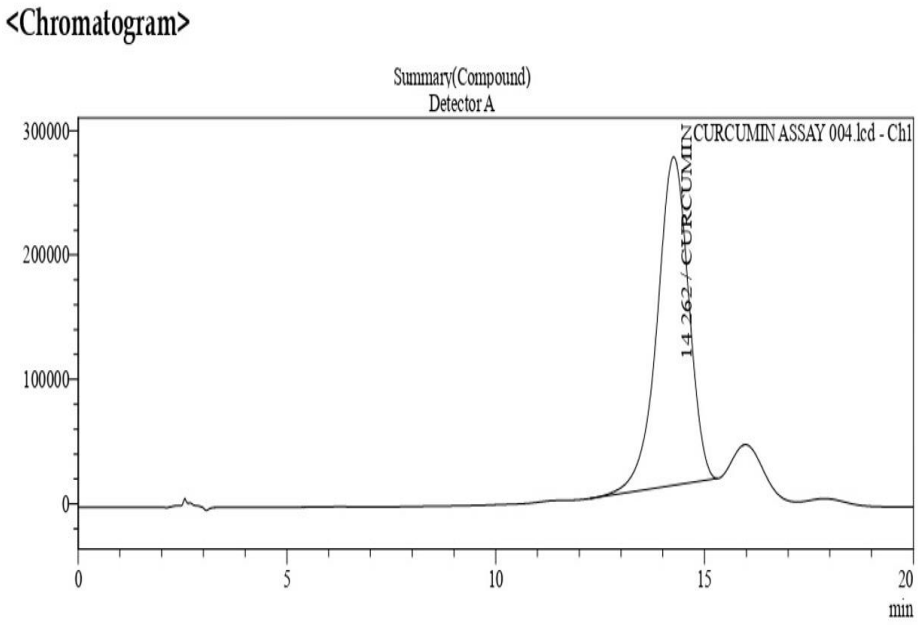

Fig 5 : chromatagram of curcumin standard

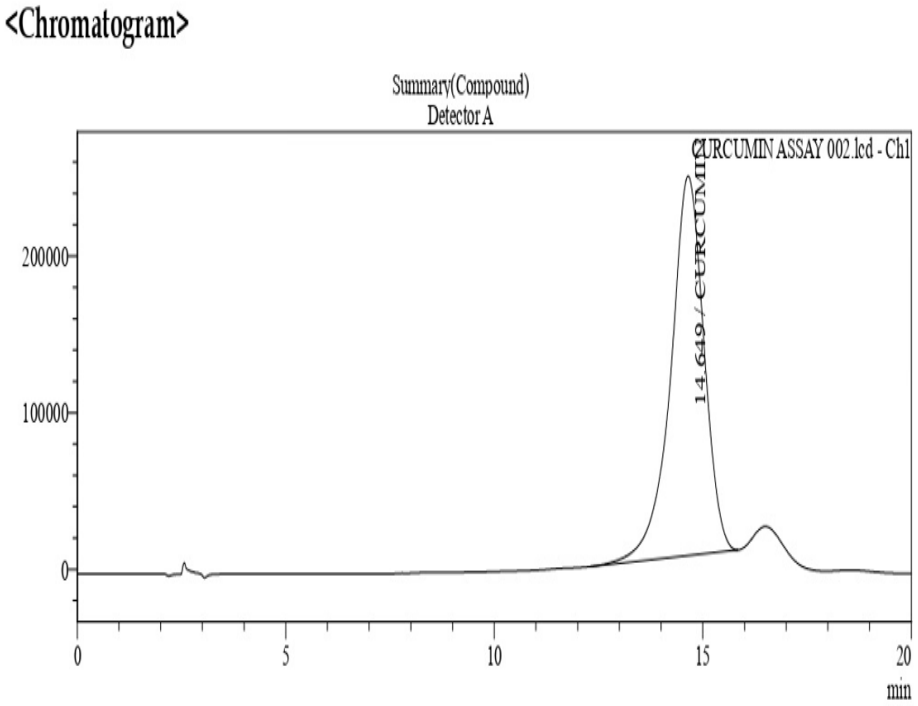

Fig 6: chromatogram of curcumin sample

Table 4: Observed values of HPLC peak Areas, retention time of Curcumin oral spray sample and standard

