IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

TASTE MASKING OF PARACETAMOL BY MICROENCAPSULATION TECHNIQUE

Vaitheeswari Nagesh[1], Satya Narayan Pradhan[1*], Renganathan Sahadevan[2]

[1,2] Centre of Biotechnology, Alagappa College of Technology, Anna University, Chennai, Tamilnadu 600 025

[*]Corresponding author - Centre of Biotechnology, Alagappa College of Technology, Anna University

Abstract: Taste (Gustation) is a chemical reaction derived from sensory responses from the four main taste perceptions: salt, sour, bitter, and sweet. The taste sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. Unfortunately, many drugs have an unpleasant taste primarily bitter. Taste masking is an effective technique to mask bitterness to make it convenient for people, especially for paediatric and geriatric populations. Several approaches include-artificial sweeteners, ion exchange resins, inclusion complexes, adsorption, gelation, solid dispersion systems have provided taste-masked drugs in the pharma market. Besides, microencapsulation of drugs using polymers specifically Eudragit EPO by Evonik® for immediate release at gastric pH within 10-15 minutes. Complex phase coacervation is one such method in which enhancement of entrapment is facilitated by another polymer like polyethylene glycol or coacervating agents like sodium alginate, sodium lauryl sulphate. The wall material (polymer) and coacervating agents are of opposite charges for the good entrapment. Paracetamol is an ideal antipyretic drug in common use among populations which is in several dosage forms. Because of the bitterness, there is a need to hinder its bitter taste by polymers. The methodology emphasized here is amorphous solid dispersion using modified complex coacervation method with comparison over the ratio of polymers and cooperating agents. The final encapsulated drug will be evaluated for physical properties like appearance, taste, moisture content, particle size distribution, particle flow, and chemical properties like UV spectroscopic assay on paracetamol, dissolution tests.

Keywords: Taste masking, Microencapsulation, Phase coacervation, Eudragit EPO, Paracetamol, Evaluation of taste

1. INTRODUCTION

Oral administration of pharmaceuticals is one of the most popular methodsof drug delivery. Many orally administered drugs elicit a bitter taste. Palatability is an extremely important factor in ensuring the likelihood that the recipient will intake pharmaceuticals. A constant problem is in treatment of patient's inability to swallow solid dosage forms such as tablets especially in pediatric and geriatricgroups. These dosage forms permit perceptible exposure of active drug ingredients to the taste bud [30].

Accordingly, masking of unpleasant taste characteristics of the drug is an important factor in the formulation of these agents. "The worse the taste of the medication, the better the cure"was once the prevailing attitude. Today a change in patient attitude and development of taste masking technique has reversed this opinion. Humans around 10,000 taste buds in the fetus for about three months. Each taste bud has 50-100 cells. Each taste cell has a receptor on its apical surface. These are transmembrane proteins bind to molecules and ions that give rise to primary tastes-salty, sweet, sour, bitter. A fifth taste is called umami, a taste of certain amino acids (monosodium glutamate) [17]. Taste masking technologies are based on the reduction of the drug to be soluble in the saliva so that the drug concentration in saliva will remain below the threshold value of the taste. Old and traditional methods include the addition of sweeteners like aspartame, sucrose, cyclamates, saccharin, mannitol, lactose. Since it will not be to all classification of bitter drugs which diabetic people are consuming [28].

Active ingredient is significantly objectionable in taste unless flavors play a major role. Though, there are some methods other than artificial sweeteners are there in market trials, we attempted microencapsulation in which polymer will entrap the drug providing high stability and high drug loading capacity [18]. For targeting immediate release, Eudragit EPO is one such polymer marketed by Evonik®, Germany. It is soluble at pH less than 5, offers immediate release within 10-15 minutes. Paracetamol, is a bitter white crystalline powder mainly used as an analgesic pain reliever and antipyretic. It is used for the relief of headaches, minor aches, and pains. In this study, paracetamol was used as a model drug for taste masking using microencapsulation [29].

1.1 PARACETAMOL

Paracetamol, an international name used in Europe and also as Acetaminophen (an international name used in the USA) is nothing but N-acetyl-para-aminophenol. It is available without the prescription of a doctor, both in mono and multi-component preparations. It is often used as an antipyretic drug and also an analgesic according to a doctor's prescription [28]. In different moderate-intensity pains, paracetamol as a weak analgesic together with nonsteroidal analgesic drugs or co-analgesics (e.g., caffeine) is a basic non-

opioid analgesic (the first step of the analgesic ladder). When pain increases, paracetamol is used as an additional analgesic with weak (e.g., caffeine, tramadol) or strong (e.g., morphine, fentanyl) opioids.

After ingestion, it is readily absorbed from the GI tract for about 30 minutes to 2 hours. In the liver, it is metabolized up to 90-95% by glucuronidation of about 40% and sulfation of about 20-40% [31]. The permeability of paracetamol to reach target tissue in the body is log p = 0.91 Paracetamol is close to classical non-steroidal anti-inflammatory drugs (NSAIDs) that act by inhibiting COX-1 and COX-2 enzymes and especially similar to selective COX-2 inhibitors. It inhibits prostaglandin synthesis by reducing the active form of COX-1 and COX-2 enzymes[13]. This occurs only when the concentration of arachidonic acid and peroxides is low. Under these conditions, COX-2 is the predominant form of cyclooxygenase, which explains the apparent COX-2 selectivity of Paracetamol [31].

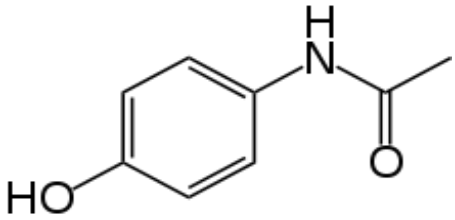

Fig 1: Chemical structure of paracetamol

S.NO	TECHNIQUES	AGENTS USED / EXAMPLES
1.	Artificial flavors and sweeteners	Eucalyptus oil – bitterness masked by fenchone ,borneol ,isoborneol ,cooling effect reduces bitterness ,produces desensitivity as in methanol ,chloroform
2.	Polymer coating	Ibuprofen (core) , methacrylic acid (polymer) by air suspension technique
3.	Ion exchange resins	Interaction of amine drugs with poly carboxylic acid ion exchange resin
4.	Inclusion complexes	Carbepentane citrate syrup – ratio 1:1 with 'β cyclodextrin
5.	Adsorption	Loperamide and phenyl propanolamine adsorbed on Mg - Al silicates (veegum F)
6.	Granulation	Drug Erythromycin is granulated with Alginic acid ratio 2.5 : 1
7.	Gelation	Water insoluble gels by sodium alginate and calcium gluconate solutions
8.	Prodrug approach	Geometric alterations of extreme bitter drugs such as chloramphenicol,erythromycin
9.	Salt / derivatives	Aspirin masked with Magnesium salt of aspirin

Table 1: Traditional approaches for taste masking

Microencapsulation is a technique by which material is encapsulated with another one to forms a protective shell or wall. It is performed to isolate and protect the material from the environment or to promote controlled release [11,14]. Microencapsulation can be used in the encapsulation of protein, because of its simple technique conditions and use of non-toxic solvent. Also, microencapsulation can be used in the packaging of tiny particles, with very small particle sizes in the form of capsules 1µm to 1000µm. The microencapsulation of drugs and their delivery keeps promise for improved therapeutical purposes. The texture, stability, foams, emulsions, and mechanical properties of dispersed systems depend on the constituent emulsifiers (low molecular weight emulsifiers) and biopolymers (proteins and some polysaccharides) adsorb and interact at liquid interfaces.

2. PHASE COACERVATION

Microencapsulation by coacervation technic consists of the separation phase of one or many hydrocolloids from the initial solution and the subsequent deposition of the newly formed coacervate phase around the active ingredient suspended or emulsified in the same reaction media. Simple coacervation is the separation phase of a liquid phase into a polymer-rich phase (coacervate) and a polymer-poor phase. It regards advantages like cost-saving and flexible operations [9]. Microcapsules by coacervation increase controlled ability based on mechanical stress, temperature, or sustained release. The most common covering materials are hydrocolloids, vegetable gums, modified starches and celluloses, dextrin and lipids, etc., and the main methods used for microencapsulation are spray drying, spray cooling, covering in a fluid bed, extrusion, centrifugal extrusion, coacervation, co-crystallization, and molecular inclusion.