S.NO	NAME OF THE SOLUTION	RETENTION TIME	HPLC AREA

1.	Curcumin standard	14.649	13432523
2.	Curcumin sample	14.262	13850446

Table 5: Observation table for curcumin oral spray sample solution:

S.NO	PARAMETERS	SPECIFICATIONS	RESULT
1.	Description	Yellow-flavoured oral syrup	Yellow-flavoured oral syrup
2.	pH	4.0 (limit 3-5)	4.31
3.	Weight per ml	1.200 gm/ml (1.050gm/ml-1.3050gm/ml)	1.1479gm/ml
4.	Assay Each 1ml (spray) contains turmeric extract (rhizome) standardized to 95% curcumin (25)	22.5mg to 27.5mg (90.0% to 110.0%)	24.407mg (97.6%)

5.	Microbial Tests		
	i. TAMC	NMT100cfu/ml	20cfu/ml
	ii. TYMC	NMT10cfu/ml	<10cfu/ml
	iii. E.Coli	Shouldbe absent	Absent
	iv. Salmonell a sp	Shouldbe absent Shouldbe absent	Absent Absent
	v. Pseudomo nas aeruginos a	Should be absent	Absent
	vi. Staphyloc occus aerues		

5. CONCLUSION: The main objective of the formulation is to increase the oral absorption of curcumin which is the pigment obtained from Curcuma longa rhizome. This is a natural colouring material from Curcuma longa rhizome. In contrast, else therapeutic activities like Anti-inflammatory, Analgesic, Antioxidant etc. oral tablets/capsule formulations are available in the market have poor absorption and bioavailability due to various biotransformation of the molecule and also first-pass metabolism. To overcome this, we formulated curcumin standardized to 95% of its potency in suitable emulsion form so that the emulsion can be

taken as a spray form which contains minute globules of curcumin directly into the oral cavity. This will help with oral inflammatory conditions and also in dental care effectively. Curcumin is a highly unstable compound that is sensitive to light, heat, and Air (oxidative decomposition). So we formulated curcumin as oral spray in the most stabilized form which contains polyoxy 40 hydrogenated castor oil derivative in optimum ratio along with other ingredients. We also formulated the emulsion according to the spray device which is a new technique so that 1ml of the liquid formulation is equivalent to 7 sprays. This formulation is very stable convenient to carry, and easy to administer. This should be the most advantageous formulation, which is most useful to people, especially during the spread of airborne infections to maintain oral hygiene as an Anti-inflammatory, Antiviral, and Antibacterial.

FUNDING SUPPORT: The authors declare that they have no funding support for this study

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest

REFERENCES:

1. Kocaadam B, Şanlier N. Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Crit Rev Food Sci Nutr. 2017 Sep 2;57(13):2889-2895. doi: 10.1080/10408398.2015.1077195.
2. Hay E, Lucariello A, Contieri M, Esposito T, De Luca A, Guerra G, Perna A. Therapeutic effects of turmeric in several diseases: An overview. Chem Biol Interact. 2019 Sep 1;310:108729. doi: 10.1016/j.cbi.2019.108729.
3. Sun W, Wang S, Zhao W, Wu C, Guo S, Gao H, Tao H, Lu J, Wang Y, Chen X. Chemical constituents and biological research on plants in the genus Curcuma. Crit

Rev Food Sci Nutr. 2017 May 3;57(7):1451-1523. doi: 10.1080/10408398.2016.1176554.