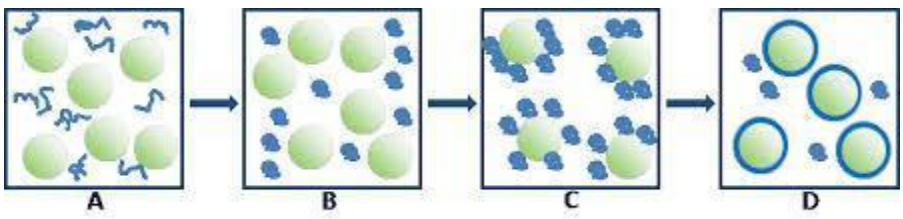

Fig 2: Microencapsulation of the drug by polymer

2.1 COMPLEX COACERVATION

Complex coacervation, in which two or more oppositely charged polymers are involved, has also been used to encapsulate fish oils. If there is an electrostatic attraction in water, associative phase separation of two polymers occurs. The interaction of two oppositely charged colloids coacervation cause complex Coacervation [8]. Encapsulation by complex coacervation is known as a potential technique for fabricating nanoparticles with a lipid core, this process could be used to design microencapsulation systems to increase desirable functions, such as preservability, miscibility, deliverability, and controlled release of the ingredients. The complex coacervation method is an emulsification step for making an oil-in-water emulsion, a coacervation step for coating the oil droplet surface by adjusting the pH of the solution, and a step for fixating the shell membrane through the gelation of the coacervate or by chemical crosslinking. The applications in the formulation of pharmaceuticals are controlled release, avoid gastric irritation, taste masking, improved stability [11].

3. OBJECTIVES

The main aim of this project is to taste mask the paracetamol by microencapsulation technique. The objectives are achieving immediate release profile with enhanced bioavailability**,** restriction of drug dissolution in mouth / oral cavity and disintegration at gastric pH**,** reduce irritation & numbness over the tongue, throat, enhance patient's compliance, convenient for pediatric and geriatric populations.

4. METHODOLOGY

Taste masking of Paracetamol was performed via microencapsulation with Eudragit EPO, which is used to target drug release in acidic mediums, e.g., gastric fluid and is used for taste masking of bitter drugs [23]. Solubility enhancer, polyethylene glycol 3350 was used to improve the inclusion of paracetamol in Eudragit EPO, by increasing Paracetamol aqueous solubility during coacervation. Several trials were prepared by varying Paracetamol: Eudragit EPO from 1: 1 to 1: 2 [15]. And the trials were split for sodium lauryl sulphate and poly ethylene glycol 3350. Before starting, the API, polymer, coacervation enhancer, adsorbent had been shifted in mesh no.20 (850 microns) individually for uniform particle size. Eudragit EPO (Evonik industries®) was dissolved in a mixture of 12ml of hydrochloric acid (1N) and 8ml of sodium hydroxide (1N) having a pH of 3.0 Then, according to the trial SLS or PEG 3350 (Gujchem surfactants Ltd) was added to the mixture and mixed uniformly using stirrer at above 1000 rpm. It was left until obtaining a clear solution. Subsequently, Paracetamol (Farmson pharmaceutical) was added and stirred until complete dissolving. If needed, the temperature was increased to 40°C to assist dissolving. 1N NaOH solution was added to the above mixture to reach alkaline pH which will lead to the complete precipitation of Paracetamol and Eudragit EPO from the solution [26]. The precipitate was then filtered using nylon mesh of 200µm and further by Whatman filter paper if required. For better particle size and nature, absorbents namely aerosil 200 or calcium silicate Florite R (Tomito Pharmaceuticals) was added in adequate quantity. The precipitate was then placed over butter paper and kept in a hot air oven at 45 - 50°C until it dried [32].

	Para: Eudragit EPO	SLS	PEG 6000	PEG 3350	Aerosil 200	Calcium Silicate FloriteR	Coacervated pH	Dried Time
Trial1	1:1		-	-	-	-	8.2	>24 hours
Trial 2	1:1	-		-		-	7.7	16 hours
Trial 3	2:1	-	-		-	-	8.16	Overnight dried
Trial 4	2:1	-	-	5.97g	-	6.4g	8.17	Overnight dried

Table 2: Trials and its composition

5. RESULTS AND DISCUSSION

5.1 APPEARANCE

The resultant coacervated product obtained from trial 4 is off-white, appears to be a fine, free-flowing powder. The figure below clearly shows the fine texture of the product.

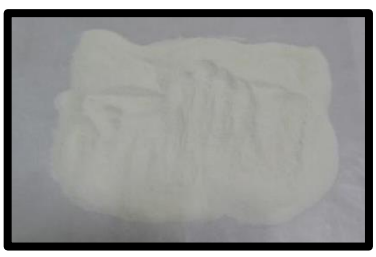

Fig 3: Trial 4 coacervated product

5.2 BULK AND TAPPING DENSITY

The bulk and tapping density were taken for 20g of trial 4 product. The bulk density value was found to be 0.38 g/cm³ and the tapped density was 0.53 g/cm³. The compressibility or Carr's index and Haussner's ratios were 16.28 % and 1.19 respectively [34].

Carr's index	Flowability	Hausner ratio
≤10	Excellent	1.00–1.11
11.0–15.0	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Awful	>1.60

Table 3: Data relating Carr's index and flow property

5.3 LOSS ON DRYING

The loss on drying value was taken for 1g of trial 4 product at 105°C for 5 minutes after drying the product in a hot air oven at 40°C for 3 hours. The LOD value was obtained to be 2.32% for the trial 4 product. The LOD value between 1-3 is said to be good powder nature as per pharma guidelines [21].

5.4 PARTICLE SIZE DISTRIBUTION

The particle size distribution was taken for 25g of trial 4 product. Accordingly, the sieves were fitted and agitated with the powder for 10 minutes with 10-watt power. The final recordings and calculation are as follows:

Sieve number	**Weight of the empty sieve (g)**	**Weight of the sieve + blend (g)**	**% Retained on the sieve**	**% Cumulative on the sieve**
20	385.2	385.6	1.67	1.67
30	370.0	370.4	1.67	3.34
40	378.4	381.4	12.5	15.84
60	370.0	373.0	12.5	28.34
80	356.8	358.4	6.67	35.01
100	360.4	362.0	6.67	41.68
Pan	443.4	457.4	58.33	100.01

Table 4: Particle size distribution

The % cumulative deposited on the sieve number 60 is taken as the number of granules present in the composition and remaining to that are fines composition. The ratio of granules: fines was found to be 1: 2.5

5.5 YIELD OF THE PRODUCT

The yield was calculated for trial 4 product by the formula below.

$$\textbf{Yield} = \frac{\textbf{Practical value of composition taken}}{\textbf{Theoretical value of the product obtained}} \textbf{ X 100}$$

The yield percentage, thus obtained for trial 4 was **77.26**

5.6 GUSTATION RESULTS

The gustation results were taken from children, adults and geriatric population for the taste and release of encapsulated

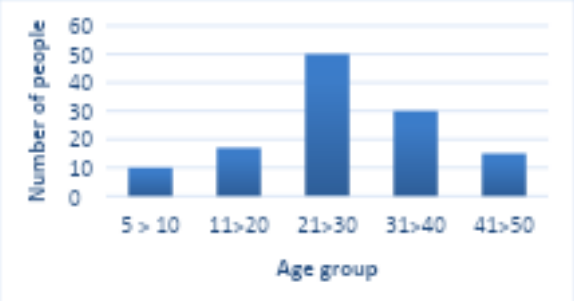

Fig 4: Population of different age groups took gustation test

Fig 5: Gustation taste scores

paracetamol orally. The population largely fall between good, better and worse. The immediate release was achieved orally within 15-30 seconds.