4. Cho MY, Kang SM, Lee ES, Kim BI. Antimicrobial activity of *Curcuma xanthorrhiza* nanoemulsions on *Streptococcus mutans* biofilms. Biofouling. 2020 Aug;36(7):825-833. doi: 10.1080/08927014.2020.1823376.
5. Slika L, Patra D. Traditional Uses, Therapeutic Effects and Recent Advances of Curcumin: A Mini-Review. Mini Rev Med Chem. 2020;20(12):1072-1082. doi: 10.2174/1389557520666200414161316.
6. Karimi A, Ghodsi R, Kooshki F, Karimi M, Asghariazar V, Tarighat-Esfanjani A. Therapeutic effects of curcumin on sepsis and mechanisms of action: A systematic review of preclinical studies. Phytother Res. 2019 Nov;33(11):2798-2820. doi: 10.1002/ptr.6467.
7. Salehi B, Stojanović-Radić Z, Matejić J, Sharifi-Rad M, Anil Kumar NV, Martins N, Sharifi-Rad J. The therapeutic potential of curcumin: A review of clinical trials. Eur J Med Chem. 2019 Feb 1;163:527-545. doi: 10.1016/j.ejmech.2018.12.016.
8. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB. Curcumin, a component of golden spice: from bedside to bench and back. Biotechnol Adv. 2014 Nov 1;32(6):1053-64. doi: 10.1016/j.biotechadv.2014.04.004.
9. Smart JD. Buccal drug delivery. Expert Opin Drug Deliv. 2005 May;2(3):507-17. doi: 10.1517/17425247.2.3.507.
10. Morales JO, McConville JT. Preface for buccal drug delivery theme issue. Drug Dev Ind Pharm. 2014 May;40(5):577-8. doi: 10.3109/03639045.2014.892961.

11. Shinkar DM, Dhake AS, Setty CM. Drug delivery from the oral cavity: a focus on mucoadhesive buccal drug delivery systems. PDA J Pharm Sci Technol. 2012 Sep-Oct;66(5):466-500. doi: 10.5731/pdajpst.2012.00877.
12. Basu S, Holbrook LT, Kudlaty K, Fasanmade O, Wu J, Burke A, Langworthy BW, Farzal Z, Mamdani M, Bennett WD, Fine JP, Senior BA, Zanation AM, Ebert CS Jr, Kimple AJ, Thorp BD, Frank-Ito DO, Garcia GJM, Kimbell JS. Numerical evaluation of spray position for improved nasal drug delivery. Sci Rep. 2020 Jun 29;10(1):10568. doi: 10.1038/s41598-020-66716-0.
13. Shen Z, Dong J, Milton-McGurk L, Cai X, Gholizadeh H, Chan HK, Lee A, Kourmatzis A, Cheng S. Numerical analysis of airflow and particle deposition in multi-fidelity designs of nasal replicas following nasal administration. Comput Methods Programs Biomed. 2023 Nov;241:107778. doi: 10.1016/j.cmpb.2023.107778.
14. Teixeira, C.C.C., Mendonça, L.M., Bergamaschi, M.M. *et al.* Microparticles Containing Curcumin Solid Dispersion: Stability, Bioavailability and Anti-Inflammatory Activity. *AAPS PharmSciTech* 17, 252–261 (2016). https://doi.org/10.1208/s12249-015-0337-6
15. Kang S, Kim M, Kim H, Hong J. Enhancement of Solubility, Stability, Cellular Uptake, and Bioactivity of Curcumin by Polyvinyl Alcohol. Int J Mol Sci. 2024 Jun 6;25(11):6278. doi: 10.3390/ijms25116278.
16. Zheng B, McClements DJ. Formulation of More Efficacious Curcumin Delivery Systems Using Colloid Science: Enhanced Solubility, Stability, and Bioavailability. Molecules. 2020 Jun 17;25(12):2791. doi: 10.3390/molecules25122791.
17. Ko WC, Chang CK, Wang HJ, Wang SJ, Hsieh CW. Process optimization of microencapsulation of curcumin in γ-polyglutamic acid using response surface

methodology. Food Chem. 2015 Apr 1;172:497-503. doi: 10.1016/j.foodchem.2014.09.100.

18. Alafiatayo AA, Lai KS, Syahida A, Mahmood M, Shaharuddin NA. Phytochemical Evaluation, Embryotoxicity, and Teratogenic Effects of *Curcuma longa* Extract on Zebrafish (*Danio rerio*). Evid Based Complement Alternat Med. 2019 Mar 5;2019:3807207. doi: 10.1155/2019/3807207.