6. CONCLUSION

The method was optimized for phase coacervation using different Eudragit EPO polymer ratios and different ratios of cooperating agents. From the data collected from physical evaluation, the coacervated product obtained from the microencapsulation technique is good enough to go for compression with the addition of extra-granular composition. The resultant product is off-white, fine, free-flowing when done using the method with trial 4 compositions as mentioned in table 2. This coacervated product provides immediate release and bitterness masked. The future work is to fix extra-granular composition for the fine coacervated product by the immediate release and to compress it into the round - 13.8 punch tablet, also to examine the microscopic view of the coacervated product before drying to confirm the efficient encapsulation of polymer over the paracetamol.

7. ACKNOWLEDGEMENTS

We would like to express our sincere gratitude to all individuals and organizations (Medreich R & D, Bangalore, Anna University, Chennai) that contributed to the successful completion of this research project on taste encapsulation using polymers.

8. REFERENCES

1. Shalini Sharma and Shaila Lewis, "Taste masking technologies: a review" International *Journal of Pharmacy and Pharmaceutical Sciences* Vol 2, Issue 2, 2010.
2. Jagtap et al., "Advance Approaches in Taste Masking for Pharmaceutical Formulation", *Journal of Medical and Pharmaceutical Innovation*; 4 (20) 2017; 1-14.
3. EP 2 646 003 B1 09.10.2013 Bulletin 2013/41 Adare Pharmaceuticals, Inc. Lawrenceville, NJ 08648 (US).
4. US 010 245 232 B2 Jan.21, 2016, SPI Pharma, Inc., Wilmington, DE (US)
5. US 010 568 832 B2 Aug. 16, 2018, Gopi M. Venkatesh, Vandalia, (US) (73) Adare Pharmaceuticals, Inc.
6. M. Maniruzzaman et al., "Taste masking of paracetamol by hot-melt extrusion: An in vitro and in vivo evaluation", *European Journal of Pharmaceutics and Biopharmaceutics* 80 (2012) 433–442, Doi: 10.1016/j.ejpb.2011.10.019.
7. P. C. Ferreira Department of Health Sciences, Portuguese Catholic University, "Drug delivery systems: Advanced technologies potentially applicable in personalized treatments", *EPMA Journal (2010)* 1:164–209, DOI: 10.1007/s13167-010-0001-x.
8. Hitabatuma Aloys, Sameh A. Korma, Tuyishime Marie Alice, Nyinawumuntu Chantal, Abdelmoneim H. Ali, Sherif M. Abed, Habinshuti Ildephonse: "Microencapsulation by Complex Coacervation: Methods, Techniques, Benefits, and Applications - A Review", *American Journal of Food Science and Nutrition Research.* Vol. 3, No. 6, 2016, pp. 188-192.
9. H.P. Merkle et al "Preparation and In Vito Evaluation of Cellulose Acetate Phthalate Coacervate Microcapsules", *J. Pharm Science* 62 pp. 1444–1448 (1973).
10. US 005 814 332 A Sep. 29, 1998 Samba Siva Rao Ghanta et al., Eurand America, Inc., Vandalia, Ohio.
11. US 6,716,456 B1 Apr. 6, 2004 Luigi Giovanni Marelli et al., Eurand International S.p.A.
12. US 2006/0105038A1 May 18, 2006, Jin-Wang Lai, Springboro, et al., Eurand Pharmaceuticals Limited.
13. Samah Hamed Almurisi, Abd Almonem Doolaanea, Muhammad Eid Akkawi, Bappaditya Chatterjee, Khater Ahmed Saeed Aljapairai & Md Zaidul Islam Sarker (2020): "Formulation development of paracetamol instant jelly for pediatric use", *Drug Development and Industrial Pharmacy*, DOI: 10.1080/03639045.2020.1791165.

14. Ghulam Murtaza, Mahmood Ahmad et al., "A Comparative Study of Various Microencapsulation techniques: Effect of polymer viscosity on Microcapsule characteristics", *Pak. J. Pharm. Sci.,* Vol.22, No.3, July 2009, pp.291-300.

15. F Lecomte et al., "Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns" *Journal of Controlled Release,* 89 (2003) 457–471, doi:10.1016/S0168-3659(03)00155-X.

16. Toshizo Isemura and Akira Imanishi, "The Dissolution of Water-Insoluble Polymers in the Surfactant Solution - The Polyelectrolyte-Like Behaviour of the Dissolved Polymers", *Journal of Polymer Science* XXXIII, PAGES 337-352 (1958).

17. Gaith Zoubari, Rebaz Ali, Andriy Dashevskiy, "Water-soluble and -insoluble polymers as binders for pellet preparation by extrusion/spherization", *Journal of Drug Delivery Science and Technology*, S1773-2247(18)31035-9 (2018).

18. Pravin Gupta1, Manish Kumar et al., "An Overview on Polymethacrylate Polymers in Gastro-retentive Dosage Forms", *Open Pharmaceutical Sciences Journal*, 2015, 2, 31-42.

19. Katarzyna Wasilewska and Katarzyna Winnicka, "Ethyl cellulose–A Pharmaceutical Excipient with Multidirectional Application in Drug Dosage Forms Development", *Materials 2019,* 12, 3386; doi:10.3390/ma12203386.

20. Juliana dos Santo, Guilherme Silveira da Silva eta l., "Eudragit®: A Versatile Family of Polymers for Hot Melt Extrusion and 3D Printing Processes in Pharmaceutics", *Pharmaceutics 2021,* 13, 1424.

21. US 2020/0170959 A1 June.4,2020 Diane Goll et al., SPI Pharma, Inc., Wilmington, DE (US).

22. US 006 139 865 A Oct. 31, 2000 David R. Friend et al., Eurand America, Inc., Vandalia, Ohio.

23. Izabela Dutra, Carlos Raimundo, "Microparticles obtained by complex coacervation: influence of the type of reticulation and the drying process on the release of the core material", *Food Science and Technology (Campinas)* December 2010, DOI: 10.1590/S0101-20612010000400036.

24. Behera S, Ghanty S, Ahmad F, Santra S, Banerjee S (2012) "UV-Visible Spectrophotometric Method Development and Validation of Assay of Paracetamol Tablet Formulation". *J Anal Bioanal Techniques* 3:151. doi:10.4172/2155-9872.1000151.

25. Jang, Hyun-Jun, et al. "Safety Evaluation of Polyethylene Glycol (PEG) Compounds for Cosmetic Use." *Toxicological research* vol. 31,2 (2015): 105-36. doi:10.5487/TR.2015.31.2.105.

26. Evonik Nutrition & Care GmbH EUDRAGIT® E 100 July 2015 EUDRAGIT® EPO, EUDRAGIT® E 12, 5.

27. Anisha A. D'souza & Ranjita Shegokar (2016): "Polyethylene glycol (PEG): A versatile polymer for pharmaceutical applications", *Expert Opinion on Drug Delivery*, DOI: 10.1080/17425247.2016.1182485.

28. Mali Kailas Krishnan et al., "Manufacturing of Paracetamol Tablets", 22 April 2018.

29. F.Aguilar, U.R. Charrondiere, et al., "Calcium silicate and silicon dioxide/silicic acid gel added for nutritional purposes to food supplements", *Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food, The EFSA Journal (2009) 1132, 1-24,* 5 June 2009.

30. David M. Kastenberg, "A Novel PEG 3350 Formulation", *New Drug Review.*

31. Marta Jèwiak-b Benista and Jerzy Z. Nowak, "Paracetamol: Mechanism of Action, Applications, and Safety Concern", *Acta Poloniae Pharmaceutica ñ Drug Research, Vol. 71 No. 1 pp. 11ñ23, 2014.*

32. Basheer Al-Kasmi et al., "Aqueous and pH-dependent coacervation method for taste masking of paracetamol via amorphous solid dispersion formation", *Nature – Scientific Reports, (2021)11:8907*.

33. Y. Kawamura et al., *Calcium silicate, 80th JECFA - Chemical and Technical Assessment (CTA), FAO 2015.*

34. Handbook of Pharmaceutical excipients, *sixth edition.*